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Sulfoxydes : nouvelle stratégie pour l'activation C(sp^3)-H asymétrique

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Monsieur David PROCTER — Directeur de recherche, Université de Manchester

« Savoir s’étonner à propos est le premier
pas fait sur la route de la découverte »

(Louis Pasteur)

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Summary

Abbreviations

* = denotes chirality

Ac = acetyl

Adam = adamantyl

APS = (*S*)-2-(*p*-tolylsulfinyl)aniline

Ar- = denotes an aromatic ring

Ar^F = 2,3,4,5,6-pentafluorophenyl

ATS = (*S*)-2-(*tert*-butylsulfinyl)aniline

AQ = 8-aminoquinoline

BHT = 2,6-di-*tert*-butyl-4-methylphenol

BINAP = (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)

Bn = benzyl

Boc = *tert*-butyloxy carbonyl

Bpin = pinacol borane

BQ = 1,4-benzoquinone

Bz = benzoyl

CMD = concerted metallation deprotonation

cod = cyclooctadiene

Cp = cyclopentadienyl

Cp* = pentamethylcyclopentadienyl

Cy = cyclohexyl

d.r. or dr = diastereomeric ratio

DAG = diacetone D-glucose

DCC = dicyclohexylcarbodiimide

DCE = 1,2-dichloroethane

DCM = dichloromethane

DFT = density functional theory

DG = directing group

DIBAL-H = di-isobutyl aluminium hydride

DKR = dynamic kinetic resolution

DMAP = *N*,*N'*-dimethylamino pyridine

2,2-DMB = 2,2-dimethylbutane

2,6-DMBQ = 2,6-dimethoxybenzoquinone

DME = dimethoxyethane

DMF = dimethylformamide

DMSO = dimethylsulfoxide

Dpen = 1,2-Diphenyl-1,2-ethylenediamine

dppf = 1,1'-bis(diphenylphosphine)ferrocene

e.r. or er = enantiomeric ratio

eq or equiv. = equivalent

FG = Functional group

HFIP = 1,1,1,3,3,3-hexafluoroisopropanol

HIMP = (3*R*,4*R*,5*S*)-4-hydroxy-5-isobutyl-3-methylpyrrolidin-2-one

IUAPC = union for pure and applied chemistry

KIE = kinetic isotope effect

KR = kinetic resolution

L = ligand

LDA = Lithium diisopropylamine

M = metal

m-CPBA = *meta*-chloroperoxybenzoic acid

MNBA = 2-methyl-6-nitrobenzoic anhydride

Ms = mesyl

NBO = Natural Bonding Orbital

NBS = *N*-bromo succinimide

NBSA = *N*-((*S*)-1-(4-(*tert*-butyl)phenyl)-2-((*R*)-*p*-tolylsulfinyl)ethyl)acetamide

NCI = Noncovalent interactions

NIS = *N*-iodo succinimide

Ns = nosyl

Nu = Nucleophile

o = *ortho*

m = *meta*

p = *para*

PCPA = (*E*)-3-((1*S*,2*S*)-2-propylcyclopropyl) acrylic acid

Phth = phthaloyl

Piv = trimethylacetyl

PMP = *para*-methoxyphenyl

*p*Tol = para-tolyl

rt = room temperature

SAM = S-adenosyl-methionine

SCF = Self-consistent field

T °C = Temperature in Celsius

T3P = Propylphosphonic anhydride

TADDOL = α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol

TBAB = *tert*-butyl ammonium bromide

TBDMS = *tert*-butyldimethylsilyl

*t*Bu = tert-butyl

TDG = transient directing group

TEMPO = 2,2,6,6-Tetramethylpiperidinyloxyl

TES = triethylsilyl

Tf = triflate

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TM = transient mediator

TMEDA = *N,N,N',N'*-tetramethylethylenediamine

TMS = trimethylsilyl

TMSO = tetramethylene sulfoxide

Tol = Toluene

Avant-propos

1. Généralités

Pendant de nombreuses années, les liaisons C-H aliphatiques ont été considérées comme dormantes, très difficilement exploitables dans le contexte de la chimie organique.[1] Le défi le plus important en considerant la fonctionnalisation directe via la conversion d'une liaison C-H vers une liaison C-X est de sélectionner une liaison C-H parmi toutes celles que contient une molécule. L'approche la plus utilisée à ce jour est l'utilisation d'un groupement directeur, qui permet, en se chélatant à un métal, de diriger l'activation d'une liaison C-H en particulier. Les premiers groupements directeurs développés, basés sur des pyridines fortement coordinantes ont peu à peu laissé place à d'autres auxiliaires plus modulables. En particulier, la découverte du potentiel particulier des groupements bicoordinants tels que la 8-aminoquinoline, l'acide picolinique ou la 2-(methylthio)aniline a permis de réaliser des avancées majeures dans l'activation de liaisons C(sp^3)-H catalysée par un métal de transition (Figure 1).[2–5]

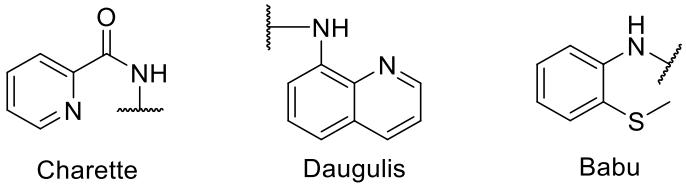


Figure 1 Exemples de groupements directeurs bicoordinants utilisés pour l'activation de liaisons C-H

De plus, la chiralité et son contrôle occupent une place majeure dans l'industrie pharmaceutique car deux énantiomères peuvent avoir des propriétés biologiques bien différentes. Ainsi le thalidomide, médicament utilisé dans les années 1950 comme anti-nauséeux chez les femmes enceintes, entraînait également de graves malformations chez le fœtus causées par l'un de ses énantiomères.[6] Dans ce cas particulier, même une synthèse asymétrique n'a pas résolu le problème puisque le centre stéréogène se racémise *in vivo* (Figure 2).[7] Plus de 50% des nouveaux médicaments ayant obtenu une autorisation de mise sur le marché après 2000 sont énantiopurs et il existe de nombreux exemples où un énantiomère a montré un effet thérapeutique supérieur à l'autre.[8]

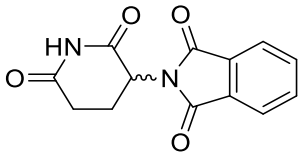


Figure 2 Structure de la thalidomide

Depuis quelques années, dans notre laboratoire, nous nous intéressons à l'activation asymétrique de liaisons C-H en utilisant un sulfoxyde comme inducteur chiral hautement modulable. Par exemple, l'utilisation du *p*-tolylsulfoxyde à la fois comme groupement directeur de fonctionnalisation C-H et comme auxiliaire de chiralité a permis d'accéder à des motifs triaryles à double chiralité axiale avec d'excellents rendements et de hautes puretés diastéréomériques (Figure 3).

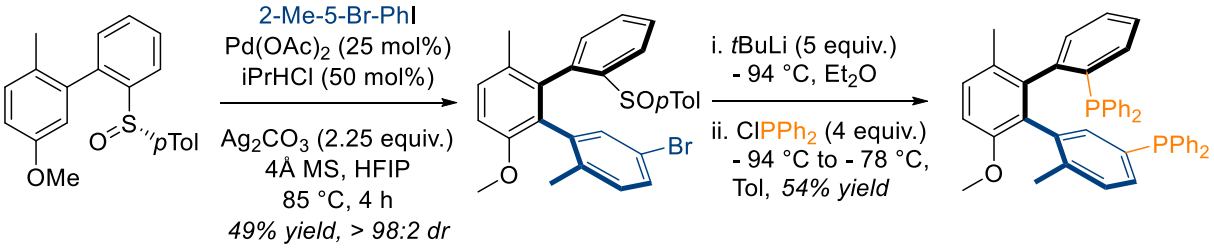


Figure 3 Synthèse d'un ligand à double axe de chiralité

Les composés obtenus peuvent être utilisés en tant que précurseurs de ligands pour des transformations asymétriques comme illustré dans la Figure 4.[9–11] La conception et l'utilisation de ligands originaux similaires est en cours de développement.

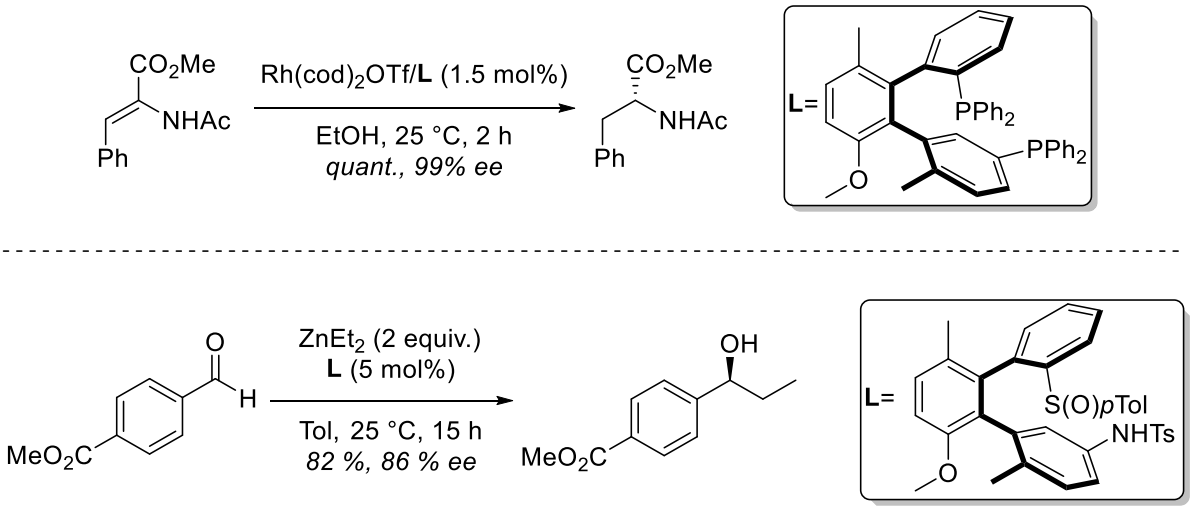


Figure 4 Exemples de ligands à chiralité axiale synthétisés au laboratoire et leurs applications

Par ailleurs, les voies de synthèse pour accéder à des sulfoxydes énantiopurs étant de plus en plus efficaces, ceux-ci sont aujourd'hui couramment utilisés en tant que ligands pour l'induction asymétrique de réactions métallo-catalysées, par White ou Itami par exemple (Schéma 1).[12,13]

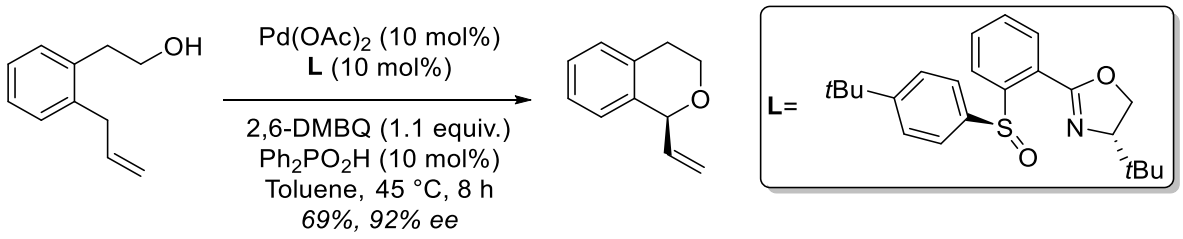


Schéma 1 Cyclisation oxydante asymétrique utilisant un ligand sulfinyloxazoline chiral

Un autre axe de recherche dans notre laboratoire porte sur la synthèse totale énantiosélective de produits naturels. Ainsi, la chiralité du sulfoxyde a été exploitée pour permettre d'accéder à des squelettes complexes et sa modularité a permis de parvenir à des synthèses efficaces.[14]

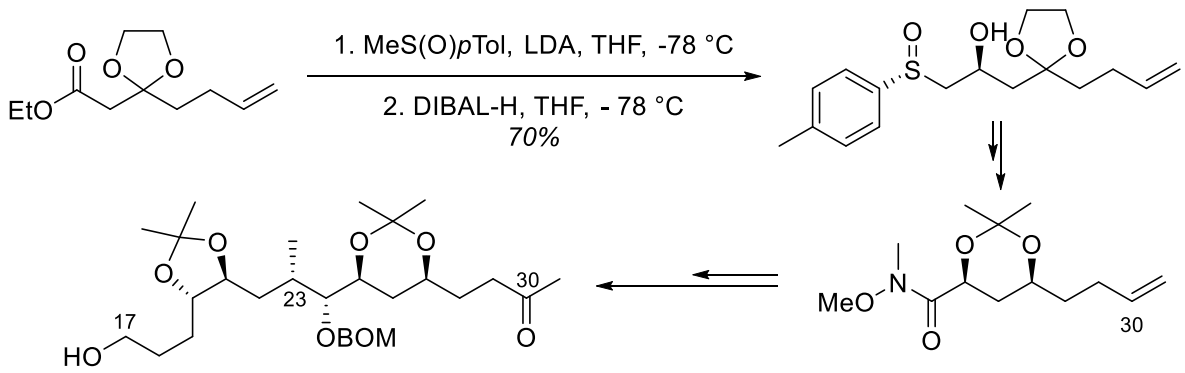


Schéma 2 Synthèse du fragment de Paquette, intermédiaire clé dans la synthèse de l'amphidinol 3

En nous inspirant à la fois des travaux du laboratoire et de Babu qui décrit l'utilisation d'un groupement directeur d'activation de liaisons C-H de type thioaniline,[3] nous nous sommes intéressés au développement de stratégies de fonctionnalisation C(sp^3)-H stéréosélectives en utilisant une sulfinylaniline énantiopure à la fois comme inducteur de chiralité et groupement directeur d'activation de liaisons C-H (Figure 5). C'est dans ce contexte que s'inscrit le projet *Sulf-As-CH*.

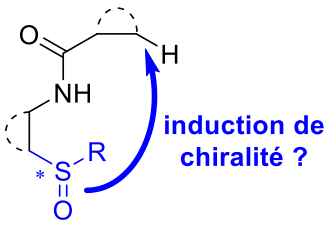


Figure 5 Rôle du sulfoxyde en tant qu'inducteur de chiralité pour l'activation de liaisons C-H

2. Résultats et discussions

Ces travaux ont été initié par Dr Faouzi Chahdoura, post-doctorant, ainsi qu'Arnaud Ferraro, étudiant en Master 2. La fonctionnalisation des cyclopropanes a été réalisée avec la participation de Clémence Rose, étudiante en Master 2. La synthèse totale de l'hoshinolactame a été réalisée avec la participation de Pauline Poutrel, étudiante en Master 2.

Afin de débuter ce projet, nous avons mis au point un nouvel auxiliaire chiral, bicoordinant, APS. Les premiers travaux en catalyse effectués au laboratoire ont porté sur la fonctionnalisation diastéréosélective de cycloalcanes, en particulier cyclopropane, en utilisant une copule chirale de type sulfinylaniline (Schéma 3).

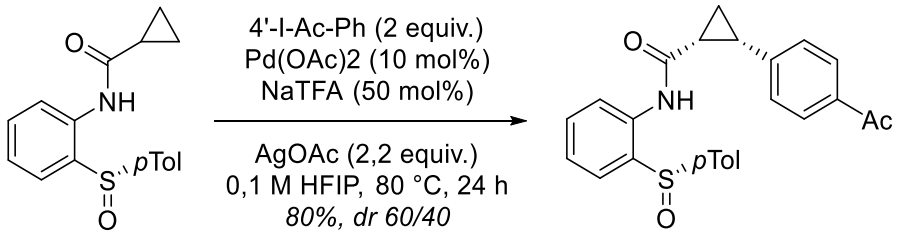


Schéma 3 Premier test d'arylation diastéréosélective utilisant une copule chirale de type sulfinylaniline

Les essais catalytiques préliminaires effectués avec le 4-iodoanisole en tant que partenaire de couplage n'ont pas conduit au produit souhaité et ceci quel que soit le catalyseur, la base, l'additif ou le solvant utilisés. Toutefois, en changeant le partenaire de couplage pour la 4'-iodoacetophenone dans les conditions décrites par Babu, le produit souhaité a été obtenu avec un rendement encourageant de 21%. Par ailleurs l'utilisation du 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) comme solvant a permis de nettement améliorer le rendement jusqu'à 80%, et ce à une température plus faible de 80 °C.[15] Toutefois, la diastéréosélectivité de la réaction est faible (excès diastéréomèrique de 20%).

Afin d'améliorer l'induction asymétrique, nous avons tenté d'optimiser l'encombrement du sulfoxyde en modifiant le groupement *p*-tolyl. De manière intéressante, en fonction des différents substituants sur le soufre (*p*-tolyl, *t*-butyl, cyclohexyl, 3,5-dimethylphenyl) le logarithme de l'excès diastéréomérique log (d.e.) est proportionnel à la conversion dans les mêmes conditions réactionnelles, avec un coefficient de corrélation $R^2 > 0,99$ (Figure 6).

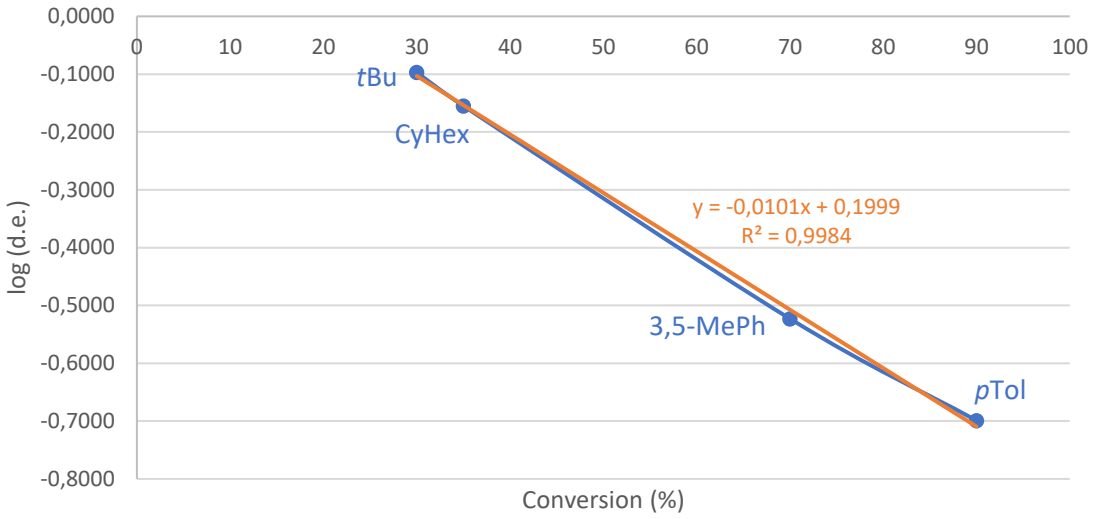


Figure 6 Corrélation entre encombrement stérique du groupement directeur, rendement et stéréosélectivité

Ainsi, une conversion et un excès diastéréomérique élevés n'ont malheureusement jamais pu être atteints. A la fois, les rendements obtenus avec le substituant *p*-tolyle et la possibilité d'isoler séparément les deux diastéréomères obtenus nous ont incité à choisir le motif *ortho*-(*p*-tolylsulfinyl)aniline comme groupement directeur. Nous avons ainsi réalisé l'arylation et l'alkylation de substrats aliphatiques cycliques avec d'excellents rendements et des rapports diastéréomériques modérés à élevés (Schéma 4).

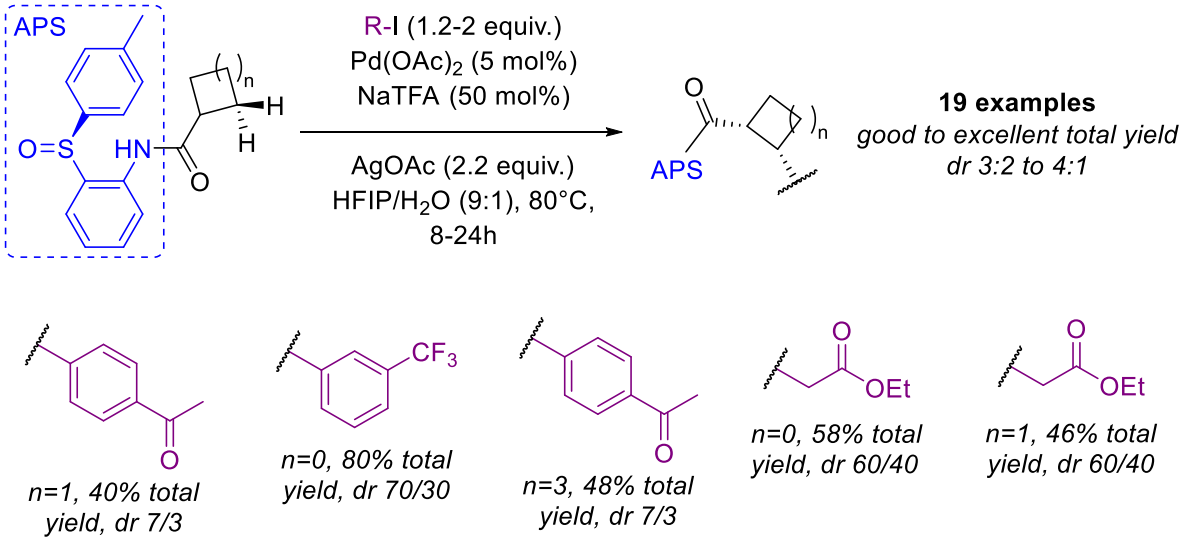


Schéma 4 Panel de transformations sur les cycloalcanes

Nous avons également pu isoler le diastéréomère majoritaire du palladacycle formé lors de la réaction d'arylation du cyclopropane et obtenir des monocristaux qui ont été analysés par diffraction des rayons X (Figure 7). Un de nos produits d'arylation ayant également cristallisé, les structures obtenues ont permis d'élucider une partie du mécanisme réactionnel par des études DFT. L'ensemble de ces résultats sera détaillé dans le Chapitre 2 et a fait l'objet d'une publication scientifique dans *Chemistry – A European Journal* en 2016, sélectionnée comme *Hot Paper*.[16]

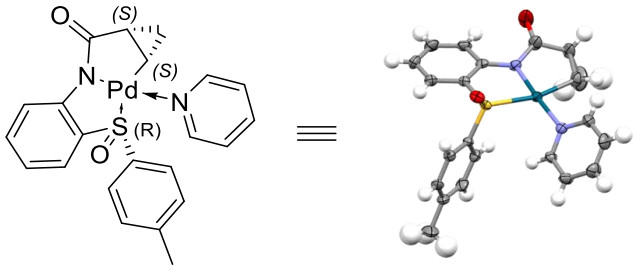


Figure 7 Structure aux rayons X du palladacycle isolé

À la suite de ces travaux, nous avons développé une voie de synthèse de produits naturels possédant un squelette cyclopropane. Nous avons notamment synthétisé l'hoshinolactame, un produit naturel découvert en 2017 et possédant d'intéressantes propriétés médicinales contre la maladie du sommeil.[17] Après introduction de notre copule chirale sur un acide 2-propylcyclopropane-1-carboxylique, nous avons effectué une transformation difficile : l'oléfination directe stéréospécifique. Après cette étape, nous avons pu déprotéger sélectivement la copule chirale dans des conditions très douces ;[18] celle-ci a pu être recyclée sans perte d'excès énantiomérique et avec un excellent rendement. Une décarboxylation dans les conditions de Barton-Motherwell[19] suivie d'une saponification puis d'une estérification nous a permis d'obtenir le composé désiré avec un excellent rendement global d'environ 30% et une totale pureté énantiomérique (Schéma 5).

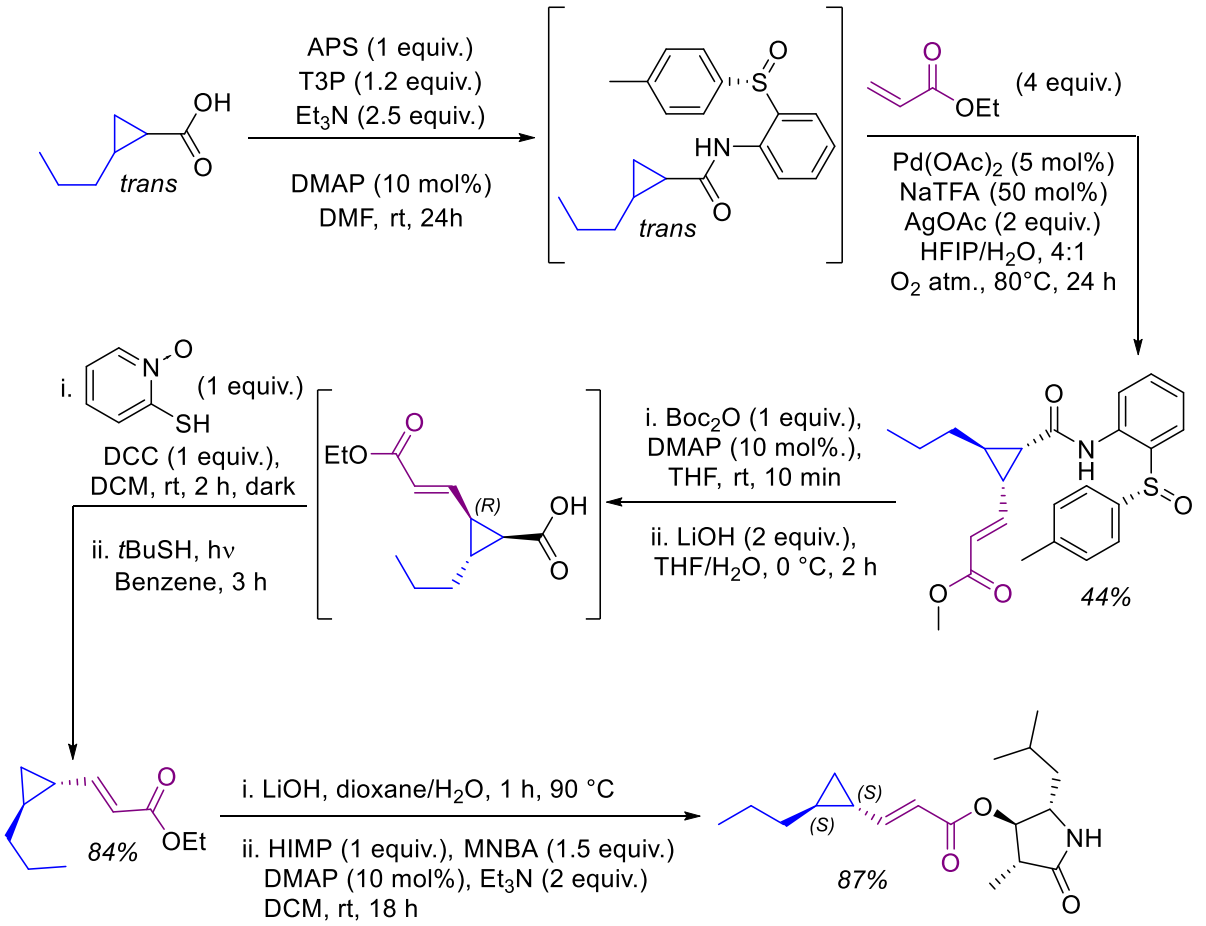


Schéma 5 Synthèse totale diastéréospécifique de l'hoshinolactame

Cette méthodologie de synthèse innovante, également appliquée à d'autres cyclopropanes naturels comme l'acide cascarillique ou la grenadamide, est également détaillée dans le Chapitre 2 et a fait l'objet d'une publication scientifique dans *Organic Chemistry Frontiers* en 2018.[20]

En parallèle de ces travaux, nous nous sommes intéressés à l'extension de notre méthodologie aux substrats aliphatiques linéaires. Après optimisation des conditions réactionnelles, en particulier les solvants utilisés, nous avons réalisé l'arylation et l'acétoxylation sur un large panel de substrats aliphatiques avec des rendements et ratios diastéréomériques modérés à bons (Schéma 6). Notre méthodologie a pu être appliquée à la synthèse de bioisostères de l'acide 2,2-diméthylcyclopropanoïque, pouvant potentiellement être utilisés comme insecticides. Ces travaux sont détaillés dans le Chapitre 3 et ont fait l'objet d'une publication scientifique dans *Chemistry – A European Journal* en 2017, sélectionnée comme *Hot Paper*.[21]

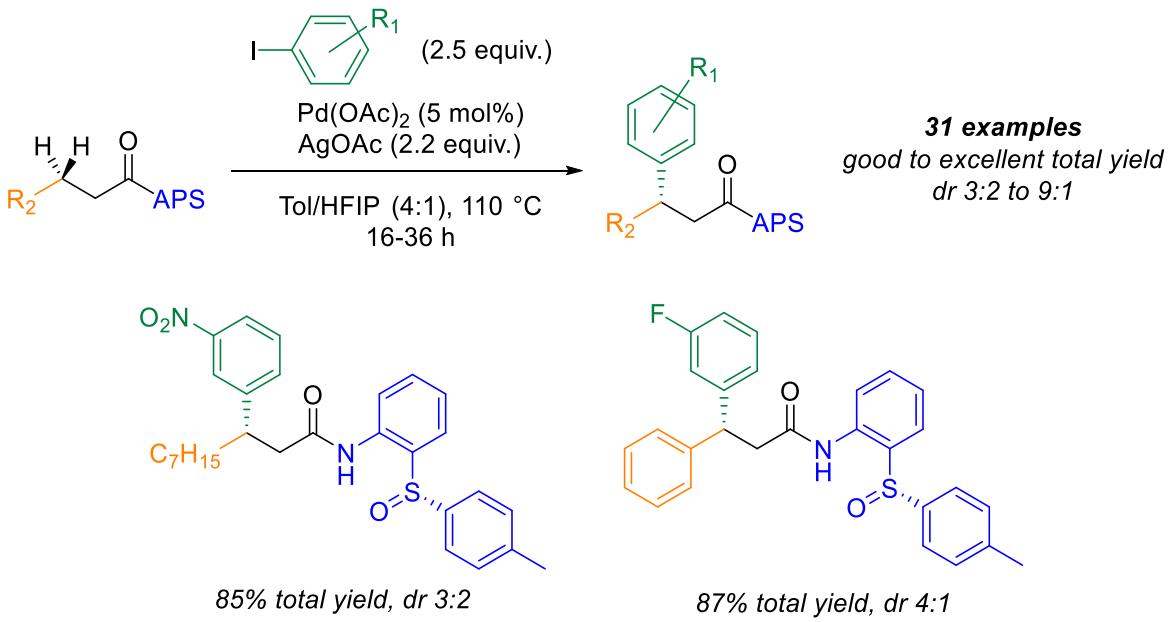


Schéma 6 Panel de transformations sur les substrats aliphatiques

Forts de nos connaissances concernant l'activation C-H diastéréosélective dirigée par un sulfoxyde chiral, nous nous sommes ensuite intéressés à une transformation plus difficile mais également plus innovante : l'activation C(sp^3)-H énantiosélective.[22,23] En corrolaire de nos travaux diastéréosélectifs, nous avons choisi de tester des ligands chiraux de type aminosulfoxyde. Nous avons tout d'abord testé un large panel de familles de ligands pour l'arylation de cyclopropanes (Schéma 7). Seuls les ligands flexibles de type *LX* (**L2**, **L3** et **L4**) ont montré une bonne réactivité et une induction de chiralité prometteuse.

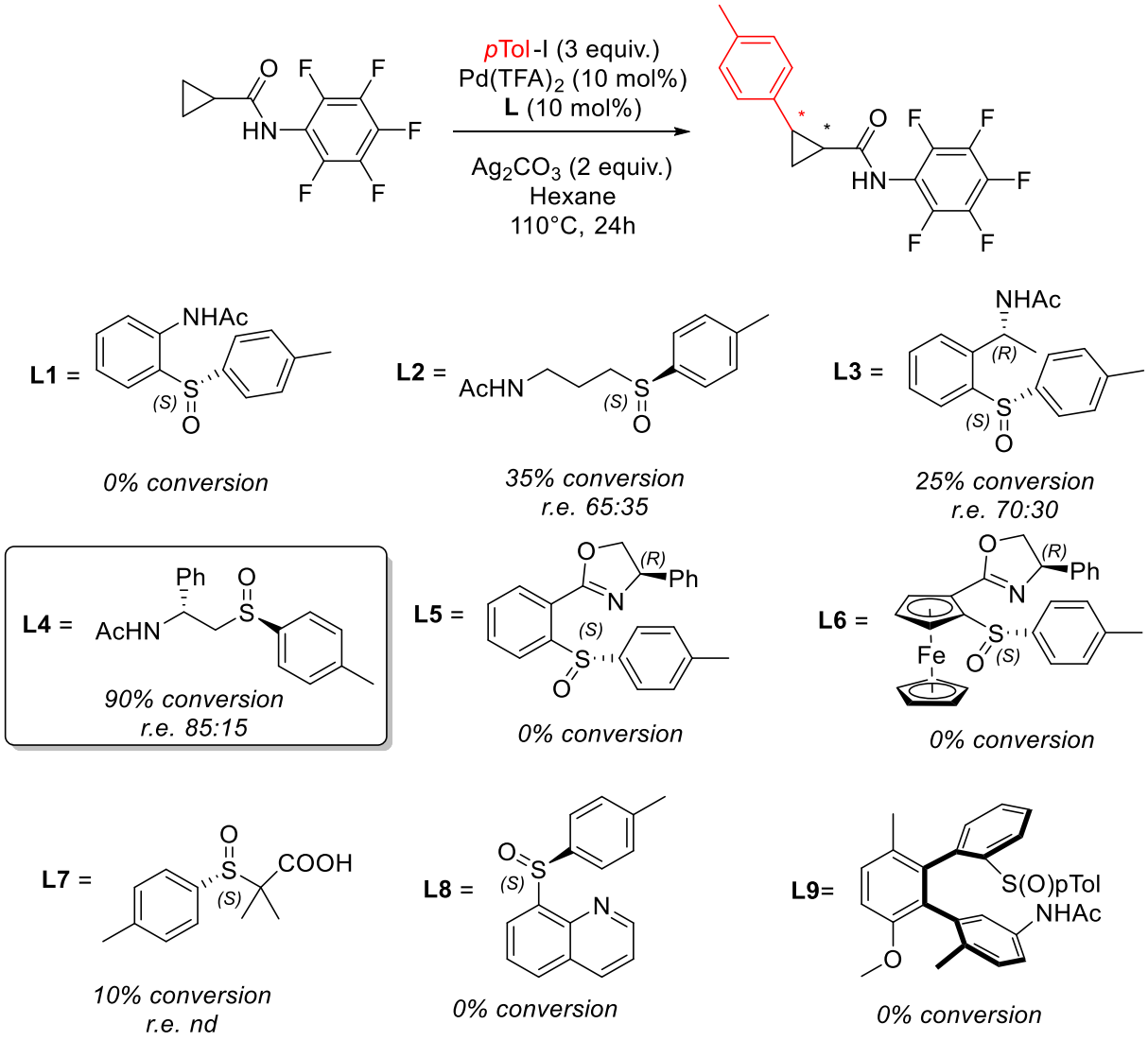


Schéma 7 Familles de ligands testées pour l'arylation énantiosélective de cyclopropanes

Les résultats préliminaires encourageants obtenus avec **L4** nous ont conduit à l'optimisation de sa structure. En particulier, l'encombrement stérique sur le phényle joue un rôle crucial dans l'induction de chiralité, puisque le ligand **L12** par exemple donne un excellent excès énantiomérique de 92% (Schéma 8).[24–26] Les conditions réactionnelles optimisées, l'arylation des cycloalcanes a pu être effectuée avec d'excellents rendements et excès énantiomériques (jusqu'à 94 % de rendement et 94 % d'excès énantiomérique pour l'arylation avec le 4-iodobenzotrifluorure).

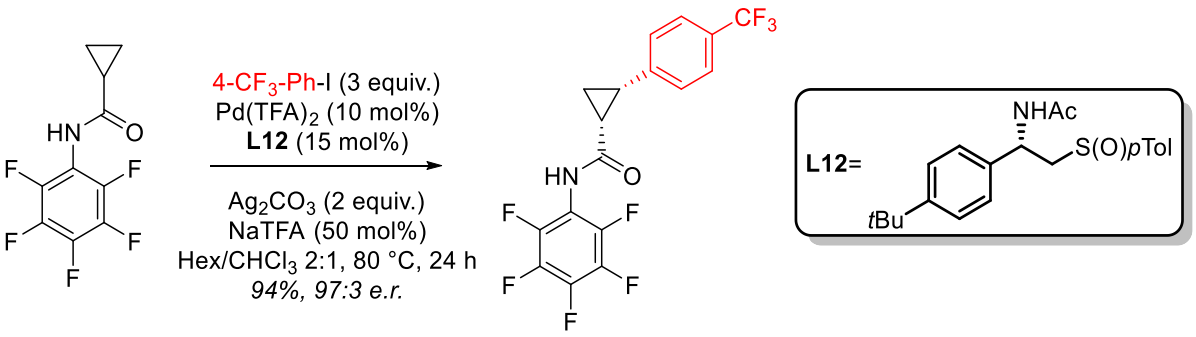


Schéma 8 Arylation énantiosélective de cyclopropanes utilisant L12

La cristallisation d'un des produits d'arylation et sa structure par diffraction des rayons X nous a permis d'attribuer avec certitude la configuration absolue des produits obtenus (Figure 8). La configuration absolue du cyclopropane est en accord avec nos études DFT préliminaires et résulte de l'intermédiaire palladacyclique le plus stable.

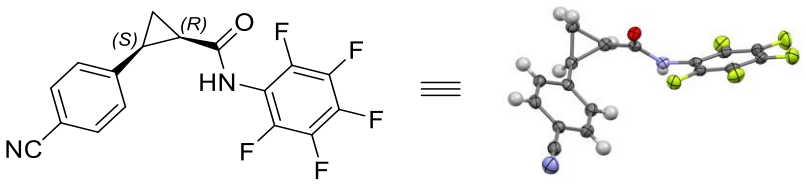


Figure 8 Structure aux rayons X d'un produit d'arylation

Les travaux qui ont suivi ont notamment porté sur l'optimisation de réactions plus difficiles, à savoir l'alkylation et l'alcynylation de cyclopropanes en utilisant **L12** (Schéma 9).

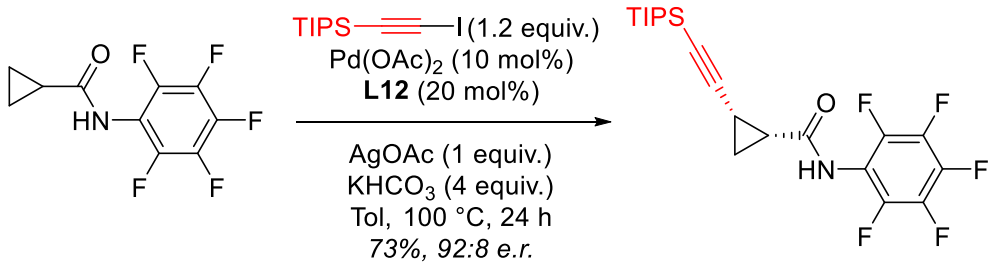


Schéma 9 Alkynylation énantiosélective de cyclopropanes utilisant L12

Il est important de noter que la réaction peut être effectuée à l'échelle du gramme avec de bonnes conversions et excès énantiomérique et que la déprotection de l'auxiliaire 2,3,4,5,6-pentafluoroanilide peut être effectuée dans des conditions douces, et sans racémisation du cyclopropane (Figure 9).

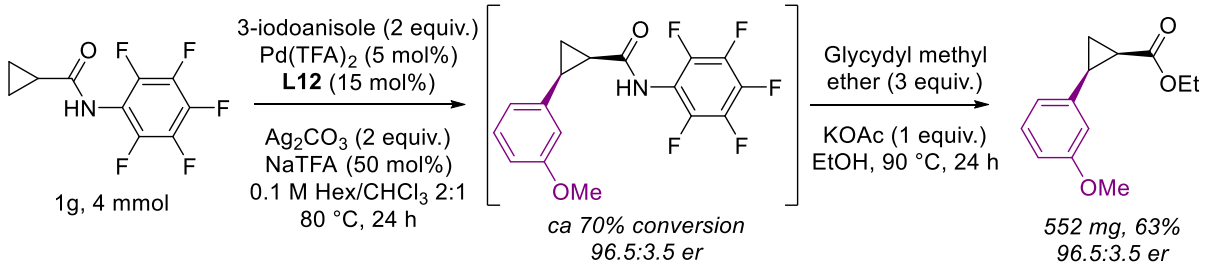


Figure 9 Arylation et déprotection énantiosélective du cyclopropane

L'un des composés déprotégés a cristallisé dans un mélange éther diéthylique/hexane et l'analyse des cristaux a montré la conservation de la configuration absolue des centres stéréogènes du cyclopropane et a permis l'enrichissement optique du composé (Figure 10).

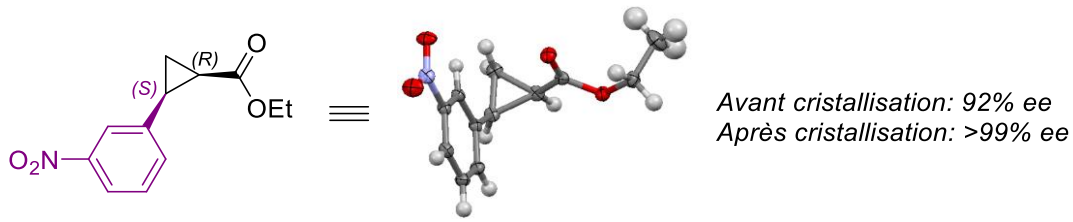


Figure 10 Structure aux rayons X d'un produit déprotégé

Des études mécanistiques préliminaires ont été menées afin de comprendre l'origine de l'excellent excès énantiomérique observé ainsi que le rôle de ce ligand original dans l'accélération de la réaction. Tous ces résultats feront l'objet d'une publication scientifique et sont détaillés dans le Chapitre 4.

3. Conclusion générale

Durant ces trois ans, nous avons développé un auxiliaire chiral, (*S*)-2-(*p*-tolylsulfinyl)aniline ou APS, que nous avons utilisé pour l'activation diastéréosélective de liaisons C-H sur des substrats aliphatiques, cycliques ou non. De multiples transformations ont alors été effectuées, telles que l'arylation, l'acétoxylation ou l'oléfination, et ont été appliquées à la synthèse stéréospécifique de produits naturels.

Suite à ces travaux, nous nous sommes intéressés au développement de nouveaux ligands chiraux, tel que *N*-((*S*)-1-(4-(*tert*-butyl)phenyl)-2-((*R*)-*p*-tolylsulfinyl)ethyl)acetamide ou NBSA, que nous avons utilisé pour l'arylation et l'alcynylation énantiosélective de cycloalcanes. En perspective, la structure du ligand NBSA sera encore optimisée pour obtenir de meilleures stéréosélectivités, mais aussi diversifier les applications de ce ligand en l'utilisant dans d'autres transformations énantiosélectives plus délicates comme les alkylations.

4. Références bibliographiques

[1] J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, *Chem. Rev.* **2016**, *117*, 8754–8786.
[2] H. M. L. Davies, D. Morton, *J. Org. Chem.* **2016**, *81*, 343–350.
[3] R. Parella, B. Gopalakrishnan, S. A. Babu, *Org. Lett.* **2013**, *15*, 3238–3241.
[4] D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965–3972.
[5] D. S. Roman, A. B. Charette, *Org. Lett.* **2013**, *15*, 4394–4397.
[6] S. K. Teo, W. A. Colburn, W. G. Tracewell, K. A. Kook, D. I. Stirling, M. S. Jaworsky, M. A. Scheffler, S. D. Thomas, O. L. Laskin, *Clin. Pharmacokinet.* **2004**, *43*, 311–327.
[7] T. Eriksson, S. Bjöurkman, B. Roth, Å. Fyge, P. Höuglund, *Chirality* **1995**, *7*, 44–52.
[8] A. M. Rouhi, *Chem. Eng. News* **2003**, *81*, 45–61.
[9] C. K. Hazra, Q. Dherbassy, J. Wencel-Delord, F. Colobert, *Angew. Chem. Int. Ed.* **2014**, *53*, 13871–13875.
[10] Q. Dherbassy, G. Schwertz, C. K. Hazra, T. Wesch, J. Wencel-Delord, F. Colobert, *Phosphorus Sulfur Silicon Relat. Elem.* **2015**, *190*, 1339–1351.
[11] Q. Dherbassy, J.-P. Djukic, J. Wencel-Delord, F. Colobert, *Angew. Chem. Int. Ed.* **2018**, *57*, 4668–4672.
[12] K. Yamaguchi, H. Kondo, J. Yamaguchi, K. Itami, *Chem. Sci.* **2013**, *4*, 3753.
[13] S. E. Ammann, W. Liu, M. C. White, *Angew. Chem. Int. Ed.* **2016**, *55*, 9571–9575.
[14] N. Rival, D. Hazelard, G. Hanquet, T. Kreuzer, C. Bensoussan, S. Reymond, J. Cossy, F. Colobert, *Org. Biomol. Chem.* **2012**, *10*, 9418.
[15] Q. Dherbassy, G. Schwertz, M. Chessé, C. K. Hazra, J. Wencel-Delord, F. Colobert, *Chem. - Eur. J.* **2016**, *22*, 1735–1743.
[16] S. Jerhaoui, F. Chahdoura, C. Rose, J.-P. Djukic, J. Wencel-Delord, F. Colobert, *Chem. - Eur. J.* **2016**, *22*, 17397–17406.
[17] H. Ogawa, A. Iwasaki, S. Sumimoto, M. Iwatsuki, A. Ishiyama, R. Hokari, K. Otoguro, S. Ōmura, K. Suenaga, *Org. Lett.* **2017**, *19*, 890–893.
[18] D. A. Evans, T. C. Britton, J. A. Ellman, *Tetrahedron Lett.* **1987**, *28*, 6141–6144.
[19] D. H. R. Barton, D. Crich, W. B. Motherwell, *J. Chem. Soc. Chem. Commun.* **1983**, 939.
[20] S. Jerhaoui, P. Poutrel, J.-P. Djukic, J. Wencel-Delord, F. Colobert, *Org. Chem. Front.* **2018**, *5*, 409–414.
[21] S. Jerhaoui, J.-P. Djukic, J. Wencel-Delord, F. Colobert, *Chem. - Eur. J.* **2017**, *23*, 15594–15600.
[22] K. S. L. Chan, H.-Y. Fu, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 2042–2046.
[23] M. Wasa, K. M. Engle, D. W. Lin, E. J. Yoo, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 19598–19601.
[24] J. L. García Ruano, A. Alcudia, M. del Prado, D. Barros, M. C. Maestro, I. Fernández, *J. Org. Chem.* **2000**, *65*, 2856–2862.
[25] P. Bravo, S. Capelli, M. Crucianelli, M. Guidetti, A. L. Markovsky, S. V. Meille, V. A. Soloshonok, A. E. Sorochinsky, F. Viani, M. Zanda, *Tetrahedron* **1999**, *55*, 3025–3040.
[26] C. Zucca, P. Bravo, E. Corradi, S. Meille, A. Volonterio, M. Zanda, *Molecules* **2001**, *6*, 424–432.

Chapter 1

C(sp^3)-H bond activation and sulfoxides, a short bibliographic study

Chapter 1 – Table of contents

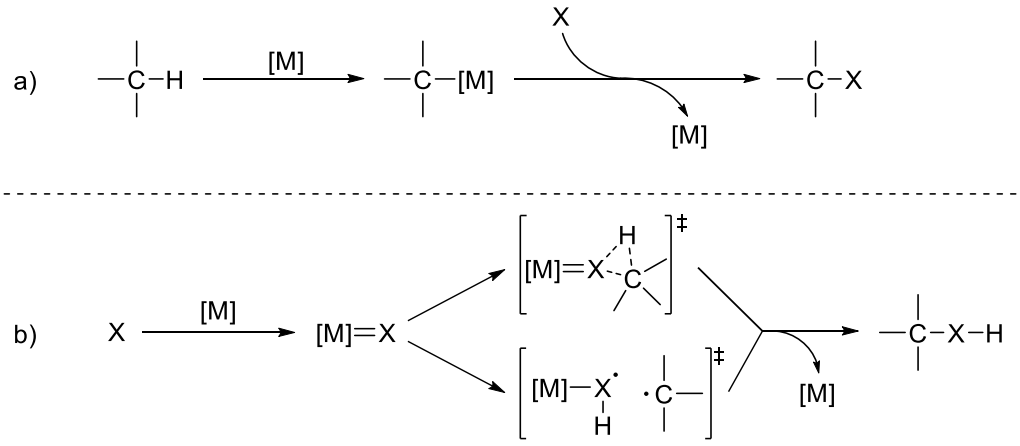
I.1. Introduction

This chapter aims to introduce the general context of this PhD work. Accordingly, two main topics are described: first and foremost, the C(sp^3)-H bond activation, focusing also on the main mechanistic studies; then, the second part of the introduction will focus on the sulfoxides with their synthesis and application in asymmetric synthesis and catalysis. For more details about these concepts, readers are invited to consult the reviews by Yu, Davies, Kagan and Trost.[1,2,27,28]

I.2. On the C(sp^3)-H bond activation

I.2.i. Definition of C-H activation

C-H activation refers to the cleavage of an unreactive C-H bond by transition metal complexes to form a C-M linked intermediate as described by Labinger and Bercaw in 2002.[29] It should be noted that the definition of C-H activation divides in two groups the reactions leading to C-H bond functionalization and involving transition metal: outer and inner sphere reactions (Scheme 1.1). Inner sphere C-H bond functionalization involves initial reaction of the C-H bond with the transition metal center [M] to form a C-M bond. Concerning outer sphere reactions, they are typically represented by carbene insertion into C-H bonds.[30]



Scheme 1.1 a) Inner and b) outer sphere mechanisms

C-H functionalization represents the overall process where the hydrogen is replaced by a functional group (Figure 1.11). This must not be confounded with processes such as Friedel-Crafts transformation in which the C-H bond cleavage follows an initial electrophilic attack on an aromatic π-system and is mediated by a base.

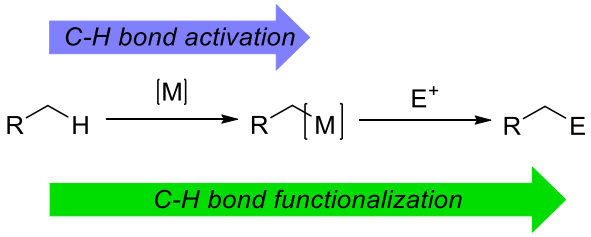
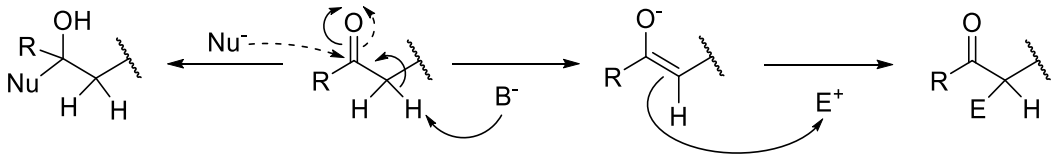


Figure 1.11 Difference between C-H bond activation and functionalisation

I.2.ii. Challenges of C(sp^3)-H activation

Carboxylic acids are ubiquitous building blocks for pharmaceutical or agrochemical applications and many of them are produced industrially on a large scale. They are involved in many chemical reactions and their diversification is a huge challenge for organic chemistry.

Ipso-functionalisation of a carboxylic acid derivative is described with Grignard reactions for example. α-functionalization of a carboxylic acid derivative has been known and developed since decades (Scheme 1.2). Due to the low pK_A of α–C-H bonds, no metal catalyst is needed. This chemistry is based on the formation of a reactive enolate, bearing an electron rich double bond. It behaves as a nucleophile and reacts which various electrophiles allowing a selective functionalization in α position to the carbonyl. Claisen condensation is one notable example of this strategy.[31,32]



Scheme 1.2 Ipso- and α-functionalisation to carbonyl group

However, β- or even more distal C-H functionalisation remains difficult because of multiple challenges:

- Low reactivity of aliphatic C-H bonds: Indeed, one of the tremendous difficulties stands in their high bond energy (typically around 100 kcal/mol), unreactive molecular orbital profile and low acidity (pK_A around 50-60). Moreover, sp^3 hybridized carbons lack π-orbitals to interact with metal centre;
- Regioselectivity: C-H bonds are ubiquitous and targeting one particular bond to break still persists to be one key challenge of metal-catalysed reactions. For some molecules, the control can be intrinsic (for example, in the case of indoles, C2 and C3 are more reactive), intramolecular or permitted by the use of directing groups (I.3);
- Harsh conditions. Often, metal-catalysed transformations require high temperature and use of a base, which could be not compatible with other functional groups.

I.2.iii. Synthetic utility of C-H activation

Over the last decades, C-H bond activation has developed significantly, and various advances have been achieved. Consequently, C-H activation approach has been establishing itself as a useful tool for organic synthesis.

C-H bond activation is currently amongst the methodology of choice to build complex molecules or to post-functionalize active ingredients. Because of these reasons, the number of publications reporting C-H activation has increased dramatically since 2000 (Figure 1.12).

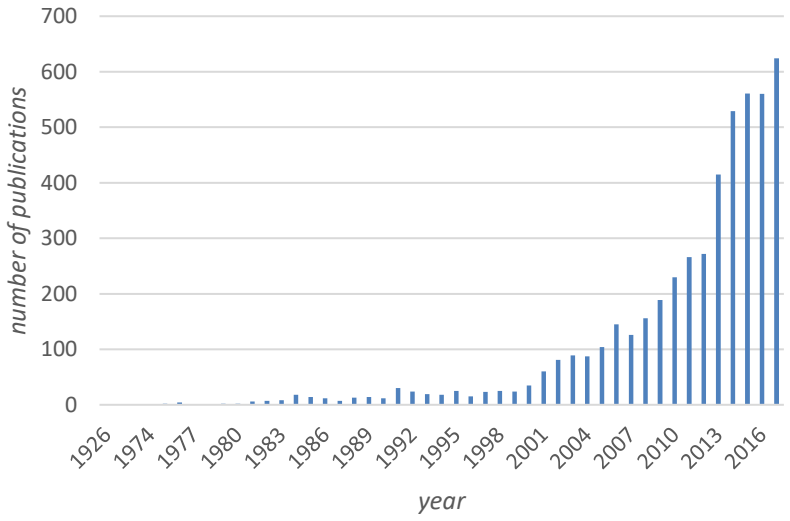
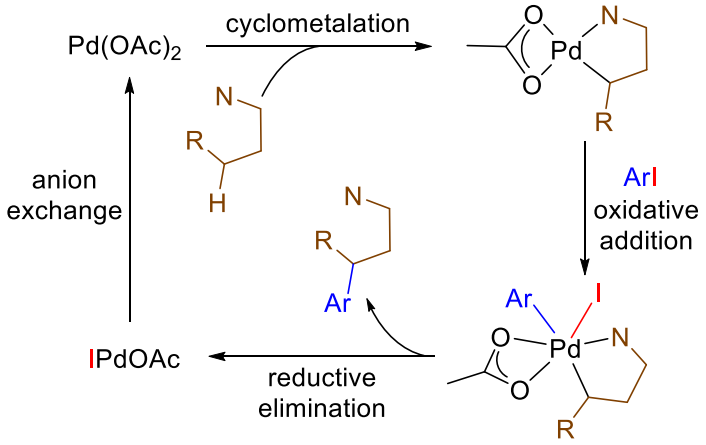


Figure 1.12 Growth of C-H activation research since 1926

I.2.iv. Mechanism of C(sp^3)-H activation: Concerted Metalation Deprotonation

In general, and in contrast with the outer sphere mechanism, inner sphere type transformations will involve generation of a M-C bond, typically as a metalacyclic intermediate. C(sp^3)-H bond functionalisation such as arylation with Ar-I (one of the most often reported reaction) typically proceeds by a Pd(II) – Pd(IV) catalytic cycle. After coordination of the substrate with the catalyst, the C-H bond is activated through cyclometallation and then oxidative addition occurs to generate Pd(IV) species. After reductive elimination and generation of a C-H functionalised product, an inactive IPdOAc species may be formed. However, the cycle is rendered catalytic due to the presence of silver salts used as iodide scavenger from the palladium coordination sphere.



Scheme 1.3 Typical catalytic cycle for directed C-H functionalisation

Three principal mechanisms are described for C-H activation: oxidative addition and σ-bond metathesis are often found for aromatic C-H bond activation while concerted metalation deprotonation occurs with both aromatic and aliphatic ones (Chart 1.1).

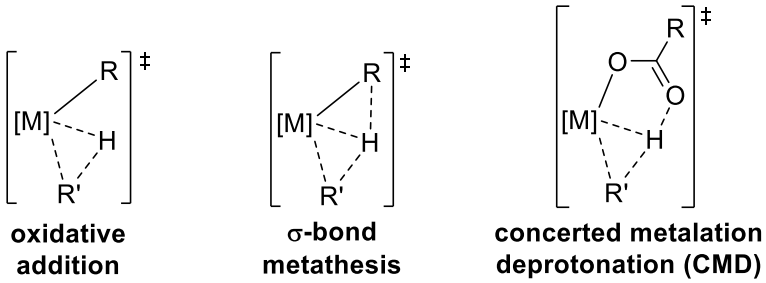
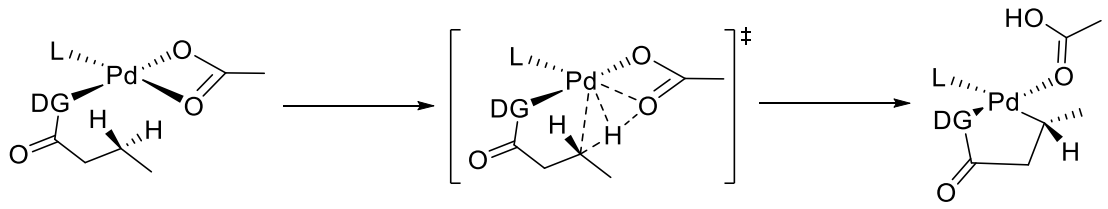


Chart 1.1 Three types of C-H bond activation mechanisms

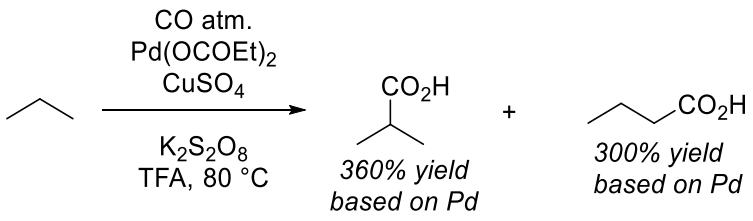
Except for some rare examples detailed later, the cyclometallation is facilitated by pre-coordination of the substrate, usually by nitrogen or oxygen atom. This coordinating motif, typically called DG (Scheme 1.4), is essential for the regioselective activation and it also enhances the efficiency of a catalytic system as the local concentration of a M increases significantly in a proximity to a C-H bond. Then, the carboxylate on the palladium helps the deprotonation by electrophilic assistance, concomitantly with Pd-C bond formation: that is the concerted metalation deprotonation (CMD).



Scheme 1.4 Focus on the inner-sphere CMD mechanism

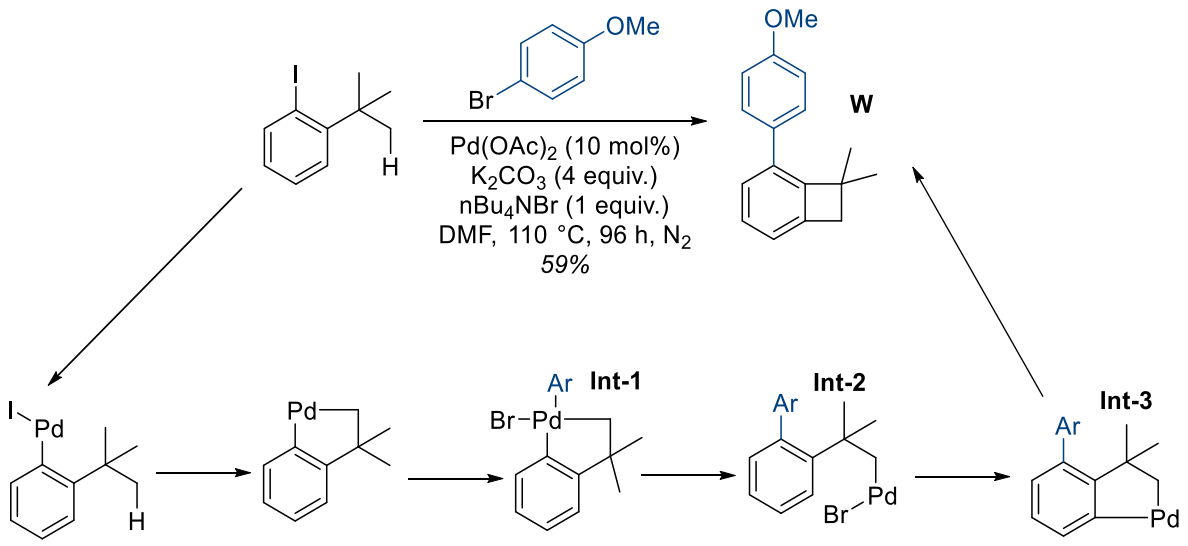
I.3. Preliminary examples of non-directed C-H bond activation

Early in 1989 and 1992, Fujiwara and co-workers showed that palladium complexes were able to activate aliphatic C-H bonds to enhance carbonylation. However, this system was not regioselective and a mixture of regioisomers was observed (Scheme 1.5).[33,34]



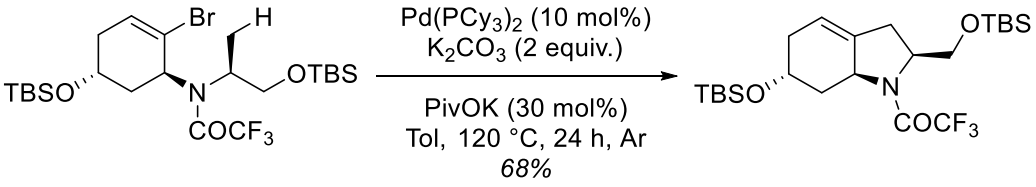
Scheme 1.5 Pd(II)-catalyzed carbonylation of propane

Due to the difficulty of activating C(sp^3)-H bonds, the pioneering examples disclosed by Dyker and co-workers corresponded to intramolecular reactions.[35] In this case, intramolecular C(sp^2)-C(sp^3) coupling occurred as a side reaction during the expected Ar-Ar cross coupling. One possible pathway to the formation of this unexpected product could be explained by the formation of a Pd(IV) intermediate **Int-1** by intramolecular aliphatic C-H activation followed by oxidative addition with the arylbromide and further reductive elimination to give the Pd(II) species **Int-2**. Reductive elimination of palladacycle **Int-3** would give the corresponding cyclobutabenzene **W** (Scheme 1.6).



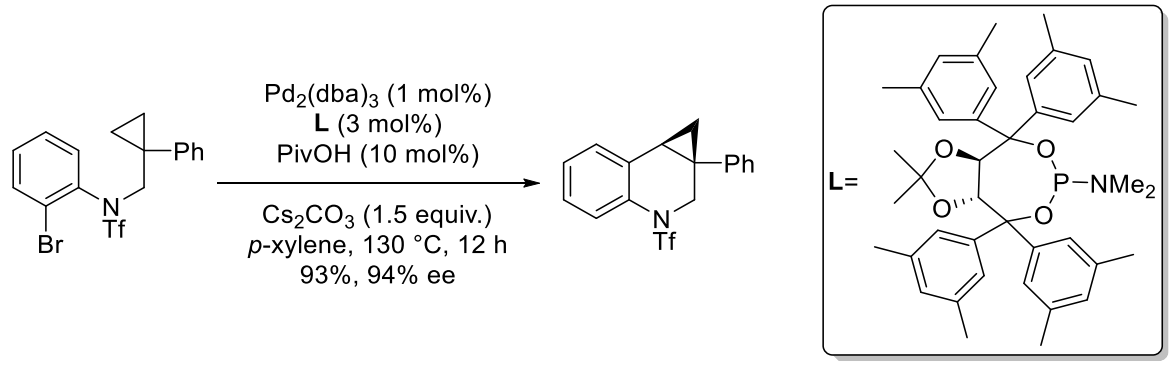
Scheme 1.6 Dyker's domino reaction

Following this pioneering work, Baudoin and co-workers demonstrated the synthetic utility of intramolecular C(sp^3)-H bond functionalization by constructing interesting bicycles such as octahydroindoles key intermediates to obtain aeruginosin marine natural products (Scheme 1.7). No homocoupling or polymerisation side products were observed due to the effect of the phosphine ligand.[36–38]



Scheme 1.7 Baudoin's key step for the synthesis of aeruginosin 98B

Since 2012, Cramer and co-workers developed a variety of interesting methodologies based on Pd(0)-catalysed intramolecular C(sp^3)-H arylation. Importantly, they have focused on stereoselective transformations targeting synthesis of chiral aliphatic substrates. The use of a chiral phosphine ligand allowed for example the enantioselective formation of tetrahydroquinoline scaffolds with good yields and enantiomeric excesses (Scheme 1.8). They also more recently used these TADDOL-type ligands for the enantioselective cyclization of chloroacetamides to lactames, with moderate to excellent yield and enantiomeric excess.[39–44] These ligands derive from natural (*R*,*R*)-tartaric acid and bind the metal through phosphorus atom.



Scheme 1.8 Cramer's enantioselective synthesis of tetrahydroquinolines

More recently, Yu and co-workers disclosed the use of a simple 2-pyridone ligand for the olefination and carboxylation of arenes and heterocycles (Figure 1.13). The development of non-directed C-H functionalisation with one equivalent of arene is a highly appealing opportunity for late-stage functionalisation of C-H bonds not accessible by directing group strategies and opens new interesting perspectives for non-directed C(sp^3)-H bond functionalisation.[45]

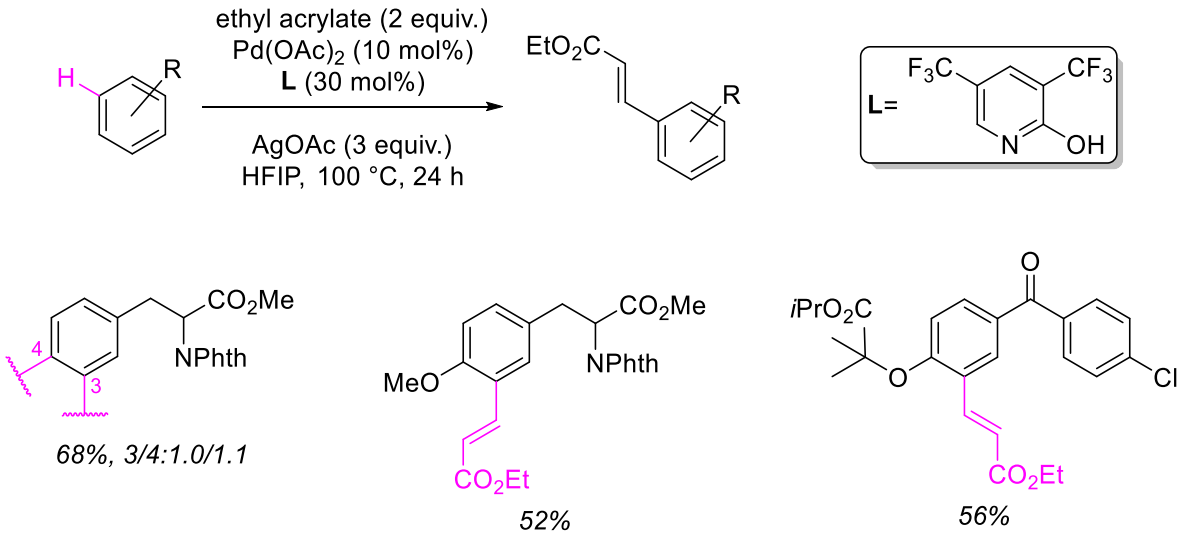
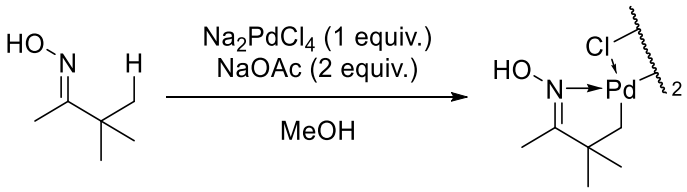


Figure 1.13 Yu's ligand-accelerated non-directed C-H functionalisation of arenes

I.4. Regioselective C(sp^3)-H activation

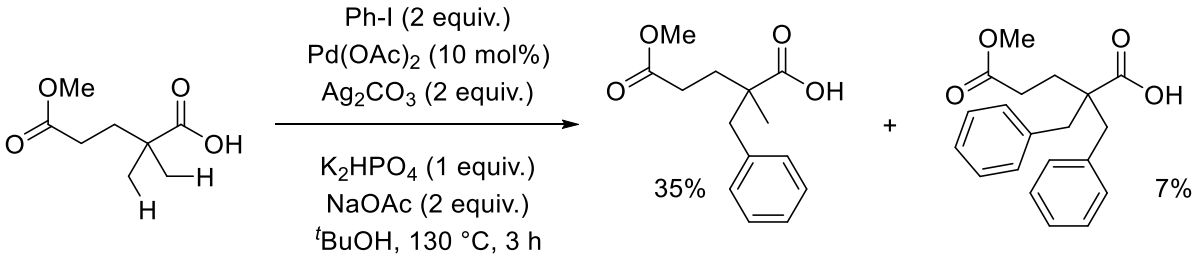
I.4.i. C(sp^3)-H activation directed by a monocoordinating group

The first example of directed aliphatic C-H bond activation was reported by Shaw and co-workers in 1978 and concerned the non-catalytic C-H bond cleavage of *tert*-butyl methyl ketone oxime, assisted by the strong coordination of the oxime with the palladium, to form a metalacyclic species (Scheme 1.9).[46] Following this work, Hiraki and co-workers demonstrated that pyridine and *N*,*N*-dimethylamine auxiliaries were also effective as directing entities for C(sp^3)-H bond cleavage.[47–49] However, these directing group strongly coordinates the metal centre due to large π-backbonding thus limiting the scope of available transformations.



Scheme 1.9 Oxime-directed C-H activation

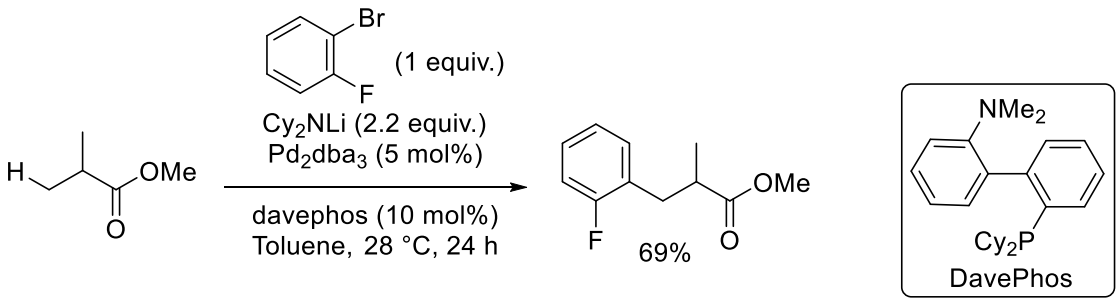
Selective β-functionalisation of carboxylic acid derivatives has not been described until the end of the twentieth century, due to the difficulty of activating these C-H bonds. The necessity of using transition metal catalysts has been demonstrated in the first example of carboxyl-directed functionalization of simple aliphatic acids by Yu and co-workers in 2007 (Scheme 1.10).[50]



Scheme 1.10 Free acid-directed C-H functionalisation

It was hypothesized that this reaction proceeds thanks to Thorpe-Ingold effect as substrates bearing substituent on the α-position did not undergo arylation. Additionally, the intermediate Pd(II)-alkyl could undergo β-hydride elimination with the α-hydrogen atom resulting in a decomposition of the starting material. Thus, many synthetically useful carboxylic acid substrates, such as amino acids, could not be functionalized.[1,51]

Then, Baudoin and co-workers described the β-arylation of esters using a palladium(0)/lithiated base system (Scheme 1.11).[52,53]



Scheme 1.11 Ester-directed C-H functionalisation

In this system, the authors assumed that after α-palladation, the β-hydride elimination is much more energetically stable than the corresponding reductive elimination which would lead to the α-arylation, thus favouring β-arylation over α-arylation. More precisely with DavePhos, the rate limiting step of the β-arylation is the Pd-enolate to homoenolate isomerization which occurs through a β-H elimination, followed by olefin-rotation and olefin-insertion sequence (Figure 1.14).

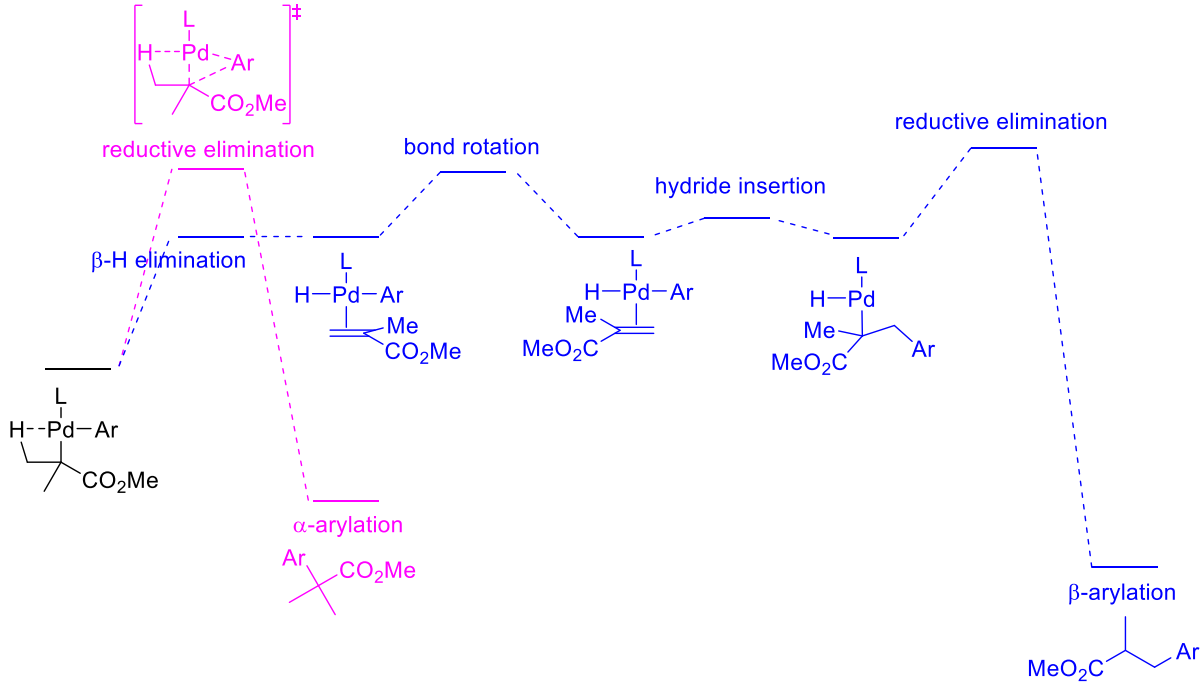
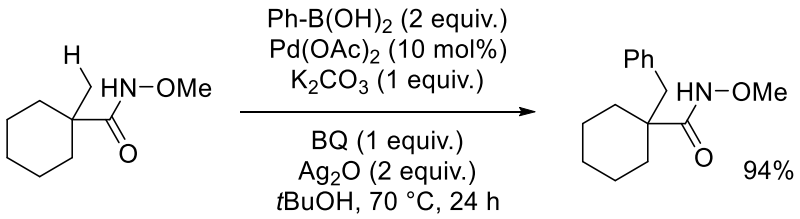


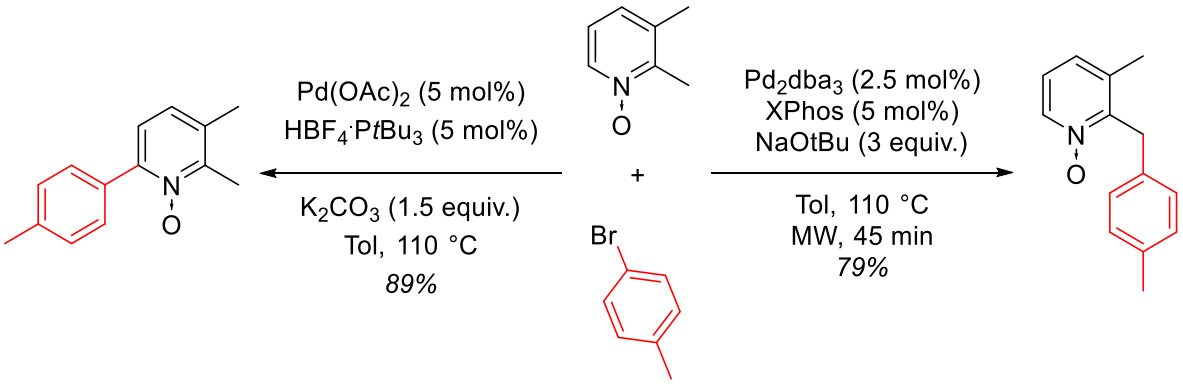
Figure 1.14 Mechanistic pathway for the α- and β-arylation (Gibbs free energies are omitted for more clarity)

These methods are however highly specific. After screening of the reaction parameters, especially the protecting group on the carboxylic acid moiety, Yu and co-workers discovered that a significantly more general system is obtained when hydroxamic acid is used as DG for the C-H arylation of cycloalkanes (Scheme 1.12).[54]



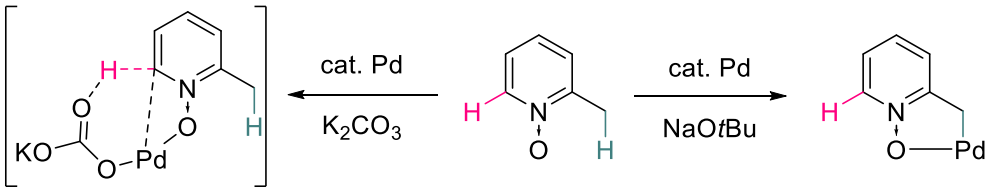
Scheme 1.12 Hydroxamic acid-directed C-H functionalisation

An elegant methodology was described by Fagnou and co-workers in 2005 and related the selective C(sp^3)-H or C(sp^2)-H bond arylation of azine *N*-oxides using a Pd(0)/Pd(II) catalytic cycle. Under finely optimized catalytic system (choice of a base), total regioselectivity for aromatic of benzylic position was observed (Scheme 1.13). [55,56] This methodology was also applied for the total synthesis of two natural products: papaverine and cryskonisine.



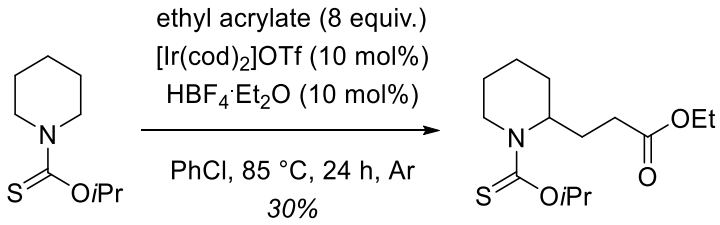
Scheme 1.13 Fagnou's divergent sp^2/sp^3 arylation

They also studied the role of the base and proposed two different mechanisms: with NaO*t*Bu, abstraction of one benzylic proton would lead to the five-membered palladacycle and to the C(sp^3)-H bond functionalisation. However, with a coordinating base such as potassium carbonate, the CMD mechanism is favoured and mainly leads to C(sp^2)-H bond functionalisation (Scheme 1.14).



Scheme 1.14 Role of the base during the azine *N*-oxide promoted C-H cleavage

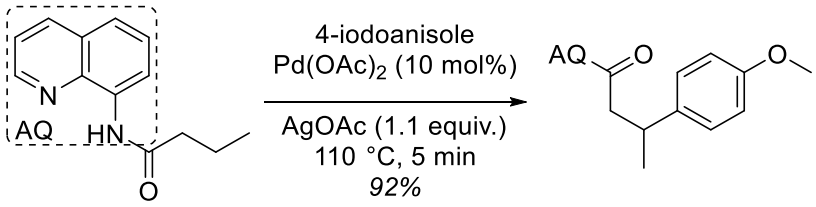
Monodentate directing groups were progressively supplanted by more robust bidentate directing groups, however only few methodologies were developed in the past few years. As notable example, Yu and co-workers developed an alkoxythiocarbonyl auxiliary for the iridium-catalysed alkylation of azacycles through monocoordination with the sulphur (Scheme 1.15). This practical approach uses an easily removable directing group and allows α-alkylation of important medicinally relevant motifs such as proline derivatives.[57]



Scheme 1.15 Yu's iridium-catalysed alkylation of azacycles

I.4.ii. Directed by a bidentate group

In 2005, only a few methods are dealing with the activation of C(sp^3)-H bonds and the development of new approaches leading to C-C bond formation was highly appealing. Daugulis and co-workers were the first to design a new class of auxiliary, 8-aminoquinoline (Scheme 1.16). This bidentate directing group allows highly efficient β-arylation of carboxylic acid derivatives and even γ-arylation of amine derivatives using iodoarenes as coupling partners.[4,58] Importantly, this auxiliary allowed activation of methylene unit, which was not possible using monodentate directing groups. A particular efficiency of the bidentate directing groups is probably due to improved stabilisation of high oxidation state metal catalysts (such as Pd^{IV} species). Moreover, in the case of aliphatic C-H activation, such double coordination is prompt to retard a β-hydride elimination by saturating the coordination sites of the metal.



Scheme 1.16 Aminoquinoline-directed C-H functionalisation

The 8-aminoquinoline auxiliary is nowadays one of the most widely used bidentate directing group, allowing various challenging transformations and using a broad range of metal catalysts (Figure 1.15).[59] Furthermore, its high chelating ability, cheap price (322 € per mole at Fluorochem supplier) and easy deprotection are the main reasons why it gained much attention for the metal-catalysed direct C-H bond functionalisation.

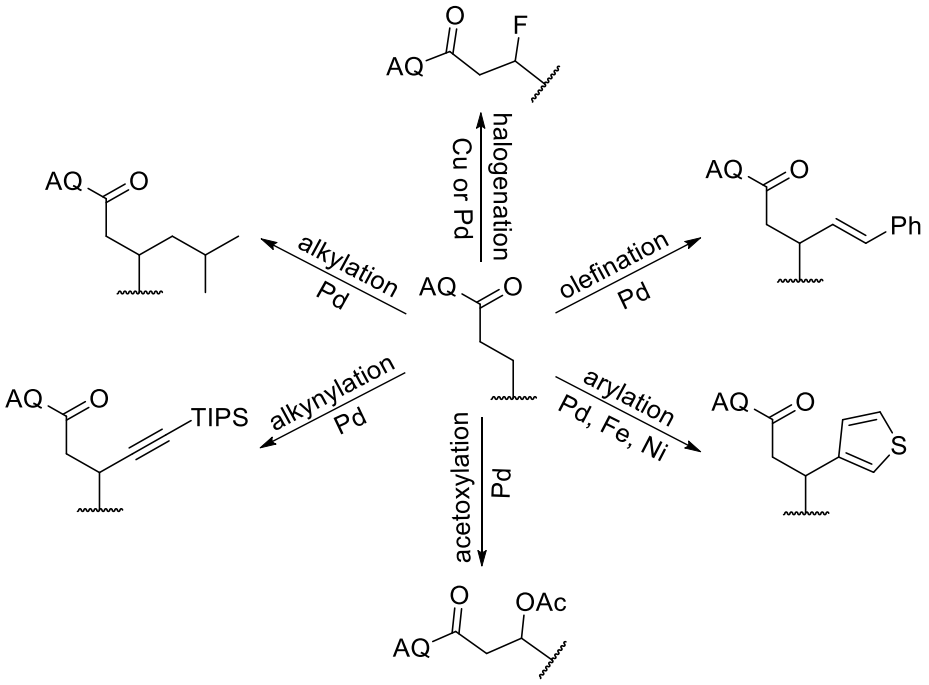


Figure 1.15 Scope of transformations using the aminoquinoline as directing group

The pioneering use of aminoquinoline as directing group opened new perspectives in C(sp^3)-H bond functionalisation and many other auxiliaries were designed in the past few years (Chart 1.2).[58,60–63]

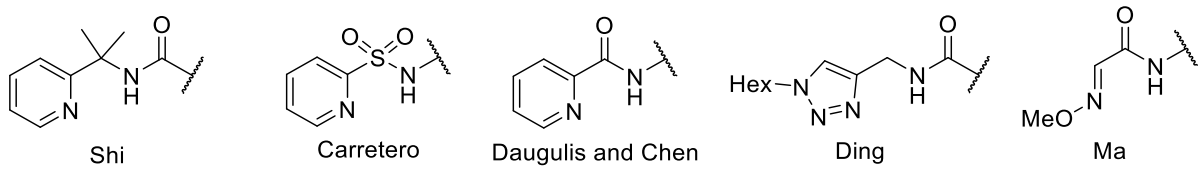
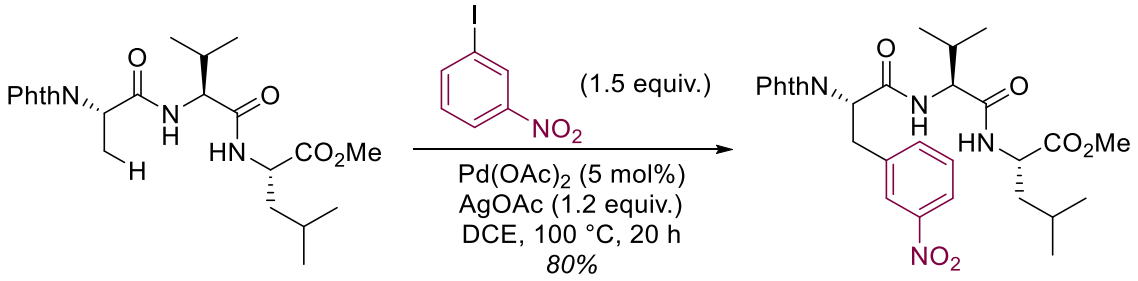


Chart 1.2 Non-exhaustive list of bidentate directing groups for C(sp^3)-H bond functionalisation

From the perspective of using cheap and easily accessible scaffolds as bidentate directing groups, Yu and co-workers were the first ones to use amino-acids and peptides for their ability to chelate metals.[64] Excellent regioselectivity for terminal C-H bonds was observed, even for more complex tri- and tetra-peptides. This methodology allowed straightforward post-synthetic modification, such as arylation or acetoxylation (Scheme 1.17).

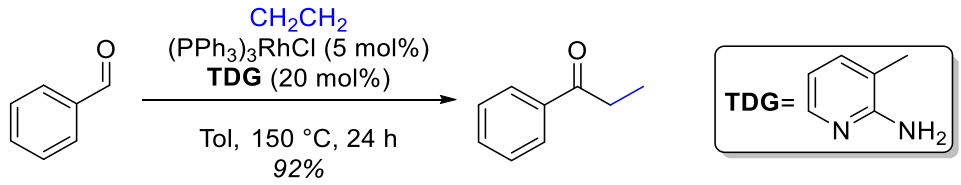


Scheme 1.17 Yu's metal-catalysed post-functionalisation of peptides

I.4.iii. C(sp^3)-H activation using a transient DG

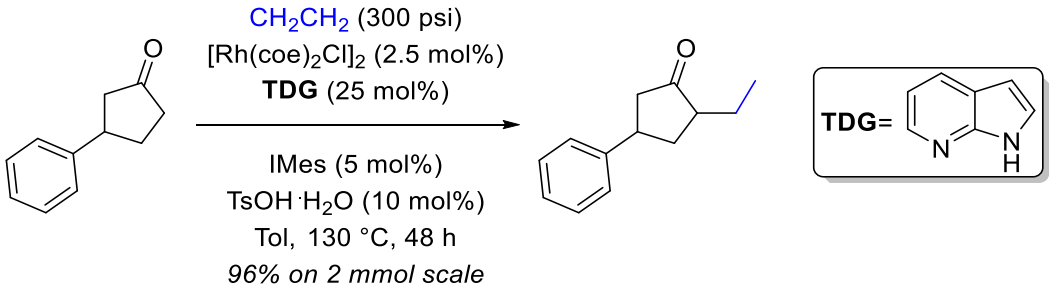
The covalent installation and removal of mono- or bi-dentate directing groups is a major drawback for synthetic use. Indeed, not only additional steps are required but also the compatibility of the installation and removal with other functional groups needs to be taken into consideration.

In this context, Hong and co-workers developed a chelation-assisted hydroacylation catalysed by Wilkinson's catalyst and promoted by *in situ* imine formation between the aldehyde starting material and 2-amino-3-picoline.[65] The advantage of this method is the catalytic use as well as *in situ* removal of the directing group (Scheme 1.18).



Scheme 1.18 Rhodium-catalysed hydroacylation of aldehydes

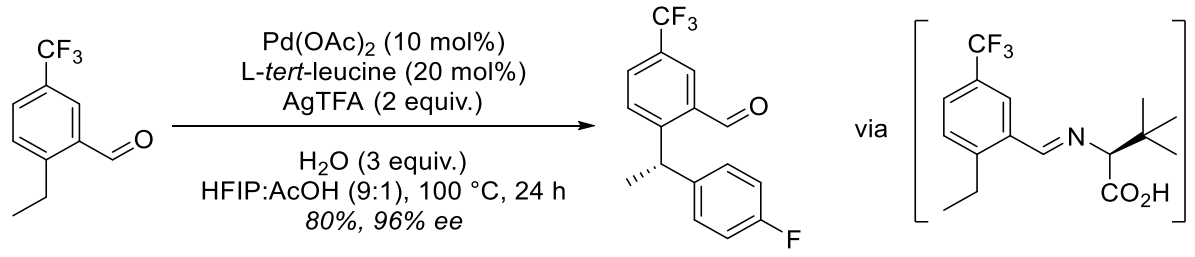
This pioneering work was extended by Mo and Dong who used 7-azaindoline as ligand for the α-alkylation of ketones.[66] The reaction is tolerant with various aryl and alkyl moieties in position 3 and various olefins react with moderate to high turnover number (Scheme 1.19).



Scheme 1.19 Rhodium-catalysed α-alkylation of ketones

In 2016, Yu and co-workers reported a breakthrough in C(sp^3)-H bond activation by using amino-acids as transient directing groups for the arylation of methylene unit.[67] Indeed, under appropriate conditions, the amino group can be tethered to an aldehyde or ketone and subsequently form a bidentate directing group to promote selective C-H bond functionalisation (Scheme 1.20). Remarkably, this reaction occurs with high enantioselectivity, delivering the expected product with up to 96 % enantiomeric excess. It should also be noted that only

catalytic amount of the amino acid auxiliary is necessary, clearly showing the transient character of the imine intermediate and the regeneration of this chiral moiety during the reaction.



Scheme 1.20 Amino-acid directed γ-arylation of aliphatic chains

This work was followed by the development of new classes of ligands suitable for *in situ* imine formation and subsequent functionalisation (Chart 1.3).[68–71]

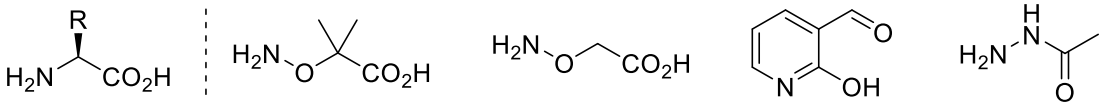
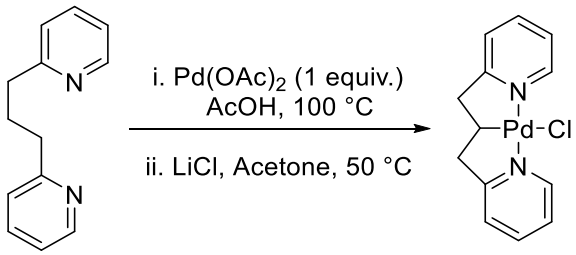


Chart 1.3 Non-exhaustive list of transient directing groups

I.4.iv. Ligand-accelerated C-H activation

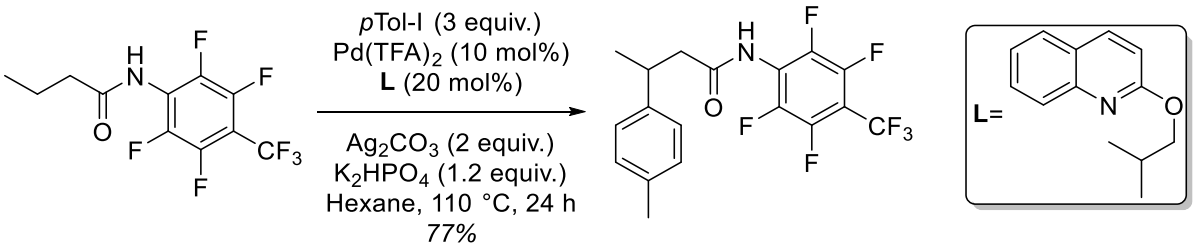
Pyridines early showed a high ability to coordinate metals and direct C-H functionalisation.[72,73] Indeed, Matsumoto and co-workers showed that a bis-pyridylpalladium complexe promote the intramolecular C-H activation and this type of molecule was further characterized in 2000 by White (Scheme 1.21).[48,74]



Scheme 1.21 Pyridine cyclopalladated complex of Matsumoto

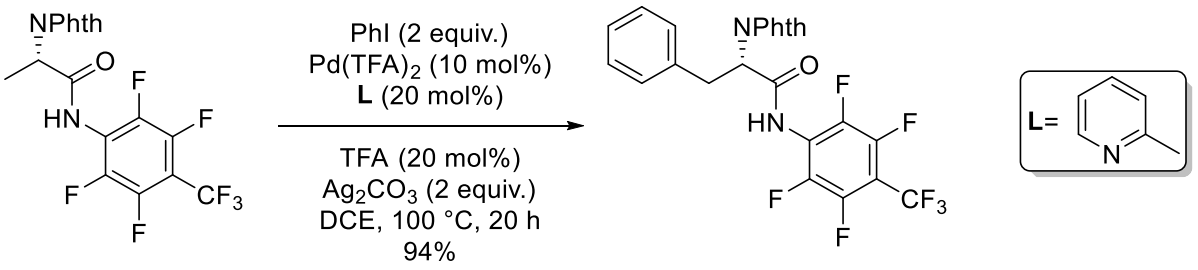
As acidic *N*-perfluoroarylamides has been demonstrated to be versatile weakly coordinating groups,[75] a ligand that strongly coordinates the metal centre and yet allows the amide moiety to bind the same centre is needed. Yu in 2009 and Sanford in 2012 showed that pyridine-type ligands permit olefination of arenes with high yields.[76,77] Guided by these encouraging works, Yu and co-workers started screening pyridine derivatives for the regioselective C(sp^3)-H activation of aliphatic chains. Simple pyridine showed 8% conversion to the desired product and further

optimisation established that optimal reactivity was achieved using 2-isobutoxyquinoline as ligand (Scheme 1.22).[78] Due to the high coordinating ability of pyridine derivatives, *ortho*-substituents are essentials to avoid formation of unreactive PdL_2 dimers. A closely related methodology was developed for the coupling of arylsilanes with alkyl chains.[79] In 2017, a similar analogue of this ligand afforded mono-arylation on α-*N*-protected amino acids without installing the perfluoroamide moiety.[80]



Scheme 1.22 Yu's quinoline-promoted C-H activation

This methodology was recently extended using either 2-picoline or a quinoline derivative to perform mono-, di-arylation and olefination of amino acid derivatives (Scheme 1.23).[81] Preliminary mechanistic studies highlighted the crucial role of the ligand in every stage of the reaction, as for example in the stabilisation of the pre-catalyst.[82]



Scheme 1.23 Yu's pyridine-promoted C-H activation

Pyridine and quinoline-type ligands also demonstrated a drastic improvement in other challenging reactions, such as alkynylation, alkylation or halogenation (Chart 1.4).[83–86]

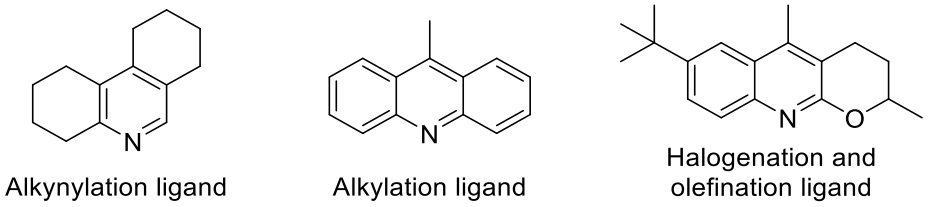
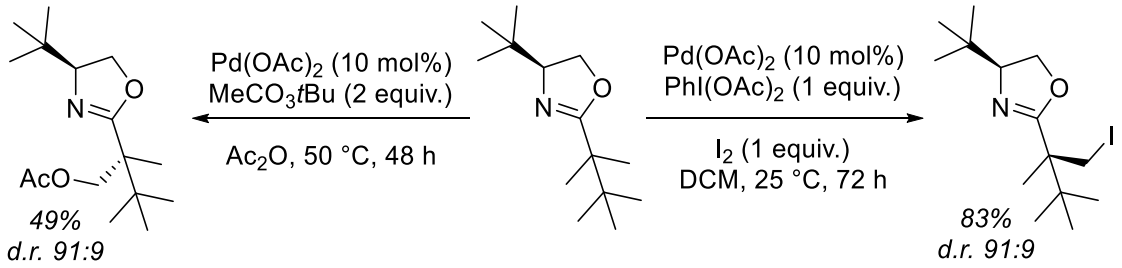


Chart 1.4 Quinoline ligands for C(sp^3)-H bond functionalisation

I.4.v. From regio- to stereo-control

Yu and co-workers were the first to use a chiral auxiliary to provide asymmetric induction during the C(sp^3)-H insertion event forming a chiral palladacycle intermediate. Following the pioneering work of Clinet and co-workers on the cyclopalladation of oxazoline-protected carboxylic acid derivative,[87] they developed their own chiral auxiliary: (*S*)-4-(*tert*-butyl)-4,5-dihydrooxazole.[88,89] They performed the diastereoselective iodination and acetoxylation under mild conditions and with moderate to high diastereomeric ratios (Scheme 1.24).



Scheme 1.24 Oxazoline-directed diastereoselective C-H functionalisation

Further insights on diastereo- and enantio-selective C-H bond activation will be detailed in both chapter 2 and 4, in their respective introductions.

I.5. Sulfoxide as auxiliaries for organic transformations

I.5.i. General introduction on sulfoxides

Sulfoxides are chemical compounds containing a sulfinyl group (S-O) attached to two carbon atoms. Regarding these two substituents, sulfoxides can be chiral or not and feature a trigonal pyramidal shape (Chart 1.5).

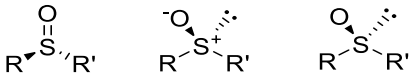
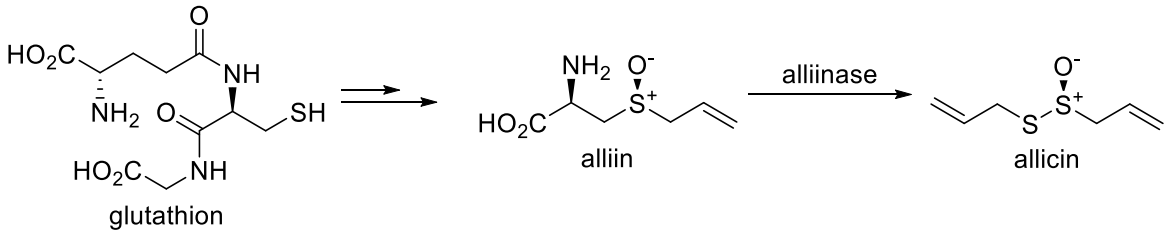


Chart 1.5 Common representation of sulfoxides

There are few examples of sulfoxide present in nature, as illustrated by alliin, a constituent of fresh garlic. When garlic is crushed or chopped, the enzyme alliinase converts it to allicin, which is responsible for the aroma of fresh garlic (Scheme 1.25).[90,91]

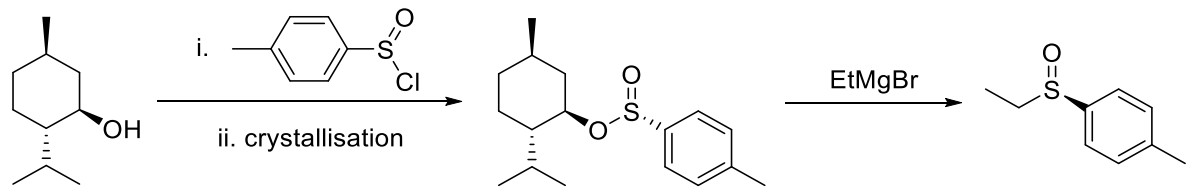


Scheme 1.25 Biosynthesis of allicin

I.5.ii. Synthesis of chiral sulfoxides

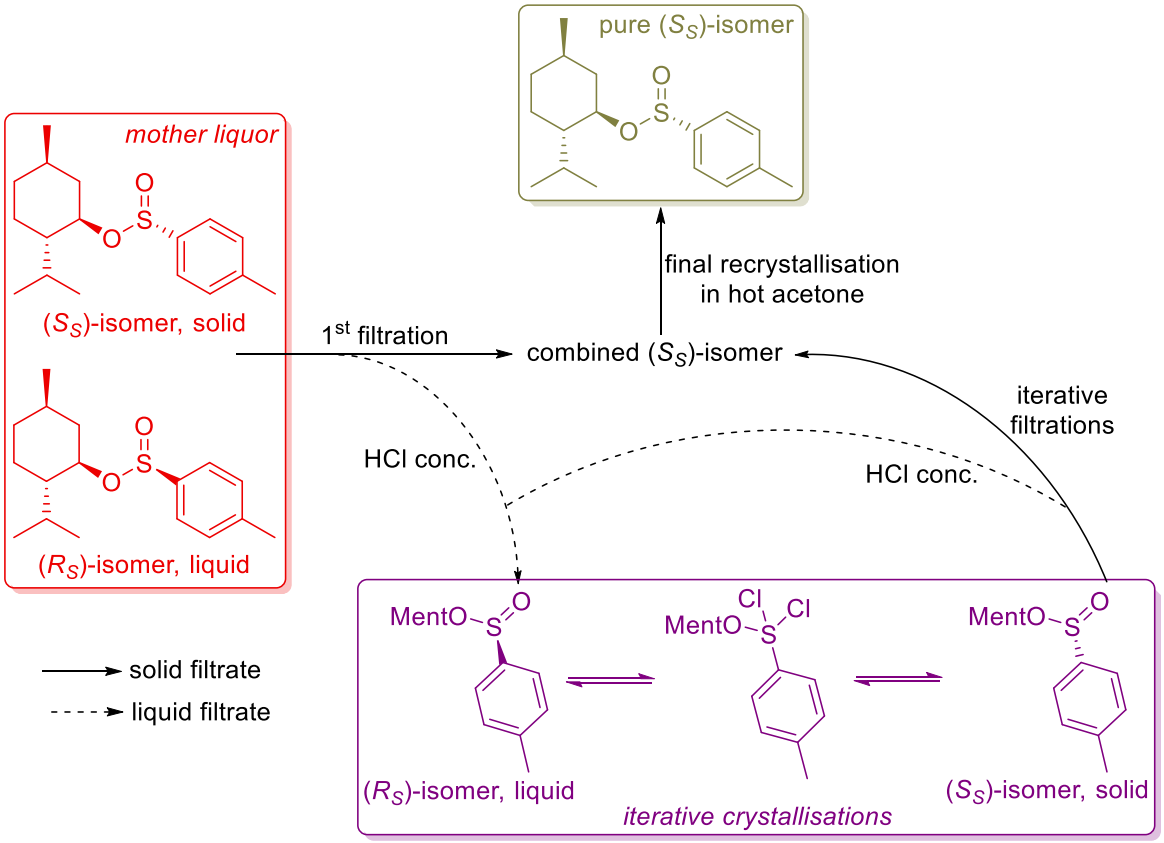
Chiral sulfoxides are crucial elements both in asymmetric synthesis and medicinal chemistry. They are often compared with phosphines as both phosphorus and sulphur atoms are close in the periodic table of elements and phosphines and sulfoxides disclose comparable properties as ligands. There are two main approaches to synthesize such compounds: enantioselective oxidation *via* chiral ligand and asymmetric induction using a chiral auxiliary.

The most common precursors for the stereoselective synthesis of sulfoxides are chiral sulfinates. The first reports were disclosed by Andersen and co-workers in the early 1960s.[92,93] Using menthol as chiral source and *in situ* generated *p*-tolyl sulfinyl chloride in presence of a base, two diastereomers of menthyl *p*-tolylsulfinate were obtained. The major diastereomer is solid and crystallized in acetone, while the minor liquid diastereomer remained in the filtrate (Scheme 1.26).



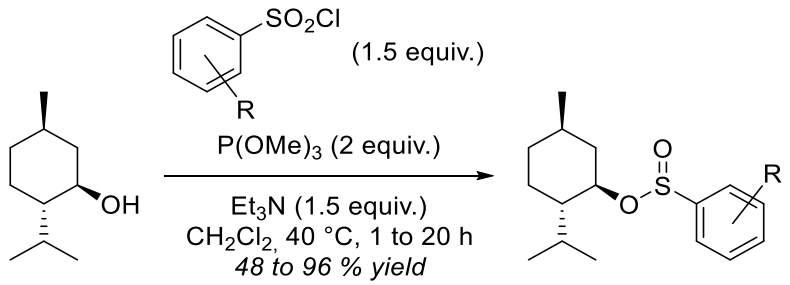
Scheme 1.26 Andersen synthesis of menthyl *p*-tolylsulfinate

Then, Solladié and co-workers significantly improved the Andersen methodology by epimerising the sulphur stereocenter in the mother liquor after each crystallization in presence of concentrated hydrochloric acid (Scheme 1.27). In consequence, the thermodynamic resolution allows high yielding procedure to access enantiopure menthyl sulfinate.[94] However, this ingenious method is limited by the scope, as none of the alkyl sulfinates is crystalline.



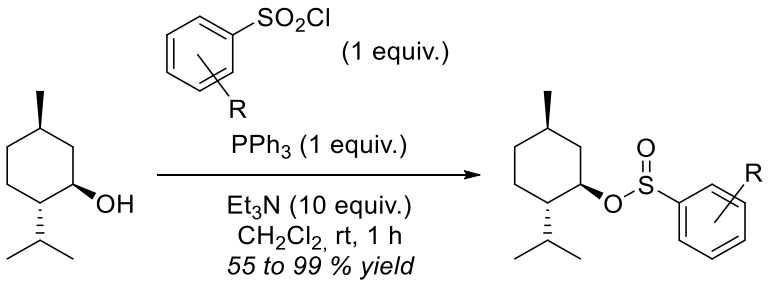
Scheme 1.27 Solladié's synthesis of menthyl *p*-tolylsulfinate

In 1987, Klunder and Sharpless disclosed a new procedure to obtain various menthyl sulfinates using sulfonyl chloride as coupling partners, which are more readily available than the corresponding sulfinic acids used in Andersen's synthesis (Scheme 1.28).[95]



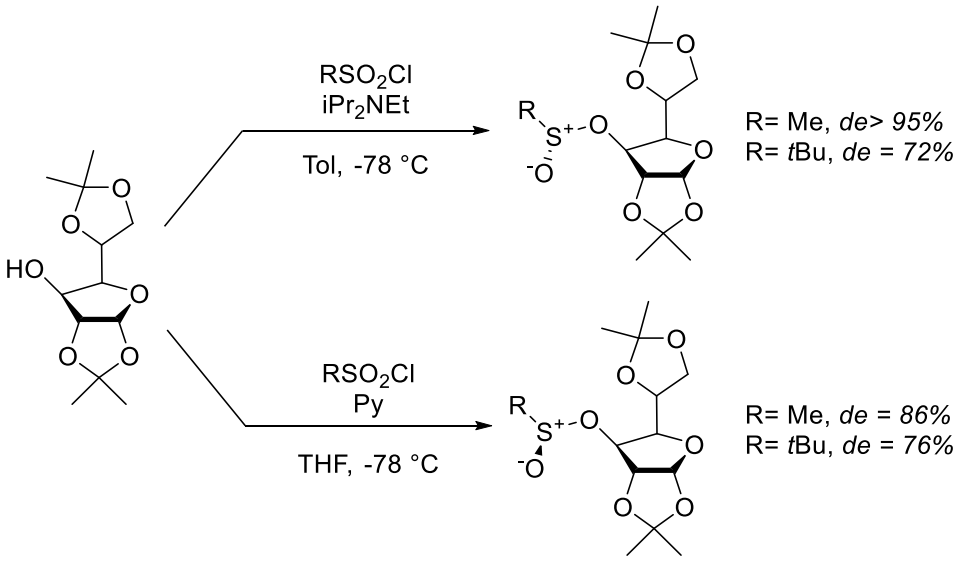
Scheme 1.28 Sharpless' synthesis of menthyl sulfinates

Later, Toru and co-workers extended this methodology, using triphenylphosphine as reducing agent, to form various sulfinates with menthol, diacetone D-glucose (DAG) and non-chiral alcohols (Scheme 1.29).[96] They obtained comparable yields and diastereomeric ratios and the main difference was the reaction time, lowered to 1 h in general. Selective crystallisation of the major diastereomer was sometimes possible but, using hydrochloric acid as racemizing agent, no sulphur epimerisation was possible, limiting the use of these sulfinates.



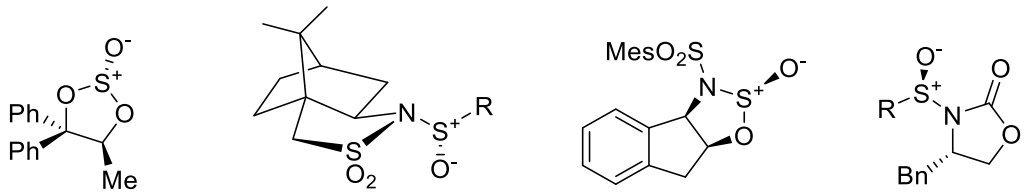
Scheme 1.29 Toru's synthesis of menthyl sulfinates

Taking inspiration from Ridley and Smal who also utilized carbohydrates to prepare optically active sulfoxides, Llera and co-workers showed that, according to the reaction conditions and especially the base used during the transformation, the stereoselectivity can be tuned.[97,98] Yet access to DAG-*tert*-butyl sulfinate gave lower diastereomeric ratios (Scheme 1.30).[99]



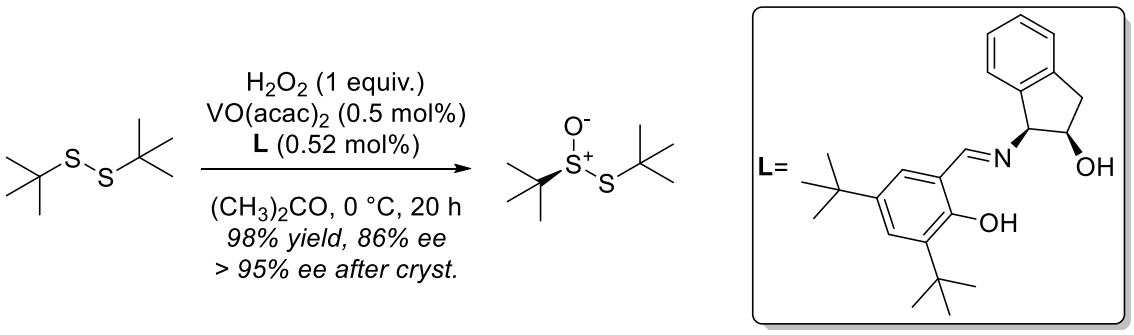
Scheme 1.30 Diastereoselective synthesis of DAG-sulfinates

Various other powerful methodologies were developed the past few years. Early in 1991, Kagan and co-workers accessed chiral sulfoxides from chiral sulphites, delivered by reaction between thionyl chloride and a chiral diol obtained from the chiral pool. [100] Oppolzer described a new chiral sulfinyl transfer agent derived from a versatile bornane-1,2-sultam.[101,102] Excellent enantiomeric excesses were obtained for the resulting sulfoxides and the chiral auxiliary could be recovered in high yields. Therefore, Evans and co-workers used its oxazolidinones, coupled with a sulfinyl chloride, to access separable sulfinamides which are 100 times more reactive with respect to nucleophiles than their corresponding menthyl sulfinate.[103] More recently, Senananyake and co-workers developed oxathiazolidine-2-oxide as chiral precursors for sulfoxides.[104]



Scheme 1.31 Various auxiliaries bearing a chiral sulfoxide

All the previous cited methods involve the diastereoselective formation of an intermediate which is then converted to a chiral sulfoxide. These methods are however not suitable for the synthesis of enantioenriched *tert*-butyl-thiosulfinate which would give access to enantiopure *tert*-butylsulfoxide moiety by addition of an organometallic reagent. Ellman and co-workers reported the synthesis of *tert*-butyl-thiosulfinate with high enantiomeric excess by means of asymmetric oxidation using low catalytic amount of both vanadium acetate and chiral Schiff base.[105,106] Further repeated recrystallizations in hexane allowed the obtention of the enantiopure *tert*-butyl-thiosulfinate and the procedure could be applied on kilogram scale with high yield. One of the advantages of the method is the easy preparation of the ligand, synthesized in one step from commercially available, enantiopure *cis*-1-amino-indan-2-ol and 3,5-di-*tert*-butylsalicylaldehyde. Notably, *tert*-butyl-thiosulfinate is the key precursor to chiral *tert*-butylsulfinamide, used in asymmetric additions of nucleophiles on imines for example.[107]



Scheme 1.32 Ellman' synthesis of *tert*-butyl-thiosulfinate

I.5.iii. Mechanistic insights about sulfoxide epimerization and its optical stability

Sulfoxides essentially racemize by pyramidal inversion and the racemization barrier is much higher than phosphines (Chart 1.6).[108–110]

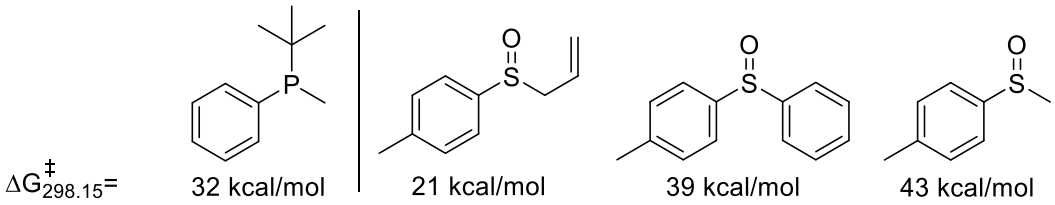
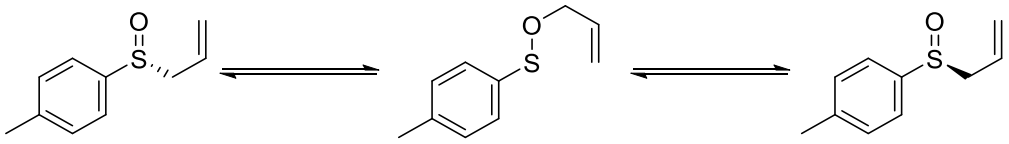


Chart 1.6 Racemization barriers of some phosphines and sulfoxides

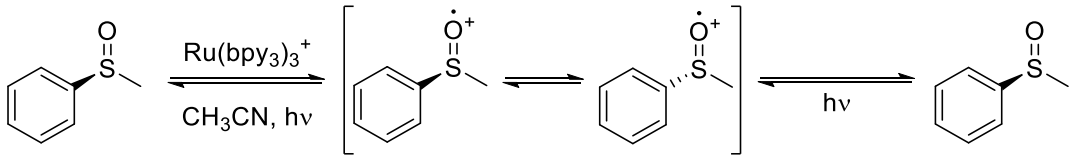
Thermal inversion usually occurs after 200 °C over a few hours by pyramidal inversion, but other mechanisms are described:

- Sigmatropic rearrangement occurs with allylsulfoxides (Scheme 1.33);[111,112]



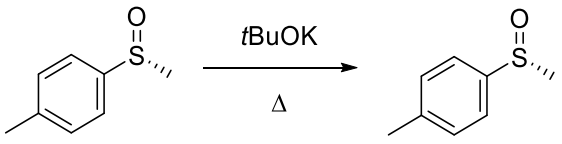
Scheme 1.33 Sigmatropic rearrangement on sulfoxides

- Homolytic cleavage with benzylsulfoxides;
- Photochemical racemization (Scheme 1.34);[113]



Scheme 1.34 Photochemical racemization of sulfoxides

- Racemization by reversible oxygen leaving under acidic conditions as observed in the synthesis of menthylsulfinate.[94] Noteworthy, sulfoxides are very stable under basic conditions, as shown by Oae and co-workers in 1966 (Scheme 1.35).[114]



Scheme 1.35 Stability of the sulphur stereocentre under basic conditions

I.5.iv. Sulfoxides and their use in asymmetric transformations

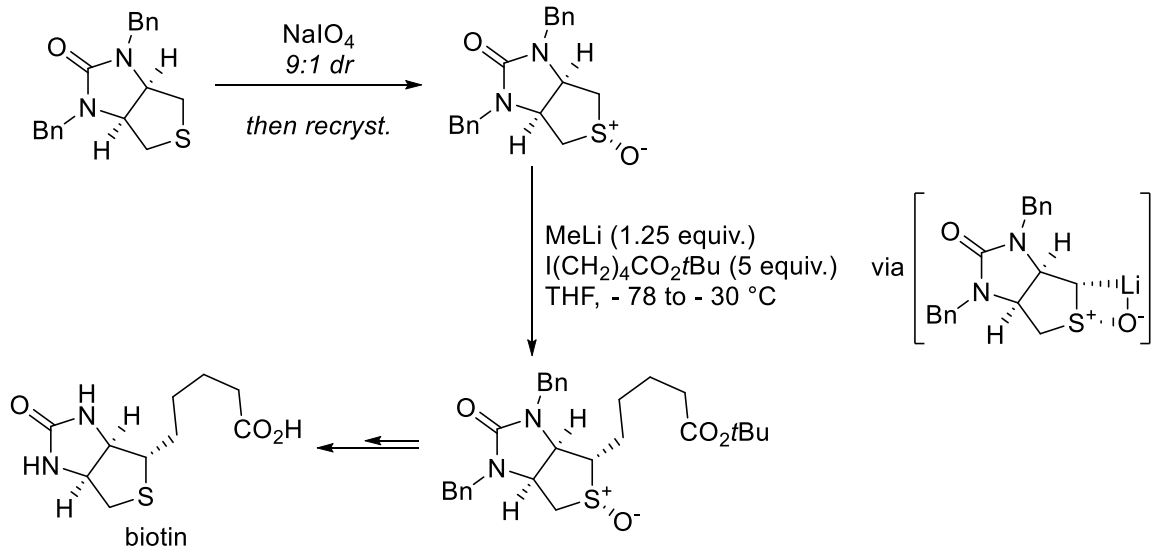
I.5.iv.1. General considerations

As this manuscript highlights the use of sulfoxides as chiral auxiliaries for asymmetric transformations, their overall application field will be quickly detailed. For a more exhaustive presentation, readers are invited to consult the nice reviews dealing with this topic.[28,115,116] In a first part, we will focus on some notable examples of the utilization of sulfoxides for the total synthesis of natural products. Then, we will discuss their use as ligand for both metal-catalysed diastereoselective and enantioselective transformations.

I.5.iv.2. Chiral sulfoxides for the synthesis of biologically active molecules

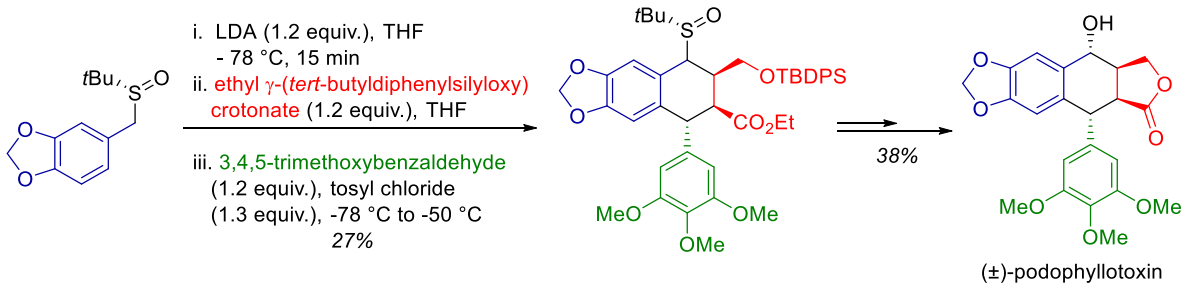
Sulfoxides are often used as chiral inductors in diastereoselective transformations during a total synthesis of active ingredients.

Back in 1978, Marquet and co-workers described the total synthesis of biotin and analogues, by diastereoselective α-alkylation followed by reduction (Scheme 1.36). Although the introduction of the sulfoxide did not occur with total stereoselectivity, column chromatography followed by recrystallisation in dichloromethane/diethyl ether afforded pure diastereomer.[117] We can hypothesize that the total diastereoselectivity for the next step may be explained by the coordination of the lithium with the oxygen of the sulfoxide, thus favouring one configuration.



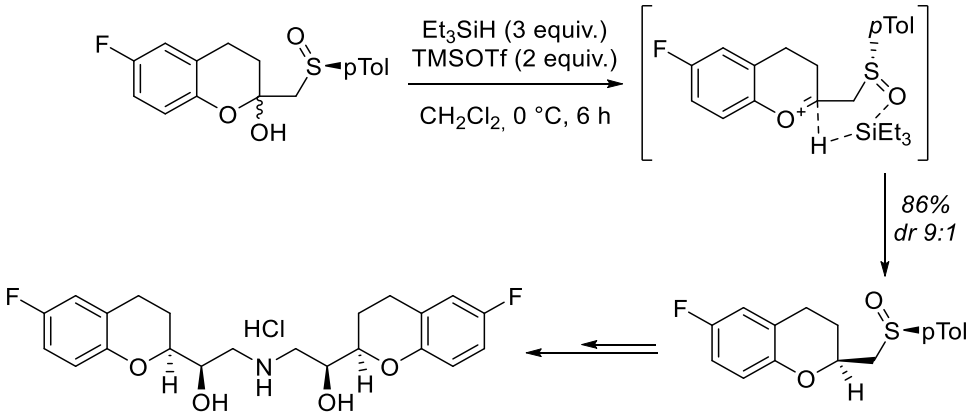
Scheme 1.36 Sulfoxide-directed total synthesis of biotin

Keaveney and co-workers published a new concise synthetic route involving sulfoxides for the total synthesis of (±)-podophyllotoxin, which involves a remarkable one-pot stereoselective three-component reaction. To complete the synthesis, they displaced the sulfoxide by water in presence of triflic anhydride and *sym*-collidine; the resulting crude alcohol was lactonized in one-pot to afford the expected product with 38% yield from the adduct (Scheme 1.37).[118]



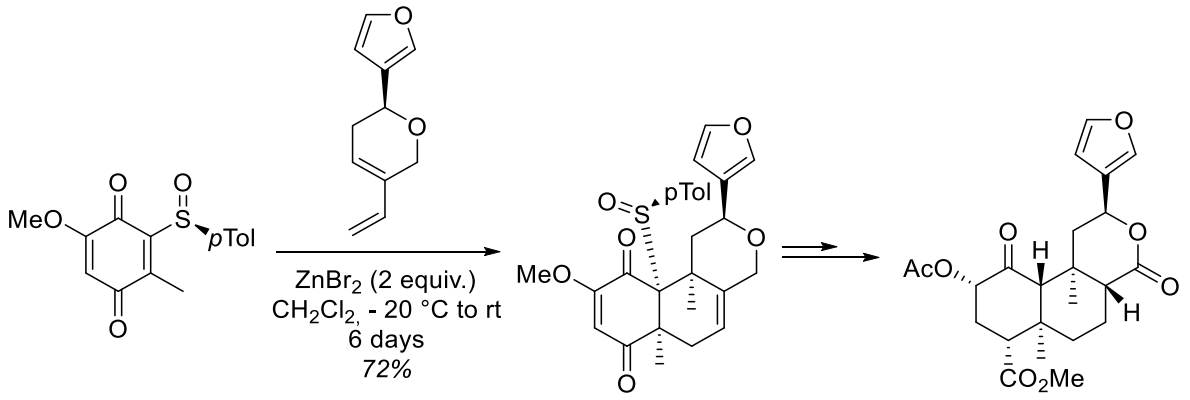
Scheme 1.37 Total synthesis of (±)-podophyllotoxin

In 2008, Colobert, Carreño and co-workers used the ability of the sulfoxide to coordinate a silane to direct a diastereoselective reductive deoxygenation process for the total synthesis of nebivolol (Scheme 1.38). Removal of the sulfoxide moiety was possible with excellent yield and complete retention of other stereocentres by means of an analogue displacement as used by Keaveney.[119]



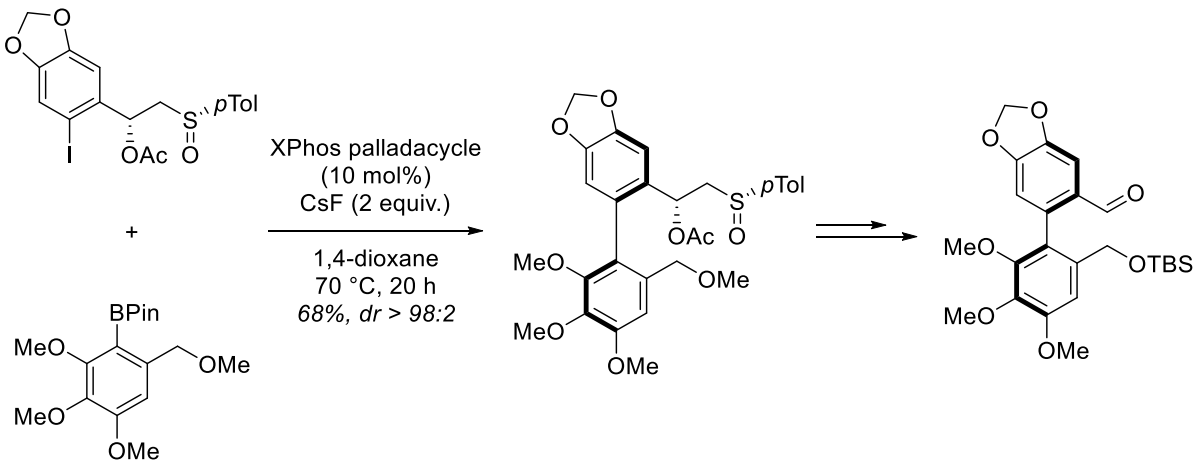
Scheme 1.38 Key step for the total synthesis of nebivolol as hydrochloride salt

Within the SynCat team in Strasbourg, sulfoxides proved to be highly efficient directing groups enabling the control of stereoselective transformations such as cycloadditions,[120] Reformatsky reactions,[121] reduction of ketones[14,122] or conjugate additions.[123] For example, Hanquet and co-workers disclosed in 2011 the use of *p*-tolylsulfoxide moiety for a diastereoselective Diels-Alder cycloaddition as the key step for the synthesis of salvinorin A and analogues (Scheme 1.39).[120,124]



Scheme 1.39 Hanquet's formal synthesis of salvinorin A using asymmetric Diels-Alder reaction

Colobert and co-workers also more recently reported an efficient pathway for the stereoselective synthesis of a key intermediate to access (-)-steganone via stereoselective Suzuki cross-coupling (Scheme 1.40).[125]

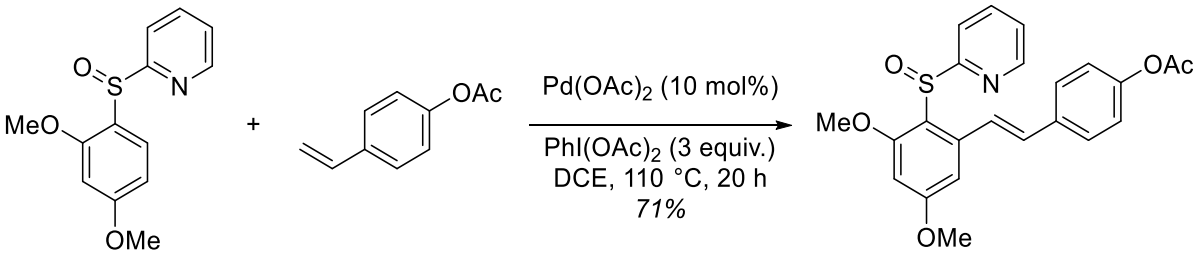


Scheme 1.40 Colobert's first stereoselective access of a key intermediate for the synthesis of (-)-steganone

I.5.iv.3. Sulfoxides in metal-catalysed diastereoselective reactions

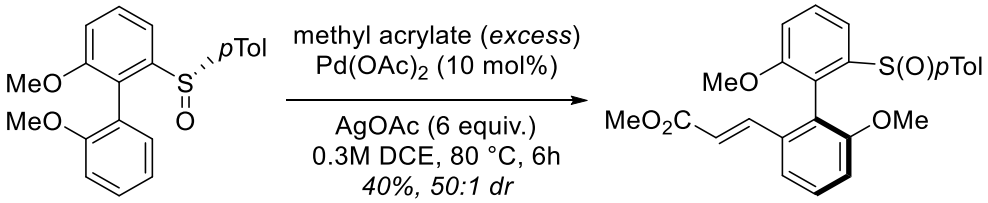
Sulfoxides can usually bind both soft metals like palladium or copper through the sulphur and hard metals like iron through the oxygen. Their high stereo-stability under harsh reaction conditions makes them auxiliaries of choice for metal-catalysed asymmetric transformations.

Carretero and co-workers developed in 2011 a 2-pyridylsulfoxide directing group for the olefination of arenes. Good control on mono- and di-functionalisation was observed, and their methodology was applied for the synthesis of the key fragment of resveratrol (Scheme 1.41). Interestingly, removal of the auxiliary occurred smoothly using *n*-butyllithium.[126]



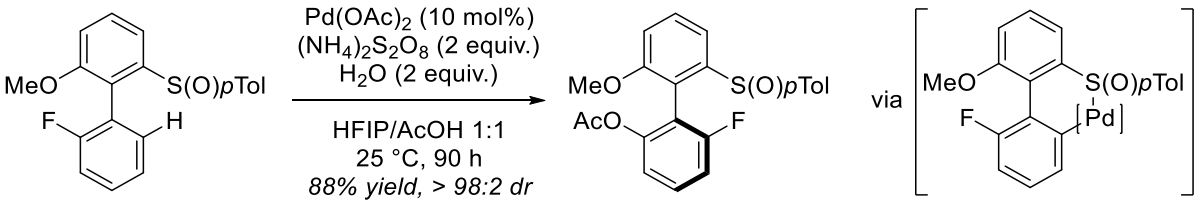
Scheme 1.41 Carretero's synthesis of a key intermediate of resveratrol

In 2013, Colobert and co-workers exploited the existing sulphur stereogenic centre in biaryl moieties to couple it with acrylates and induce atropoisomerism via dynamic kinetic resolution (Scheme 1.42).[127]



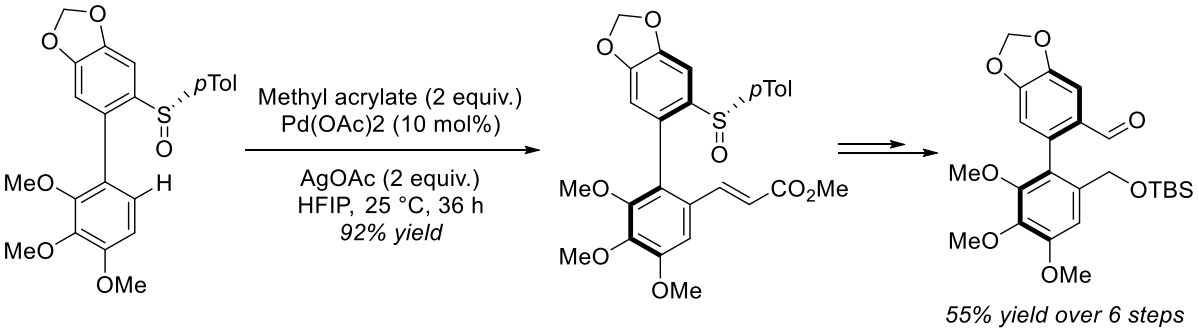
Scheme 1.42 Diastereoselective olefination of biaryl scaffolds using a chiral sulfoxide

In 2014, two other procedures for the stereoselective iodination and acetoxylation of biaryls were developed.[9] Mild C(sp^2)-H bond activation occurred and both excellent yields and diastereomeric ratios were observed (Scheme 1.43).



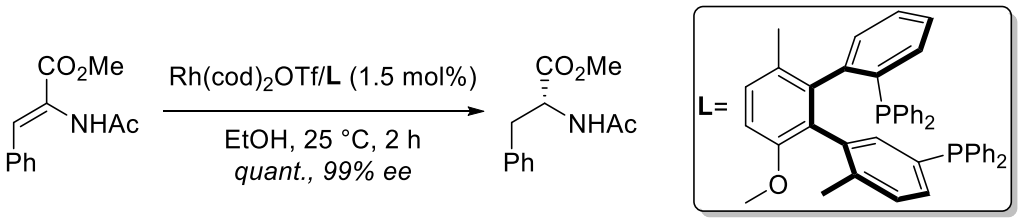
Scheme 1.43 Colobert's atroposelective acetoxylation and iodination

Atroposelective Heck oxidative addition was later used for an expedient access of the key intermediate for the synthesis of (-)-steganone (Scheme 1.44).[128] Under extremly mild reaction conditions, full conversion of the biaryl precursor into the olefinated profuct was achieved and the atropopure product was isolated in 92 % yield.



Scheme 1.44 Colobert's first stereoselective access of a key intermediate of (-)-steganone

In 2018, sulfoxide proved to be an excellent chiral inductor for atroposelective synthesis of multiarene scaffolds; Colobert and co-workers discovered a route towards new terphenyl ligands with two atropoisomeric axes. After functionalisation of the terphenyl moiety, completed or not by traceless removal of the sulfoxide, the resulting ligands showed excellent enantiomeric induction for various reactions (Scheme 1.45).[9–11]



Scheme 1.45 Asymmetric hydrogenation using new terphenyl-type ligands

I.5.iv.4. Sulfoxides as ligands in metal-catalysed transformations

Sulfoxides were early used as ligands for a large variety of transformations. Many metal complexes were prepared since the 1970s, with ruthenium,[129] iridium,[130] rhodium[131,132] and palladium[131] for example (Chart 1.7). The following part will mainly relate on bis-sulfoxide and aminosulfoxide type ligands. For more exhaustive information, readers are invited to consult the reviews of Dorta, Procter and Trost.[28,115,133]

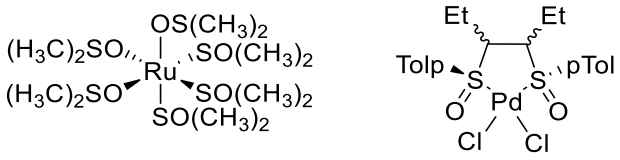
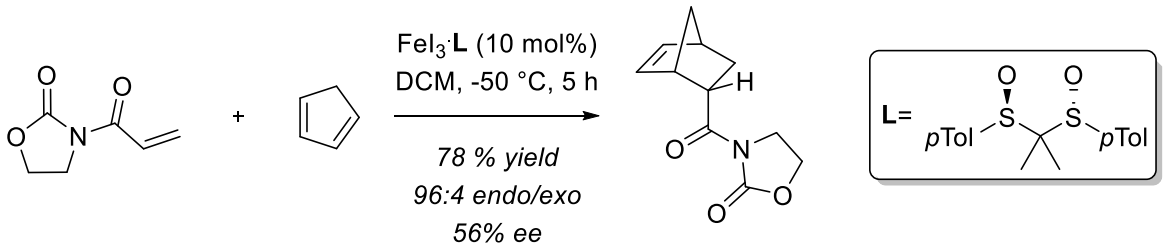


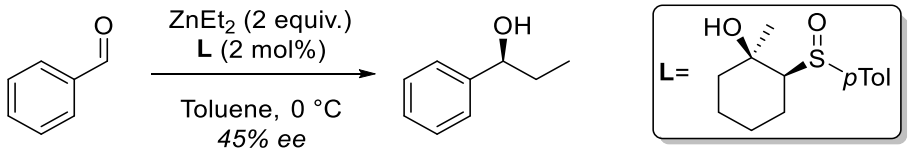
Chart 1.7 Two metal-sulfoxide complexes

Early in 1993, Khiar and co-workers synthesized the first chiral sulfoxide ligand bearing chirality only on the sulphur atom and used it for iron-catalyzed Diels-Alder reaction (Scheme 1.46).[134] In this case, the metal-ligand complex was preliminary formed by reaction between iron, iodine and the bis-sulfoxide.



Scheme 1.46 Khiar's asymmetric Diels-Alder reaction

The same year, Carreño and co-workers disclosed the enantioselective addition of diethylzinc on benzaldehyde using β-hydroxysulfoxide ligands.[135]



Scheme 1.47 Carreño's asymmetric addition of diethylzinc on benzaldehyde

The pioneering studies of Khiar and Carreño were followed in 1995 by the synthesis of another bis-sulfoxide ligand used by Shibasaki and co-workers for an enantioselective Tsuji-Trost reaction which showed moderate activity.[136] An array of bidentate ligands bearing a chiral sulfoxide were then synthesized and some of them showed excellent enantiomeric induction for this type of reaction (Figure 1.16).[137,138]

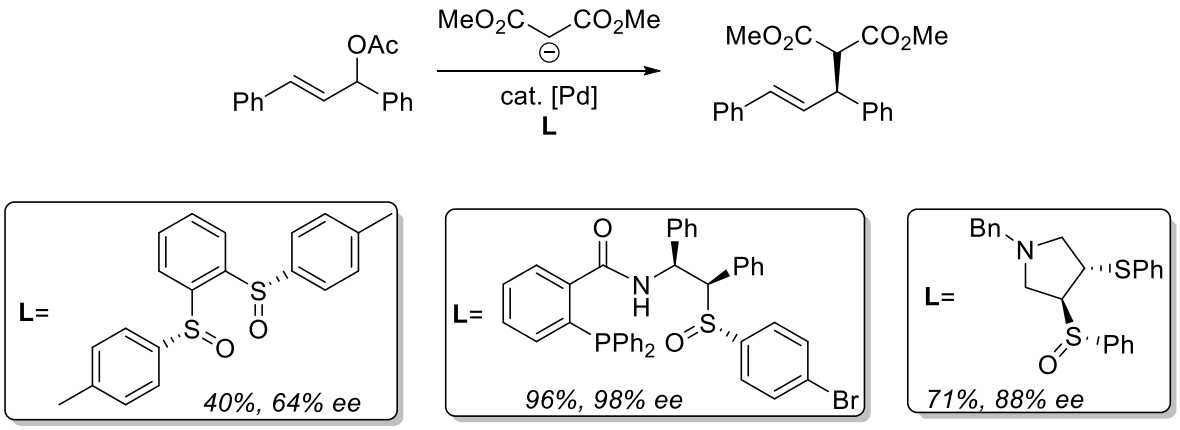
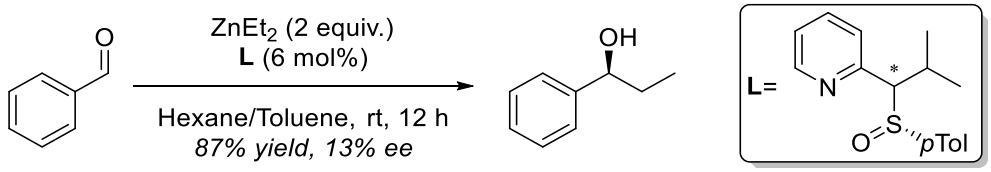


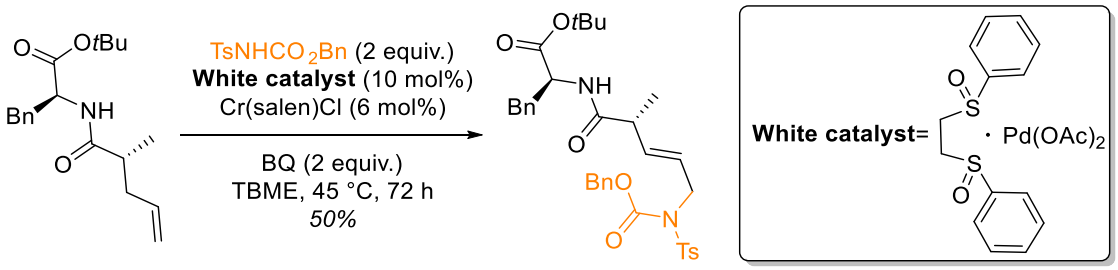
Figure 1.16 Examples of chiral ligands for the asymmetric Tsuji-Trost reaction

Chelucci and co-workers also developed a sulfoxide-containing ligand for the asymmetric Tsuji-Trost reaction, although showing moderate enantiomeric induction. Interestingly, the very same ligand is also capable of induing a chiral information during an addition of diethyl zinc to benzaldehyde (Scheme 1.48).[139]



Scheme 1.48 Asymmetric addition to benzaldehyde using a pyridylsulfoxide ligand

In 2007, White and co-workers developed a new air-stable catalyst, known today as White catalyst, used in numerous allylic C-H bond functionalisation reactions of olefins and oxidative Heck additions.[140,141] Challenging allylic amination could be performed with this exceptional catalyst using methyl *N*-tosyl carbamate as nucleophile to obtain linear E-allylic amine products (Scheme 1.49).[142]



Scheme 1.49 White allylic amination using bis-sulfoxide-Pd(II) catalyst

Later, Dorta and co-workers used a chiral atropopure bis-sulfoxide ligand for the asymmetric 1,4-addition of boronic acids to cyclohexenone.[143] A comparison of this ligand with the bis-phosphine analogue revealed that the sulfoxide complex is far more reactive and give better enantiomeric excess than the corresponding phosphine (Figure 1.17). The authors suggest that the high σ-donation of sulfoxides improves the reactivity of the system.

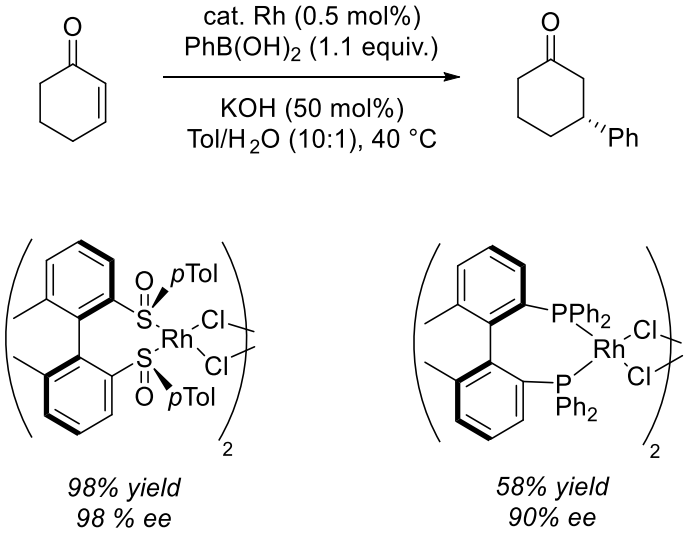


Figure 1.17 Dorta 1,4-addition using chiral sulfoxide and phosphine ligands

S,N bidentate ligands with chirality present at both the carbon backbone and sulphur atom have emerged as valuable ligands for asymmetric catalysis. In 1994, Williams and co-workers synthesized the first sulfinyloxazoline ligands for asymmetric Tsuji-Trost reaction; the desired compound was afforded in 96% yield and 88% enantiomeric excess.[144] This skeleton was later used by Hiroi and co-workers for an asymmetric Diels-Alder reaction between protected acrylamide and cyclopentadiene; high yield and selectivity were observed.[145] More recently, Itami and co-workers reported an asymmetric Suzuki-type coupling using William's ligand to get axial chirality with good yield and moderate 61% enantiomeric excess.[12] In 2016, White and co-workers optimized the structure of sulfinyloxazoline ligands for the enantioselective allylic C-H oxidation of olefins to isochromans (Chart 1.8).[13] Many other types of ligands have also been disclosed, such as (S,O), (S,S) or (S,P).

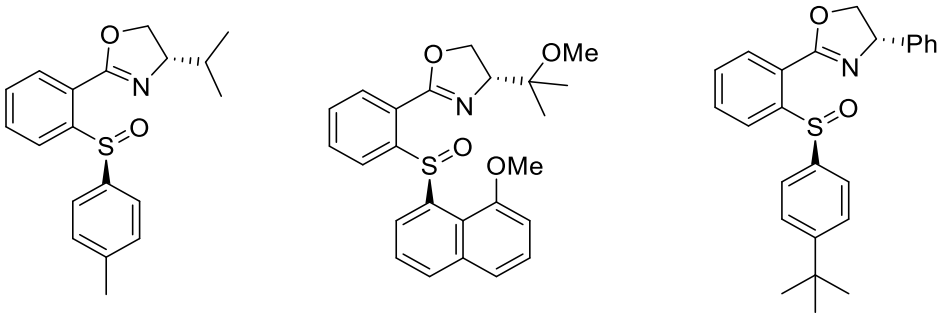


Chart 1.8 Examples of sulfinyloxazoline-type ligands

More exotic ligands such as sulfoxide-olefin or ferrocene hybrid ligands,[146] were developed for rhodium catalysed 1,4-additions (Chart 1.9). Du and co-workers established that both sulfoxide and olefin were bound to the metal centre during catalysis.[147]

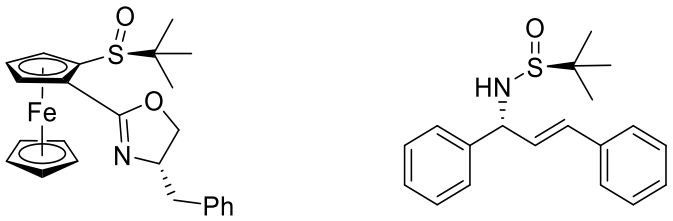
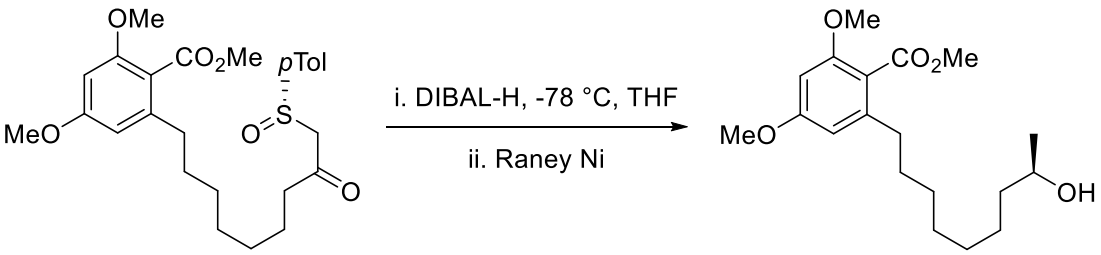


Chart 1.9 Examples of hybrid ligands

I.5.v. Sulfoxides: traceless directing groups

One of the key advantages of using the sulfoxide in particular as chiral auxiliary is its traceless character due to the ability to cleave or to transform it into a myriad of functionalities. This appealing feature was often used in total synthesis, as mentioned before.

Desulfinylation is usually performed using Raney Nickel.[148,149] This reaction has found numerous applications as for example in the total synthesis of lasiodiplodin (Scheme 1.50).[150]



Scheme 1.50 Raney Ni desulphurisation in the total synthesis of lasiodiplodin

Another important transformation regarding these moieties is the Pummerer reaction whereby alkylsulfoxides rearrange to α-acyloxy-thioethers.[151–153] Originally developed with acetic anhydride as promoter, many variants have been published as for example using Lewis acids which allow the reaction to proceed smoothly at lower temperatures.[154] Acylation of the sulfoxide followed by elimination of acetic acid produces a reactive thionium ion. Then, acetate adds to the sulfonium to give the final product (Figure 1.18).

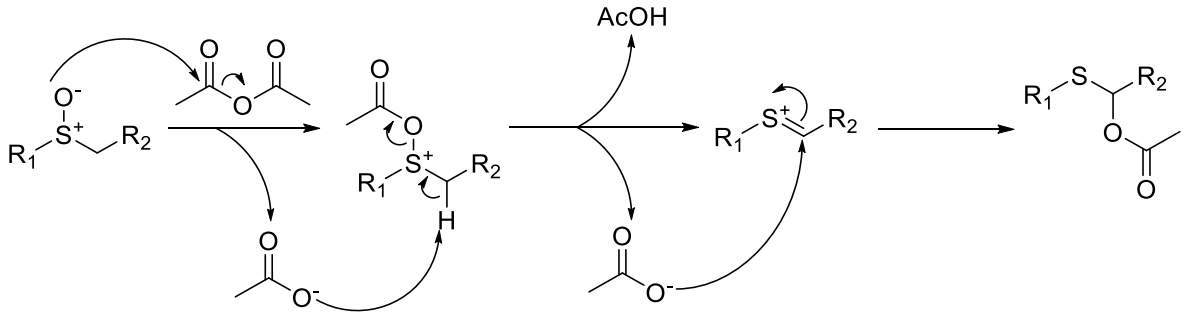
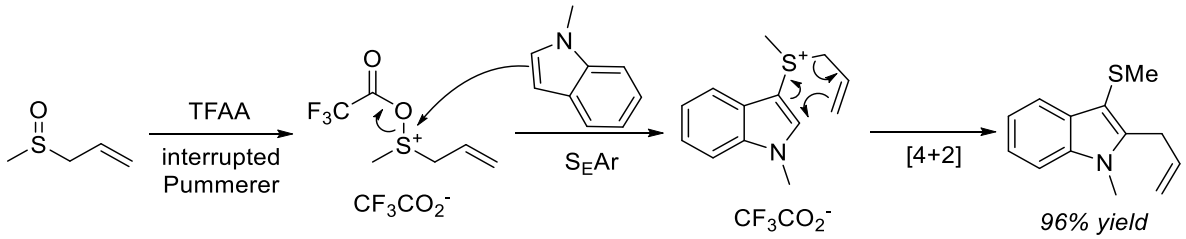


Figure 1.18 General mechanism for Pummerer rearrangement

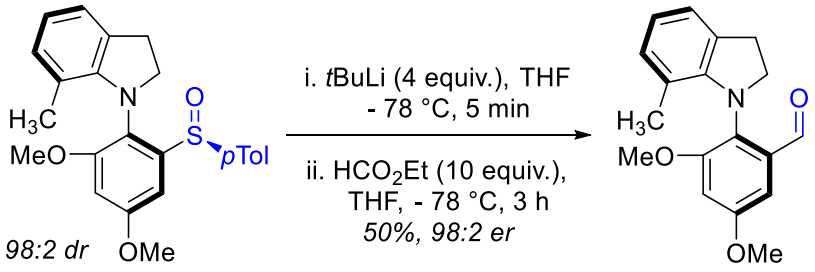
For example, Procter and co-workers remarkably used other nucleophiles than acetate to interrupt the Pummerer rearrangement and promote other challenging transformations such as [3+3] sigmatropic rearrangements (Scheme 1.51).[155,156]



Scheme 1.51 Procter synthesis of 3-thioindoles

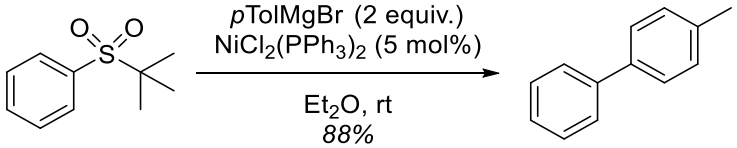
But sulfoxides are also easily transformed by exchange with lithium species (without affecting other functions or stereocentres) and quenching with numerous electrophiles as shown by Fujihara and co-workers in 1991.[157] From chiral auxiliary, the sulfoxide thus becomes an interchangeable functional group. As only few target products bear this motif, this reaction reaches high significance to broaden their application scope.

Remarkably, Colobert and co-workers showed recently that removal of the sulfoxide on axially chiral C-N scaffolds did not affect the chiral axis.[158] Generation of the lithium species after addition of excess *tert*-butyllithium followed by quenching with a formyl source afforded the desired aldehyde with good yield and excellent enantiomeric excess (Scheme 1.52).



Scheme 1.52 Lithium-promoted sulfoxide exchange

Finally, Julia and co-workers also developed a methodology to remove *tert*-butylsulfoxide moieties by oxidizing them to sulfones and then performing a nickel-catalysed cross-coupling with Grignard reagents (Scheme 1.53).[159,160] While interesting, this reaction suffers from a limited field of application.



Scheme 1.53 Julia's sulfoxide coupling with Grignard reagents

I.6. Objectives of the doctoral thesis

First and foremost, the emergence of numerous methodologies for auxiliary-assisted C(sp^3)-H bond activation and the high potential of sulfoxides to promote highly efficient asymmetric transformations urged us to design and explore a new chiral bicoordinating directing group. When the *Sulf-As-CH* project started, there were only two examples of chiral auxiliary for the asymmetric C(sp^3)-H bond functionalisation and none was containing a chiral sulfoxide. This innovative project originally aimed to design a new bidentate directing group bearing a chiral sulfoxide and to apply it for the arylation of the most reactive aliphatic skeleton: cyclopropanes. Rewardingly, we were able to construct stereoselectively complex scaffolds via arylation and even challenging alkylation and olefination using (*S*)-2-(*p*-tolylsulfinyl)aniline (APS) as the DG (Figure 1.19). This work will be detailed in the next chapter.

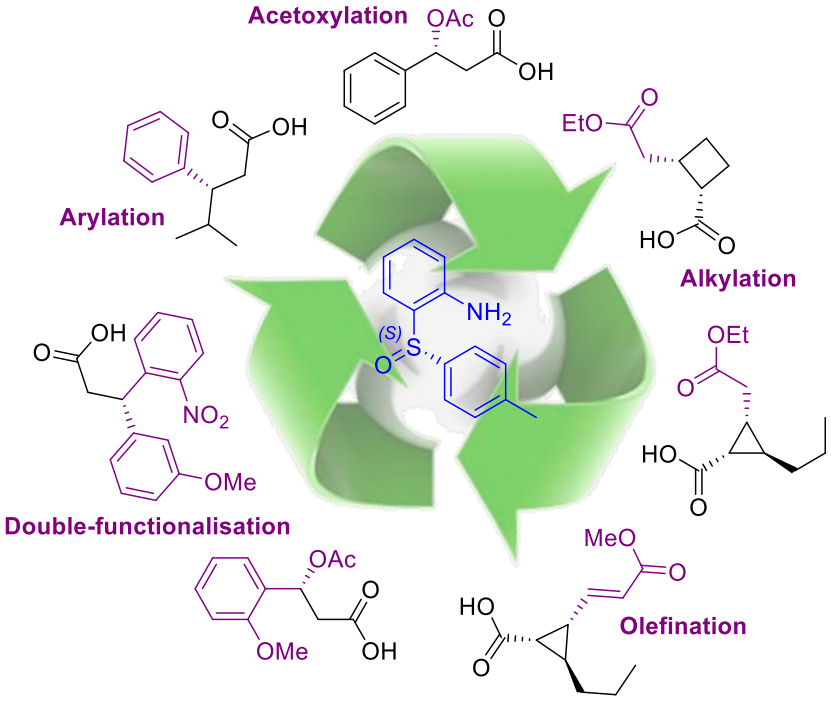


Figure 1.19 Scope of transformations allowed by (*S*)-2-(*p*-tolylsulfinyl)aniline

In the continuity of this first work, we developed a new methodology to access enantiopure cyclopropane key intermediate for natural product synthesis. We performed challenging olefination and alkylation and obtained three intermediates for the synthesis of cyclopropane-based biologically active scaffolds: hoshinolactam, cascarillic acid and grenadamide total synthesis. To exemplify our method, the total synthesis of hoshinolactam was achieved with good yield and excellent enantiomeric excess (Figure 1.20). This work will also be detailed in the next chapter.

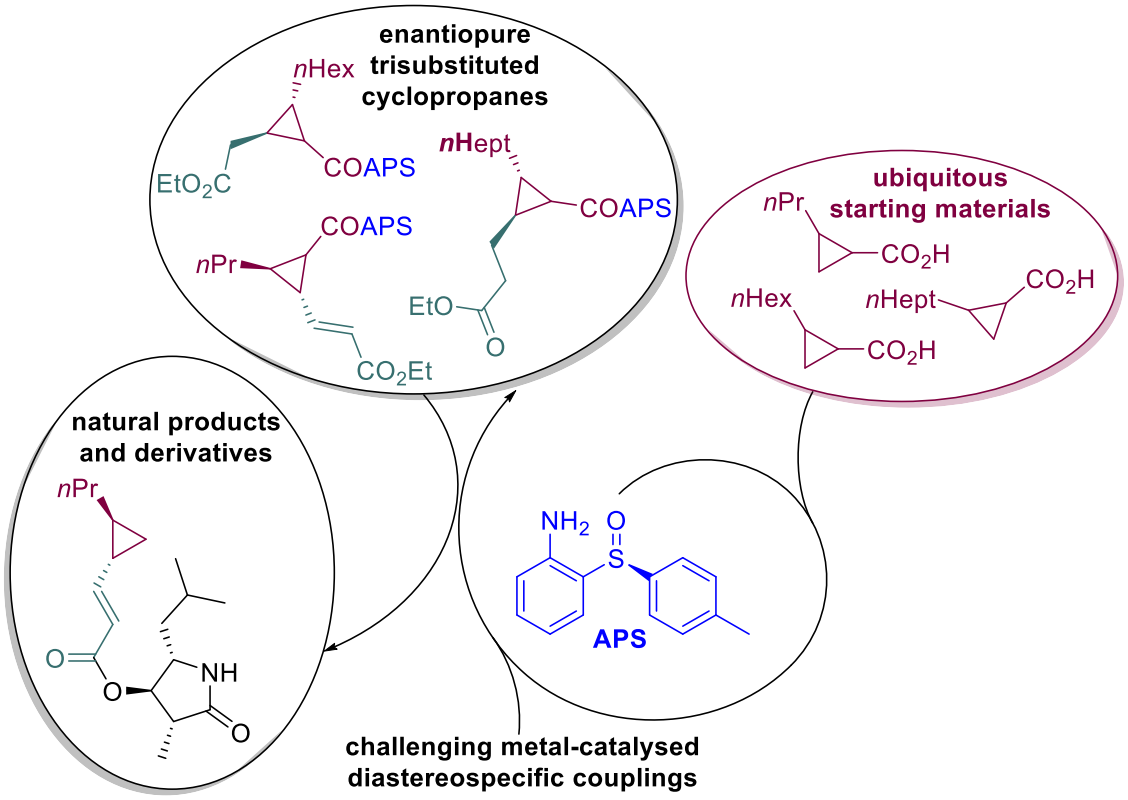


Figure 1.20 APS-based strategy for the synthesis of cyclopropane-containing natural products

With our knowledge in diastereoselective APS-promoted C-H activation of cycloalkane, we then studied the functionalisation of simple aliphatic chains. We succeded in developing a catalytic system for performing arylation with good yields and moderate to good diastereomeric ratios, but also more challenging acetoxylation or one-pot double functionalisation of hydrocinnamic acid derivatives. This work will be detailed in the third chapter.

Finally, even if APS showed high potential in promoting various transformations, the moderate diastereoselectivity observed for the different transformations is a major limitation of this technology. Accordingly, targeting more efficient, powerful and stereoselective protocols, we endeavoured on developing an enantioselective transformation. Consequently, we developed a new scaffold for the ligand-enabled enantioselective arylation and alkynylation of cycloalkanes. This study will be developed in the fourth chapter and opens new perspectives for the synthesis of highly functionalised enantioenriched products.

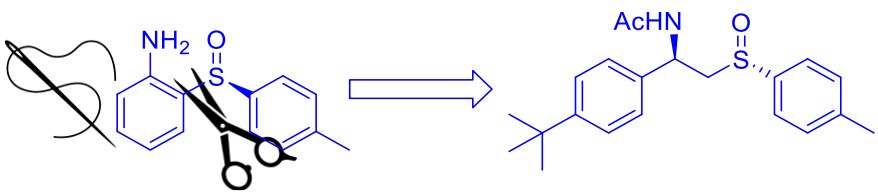


Figure 1.21 From diastereo- to enantio-selective sulfinylamine-promoted C-H activation

I.7. Conclusion

Over the years, sulfoxides proved to be excellent ligands and chiral inductors for metal-catalysed asymmetric transformations. In parallel, the ingenious development of numerous efficient catalytic systems unlocked the door towards direct metalation of C(sp^3)-H bonds. A widespread use of C-H activation is yet hampered by the need for finely designed starting material bearing, often hardly transformable, directing groups. Encouraged by our pioneering work on diastereoselective C(sp^2)-H bond functionalisation, the design of new sulfoxide-bearing ligands for the C(sp^3)-H bond activation seems appealing.

In this context, the *Sulf-As-CH* project was dedicated to the design, the synthesis and the applications of new sulfoxide scaffolds for highly stereoselective transformations and the following will disclose 1) the design and use of (*S*)-2-(*p*-tolylsulfinyl)aniline (APS) as chiral auxiliary for the diastereoselective C(sp^3)-H bond arylation, acetoxylation, alkylation and olefination as well as 2) the development of *N*-((*S*)-1-(4-(tert-butyl)phenyl)-2-((*R*)-*p*-tolylsulfinyl)ethyl)acetamide (NBSA) as ligand for the enantioselective C(sp^3)-H bond arylation and alkynylation (Figure 1.22).

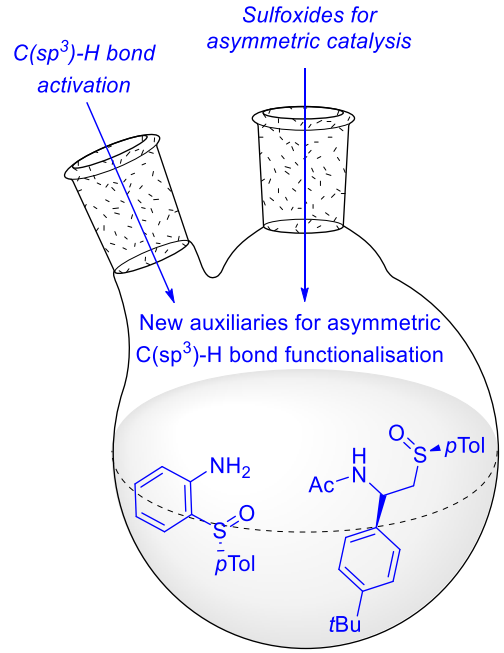


Figure 1.22 Merging C-H activation and sulfoxides to design new efficient ligands

I.8. Bibliographic references

[27] T. Toru, Ed. , *Organosulfur Chemistry in Asymmetric Synthesis*, Wiley-VCH-Verl, Weinheim, **2008**.
[28] B. M. Trost, M. Rao, *Angew. Chem. Int. Ed.* **2015**, *54*, 5026–5043.
[29] J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507–514.
[30] H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861–2904.
[31] L. Claisen, A. Claparède, *Berichte Dtsch. Chem. Ges.* **1881**, *14*, 2460–2468.
[32] L. Claisen, *Berichte Dtsch. Chem. Ges.* **1887**, *20*, 655–657.
[33] Y. Fujiwara, K. Takaki, J. Watanabe, Y. Uchida, H. Taniguchi, *Chem. Lett.* **1989**, *18*, 1687–1688.
[34] T. Nishiguchi, K. Nakata, K. Takaki, Y. Fujiwara, *Chem. Lett.* **1992**, *21*, 1141–1142.
[35] G. Dyker, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 103–105.
[36] J. Sofack-Kreutzer, N. Martin, A. Renaudat, R. Jazzar, O. Baudoin, *Angew. Chem. Int. Ed.* **2012**, *51*, 10399–10402.
[37] D. Dailler, G. Danoun, O. Baudoin, *Angew. Chem. Int. Ed.* **2015**, *54*, 4919–4922.
[38] P. M. Holstein, D. Dailler, J. Vantourout, J. Shaya, A. Millet, O. Baudoin, *Angew. Chem. Int. Ed.* **2016**, *55*, 2805–2809.
[39] T. Saget, N. Cramer, *Angew. Chem. Int. Ed.* **2012**, *51*, 12842–12845.
[40] T. Saget, S. J. Lemouzy, N. Cramer, *Angew. Chem. Int. Ed.* **2012**, *51*, 2238–2242.
[41] J. Pedroni, M. Boghi, T. Saget, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 9064–9067.
[42] J. Pedroni, N. Cramer, *Angew. Chem. Int. Ed.* **2015**, *54*, 11826–11829.
[43] J. Pedroni, T. Saget, P. A. Donets, N. Cramer, *Chem. Sci.* **2015**, *6*, 5164–5171.
[44] J. Pedroni, N. Cramer, *Org. Lett.* **2016**, *18*, 1932–1935.
[45] P. Wang, P. Verma, G. Xia, J. Shi, J. X. Qiao, S. Tao, P. T. W. Cheng, M. A. Poss, M. E. Farmer, K.-S. Yeung, et al., *Nature* **2017**, *551*, 489–493.
[46] A. G. Constable, W. S. McDonald, L. C. Sawkins, B. L. Shaw, *J. Chem. Soc. Chem. Commun.* **1978**, 1061.
[47] Y. Fuchita, K. Hiraki, T. Uchiyama, *J. Chem. Soc. Dalton Trans.* **1983**, 897.
[48] K. Hiraki, Y. Fuchtta, Y. Matsumoto, *Chem. Lett.* **1984**, *13*, 1947–1948.
[49] Y. Fuchita, K. Hiraki, Y. Matsumoto, *J. Organomet. Chem.* **1985**, *280*, c51–c54.
[50] R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders, J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510–3511.
[51] R. M. Beesley, C. K. Ingold, J. F. Thorpe, *J Chem Soc Trans* **1915**, *107*, 1080–1106.
[52] A. Renaudat, L. Jean-Gérard, R. Jazzar, C. E. Kefalidis, E. Clot, O. Baudoin, *Angew. Chem. Int. Ed.* **2010**, *49*, 7261–7265.
[53] P. Larini, C. E. Kefalidis, R. Jazzar, A. Renaudat, E. Clot, O. Baudoin, *Chem. - Eur. J.* **2012**, *18*, 1932–1944.
[54] D.-H. Wang, M. Wasa, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 7190–7191.
[55] L.-C. Campeau, D. J. Schipper, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3266–3267.
[56] D. J. Schipper, L.-C. Campeau, K. Fagnou, *Tetrahedron* **2009**, *65*, 3155–3164.
[57] A. T. Tran, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 10530–10534.
[58] V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155.
[59] M. Corbet, F. De Campo, *Angew. Chem. Int. Ed.* **2013**, *52*, 9896–9898.
[60] K. Chen, B.-F. Shi, *Angew. Chem. Int. Ed.* **n.d.**, *53*, 11950–11954.
[61] N. Rodríguez, J. A. Romero-Revilla, M. Á. Fernández-Ibáñez, J. C. Carretero, *Chem. Sci.* **2012**, *4*, 175–179.
[62] G. Zhang, X. Xie, J. Zhu, S. Li, C. Ding, P. Ding, *Org. Biomol. Chem.* **2015**, *13*, 5444–5449.

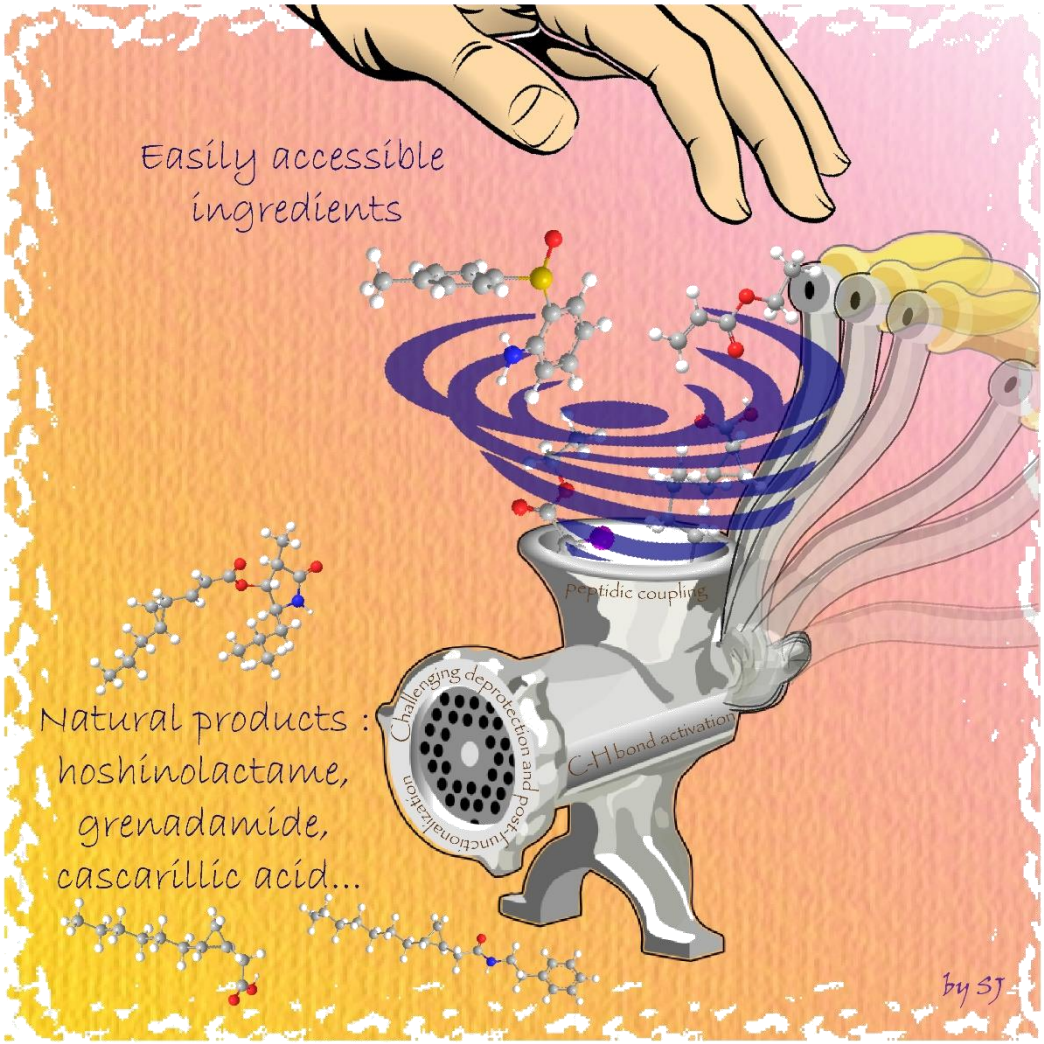
[63] M. Fan, D. Ma, *Angew. Chem. Int. Ed.* **n.d.**, *52*, 12152–12155.
[64] W. Gong, G. Zhang, T. Liu, R. Giri, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 16940–16946.
[65] C.-H. Jun, H. Lee, J.-B. Hong, *J. Org. Chem.* **1997**, *62*, 1200–1201.
[66] F. Mo, G. Dong, *Science* **2014**, *345*, 68–72.
[67] F.-L. Zhang, K. Hong, T.-J. Li, H. Park, J.-Q. Yu, *Science* **2016**, *351*, 252–256.
[68] F. Ma, M. Lei, L. Hu, *Org. Lett.* **2016**, *18*, 2708–2711.
[69] Y. Wu, Y.-Q. Chen, T. Liu, M. D. Eastgate, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, DOI 10.1021/jacs.6b09653.
[70] R.-Y. Zhu, L.-Y. Liu, H. S. Park, K. Hong, Y. Wu, C. H. Senanayake, J.-Q. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 16080–16083.
[71] R.-Y. Zhu, L.-Y. Liu, J.-Q. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 12394–12397.
[72] K. D. Otley, J. A. Ellman, *Org. Lett.* **2015**, *17*, 1332–1335.
[73] H. Kinuta, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2015**, *137*, 1593–1600.
[74] A. J. Canty, J. Patel, B. W. Skelton, A. H. White, *J. Organomet. Chem.* **2000**, *607*, 194–202.
[75] M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 9886–9887.
[76] Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 5072–5074.
[77] A. Kubota, M. H. Emmert, M. S. Sanford, *Org. Lett.* **2012**, *14*, 1760–1763.
[78] M. Wasa, K. S. L. Chan, X.-G. Zhang, J. He, M. Miura, J.-Q. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 18570–18572.
[79] J. He, R. Takise, H. Fu, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 4618–4621.
[80] G. Chen, Z. Zhuang, G.-C. Li, T. G. Saint-Denis, Y. Hsiao, C. L. Joe, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 1506–1509.
[81] J. He, S. Li, Y. Deng, H. Fu, B. N. Laforteza, J. E. Spangler, A. Homs, J.-Q. Yu, *Science* **2014**, *343*, 1216–1220.
[82] Y. Dang, S. Qu, J. W. Nelson, H. D. Pham, Z.-X. Wang, X. Wang, *J. Am. Chem. Soc.* **2015**, *137*, 2006–2014.
[83] H. Fu, P.-X. Shen, J. He, F. Zhang, S. Li, P. Wang, T. Liu, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 1873–1876.
[84] R.-Y. Zhu, J. He, X.-C. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 13194–13197.
[85] R.-Y. Zhu, T. G. Saint-Denis, Y. Shao, J. He, J. D. Sieber, C. H. Senanayake, J.-Q. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 5724–5727.
[86] S. Li, G. Chen, C.-G. Feng, W. Gong, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 5267–5270.
[87] G. Balavoine, J. C. Clinet, *J. Organomet. Chem.* **1990**, *390*, c84–c88.
[88] R. Giri, X. Chen, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2005**, *44*, 2112–2115.
[89] R. Giri, J. Liang, J.-G. Lei, J.-J. Li, D.-H. Wang, X. Chen, I. C. Naggar, C. Guo, B. M. Foxman, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2005**, *44*, 7420–7424.
[90] A. Rabinkov, T. Miron, L. Konstantinovski, M. Wilchek, D. Mirelman, L. Weiner, *Biochim. Biophys. Acta BBA - Gen. Subj.* **1998**, *1379*, 233–244.
[91] N. Yoshimoto, M. Onuma, S. Mizuno, Y. Sugino, R. Nakabayashi, S. Imai, T. Tsuneyoshi, S. Sumi, K. Saito, *Plant J.* **2015**, *83*, 941–951.
[92] K. K. Andersen, *Tetrahedron Lett.* **1962**, *3*, 93–95.
[93] K. K. Andersen, W. Gaffield, N. E. Papanikolaou, J. W. Foley, R. I. Perkins, *J. Am. Chem. Soc.* **1964**, *86*, 5637–5646.
[94] C. Mioskowski, G. Solladie, *Tetrahedron* **1980**, *36*, 227–236.
[95] J. M. Klunder, K. B. Sharpless, *J. Org. Chem.* **1987**, *52*, 2598–2602.
[96] Y. Watanabe, N. Mase, M. Tateyama, T. Toru, *Tetrahedron Asymmetry* **1999**, *10*, 737–745.
[97] D. D. Ridley, M. A. Smal, *J. Chem. Soc. Chem. Commun.* **1981**, *0*, 505–506.
[98] J. M. Llera, I. Fernández, F. Alcudia, *Tetrahedron Lett.* **1991**, *32*, 7299–7302.

[99] I. Fernández, B. Gori, F. Alcudia, N. Khiar, *Phosphorus Sulfur Silicon Relat. Elem.* **2005**, *180*, 1511–1512.
[100] F. Rebiere, O. Samuel, L. Ricard, H. B. Kagan, *J. Org. Chem.* **1991**, *56*, 5991–5999.
[101] W. Oppolzer, M. Wills, C. Starkemann, G. Bernardinelli, *Tetrahedron Lett.* **1990**, *31*, 4117–4120.
[102] W. Oppolzer, O. Froelich, C. Wiaux-Zamar, G. Bernardinelli, *Tetrahedron Lett.* **1997**, *38*, 2825–2828.
[103] D. A. Evans, M. M. Faul, L. Colombo, J. J. Bisaha, J. Clardy, D. Cherry, *J. Am. Chem. Soc.* **1992**, *114*, 5977–5985.
[104] Z. Han, D. Krishnamurthy, P. Grover, Q. K. Fang, C. H. Senanayake, *J. Am. Chem. Soc.* **2002**, *124*, 7880–7881.
[105] D. A. Cogan, G. Liu, K. Kim, B. J. Backes, J. A. Ellman, *J. Am. Chem. Soc.* **1998**, *120*, 8011–8019.
[106] D. J. Weix, J. A. Ellman, *Org. Lett.* **2003**, *5*, 1317–1320.
[107] M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600–3740.
[108] D. R. Rayner, A. J. Gordon, K. Mislow, *J. Am. Chem. Soc.* **1968**, *90*, 4854–4860.
[109] A. Rauk, L. C. Allen, K. Mislow, *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 400–414.
[110] K. Mislow, *Trans. N. Y. Acad. Sci.* **1973**, *35*, 227–242.
[111] D. A. Evans, G. C. Andrews, *Acc. Chem. Res.* **1974**, *7*, 147–155.
[112] R. W. Hoffmann, R. Gerlach, S. Goldmann, *Tetrahedron Lett.* **1978**, *19*, 2599–2602.
[113] C. Aurisicchio, E. Baciocchi, M. F. Gerini, O. Lanzalunga, *Org. Lett.* **2007**, *9*, 1939–1942.
[114] Y.-H. Khim, W. Tagaki, M. Kise, N. Furukawa, S. Oae, *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2556–2557.
[115] G. Sipos, E. E. Drinkel, R. Dorta, *Chem Soc Rev* **2015**, *44*, 3834–3860.
[116] J. Han, V. A. Soloshonok, K. D. Klika, J. Drabowicz, A. Wzorek, *Chem. Soc. Rev.* **2018**, *47*, 1307–1350.
[117] S. Lavielle, S. Bory, B. Moreau, M. J. Luche, A. Marquet, *J. Am. Chem. Soc.* **1978**, *100*, 1558–1563.
[118] M. Casey, C. M. Keaveney, *Chem Commun* **2004**, 184–185.
[119] M. C. Carreño, G. Hernández-Torres, A. Urbano, F. Colobert, *Eur. J. Org. Chem.* **2008**, *2008*, 2035–2038.
[120] M. C. Carreño, J. L. García Ruano, M. A. Toledo, A. Urbano, C. Z. Remor, V. Stefani, J. Fischer, *J. Org. Chem.* **1996**, *61*, 503–509.
[121] F. Colobert, M. Obringer, G. Solladié, *Eur. J. Org. Chem.* **2006**, *2006*, 1455–1467.
[122] G. Solladié, M. Adamy, F. Colobert, *J. Org. Chem.* **1996**, *61*, 4369–4373.
[123] S. Beauvière, F. Brebion, S. Chelli, B. Delouvrié, C. Gomez, O. Kwasnieski, R. M. Mallorquin, F. Najera, G. Vincent, M. R. Vitale, et al., *Phosphorus Sulfur Silicon Relat. Elem.* **2013**, *188*, 367–376.
[124] D. A. Lanfranchi, C. Bour, G. Hanquet, *Eur. J. Org. Chem.* **2011**, *2011*, 2818–2826.
[125] B. Yalcouye, S. Choppin, A. Panossian, F. R. Leroux, F. Colobert, *Eur. J. Org. Chem.* **2014**, *2014*, 6285–6294.
[126] A. García-Rubia, M. Á. Fernández-Ibáñez, R. Gómez Arrayás, J. C. Carretero, *Chem. - Eur. J.* **2011**, *17*, 3567–3570.
[127] T. Wesch, F. R. Leroux, F. Colobert, *Adv. Synth. Catal.* **2013**, *355*, 2139–2144.
[128] Q. Dherbassy, J. Wencel-Delord, F. Colobert, *Tetrahedron* **2016**, *72*, 5238–5245.
[129] B. R. James, E. Ochiai, G. L. Rampel, *Inorg. Nucl. Chem. Lett.* **1971**, *7*, 781–784.
[130] R. Dorta, H. Rozenberg, L. J. W. Shimon, D. Milstein, *J. Am. Chem. Soc.* **2002**, *124*, 188–189.

[131] C. Pettinari, M. Pellei, G. Cavicchio, M. Crucianelli, W. Panzeri, M. Colapietro, A. Cassetta, *Organometallics* **1999**, *18*, 555–563.
[132] R. Dorta, H. Rozenberg, D. Milstein, *Chem. Commun.* **2002**, 710–711.
[133] A. P. Pulis, D. J. Procter, *Angew. Chem. Int. Ed.* **2016**, *55*, 9842–9860.
[134] N. Khiar, I. Fernández, F. Alcudia, *Tetrahedron Lett.* **1993**, *34*, 123–126.
[135] M. C. Carreño, J. L. García Ruano, M. C. Maestro, L. M. Martín Cabrejas, *Tetrahedron Asymmetry* **1993**, *4*, 727–734.
[136] R. Tokunoh, M. Sodeoka, K. Aoe, M. Shibasaki, *Tetrahedron Lett.* **1995**, *36*, 8035–8038.
[137] H.-G. Cheng, B. Feng, L.-Y. Chen, W. Guo, X.-Y. Yu, L.-Q. Lu, J.-R. Chen, W.-J. Xiao, *Chem Commun* **2014**, *50*, 2873–2875.
[138] R. Siedlecka, E. Wojaczyńska, J. Skarżewski, *Tetrahedron Asymmetry* **2004**, *15*, 1437–1444.
[139] G. Chelucci, D. Berta, A. Saba, *Tetrahedron* **1997**, *53*, 3843–3848.
[140] K. J. Fraunhoffer, M. C. White, *J. Am. Chem. Soc.* **2007**, *129*, 7274–7276.
[141] M. S. Chen, N. Prabagaran, N. A. Labenz, M. C. White, *J. Am. Chem. Soc.* **2005**, *127*, 6970–6971.
[142] S. A. Reed, A. R. Mazzotti, M. C. White, *J. Am. Chem. Soc.* **2009**, *131*, 11701–11706.
[143] J. J. Bürgi, R. Mariz, M. Gatti, E. Drinkel, X. Luan, S. Blumentritt, A. Linden, R. Dorta, *Angew. Chem. Int. Ed.* **2009**, *48*, 2768–2771.
[144] J. V. Allen, J. F. Bower, J. M. J. Williams, *Tetrahedron Asymmetry* **1994**, *5*, 1895–1898.
[145] K. Hiroi, K. Watanabe, I. Abe, M. Koseki, *Tetrahedron Lett.* **2001**, *42*, 7617–7619.
[146] S. Nakamura, T. Fukuzumi, T. Toru, *Chirality* **2004**, *16*, 10–12.
[147] X. Feng, B. Wei, J. Yang, H. Du, *Org. Biomol. Chem.* **2011**, *9*, 5927.
[148] G. Tsuchihashi, S. Iriuchijima, M. Ishibashi, *Tetrahedron Lett.* **1972**, *13*, 4605–4608.
[149] N. Kunieda, M. Kinoshita, J. Nokami, *Chem. Lett.* **1977**, *6*, 289–292.
[150] G. Solladié, A. Rubio, M. C. Carreño, J. García Ruano, *Tetrahedron Asymmetry* **1990**, *1*, 187–198.
[151] R. Pummerer, *Berichte Dtsch. Chem. Ges.* **1909**, *42*, 2282–2291.
[152] R. Pummerer, *Berichte Dtsch. Chem. Ges.* **1910**, *43*, 1401–1412.
[153] O. de Lucchi, U. Miotti, G. Modena, in *Org. React.* (Ed.: John Wiley & Sons, Inc.), John Wiley & Sons, Inc., Hoboken, NJ, USA, **1991**, pp. 157–405.
[154] I. K. Stamos, *Tetrahedron Lett.* **1986**, *27*, 6261–6262.
[155] M. Šiaučiulis, S. Sapmaz, A. P. Pulis, D. J. Procter, *Chem. Sci.* **2018**, *9*, 754–759.
[156] Z. He, H. J. Shrives, J. A. Fernández-Salas, A. Abengózar, J. Neufeld, K. Yang, A. P. Pulis, D. J. Procter, *Angew. Chem. Int. Ed.* **2018**, *57*, 5759–5764.
[157] N. Furukawa, S. Ogawa, K. Matsumura, H. Fujihara, *J. Org. Chem.* **1991**, *56*, 6341–6348.
[158] J. Rae, J. Frey, S. Jerhaoui, S. Choppin, J. Wencel-Delord, F. Colobert, *ACS Catal.* **2018**, *8*, 2805–2809.
[159] J. Clayden, M. Julia, *J. Chem. Soc. Chem. Commun.* **1993**, 1682.
[160] J. Clayden, J. J. A. Cooney, M. Julia, *J. Chem. Soc. Perkin 1* **1995**, 7.

Chapter 2

Development and applications of an enantiopure sulfinyl aniline as chiral directing group for the C(sp^3)-H activation of cycloalkanes



Chapter 2 – Table of contents

II.1. Introduction

II.1.i. Summary of this work

This chapter is dedicated to the diastereoselective β-functionalization of cycloalkanes, by means of the C-H activation and using a bidentate sulfinylaniline auxiliary as the chiral inductor. Our first objective was to develop for such transformation a suitable directing group bearing a chiral sulfoxide as a potential chiral source. Our second objective was the application of this directing group to the C-H activation of cycloalkane carboxylic acid derivatives to access complex scaffolds. In the course of this work, we developed an efficient reaction for the synthesis of trisubstituted cycloalkanes, showing a *cis*-configuration between the carbonyl motif and the newly installed functional group. In addition, we applied this methodology to the obtention of *trans*-disubstituted cyclopropanes key intermediates for the total synthesis of natural products. This part of our work will focus on three natural products, hoshinolactam, cascarillic acid and grenadamide.

II.1.ii. Biological interest and properties of cyclopropanes

Most organic compounds found in nature contains rings in their molecule (Chart 2.10). Among all these natural products, which are important medicinal molecules or pigments, all size of cycloalkane can be found, in particular cyclopropane core in insecticides.[161] There is a strong interest in first synthesizing these natural products in an efficient way, considering their numerous stereocentres; secondly synthesizing analogues of these compounds for medicinal chemistry applications.

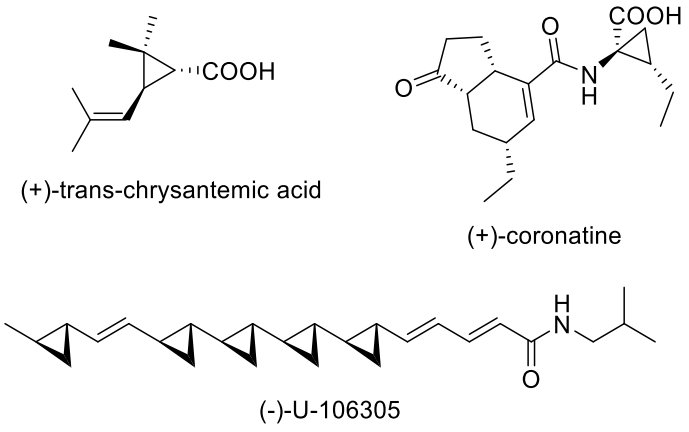


Chart 2.10 Representative cyclopropane natural products

Cyclopropanes have unique properties and reactivity related to their high ring strain, which also render their synthesis highly challenging. The triangular structure of the molecule imposes the bond angles to be 60 °, almost twice less than the thermodynamically most stable angle of 109.5 ° computed for sp^3 hybridized orbitals. The distortion of the bonds due to the orbitals is called bent bonds and is typical from cyclopropane rings.[162,163]

They also exhibit unique properties related to this distortion: a pseudo-aromatic character and a specific reactivity (Figure 2.23).[164,165] In an analogy to epoxides, Walsh proposed that cyclopropanes could be considered as insertion of methylene into ethylene.[166]

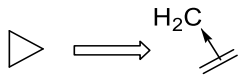


Figure 2.23 Pseudo-aromaticity of cyclopropane

The Walsh orbital diagram of the cyclopropane explains the full delocalization of the electrons all over the ring, giving it a pseudo-aromaticity also called σ-aromaticity.[167] Therefore the significant sp^2 character of the cyclopropane ring explains their particular reactivity that may be considered as olefin surrogates (Figure 2.24).

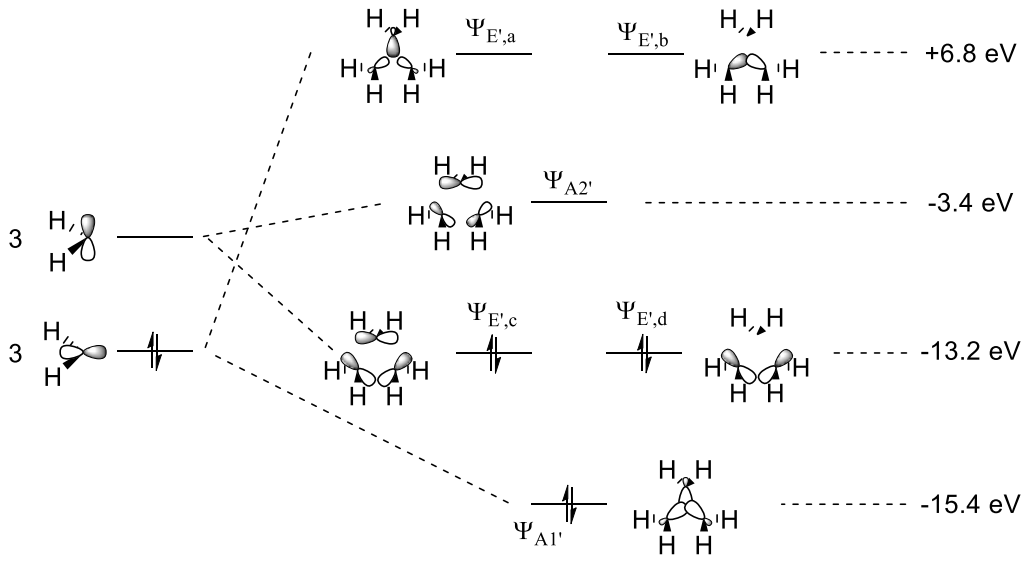
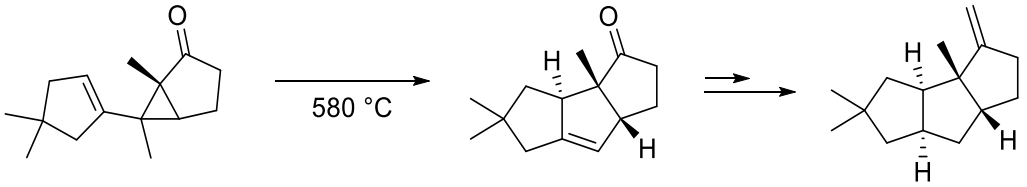


Figure 2.24 Orbital diagram of cyclopropane

For instance, methylcyclopropane can open and rearrange in cyclobutene under heat, as well as the vinylcyclopropane will rearrange to cyclopentene (Figure 2.25). These reactions proceed through radical processes and allow the formation of numerous interesting rings.[164,168–171]

Figure 2.25 Representative thermal rearrangements of cyclopropane rings

Hudlicky and co-workers used this methodology for the total synthesis of an important sesquiterpene precursor, hirsutene, in 1980 (Scheme 2.54).[172,173]



Scheme 2.54 Key step of the total synthesis of hirsutene

Among all types of reactivity found with small rings, reactions related to donor-acceptor cyclopropanes are also of major importance as they allow access to various complex scaffolds.[174,175] As previously, the main driving force for these transformations is the high ring strain of the cyclopropane that enhances its opening (Figure 2.26).

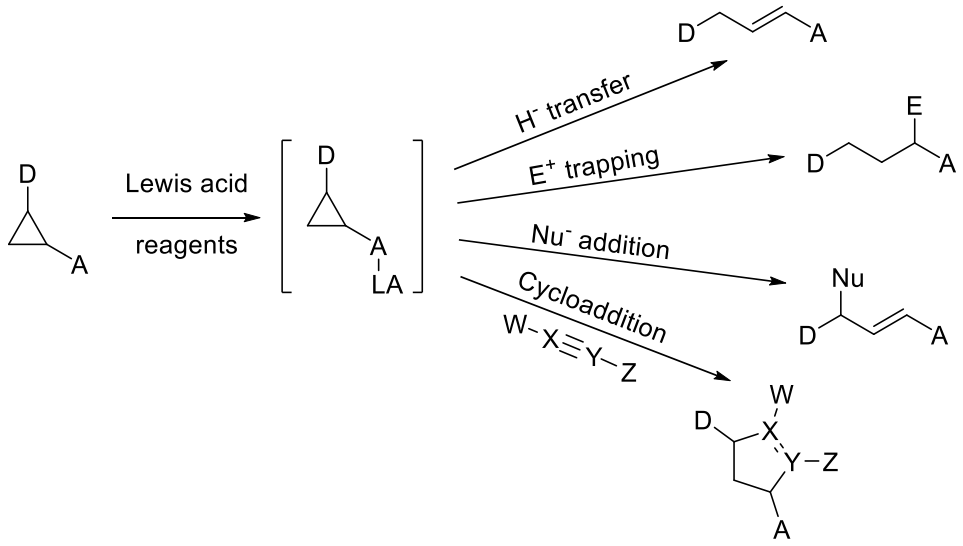
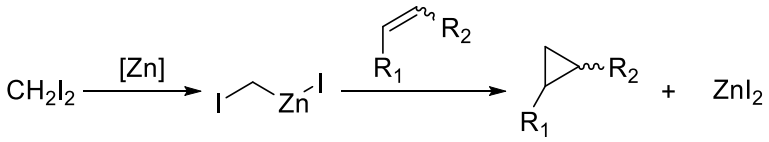


Figure 2.26 Representative reactions with donor-acceptor cyclopropanes

II.1.iii. Standard methods to build up functionalized cyclopropanes

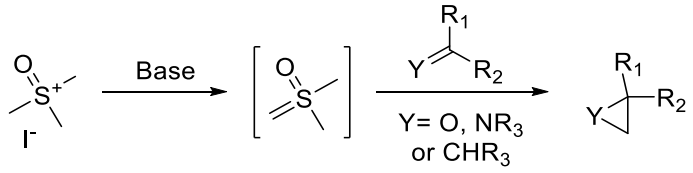
As seen before, cyclopropanes are important motives in organic chemistry.[176]

One of the first example of cyclopropanation was achieved by Simmons and Smith in 1958.[177] Alkenes react with diiodomethane in presence of activated zinc to afford substituted cyclopropanes in high yield (Scheme 2.55). This reaction is tolerant with various alkenes and the relative stereochemistry of the cyclopropane depends on the configuration of the double bond, allowing the formation of *cis*- and *trans*-cyclopropanes.



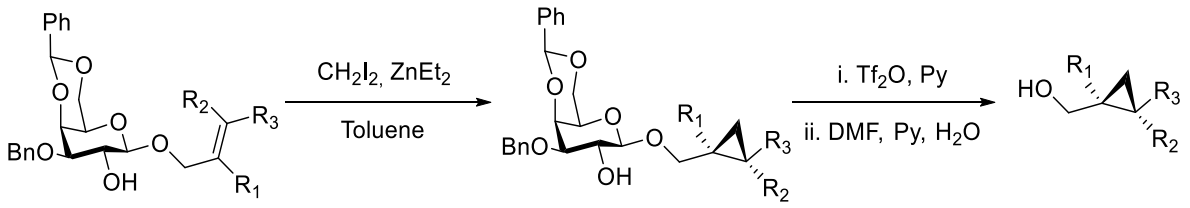
Scheme 2.55 Simmons-Smith cyclopropane synthesis

Discovered by Johnson in 1961 and further improved by Corey and Chaykovsky in 1965, the eponym transformation uses the addition of *in situ* generated sulphur ylide on ketone and aldehyde, imine or enone to get the corresponding epoxide, aziridine or cyclopropane (Scheme 2.56).[178,179] This efficient method is an alternative to the Simmons-Smith reaction.



Scheme 2.56 Corey-Chaykovsky cyclopropane, epoxide and aziridine synthesis

To perform an asymmetric Simmons-Smith reaction, a few chiral auxiliaries have been reported. For example, based on zinc-mediated reaction, Iglesias-Guerra and co-workers recently developed a sugar chiral auxiliary for diastereoselective Simmons-Smith cyclopropanation reaction.[180–182] In 2007, Hsung and co-workers used a chiral oxazolidine-2-one derivative to achieve, with high diastereoisomeric excess, the cyclopropanation reactions.[183] Bull and co-workers designed a similar system and applied it to the synthesis of natural products.[184] In 2012, Yun and co-workers employed a chiral 1,3-oxathiane 3-oxides derived from (+)-camphor to obtain with high diastereoselectivity and moderate yield *trans*-cyclopropanes (Scheme 2.57).[185]



Scheme 2.57 Iglesias-Guerra cyclopropane synthesis

With the development of ligand-assisted chemistry, Simmons-Smith cyclopropanation reaction has also been carried out with several asymmetric systems involving different ligands, such as Charette's chiral dioxaborolane, Nugent's isoborneol-based amino alcohol ligand or Deng-gao's sulfonamide (Chart 2.11).[186–189]

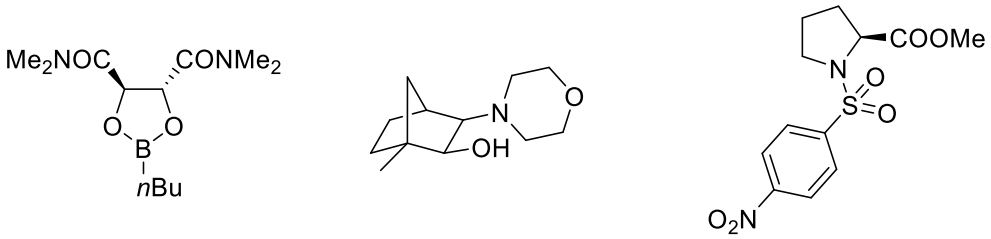
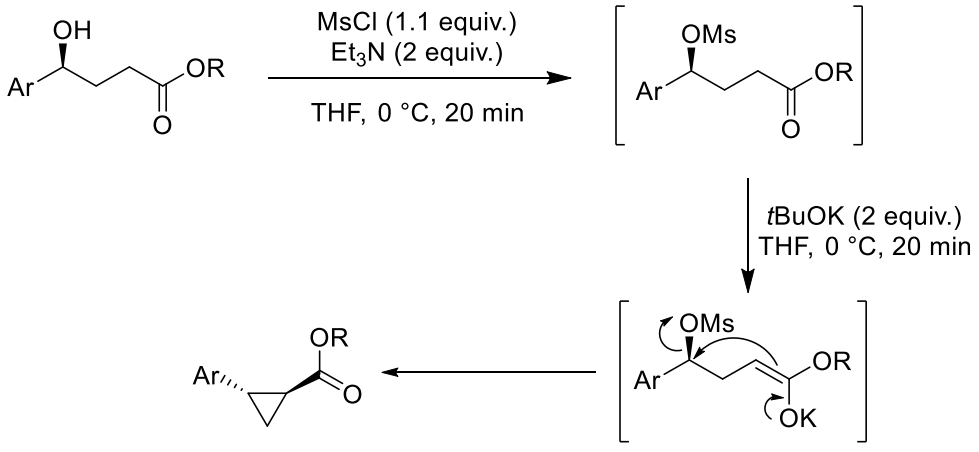


Chart 2.11 Representative chiral ligands for the asymmetric Simmons-Smith reaction

Intramolecular asymmetric cyclopropanation was also performed by Ku and co-workers via displacement of an enantiopure benzylic mesylate moiety by intramolecular addition of a potassium enolate delivering the corresponding *trans*-cyclopropane with high enantiomeric purity (Scheme 2.58).[190]



Scheme 2.58 Ku's asymmetric cyclopropanation

In recent years, many elegant organocatalyzed approaches for the asymmetric cyclopropanation were published. They involved different type of catalysts, such as carbenes, diamines or more complex oxazaborolidinium ions and camphor derivatives (Chart 2.12).

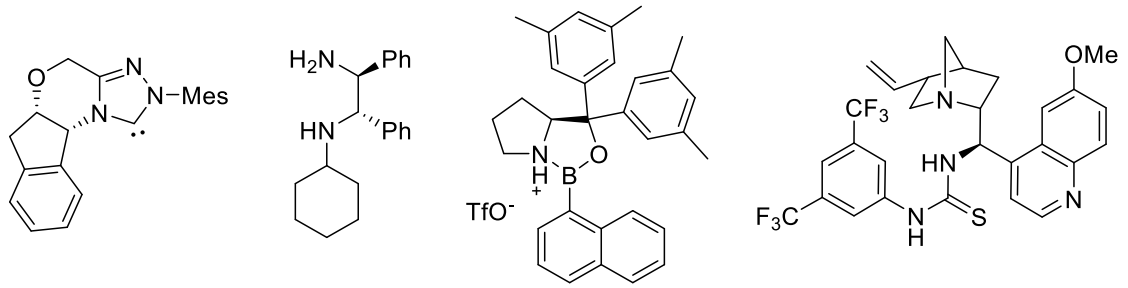
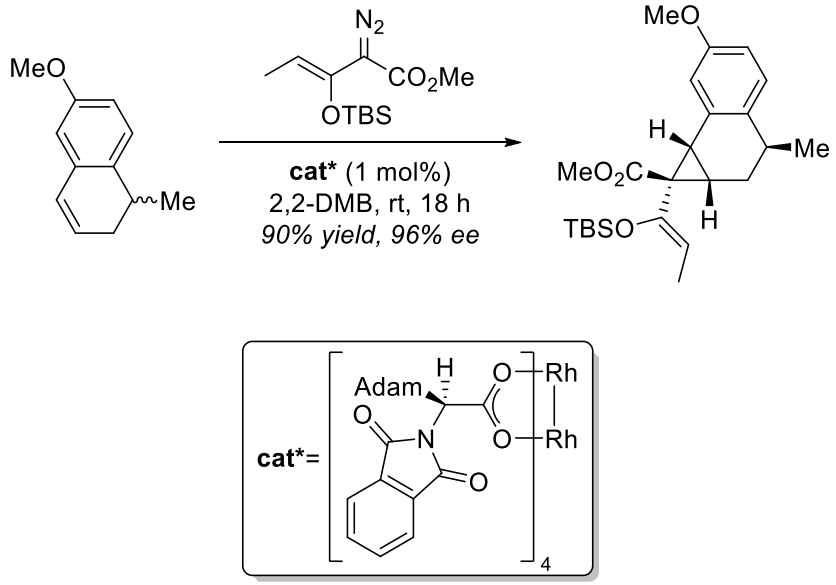


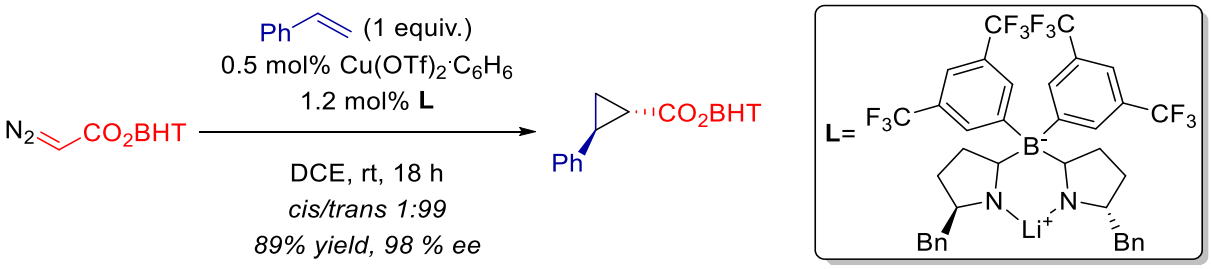
Chart 2.12 Representative chiral organocatalysts for cyclopropanation

With the tremendous development of metal-catalysed transformations, some research groups reported organometallic synthesis of cyclopropanes. Numerous asymmetric reactions were developed using rhodium and ruthenium catalysts and carbene precursors as starting materials. For example, Davies and co-workers developed a rhodium-catalysed C-H bond activation strategy to build trisubstituted cyclopropane rings (Scheme 2.59).[191]



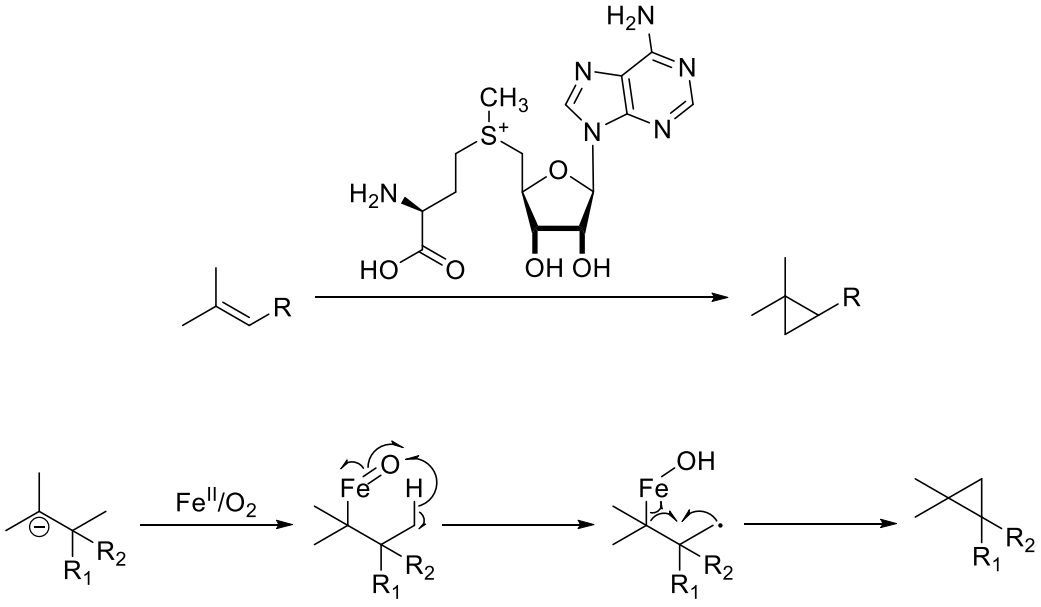
Scheme 2.59 Davies asymmetric cyclopropanation

The synthesis of cyclopropane rings using a diazo as carbene precursor and an olefin as precursors was also performed with other systems, such as copper and a chiral ligand reported by Pfaltz (Scheme 2.60) or a complex cobalt/porphyrin catalyst reported by Zhang.[192–194] Most of these methods to build enantioenriched cyclopropanes proved their efficiency on a large panel of systems but generally limited to the synthesis of *trans*-cyclopropanes because of the poor availability and stability of (*Z*)-alkenes to construct *cis*-cyclopropanes.



Scheme 2.60 Pfaltz cyclopropane synthesis

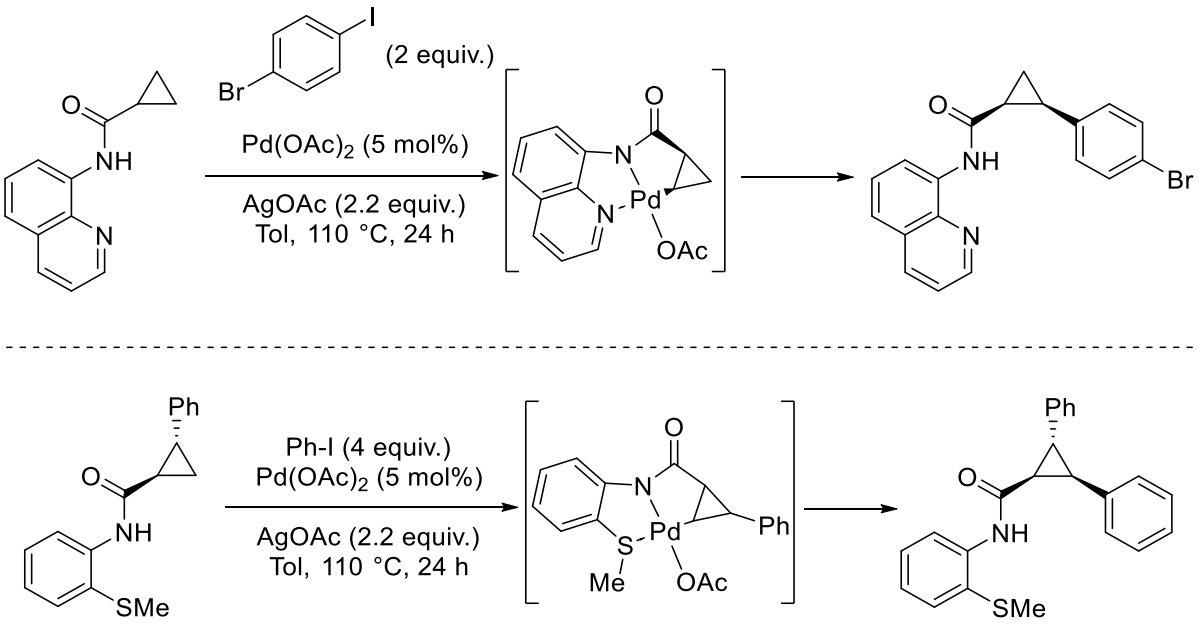
Finally, in nature, cyclopropane can be built in many ways. For example, the coenzyme S-adenosyl-methionine (SAM) can give its methylene to a double bond to generate a three-membered ring. Iron contained in metalloenzymes can also promote a radical cyclization.[165] Due to the formation of covalent intermediates, most of the cyclopropanes contained in natural products are in relative *trans* configuration (Scheme 2.61).



Scheme 2.61 Biosynthesis of cyclopropane rings

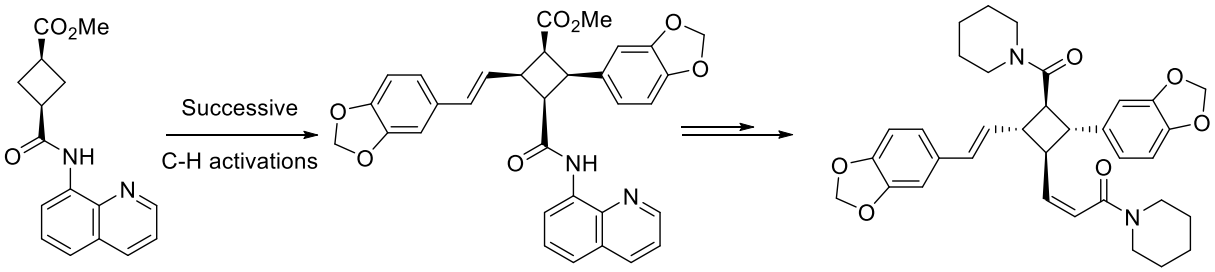
II.1.iv. C-H functionalisation of cyclopropanes using a bidentate DG

As previously mentioned (I.2.ii), selective ipso- and α-functionalization to carbonyl group are widely described. To facilitate the activation of unreactive β-C(sp^3)-H bond in carboxylic acid derivatives, and with the emergence of nitrogen-directed cyclopalladation, many research groups started working on the selective β-functionalization of amides as masked carboxylic acids and developed bidentate directing groups, which would promote the metal chelation and indirectly assist the proton abstraction (Scheme 2.62). These directing groups were applied for the selective *cis*-arylation of substituted cycloalkanes due to the steric constraints which force the intermediate palladacycle to adopt a *cis*-geometry.[3,195]



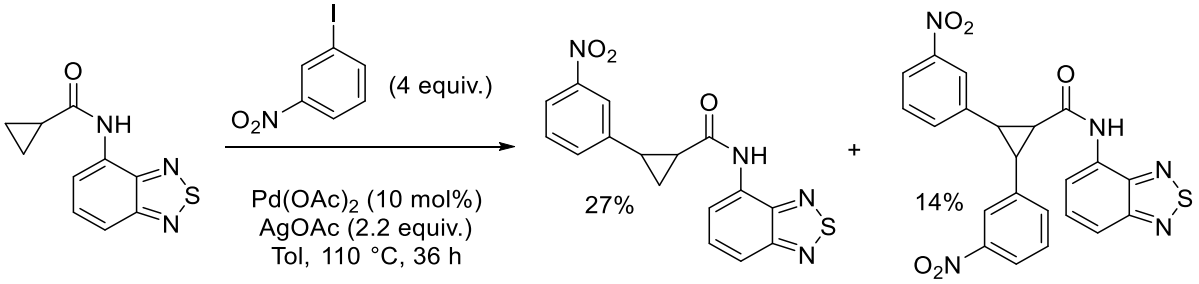
Scheme 2.62 *cis*-Arylation of cyclopropane using a bidentate directing group

These methodologies, widely using 8-aminoquinoline as powerful directing group, were also applied for the total synthesis of various cyclobutane-containing natural products (Scheme 2.63).[196,197]



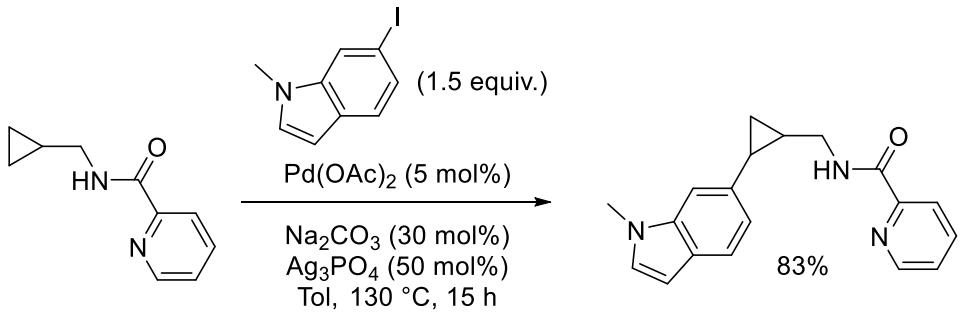
Scheme 2.63 Arylation and olefination of cyclobutane using a bidentate directing group for the total synthesis of pipercyclobutanamide A

In 2017, Babu and co-workers developed a new bidentate directing group based on a benzothiadiazole core, allowing arylation and alkylation of cycloalkanes, and arylation of simple alkyl chains (Scheme 2.64). However, this system suffers from the lack of control over the rate of arylation, resulting in a mixture of mono and biarylated species.[198]



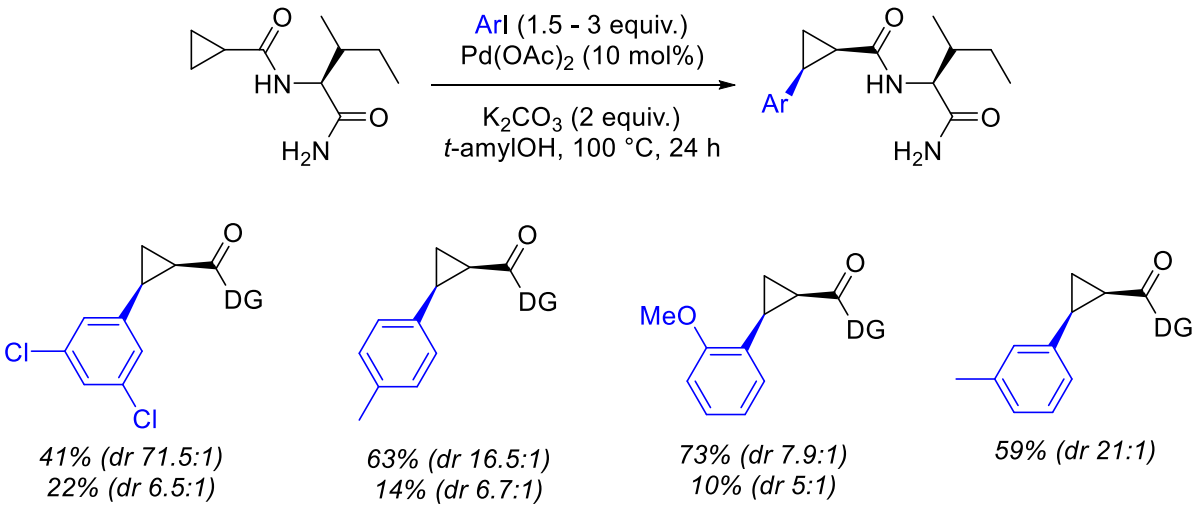
Scheme 2.64 *cis*-Arylation of cyclopropane using a bidentate directing group

Besides these contributions to the C-H bond activation of masked cyclopropane carboxylic acids, Charette and co-workers developed a practical approach for the functionalisation of cyclopropylmethanamine, masked as picolamide derivatives, with excellent yields and broad scope tolerance (Scheme 2.65).[5]



Scheme 2.65 *cis*-Arylation of cyclopropane using a bidentate directing group

Now if we consider a diastereoselective approach, chiral DG must be designed considering that accessing stereogenic carbons by means of asymmetric C(sp^3)-H bond functionalisation presents an additional difficulty. Recently, Yu and Hong independently performed the diastereoselective arylation of chiral amino-acid derivatives and hence the stereoselectivity was imposed by the proximal stereogenic centre (Scheme 1.23).[81,199] Hong and co-workers designed a chiral bidentate directing group for the C(sp^3)-H bond functionalization of cycloalkanes (Scheme 2.66). In 2016, these two reports were the only examples of diastereoselective cyclic C-H bond activation described in the literature.



Scheme 2.66 Hong diastereoselective arylation of cyclopropanes

II.2. On the way to the first diastereoselective sulfoxide-directed C(sp^3)-H activation of cyclopropanes

II.2.i. Development of a new sulfinyl aniline chiral directing group

The following was realized with Dr Faouzi Chahdoura, post-doctoral student.

II.2.i.1. Background of the work

Regarding the widely recognized potential of bicoordinating directing groups to facilitate challenging functionalisation of aliphatic substrates, the conception of original chiral bidentate directing groups, implying various sources of chirality, is highly appealing. Indeed, and when we started working on this subject, no chiral bicoordinating directing group has ever been disclosed for the C(sp^3)-H bond activation. Drawing inspiration from Daugulis and Babu's work on C-H bond functionalization of cycloalkanes using 2-(methylthio)-aniline as directing group, we designed a 2-(sulfinyl)-aniline as potential directing group and chiral inductor for the asymmetric functionalisation of cycloalkanes (Figure 2.27).[3,4]

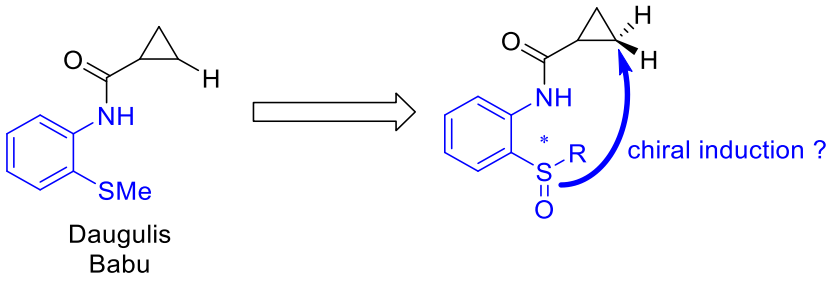
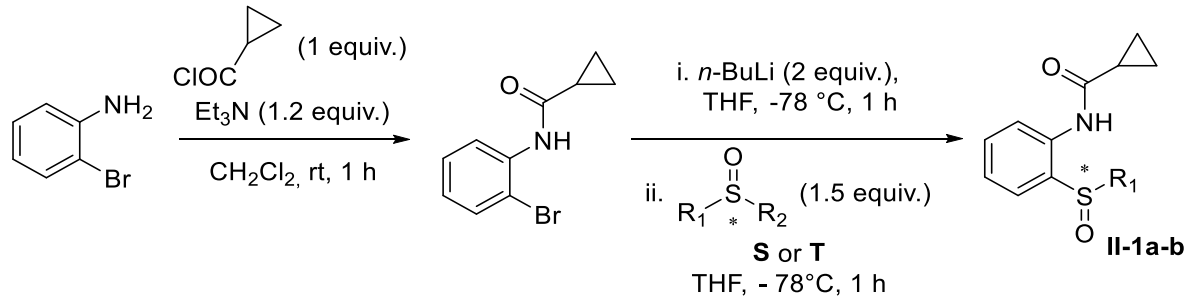


Figure 2.27 From regio- to diastereo-selective C-H bond activation

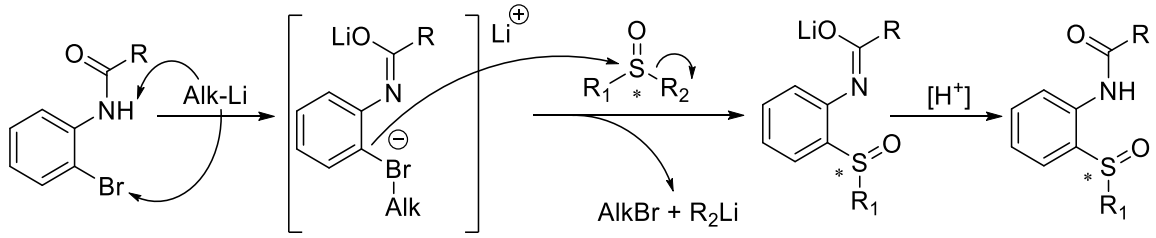
II.2.i.2. Synthesis of the substrates and chiral auxiliaries

The first synthesis of the sulfinylaniline directing group was performed by coupling the 2-bromoaniline with cyclopropane carbonyl chloride in presence of triethylamine as base. Then, the newly formed amide was deprotonated with one equivalent of *n*-butyllithium, and another equivalent promoted the halogen-metal exchange. The generated aryllithium species were quenched with chiral electrophiles such as menthyl sulfinate **S** or *tert*-butyl thiosulfinate **T** to access various sulfoxide substrates (Scheme 2.67).



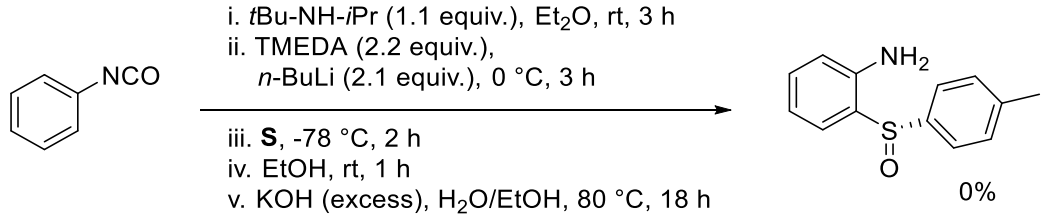
Scheme 2.67 First synthesis of cyclopropane substrates

As described by O'Brien and co-workers, the second step follows certainly a nucleophilic mechanism with the formation of an ate-complex, which then attacks the sulfoxide to release the leaving group (Scheme 2.68).[200]



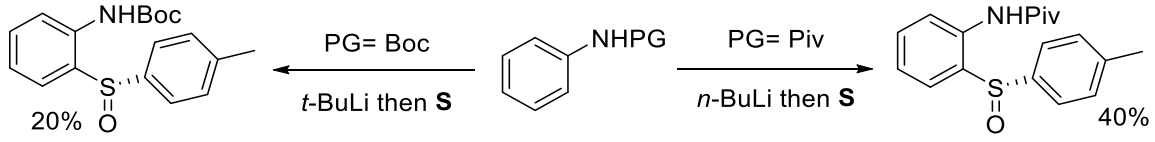
Scheme 2.68 Mechanistic insights for the *ortho*-functionalization of aniline derivatives

Then, we tried to improve the synthesis of the (*S*)-2-(*p*-tolylsulfinyl)aniline (APS), as no general way to access chiral *ortho*-sulfinylaniline has been disclosed in the literature. Accordingly, different strategies were evaluated using (-)-menthyl-(*S*)-*p*-toluenesulfinate **S** as chiral precursor. An appealing one-pot approach, inspired by Booker-Milburn and co-workers, consisted of the *ortho*-lithiation of an *in-situ* generated urea, followed by quenching with **S**. Deceivingly, no product formation was ever observed (Scheme 2.69).[201,202]



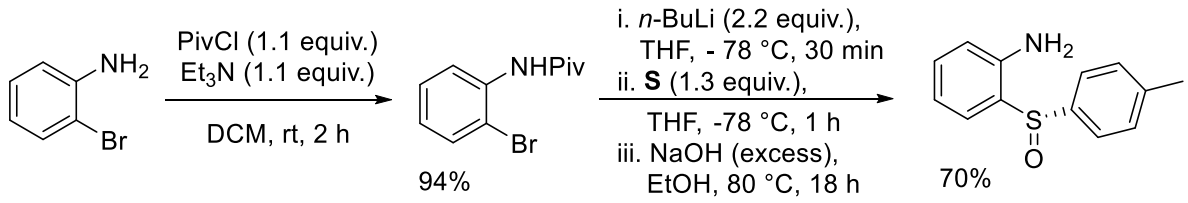
Scheme 2.69 APS synthesis using Booker-Milburn conditions

Concerned about atom economy, we envisaged the ortholithiation of a protected aniline to get our chiral auxiliary. These methodologies only gave low yields (Scheme 2.70).



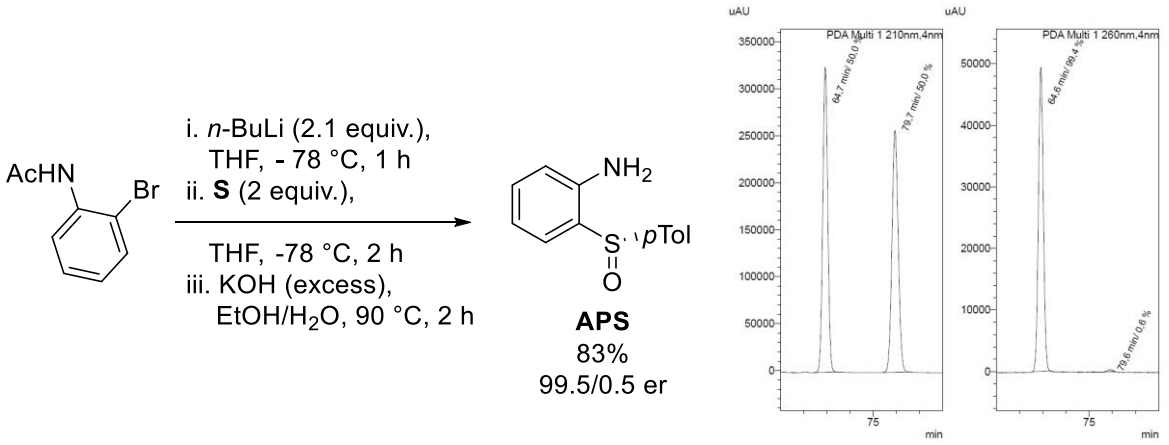
Scheme 2.70 APS synthesis from protected aniline

All other methods consisted in the lithium/halogen exchange of a protected 2-bromoaniline or *ortho*-lithiation of a protected aniline. Using 2-bromo-*N*-pivanilide as substrate, lithium/halogen exchange with *n*-butyllithium followed by trapping with **S** afforded the pivaloyl-protected directing group, which was subsequently deprotected under basic conditions to deliver enantiopure APS with 70% isolated yield over three steps (Scheme 2.71). This convenient methodology is only limited by the reaction time for the deprotection of the pivaloyl group, stable under mild basic conditions.



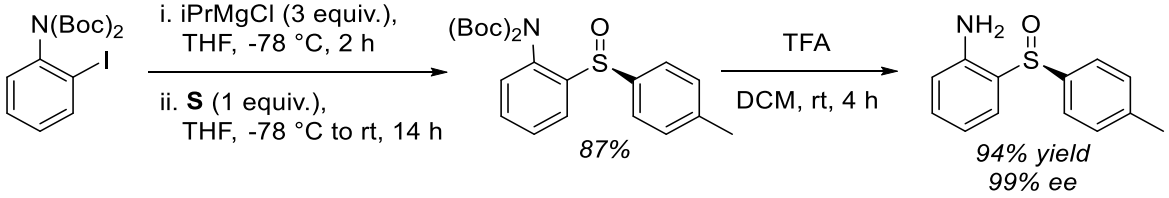
Scheme 2.71 APS synthesis from 2-bromoaniline

During our optimization of the APS synthesis and drawing inspiration from Terry-Lorenzo and co-workers who studied metal/halogen exchange on mono-acetamide-protected anilines, the amide group was selected instead of pivalamide to acetamide, which would be more easily deprotected under basic conditions.[203] Cheap and commercially available 2-bromo-*N*-acetanilide was thus used as starting material and in one-pot procedure APS was obtained with an excellent 83% yield and total enantiomeric purity (Scheme 2.72). Other easily removable amino-protecting groups, such as trifluoroacetamide, did not give any conversion to the desired product, but side reactions such as nucleophilic attack of the *n*-butyllithium on the carbonyl group were observed.



Scheme 2.72 APS synthesis from 2'-bromoacetanilide and associated chiral HPLC chart

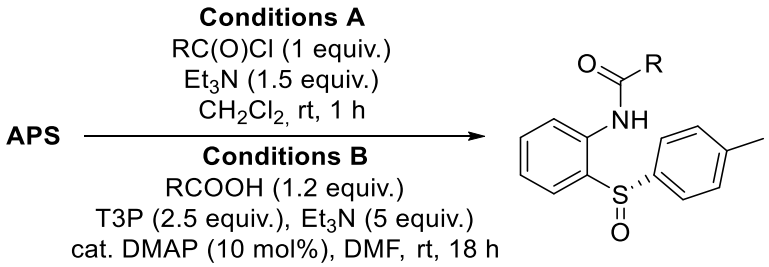
Recently He and co-workers also reported an efficient two-step methodology for the synthesis of enantiopure APS by the usual metal/halogen exchange to introduce the sulfoxide on a Boc-protected iodoaniline (Scheme 2.73).[204] However, the *N,N'*-di-Boc-2-iodoaniline used in this method is rather expensive compared to the 2'-bromoacetanilide precursor used in our protocol.



Scheme 2.73 He's APS synthesis from *N,N*-di-Boc-2-iodoaniline

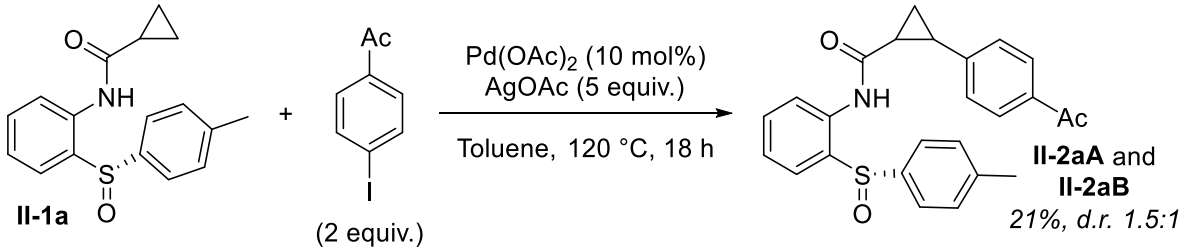
II.2.i.3. First catalytic tests using sulfinylaniline directing groups

Using our protocol described in Scheme 2.72, we accessed the first substrate **II-1a** with an excellent enantiomeric excess. Usually, our substrates were obtained by simple coupling with an acyl chloride in presence of triethylamine or with an acid under standard peptidic coupling conditions (Scheme 2.74).[205]



Scheme 2.74 Obtention of the substrates

Rapidly, we initiated our catalytic testes by studying arylation of cyclopropane ring with 4'-iodoacetophenone in presence of palladium catalyst and a silver salt in toluene (Scheme 2.75).



Scheme 2.75 First test of palladium-catalysed C-H arylation using the APS directing group

Drawing inspiration from a clear improvement of the reactivity assessed by the drastic jump reported by other research groups when performing the direct functionalisation in polar solvents, we attempted the arylation reaction in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at lower temperature. Rewardingly, the mixture of the two diastereomers **II-2aA** and **II-2aB** was afforded in high 80% yield and encouraging 20% diastereoisomeric excess. Further insights about the optimisation of the reaction conditions will be detailed later (II.2.ii).

As first attempts to improve the diastereomeric excess of the diastereoselective C(sp^3)-H bond activation of cyclopropane, a screening of various alkyl and aryl groups on the sulfoxide moiety for the diastereoselective C(sp^3)-H bond activation of cyclopropane showed an interesting logarithmic correlation between the conversion and the diastereoselectivity: generally, using aryl sulfoxides high conversions could be reached, nevertheless to the detriment of the diastereomeric ratio; in contrary, alkyl sulfoxides suffered from low yield but high diastereoisomeric excess. Using highly hindered groups such as adamantane on the sulfoxide resulted in total inhibition of the reaction (Figure 2.28).

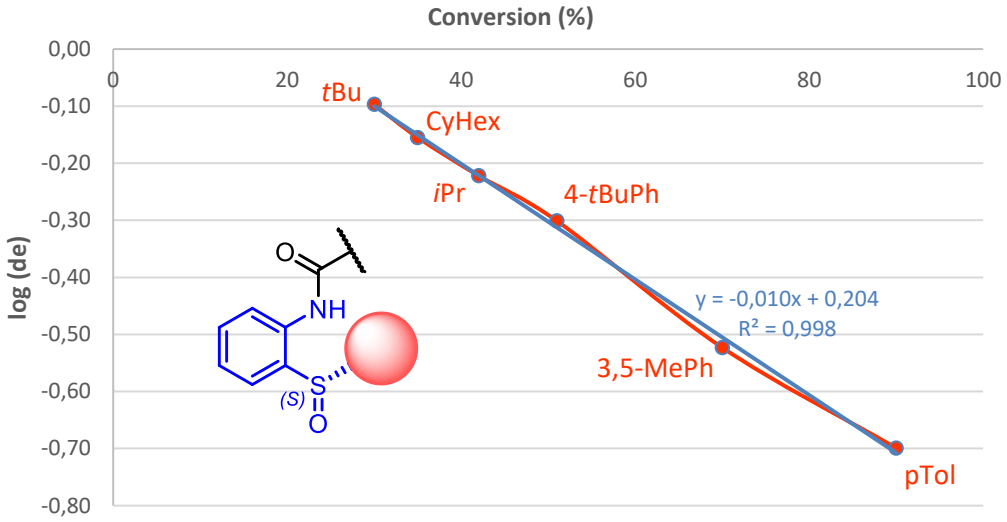
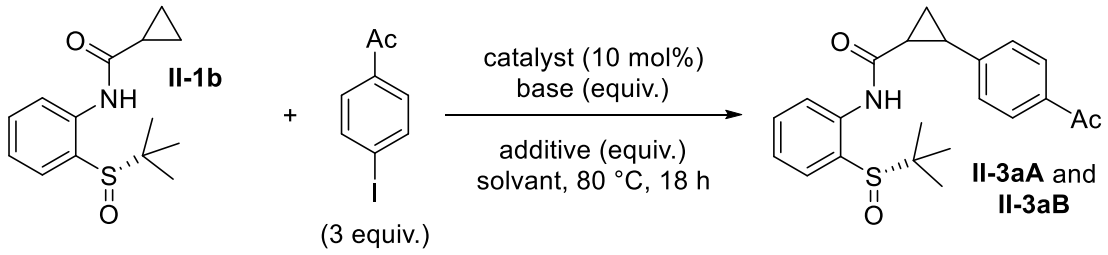


Figure 2.28 Relation between conversion, diastereomeric excess and steric hindrance of the directing group

During this study, SO^{t}Bu moiety appeared highly promising as the desired product was furnished with a good stereoselectivity of about 9:1 and 30 % conversion. However, despite extensive optimisation study, we did not manage to improve the reactivity of this catalytic system. Indeed, while the diastereomeric ratio was maintained around 90/10, the reactivity was not better as the initial conditions (Table 2.1). This drastic difference in reactivity could be explained by the difficulty of the aryl iodide to approach the palladacycle for oxidative addition because of the steric hindrance of the *tert*-butyl group.

Table 2.1 Optimization of the arylation using (*tert*-butylsulfinyl)aniline as directing group



Entry	Base (equiv.)	Additive (equiv.)	Solvant T °C	NMR Yield (%)
1	AgOAc (4)	NaTFA (0.5)	HFIP	24
2	AgOAc (4)	K_2CO_3 (0.5)	HFIP	19
3	Ag_2CO_3 (4)	-	HFIP	13
4	AgOAc (4)	KF (1)	HFIP	16
5	AgOAc (4)	K_2HPO_4 (0.5)	HFIP	<10
6	AgOAc (2)	NaTFA (0.5)	HFIP	16
7	AgOAc (6)	NaTFA (0.5)	HFIP	23

As the reasonable level of conversion of **II-1b** was not achieved, we retained (*S*)-2-(*para*-tolyl-sulfinyl)aniline (APS) as directing group for our transformation for two mains reasons: first of all, high yielding reactions compared to the *tert*-butyl moiety would allow the efficient access to arylated compounds; secondly, the two diastereisomers obtained during the reaction are easily separable by simple column chromatography on silica gel, yielding to two enantiopure diastereoisomers, useful for medicinal chemistry applications.

II.2.i.4. Ineffective bidentate directing groups

Apart from sulfinyl-aniline-based directing group, various other bidentate auxiliaries were synthesized and tested for C-H bond arylation of aliphatic cyclic substrates (Chart 2.13).

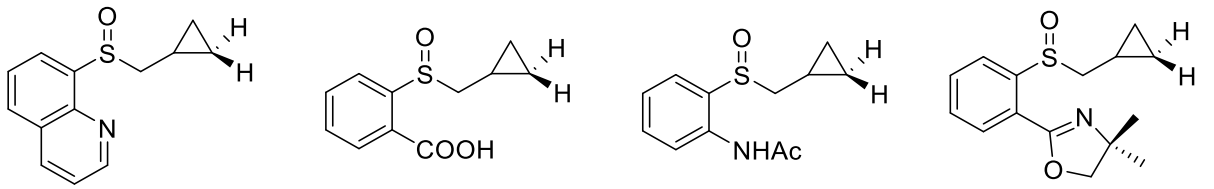
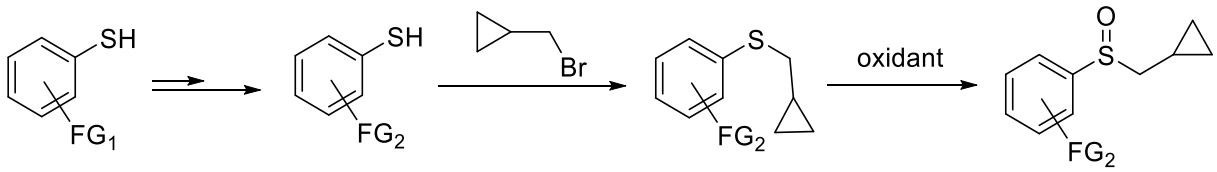


Chart 2.13 Other classes of directing groups considered

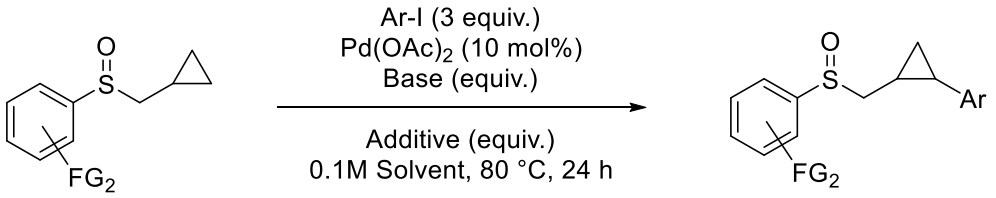
All these compounds were generally synthesized as racemates by functionalisation of an arylthiol precursor, followed by nucleophilic addition to (bromomethyl)cyclopropane and racemic oxidation of the thioether into sulfoxide either using *m*-CPBA or $FeCl_3/H_5IO_6$ as oxidizing agents (Scheme 2.76).[206]



Scheme 2.76 General racemic synthesis of the other substrates

Unfortunately, under various reaction conditions described in the literature,[22,50,207] the desired arylation product could not be observed (Table 2.2). Moreover, this type of substrate suffers from a tedious asymmetric synthesis as the starting (bromomethyl)cyclopropane tends to rearrange to the corresponding methylenecyclopropane in the presence of lithium bases or Grignard reagents.

Table 2.2 Arylation tests with other directing groups



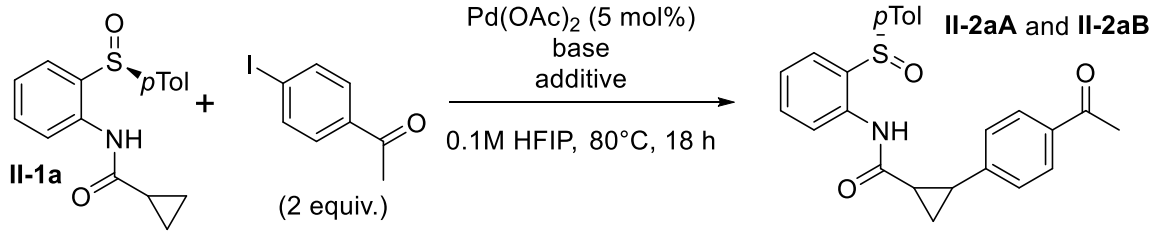
Entry	FG_2	Ar	Base (equiv.)	Additive (equiv.)	Solvent	Conversion
1	2-Pyr	4-Ac-Ph	AgOAc (4)	NaTFA (0.5)	HFIP/H_2O	0
2	2-Pyr	4-Ac-Ph	Ag_2CO_3 (2)	NaTFA (0.5)	HFIP	0
3	2-Pyr	Ph	AgOAc (2)	NaTFA (0.5)	DCE	0
4	2-Pyr	Ph	Ag_2CO_3 (2)	NaTFA (0.5)	tBuOH	0
5	2-COOH	4-Ac-Ph	Ag_2CO_3 (2)	NaOAc (1) K_2HPO_4 (0.5)	HFIP	0
6	2-NHAc	4-Ac-Ph	AgOAc (4)	NaTFA (0.5)	HFIP	0
7	2-Oxa	4-Ac-Ph	AgOAc (4)	NaTFA (0.5)	HFIP	0
8	2-Oxa	Ph	AgOAc (4)	NaTFA (0.5)	HFIP	0

II.2.ii. Optimization of the C-H functionalization of cyclopropane carboxylic acid

With a first hit in term of reactivity and an optimized synthesis for the chiral directing group APS, we endeavoured on optimizing the yield for the arylation of **II-1a** with 4'-iodoacetophenone.

First of all, using palladium(II) acetate as catalyst and HFIP as solvent, we optimized the base and additive. Using a silver salt as base no matter its counter anion, gave good NMR yield. When using an *N*-heterocyclic carbene precursor imidazolium salt as additive, the conversion dropped drastically, surely explained by the strongly coordinating character or the carbene that could avoid formation of the desired metalacyclic species (Entry 3). It was found that adding 0.5 equivalents of sodium trifluoroacetate in the reaction mixture helped rising the conversion up to 90% while diminishing the amount of expensive silver acetate (Entry 4). Its exact action mode is yet not known but we can suspect the formation of a hybrid Pd(OAc)(TFA) species that would be more reactive that both $Pd(OAc)_2$ and $Pd(TFA)_2$ (Table 2.3).

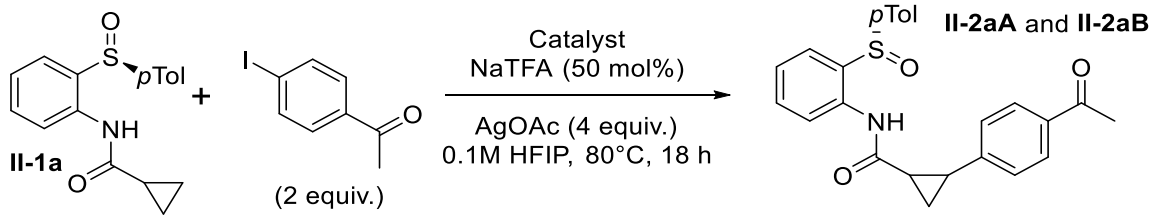
Table 2.3 Optimisation of the base and additive for cyclopropane arylation



Entry	Base (equiv.)	Additive (equiv.)	NMR Yield (%)
1	AgOAc (4)	-	80
2	Ag_2CO_3 (2.2)	-	81
3	AgOAc (4)	iPrHCl (0.2)	54
4	AgOAc (4)	NaTFA (0.5)	90
5	AgOAc (2.2)	NaTFA (0.5)	90
6	AgOAc (4)	AdamOH (0.5)	75
7	$AgBF_4$ (4)	NaTFA (0.5)	60
8	$AgBF_4$ (4)	AdamOH (0.5)	55

Then we investigated the catalyst source. We showed that the reaction need a palladium(II) catalyst to proceed, as with a source of Pd(0) (Entry 2) or without catalyst (Entry 3) no reaction occurred. Thus, the catalytic cycle certainly involves Pd(II)/Pd(IV) species. Based on the previous results concerning the addition of NaTFA in the reaction mixture, we tried using palladium(II) trifluoroacetate, however only low conversion was obtained, supporting the theory of the formation of a dual Pd(OAc)(TFA) species (Entry 5). The efficiency of the system allowed us to decrease the catalyst loading from 10 to 5 mol% (Table 2.4).

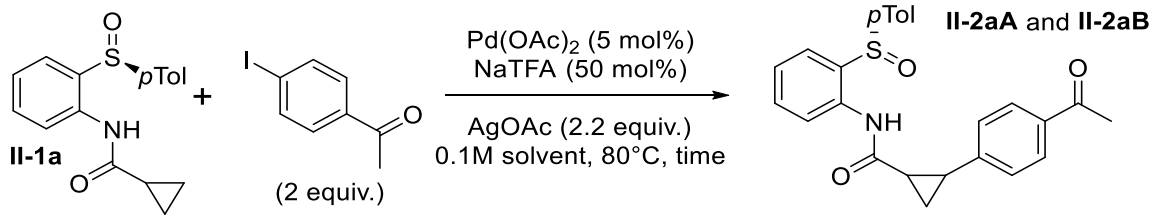
Table 2.4 Optimisation of catalyst for cyclopropane arylation



Entry	Catalyst (loading)	NMR Yield (%)
1	$Pd(OAc)_2$ (10 mol%)	90
2	Pd_2dba_3 (10 mol%)	0
3	none	0
4	$Pd(OAc)_2$ (5 mol%)	90
5	$Pd(TFA)_2$ (10 mol%)	30

Final optimization was done on both solvent and reaction time, while keeping the mixture at 80 °C. Compared to other solvents like 1,2-dichloroethane or 1,1,1-trifluoroethanol (Entries 1 and 2), HFIP showed a drastic beneficial effect in term of reactivity. Interestingly, by adding a small amount of water in the reaction mixture, the conversion was further improved, and the reaction time could be decreased to only 8 h (Entry 5). Based on the experimental observations done during the experiments, we suspect a better dissolution of all compounds, in particular the silver and sodium salts, in this pseudo-homogeneous mixture. When rising the proportions of water from 9:1 to 4:1 and 1:1, the mixture started to be biphasic and the reactivity was lowered. However, the reactivity was high in a mixture of surfactant and HFIP, suggesting that in our system, HFIP may also form micelles as suggested in various studies (Table 2.5).[208,209]

Table 2.5 Optimisation of solvent and time for cyclopropane arylation



Entry	Solvent	Time (h)	NMR yield (%)	dr
1	DCE	18	15	1:1
2	CF_3CH_2OH	18	50	55:45
3	HFIP	18	90	60:40
4	HFIP/H_2O (9:1)	18	90	60:40
5	HFIP/H_2O (9:1)	8	90	60:40
6	2% w/w TPGS-750 in H_2O/HFIP (9:1)	24(35 °C)	90	60:40

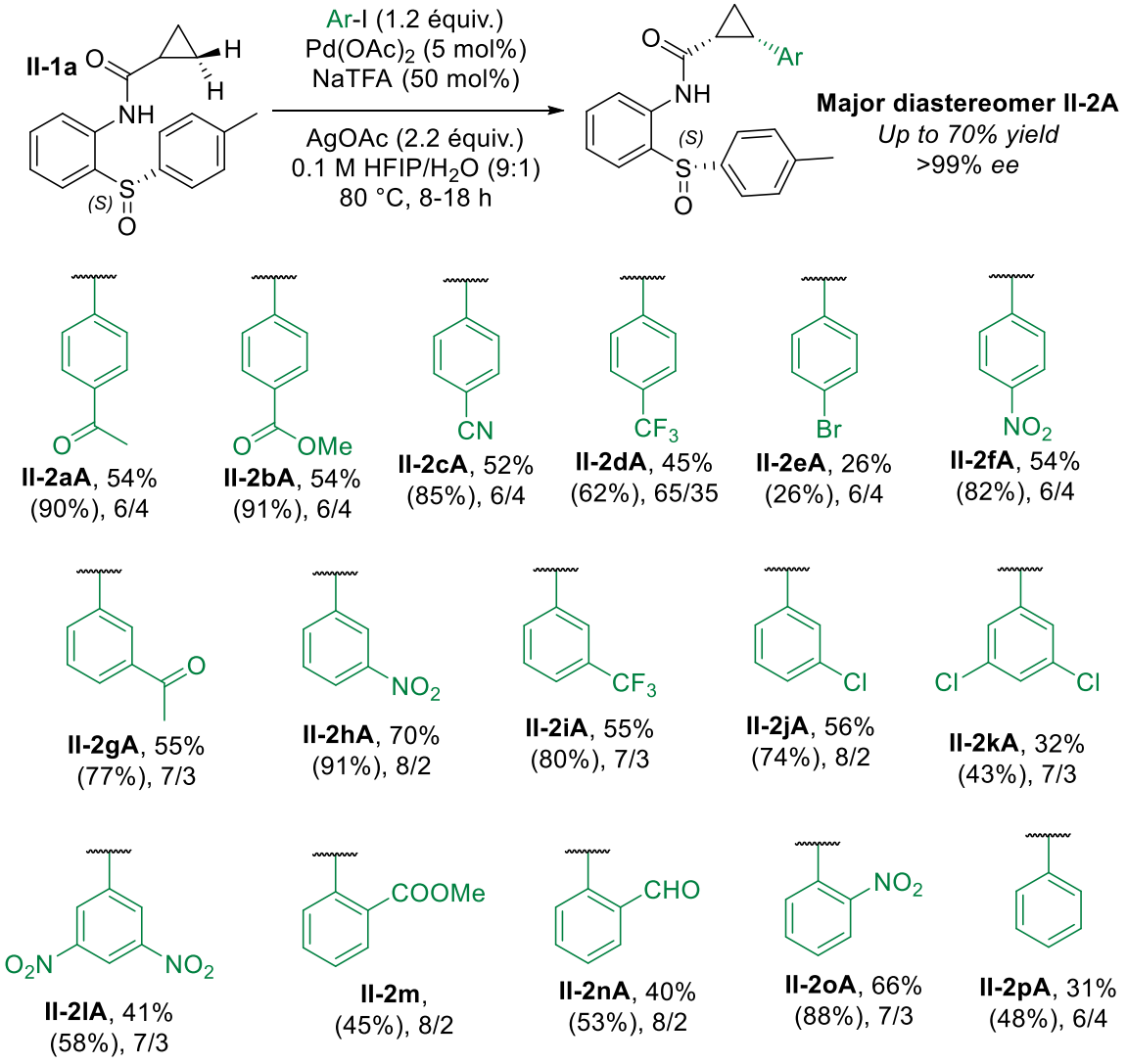
At the end, we could even lower the excess of iodoarene coupling partner from 2 to 1.2 equivalent, using 5 mol% of $Pd(OAc)_2$ as catalyst, 50 mol% of NaTFA as additive and 2.2 equivalents of AgOAc as base in a 9:1 mixture of HFIP and water, to get efficient arylation of non-substituted cyclopropane substrate while maintaining the diastereoisomeric ratio to 60/40.

II.3. Non-substituted cycloalkane functionalization

II.3.i. Arylation of naked cyclopropane

Under the optimized reaction conditions, direct arylation of **II-1a** with a large panel of iodoarene coupling partners was performed, affording selectively mono-*cis*-arylated cyclopropanes **II-2** with good to excellent total yield and moderate to good diastereoselectivity (Table 2.6).[16] All type of functional groups on the iodoarene coupling partner were well tolerated, from ketone to sensitive aldehyde or halogen. However, the reactivity of the system dropped while using electron-rich coupling partners such as iodoanisole. Moreover, the diastereoselectivity was influenced by the substitution of the coupling partner: *para*-substituted ones gave generally 20 % diastereomeric excess, *meta*-susbtituted from 30 to 40 % and *ortho*-susbtituted up to 40 %.

Table 2.6 Scope of arylation on naked cyclopropane ring using APS as chiral directing group (total yields are given; between bracket, yield of the major diastereomer, with the diastereomeric ratio)



In almost all the cases (except for **II-2m**), the major diastereomer was easily separated from the minor diastereomer by silica gel chromatography. The relative *cis*-configuration was proved by NOESY analysis of compound **II-2fA** (Figure 2.29).

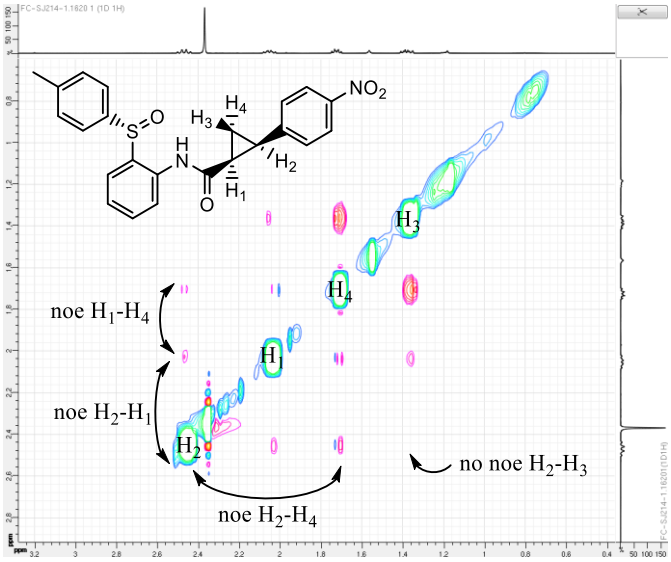


Figure 2.29 NOE experiment on arylated product II-2fA

Notably, **II-2aA** crystallized in CH_2Cl_2/$CHCl_3$/Et_2O affording single crystals suitable for X-Ray diffraction analysis (Figure 2.30.a). The absolute configuration for the other products was attributed accordingly. In the asymmetric unit, the absolute configuration of both chiral carbons on the cyclopropane was proven to be (1*R*, 2*S*). The amide moiety is antiparallel to the adjacent C-H bond in the cyclopropane ring, which can be explain by the orbital repulsion between these atoms. Furthermore, the distance between the tolyl and the acetylphenyl (around 3.7 Å) suggests a possible π-interaction between these two rings.[210] Unit packing shows multiple hydrogen bonds between the sulfoxide and the amide moiety (Figure 2.30.b).

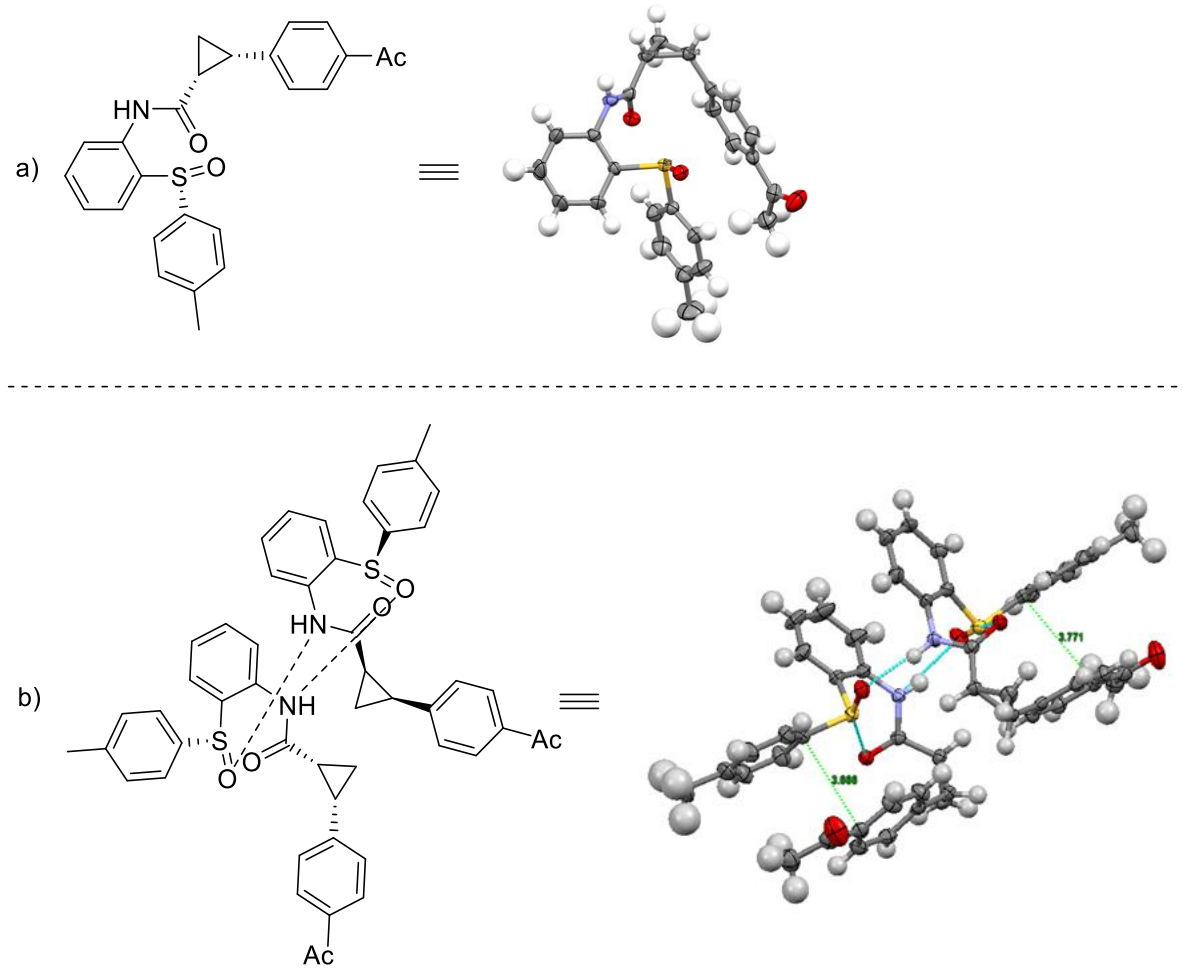
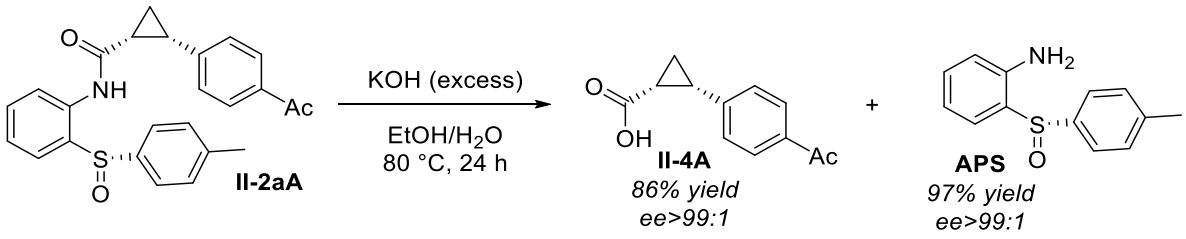


Figure 2.30 ORTEP views of II-2aA

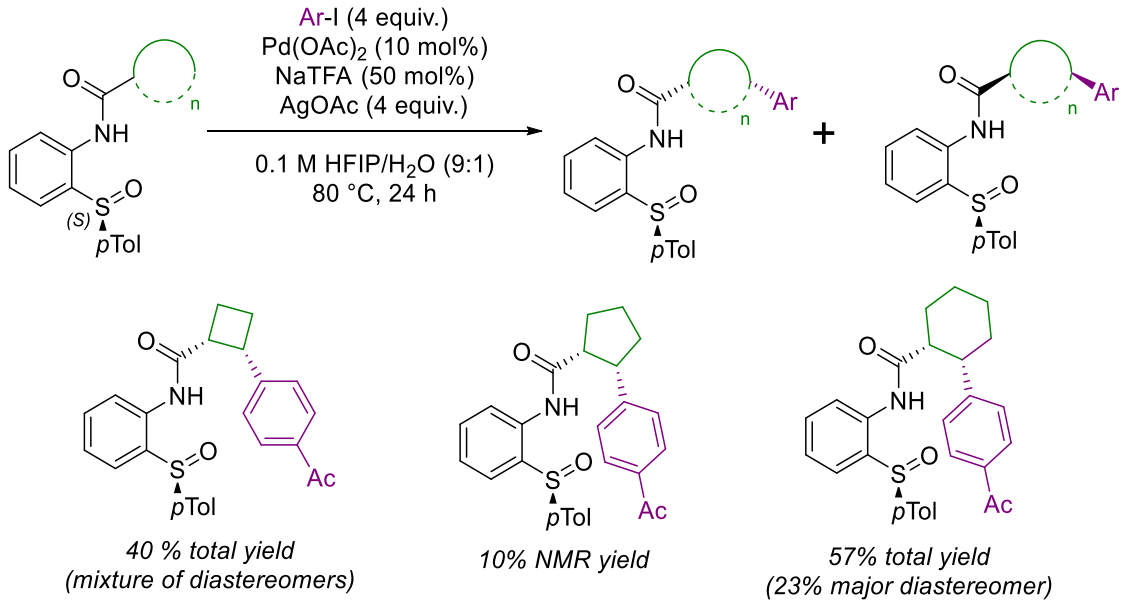
To illustrate the synthetic value of this methodology, deprotection of one of the products was performed under basic conditions, to regenerate arylated cyclopropane carboxylic acid. One of the advantages of our method is the ability to recover in quantitative yield the chiral auxiliary with no loss of its enantiomeric purity, by a simple acido-basic work-up after deprotection. The carboxylic **II-4A** could not be separated by chiral HPLC but optical rotation suggested full enantiomeric purity (Scheme 2.77).



Scheme 2.77 Deprotection of APS under basic conditions

II.3.ii. Extension to the arylation of larger cycloalkanes

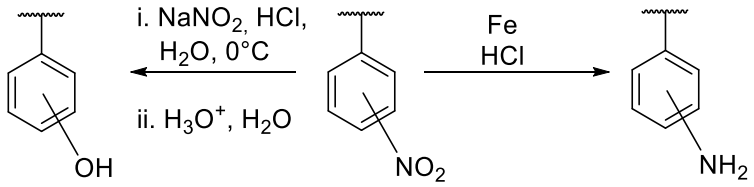
Encouraged by the excellent directing ability of our chiral auxiliary for the arylation of cyclopropane carboxylic acid, we pursued by extending the scope to the arylation towards larger cycloalkanes (Scheme 2.78). Selective *cis*-arylation of cyclobutane ring was achieved with a modest yield of 40% and the two diastereomers were not separable in this case. Surprisingly, low reactivity was observed using cyclopentane carboxamide derivative. When using cyclohexane-derived as substrate, four products were isolated: two *cis*- and two *trans*-diastereomers in around a 4:1 *cis*:*trans* ratio. Indeed, the ring constraints are lower in the cyclohexane, which allowed the *trans*- functionalization.[211]



Scheme 2.78 Diastereoselective arylation of larger cycloalkanes

II.3.iii. Limitation of the scope

Even though our method proved to be efficient for the functionalisation of small ring substrates and using various iodoarenes bearing electron-withdrawing functional groups, the reaction performed poorly using electron-donating functional groups on the aromatic ring, such as 4-iodoanisole or 4-iodotoluene. However, regarding the high yields and good diastereomeric ratio obtained using nitro-substituted iodobenzene, an alternative solution could consist in the conversion to aniline by simple reduction or to phenol by diazotization followed by hydrolysis, thus allowing access to a larger variety of compounds (Scheme 2.79).[212]



Scheme 2.79 Post-modification of nitro derivatives

One other serious limitation relates to the low reactivity with linear alkyl chains under our optimized reaction conditions. Even more activated benzylic position did not undergo any C-H bond activation (Chart 2.14). Fortunately, we overcame this issue and another part of this manuscript will be devoted to the functionalization of linear chains using modified conditions (III.2.i).

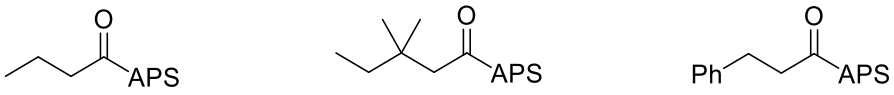
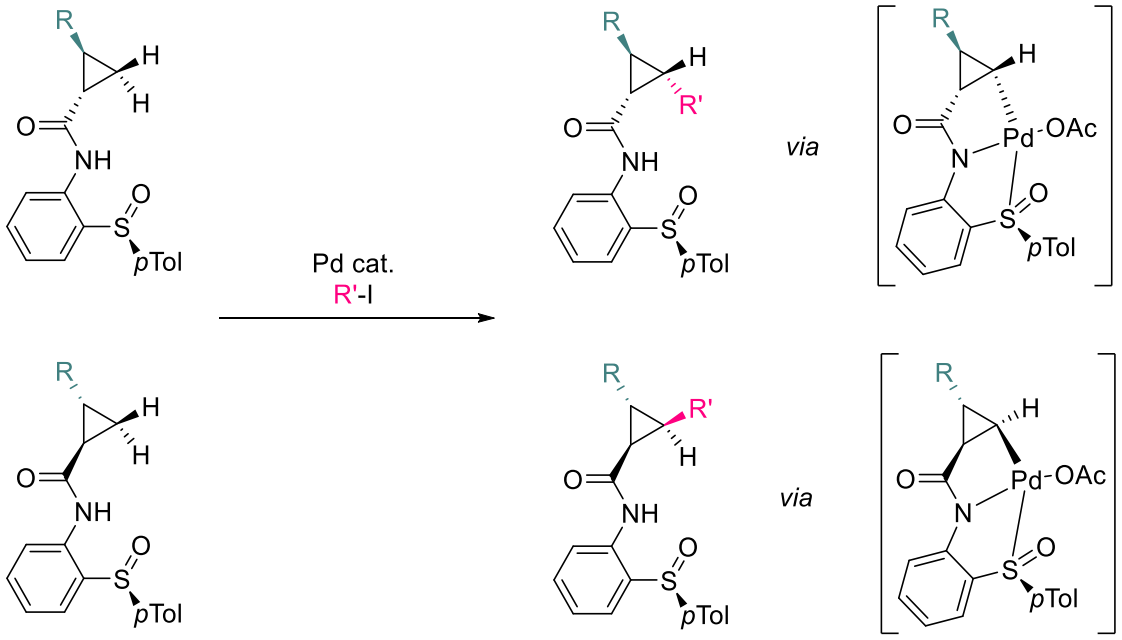


Chart 2.14 Unreactive substrates for diastereoselective arylation

II.3.iv. Extension to the arylation of substituted cyclopropanes

The following was realized with Clémence Rose, Master student.

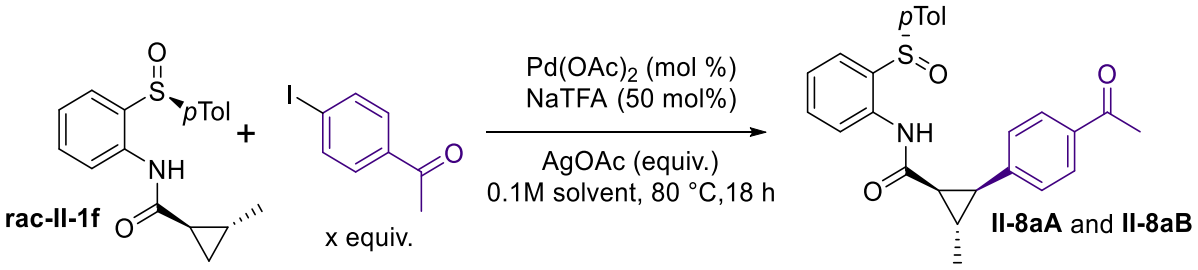
Encouraged by the high reactivity of our catalytic system and the easy separation of the two diastereomers formed, we investigated the more challenging stereoselective C(sp^3)-H bond arylation of disubstituted cyclopropanes to access original trisubstituted cyclopropanes (Scheme 2.80). Notably, cyclopropane carboxylic acids bearing both alkyl and aryl substituents are key biologically active scaffolds, involved in cardiovascular disease treatment, pyrethroid insecticides and peptide isosters.[213–215]



Scheme 2.80 Stereospecific functionalisation of substituted cyclopropanes

Thus, we investigated the *cis*-arylation of *trans*-2-methylcyclopropane-1-carboxylic acid derivative with 4'-iodoacetophenone. The system is less reactive due to the steric hindrance of the methyl and both low coupling partner and catalyst loading afforded only traces of the desired product (Entry 1). Nevertheless, with an excess of iodoarene (Entry 4), the reaction proceeds smoothly under our conditions. Further increase of the reaction time allowed full conversion to two isolable diastereomers (Entry 5, Table 2.7).

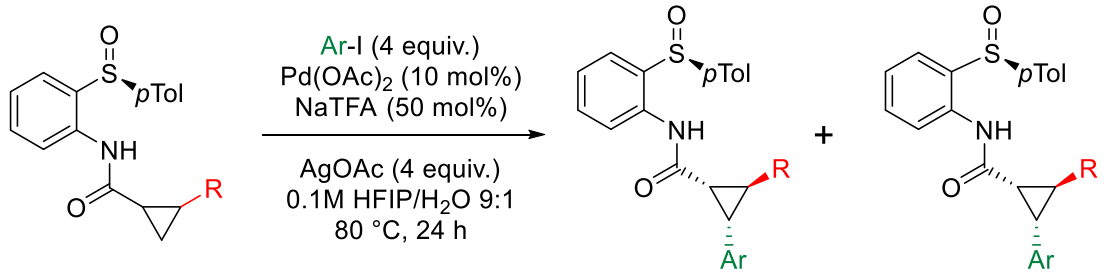
Table 2.7 Optimisation of the arylation of substituted cyclopropane derivatives



Entry	x	Catalyst loading (mol%)	Base (equiv.)	Solvent	NMR yield (%)
1	1.2	5	AgOAc (2.2)	HFIP	traces
2	4	10	Ag_2CO_3 (2.2)	HFIP	traces
3	4	10	AgOAc (4)	HFIP	43
4	4	10	AgOAc (4)	HFIP/H_2O (9:1)	80
5	4	10	AgOAc (4)	HFIP/H_2O (9:1), 24h	100

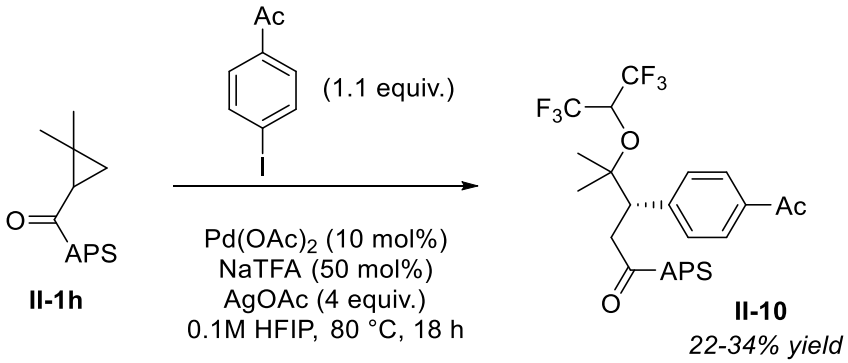
With optimised reaction conditions in hand, we applied our strategy to the synthesis of novel enantiopure 1,2,3-trisubstituted cyclopropane carboxylic acid derivatives from racemic precursors. Independently from the alkyl chain size, arylation could be performed with high yield and complete separation of the two diastereomers. The reaction is tolerant with various functional groups on the arene moiety regardless their position (Table 2.8). Among all described methods to access 1,2,3-trisubstituted cyclopropanes carboxylic acid derivatives, our method offers large tolerance in the aryl substituents and allow access to the two enantiomers that are both valuable considering medicinal chemistry applications (II.5).[216–218]

Table 2.8 Scope of the diastereoselective arylation of substituted cyclopropanes using APS as directing group



Entry	R	Substrate	Ar	Product	A yield (%)	B yield (%)	Total yield (%)
1	Me	II-1f	4-Ac-C_6H_4	II-8a	52	31	83
2	Me	II-1f	3-Ac-C_6H_4	II-8g	56	36	92
3	Me	II-1f	3-NO_2-C_6H_4	II-8h	54	31	85
4	Me	II-1f	C_6H_5	II-8p	50	36	86
5	*n*Pr	II-1g	4-Ac-C_6H_4	II-9a	56	34	90
6	*n*Pr	II-1g	4-NO_2-C_6H_4	II-9f	47	40	87

We were also interested in the arylation of 2,2-dimethylcyclopropane carboxamide substrate **II-1h** in order to synthesize analogues of chrysanthemic acid. However, **II-1h** revealed to be a strong donor-acceptor cyclopropane and we found that it underwent arylation, followed by ring-opening and addition of one HFIP molecule in one-pot (Scheme 2.81). We suspected that the arylation occurred first, followed by ring opening. The *in situ* generated tertiary carbocation could then be attacked by HFIP to get to **II-10**. Nonetheless interesting, this transformation was restricted to a small scope of electron-poor iodoarenes and no conditions proved to be efficient to avoid ring opening.

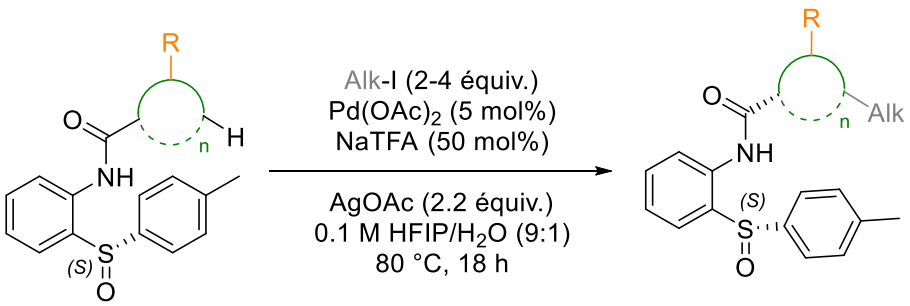


Scheme 2.81 Arylation of 2,2-dimethylcyclopropane derivative

II.3.v. Other challenging transformations: alkylation and olefination

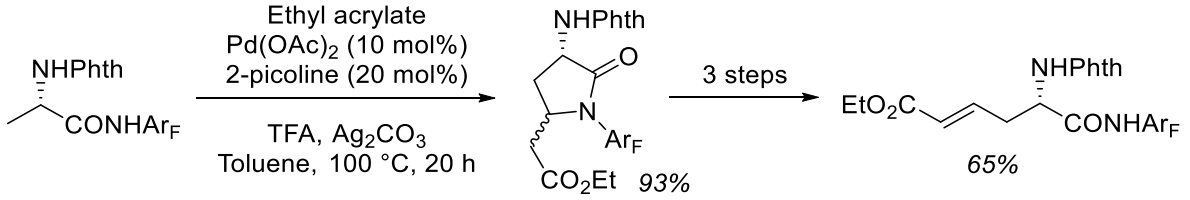
Palladium-catalysed alkylation reactions have already been performed in a regioselective way, either on sp^2 or sp^3 carbons.[4,219] Using our chiral APS, we succeeded in performing challenging C(sp^3)/C(sp^3) coupling using various alkyl iodides as coupling partners, and even with a more sterically hindered disubstituted cyclopropane as substrate (Entry 3). Even if the yields are relatively moderate, these are one of the first examples of diastereoselective and diastereoselective alkylation on cyclopropane ring (Table 2.9). Using the ATS chiral auxiliary with the *tert*-butyl group on the sulphur atom, low yield of 13% of **II-13** was isolated, however with a high diastereomeric ratio of 90:10 (Entry 4). Selective mono-alkylation of cyclobutene **II-1c** was also effective and the two diastereomers **II-14A** and **II-14B** were obtained with 46 and 21% yield respectively (Entry 5).

Table 2.9 Alkylation of cycloalkanes



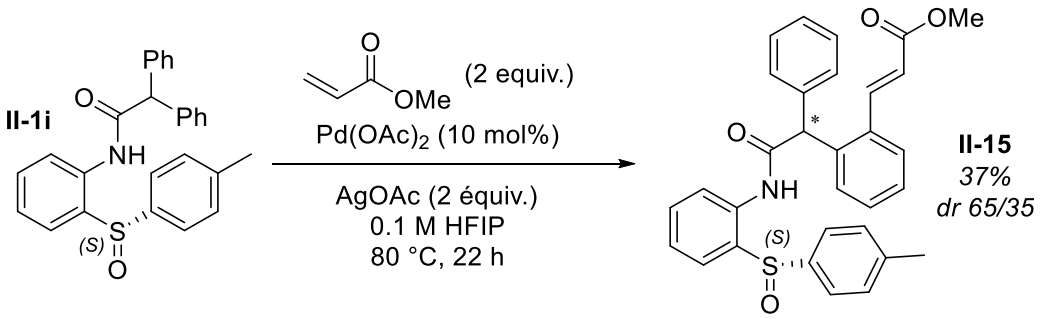
Entry	n	R	Substrate	Alk	Product	Total yield A+B (%)
1	0	H	**II-1a**	CH_2CO_2Et	**II-11a**	58 (34 + 24)
2	0	H	**II-1a**	Me	**II-11b**	34
3	0	*n*Pr	**II-1g**	CH_2CO_2Et	**II-12**	62 (40 + 22)
4	0	H	**II-1b (with ATS auxiliary)**	CH_2CO_2Et	**II-13**	13
5	1	H	**II-1c**	CH_2CO_2Et	**II-14**	67 (46 + 21)

Direct olefination of the aliphatic substrates is particularly challenging with only few precedents. Various examples of catalytic olefination lead a side reaction, ie. irreversible Michael addition of the amide to the alkene and further transformations need to be performed to regenerate the double bond (Scheme 2.82).[81,220–222]



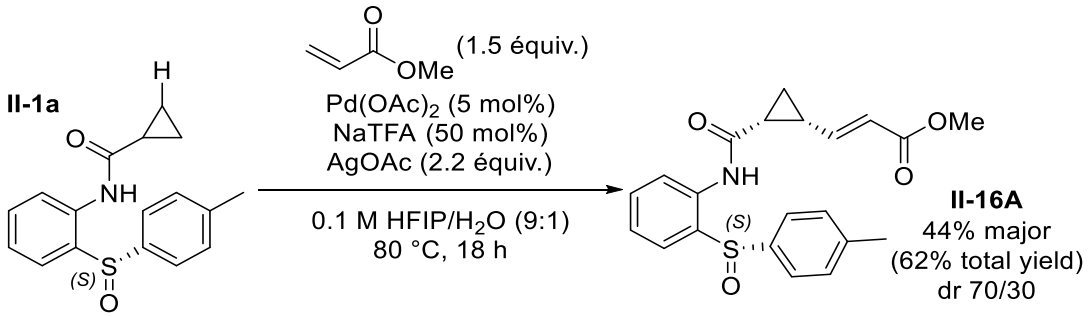
Scheme 2.82 Yu's methodology to access olefins

In pursuance of evaluating the potential of our bicoordinating DG in this transformation, the diastereoselective olefination was performed on an aromatic ring, rewardingly with no 1,4-addition, delivering **II-15** in promising 37% total yield and moderate 65/35 diastereomeric ratio (Scheme 2.83).



Scheme 2.83 Diastereoselective C(sp^2)-H olefination using APS as chiral directing group

Following this hit, we applied the same reaction conditions to **II-1a** and were pleased to observe formation of the desired product in good total yield (Scheme 2.84). The major diastereomer **II-16A** was isolated by column chromatography.

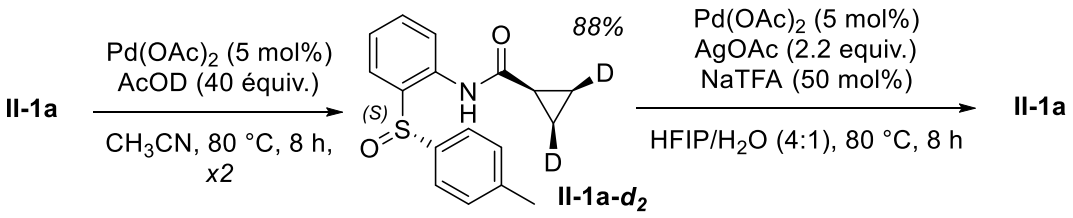


Scheme 2.84 First diastereoselective C(sp3)-H olefination using APS as chiral directing group

II.4. Mechanistic aspects

In order to elucidate the mechanism and the mode of action of our sulfinylaniline DG, preliminary mechanistic studies have been undertaken.

Firstly, the reversibility of the C-H bond activation step was investigated. Deuterated substrate **II-1a-*d*$_2$** was efficiently obtained using acetic acid-*d* as internal source of deuterium. Using a similar protocol to our arylation, nonetheless without coupling partner, full conversion to **II-1a** was observed after 8 h (Scheme 2.85). This suggests total reversibility of the C-H bond activation step.



Scheme 2.85 Deuteration experiment on naked cyclopropane

Kinetic isotopic effects were also studied by reacting separately **II-1a** and **II-1a-*d*$_2$** in our reaction conditions with 4'-iodoacetophenone as model coupling partner. The kinetic isotope effect was found to be 1.2, which is coherent with the hypothesis that the C-H bond activation step is not the rate-determining step of the transformation (Figure 2.31).

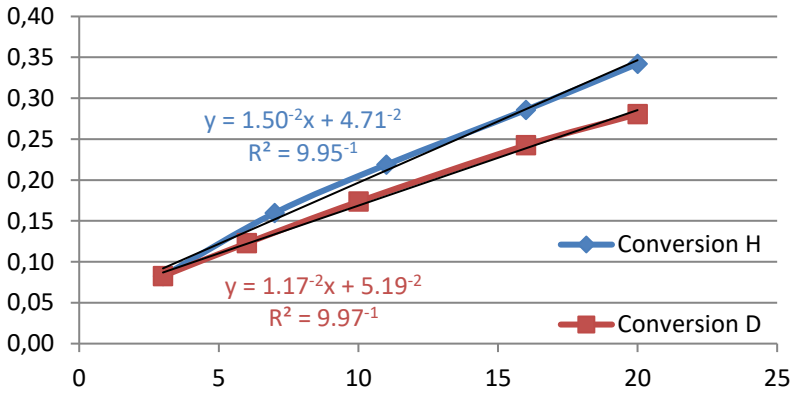
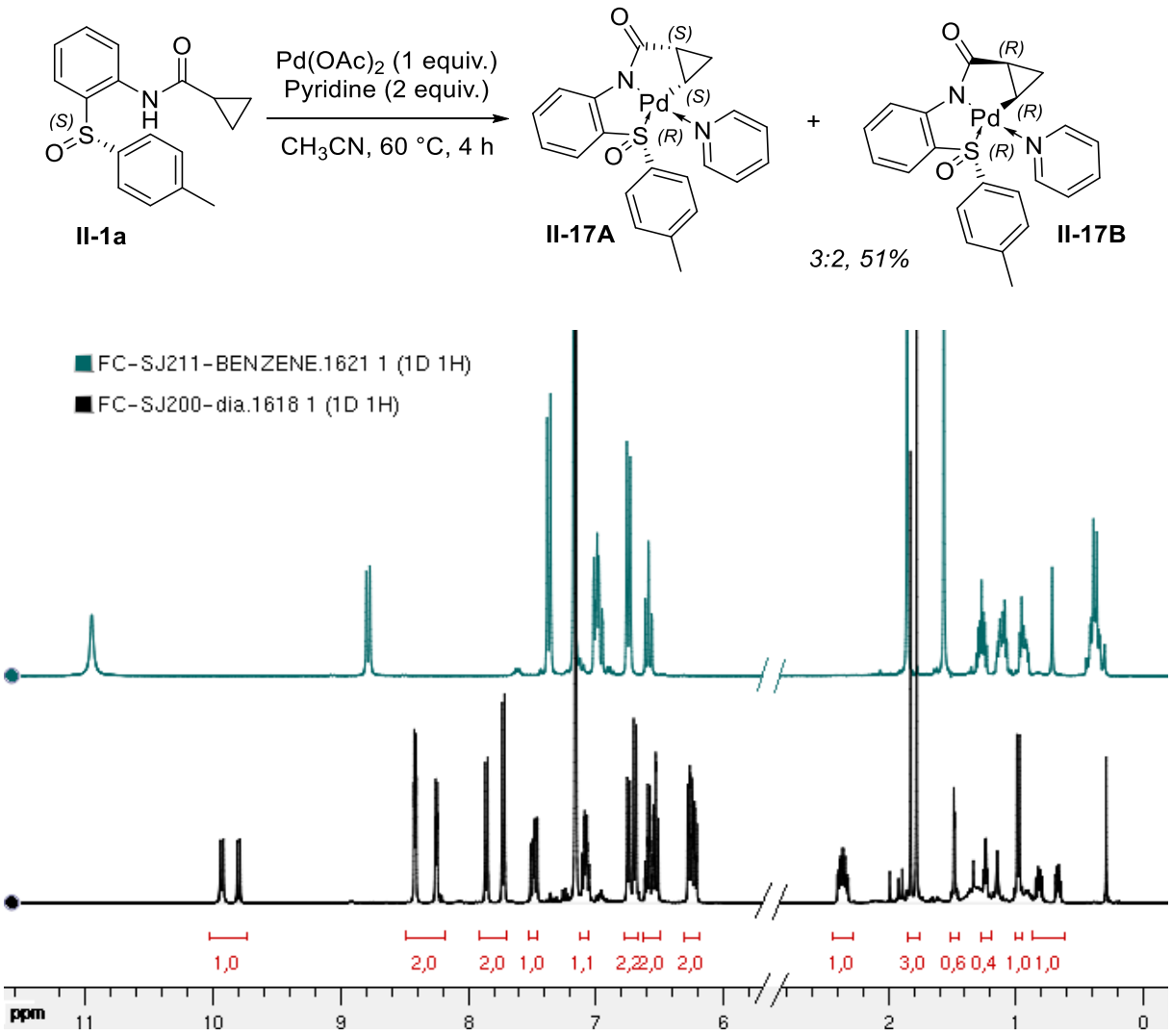


Figure 2.31 KIE effects on non-substituted cyclopropane

Subsequently, attempts to isolate palladacyclic species were undertaken to support the mechanism of this transformation. Isolation of stabilized palladacycle **II-17** was possible using conditions developed by Rao and co-workers (Scheme 2.86).[211]



Scheme 2.86 Palladacycle I-17A synthesis and comparison between the starting material and palladacycle NMR

Crystallisation in benzene of the major diastereomer **II-17A** afforded mono-crystals, suitable for X-Ray diffraction analysis (Figure 2.32). The crystallographic data give several key information about the original cyclopropane-derived palladacycle. Firstly, the bidentate character of the APS directing group is proven and amide group coordinates *via* its deprotonated form. Moreover, although the sulfoxide moiety contains potentially two chelating atoms, *i.e.* O- and S-, the Pd-S coordination is favored resulting in a formation of 5,5-bicyclic species. Importantly, the rare examples of isolated palladacyclic intermediates generated *via* C(sp^3)-H activation of aliphatic, linear substrates bearing quinolin-8-amine derived *N*,*N*-bicoordinating directing group show a related, 5,-5-bicyclic structure.[4] A rapid comparison of **II-17A** with the literature described structures show that APS moiety leads to a formation of larger metallacyclic species; for **II-17A** the amide-Pd bond is of 2.014 Å, whereas for quinolone-type intermediates, the values of 1.971 Å and 1.969 Å were determined. Besides, S-Pd bond of 2.329 Å is significantly longer than the

N(quinoline)-Pd linkages (2.126 Å and 2.124 Å). In contrast, Pd-C bond in **II-17A** is shorter in comparison to its quinolin-8-amine congeners (2.001 Å vs. 2.023 Å and 2.012 Å). The N(1)-Pd-C(17) angle of 83.1° shows distortion from an idealized square planar geometry at the palladium center as is coherent with the literature. In addition, slight torsion of the second ring is also observed, as suggested by the S(1)-Pd-N(1) angle of 84.09 Å and S(1)-C(8)-C(13) and C(8)-C(13)-N(1) angles of 118.92° and 117.09° respectively, together with S(1)-C(8)-C(13)-N(1) torsion of -0.90°. Finally, the X-ray structure of the palladacyclic compound clearly shows that *p*Tol substituent of the sulfoxide moiety points in an opposite direction to the cyclopropane ring, yet impacting only moderately the steric hindrance between diastereotopic positions at C(17) and C(16), resulting in low stereoselectivity observed.

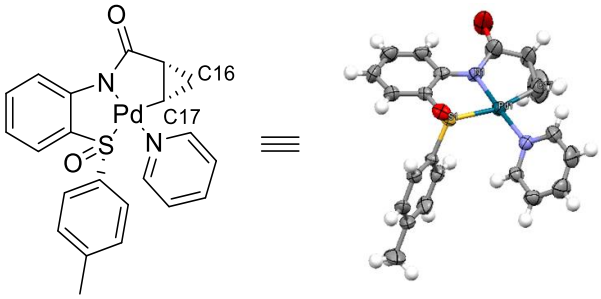


Figure 2.32 ORTEP view of the palladacycle II-17A

Furthermore, preliminary density functional theory (DFT-D) computations were carried out without thorough investigation of the reaction energy profile. Given the conditions required for the catalysis to take place and the central role of palladacyclic intermediates in the overall process, a mere comparison of the energies of metallacycles **Int-2aA-1** and **Int-2aB-1** (Figure 2.34) that are formed indicated that they were almost all isoenergetic within 2 kcal/mol (gas phase ground state geometries at 298.15 K, ZORA-PBE-D3(BJ)/all electron TZP), with a slight bias in favour of the tridentate complex **II-17A** depicted in Figure 2.32 where the cyclopropyl's methylene orientation is antara-facial with respect to the sulfoxide's oxygen atom. As a matter of fact, in the present stage of the study, it was not possible to confirm that the deprotonation of the amidic NH position that leads to neutral **II-17** takes place before the cyclopalladation step or after.[223,224] Computation of the energies of the two-low lying tridentate palladium acetate chelates, *i.e.* the precursors of **Int-2a-1** (noted **pre-Int-2a-1**), indicates however that the *N*-bound proton bears a rather high positive charge that makes it potentially prone to abstraction by any moderate base such as the acetate. This can be intuitively noted from the map of electrostatic potential drawn in Figure 2.33 which denotes a dark blue coloured isosurface area symptomatic here of an important charge density depletion at the amide's proton. Deprotonation of this

position is key to the stabilization of the palladacycle as it releases nitrogen's lone electron pair leading to enhanced electron conjugation and planarization of the whole chelate. Natural charges (extracted from Natural Bonding Orbital - Natural Population analysis)[225] clearly support the acidic character of this position ($q(H_{amide})$ = +0.43, $q(H)_{average}$~+0.22) in **pre-Int-2aA-1**. When comparing relevant interatomic distances around the central Pd atom on going from **pre-Int-2aA-1** to **Int-2aA-1**, one can note that the largest variation of distance is observed by order of importance for the N_{amide}-Pd bond (shortening by 0.10 Å), the S-Pd bond (shortening by 0.05 Å) and the C-Pd bond (shortening by 0.01 Å). Therefore, the amide's C-O and sulfoxide's S-O distances undergo a slight elongation by ca. 0.010-0.020 Å. Further NBO analysis of **Int-2aA-1** indicates that in the assumed Lewis structure the lowest bond electron populations around the the Pd center are found for the S-Pd and $N_{pyridine}$-Pd bonds, which fall below the detection threshold of 1.7 e. Their Wiberg bond indices *w* (NBO) are respectively *w*(S-Pd) = 0.14 and *w*($N_{pyridine}$-Pd) = 0.05. Interestingly, in the computed NBO Lewis structure the bonds that actually seem to scaffold the chelate are the N_{amide}-Pd and $C_{cyclopropyl}$-Pd, which are both computed as the following linear combinations of atom centered orbitals: ψN_{amide}-Pd) (1.89 e)= 0.90($sp^{2.99}$)$_N$ + 0.43($sd^{0.95}$)$_{Pd}$, *w*(N_{amide}-Pd)= 0.10; $\psi C_{cyclopropyl}$-Pd) (1.83 e)= 0.78($sp^{3.54}$)$_C$ + 0.62($sd^{1.21}$)$_{Pd}$, *w*(C-Pd)= 0.53.

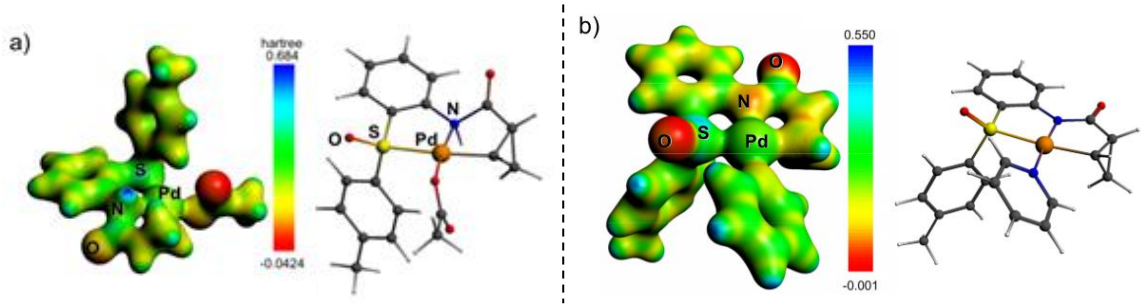


Figure 2.33 Palladacyclic intermediates and the associated charge density maps over an isosurface of the SCF electron density

Based on this study and in accordance with literature precedents, a simplified catalytic scenario can be proposed. A substrate binding to the metal by coordinating S- and N-atoms is believed to initiate the overall transformation. The chelation with the deprotonative amide group, bearing a negative charge, enhances formation of Pd-intermediate **pre-Int-2aA-1** bearing one anionic acetate ligand and allows the C-H preactivation via favourable Pd-CH agostic geometry. However, at the moment, the order of the elemental steps of NH-deprotonation and palladation, remains ambiguous. This intermediate could not be isolated, though it was possible to observe by infrared spectrometry analysis shifts in the S-O and C-O stretches, as well as disappearance of

the N-H stretch. Subsequently, the reversible C-H activation takes place, probably via Concerted Metalation-Deprotonation Pathway, enhanced in a presence of NaTFA additive. This metalation step is believed to be stereodeterminant, as the same diastereomeric ratio of the palladacyclic intermediates **Int-2aA-1** and the arylated products is usually observed. Subsequent oxidative addition of Ar-I leads to a formation of the Pd(IV) intermediates **Int-2aA-2** and a final reductive elimination delivers both diastereomers of the product and the catalyst is regenerated in a presence of AgOAc. Noteworthy, the scope of the arylation of **II-1a** clearly indicates that the diastereoselectivity is improved when *meta*- and *ortho*-substituted iodoarenes are used. It can be hypothesized that when more sterically demanding iodoarenes are used, the rate of the reductive elimination from the two diastereomeric metallacycles **Int-2aA-2** is different. Accordingly, one diastereomer of **Int-2aA-2** is converted into the final product more rapidly and the reversibility of the previous steps allows the re-equilibration of the ratio **Int-2aA-1: Int-2aB-1**. Therefore, in this case the overall stereoinduction would be impacted by both, the diastereoselectivity of the C-H activation step and the rate of the reductive elimination from the two diastereomeric intermediates (Figure 2.34).

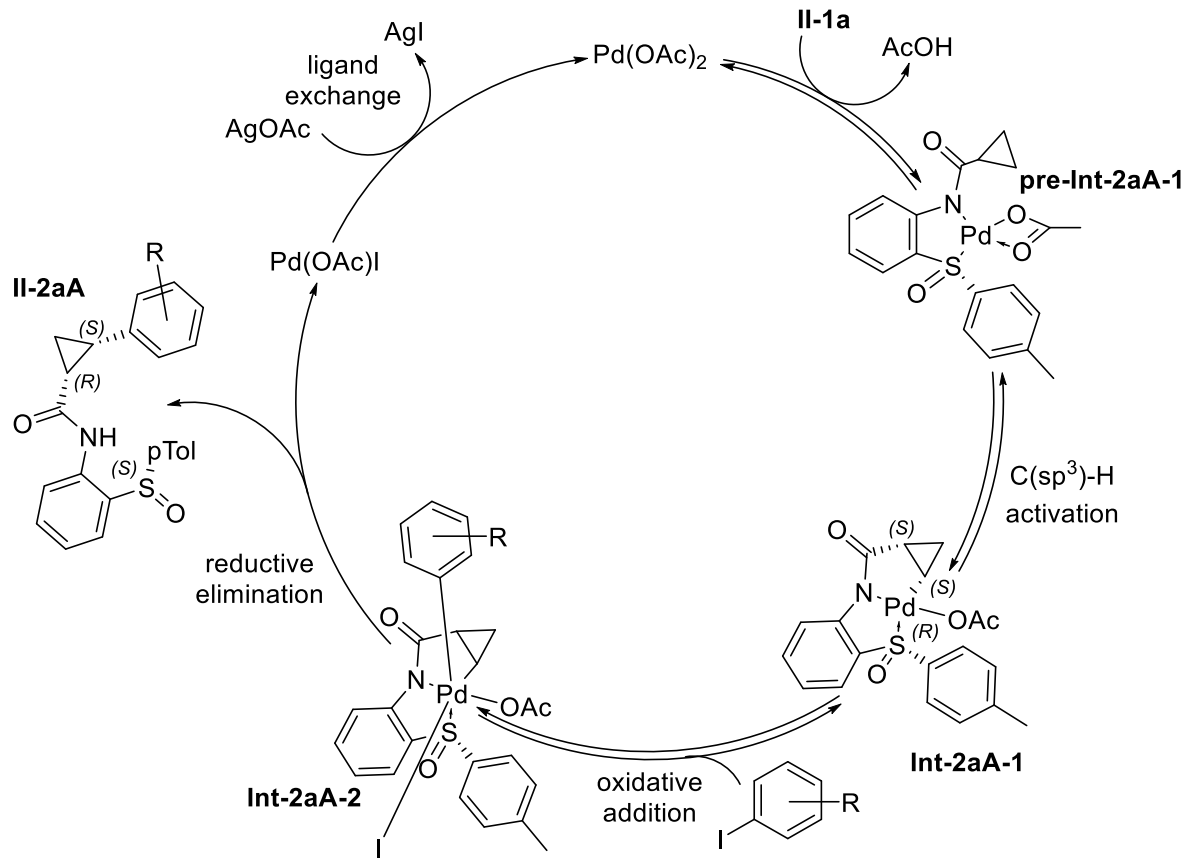
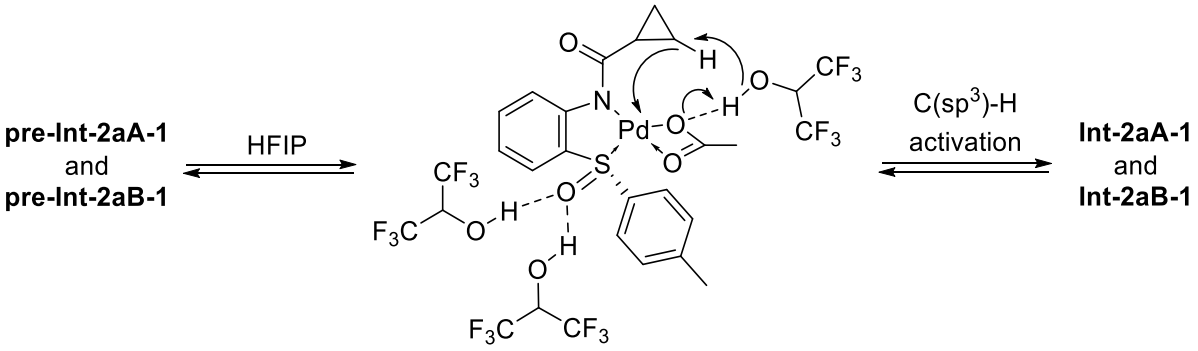


Figure 2.34 Mechanism for C-H activation of cycloalkanes using APS as chiral directing group

In this catalytic cycle, the role of HFIP remains ambiguous although we suspect the formation of a coordination sphere around the sulfoxide that could enhance its coordinating ability.[15] Regarding its low pKa (9.3) compared to 2,2,2-trifluoroethanol (12.9) or isopropanol (17.1), HFIP could also play a role in the assisted deprotonation mechanism (Scheme 2.87).



Scheme 2.87 Possible role of HFIP in the CMD

Transition state from **pre-Int-2aA-1** to **Int-2aA-1** has been calculated and shows coherent distances for a CMD mechanism (I.2.iv). However, integration of one HFIP molecule in this model was not successful and resulted in high destabilisation of the system (Figure 2.35).

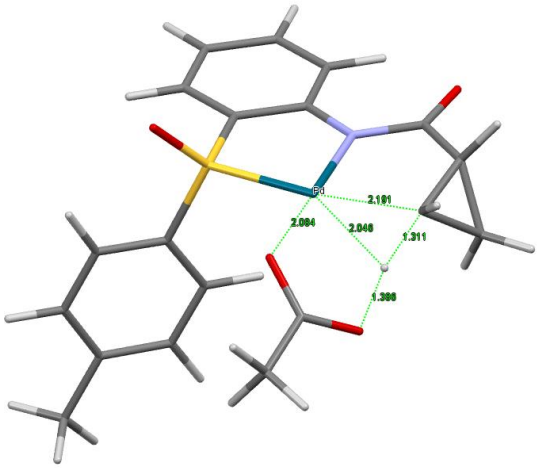


Figure 2.35 Calculated transition state for the diastereoselective C-H bond activation of cyclopropane ring

Concerning the *tert*-butyl substrate, even though no palladacycle was isolated, we hypothesized its similarity with **II-17**, and supposed that one of the C-H bonds in the cyclopropane, by clashing sterically with the directing group, would be the origin of the diastereoselectivity. The increased stereoselectivity arises from the important steric hindrance between of the cyclopropane C-H bonds and the directing group. In contrast, the flat nature of the *p*-tolyl moiety, the C(16)-H would not lead to high destabilisation of the minor diastereomer (Chart 2.15).

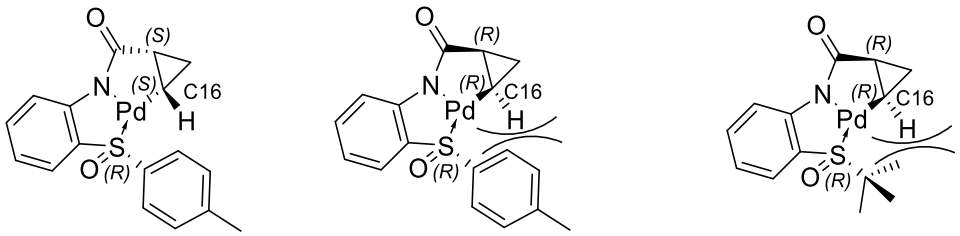


Chart 2.15 Origin of the diastereoselectivity in APS-based systems

II.5. Application to the synthesis of natural products

II.5.i. Introduction

As mentioned before (II.1.ii), many natural products bear cyclopropane and cyclobutane skeletons. In particular, the smallest cycloalkanes are fascinating subunits, privileged scaffolds in medicinally active compounds, drugs, agrochemicals, food and fragrances but have also been widely exploited as versatile synthetic blocks and intermediates.[175]

II.5.ii. Isolation and synthesis of hoshinolactam

Hoshinolactam was discovered recently by Japanese scientists near Hoshino, Okinawa. As many other compounds isolated from marine cyanobacterium, it showed biological activity, particularly antitrypanosomal activity.[17,226]

Retrosynthetic analysis of hoshinolactam clearly indicates two fragments: (*E*)-3-((1*S*,2*S*)-2-propylcyclopropyl) acrylic acid (PCPA) and (3*R*,4*R*,5*S*)-4-hydroxy-5-isobutyl-3-methylpyrrolidin-2-one (HIMP) (Chart 2.16). The optimized synthesis of the HIMP moiety has already been described and hence will not be detailed in this manuscript.[227–229]

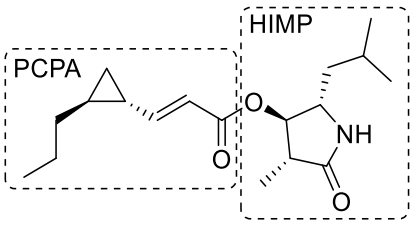
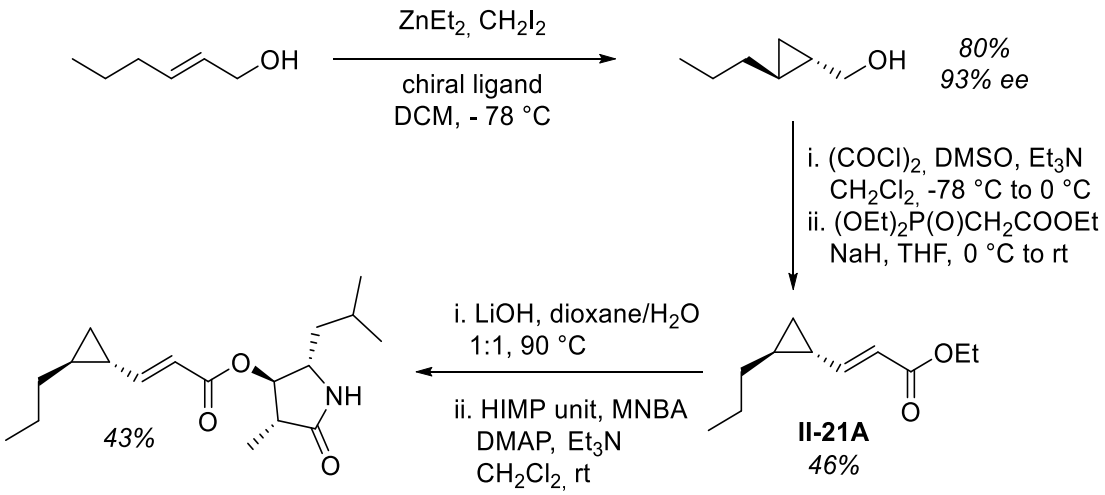


Chart 2.16 Hoshinolactam

The unique synthesis developed by Ogawa and co-workers started with the enantioselective construction of the cyclopropane unit using Charette's methodology from the corresponding allylic alcohol.[186] The intermediate was subsequently oxidized under Swern conditions followed by Homer-Wadsworth-Emmons reaction. The key intermediate **II-21A** was then saponified and coupled with HIMP unit to afford hoshinolactam with 20% overall yield and assumed 93% enantiomeric excess (Scheme 2.88).

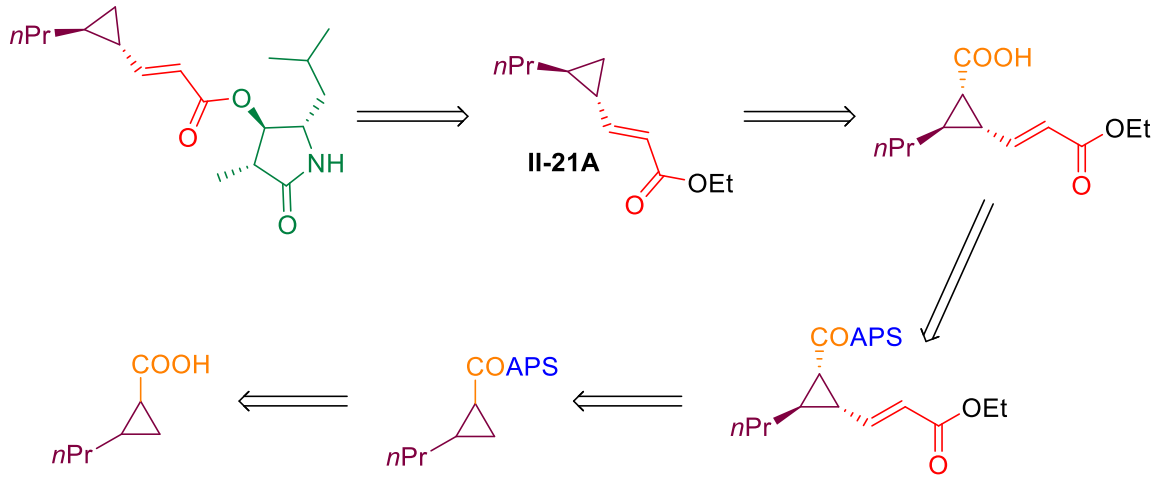


Scheme 2.88 Ogawa's synthesis of hoshinolactam

II.5.iii. APS-based total synthesis of hoshinolactam

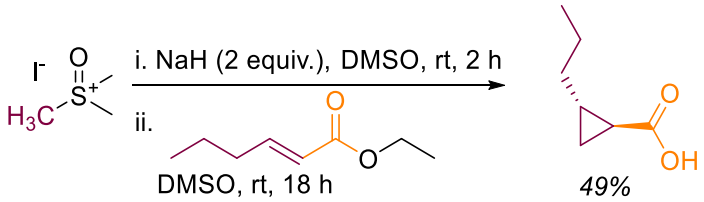
The following was realized with Pauline Poutrel, Master student.

In this project, our aim was to develop a new synthetic approach towards the PCPA unit of hoshinolactam. The key *trans*-cyclopropane **II-21A** is obtained from the decarboxylation of a 1,2,3-trisubstituted cyclopropane. This carboxylic acid results from the deprotection of our chiral auxiliary, which allows installing the olefin moiety through C(sp^3)-H bond functionalization on a racemic-*trans*-cyclopropane carboxamide derivative.



Scheme 2.89 Retrosynthetic pathway for APS-based synthesis of hoshinolactam

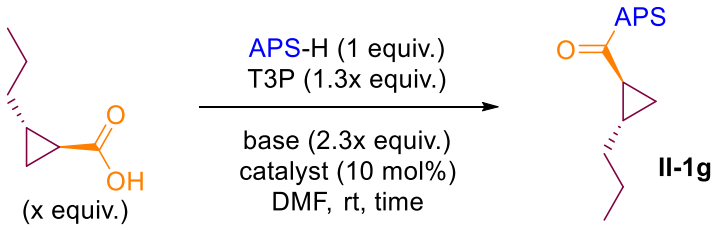
To debute this synthesis, the racemic *trans-n*-propyl-cyclopropane carboxylic acid was prepared according to a modified Corey-Chaykowsky procedure, using ethyl 2-(*E*)-hexenoate as starting material and trimethylsulfoxonium iodide as carbanion source. We screened different bases and protocols to optimize the conditions and we found that the procedure implying sodium hydride in the first step followed by direct hydrolysis of the ester after cyclopropanation was the most efficient. The reaction proceeded smoothly, and the pure carboxylic acid was furnished in almost 50% yield over two steps. Moderate yields can be explained by the high affinity of the compound to the aqueous medium, thus resulting in a difficult extraction.



Scheme 2.90 APS-based synthesis of hoshinolactam

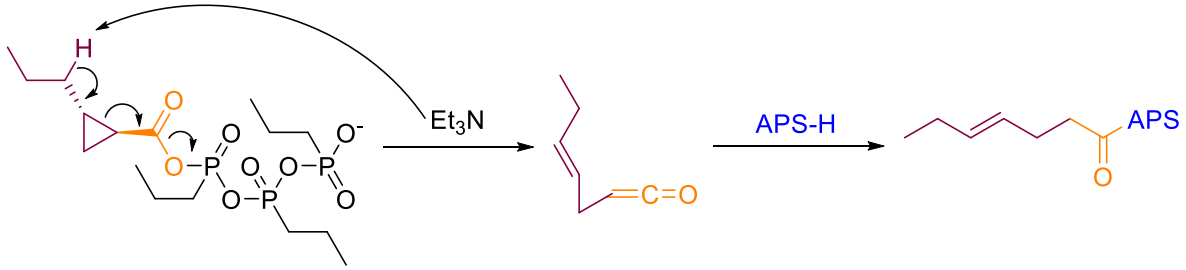
The crude carboxylic acid was subsequently coupled with our chiral auxiliary APS using propylphosphonic anhydride (T3P) as coupling agent and triethylamine as base. This coupling reagent presents many advantages; racemization of the C1 could be avoided and smooth purification *via* extraction (high solubility in the aqueous layer) was performed. However, the main drawback results in its price (100€/mole compared to 40€/mole for *N*,*N*'-dicyclohexylcarbodiimide). The desired product was obtained, however with low yield compared to the conversion. Optimization of the stoichiometry of the starting material, nature of the base and reaction time allowed full conversion to the desired carboxamide **II-1g** derivative as a 1:1 mixture of diastereomers. Switch from nucleophilic base (Entry 1, triethylamine) to non-nucleophilic base (Entry 2, pyridine), even in absence of 4-(dimethylamino)-pyridine as catalyst, significantly raised the conversion (Entries 3 and 4, Table 2.10).

Table 2.10 Optimisation of the peptidic coupling between APS-H and cyclopropane acid



Entry	x	Base	Catalyst	Time	Conversion
1	1	Et_3N	DMAP	17 h	46%
2	1	Pyr	DMAP	17 h	72%
3	1	Pyr	-	17 h	76%
4	2	Pyr	-	24 h	100%

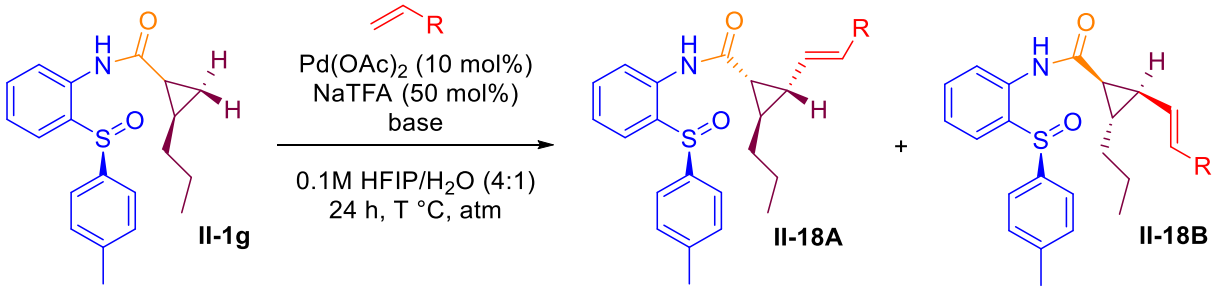
According to the mechanistic studies of Skobridis and co-workers, we can hypothesize a side-reaction occurring in presence of triethylamine and due to the specific reactivity of the cyclopropane ring (Scheme 2.91).[230] The resulting product has never been isolated, however presence of olefinic protons and amide carbon suggests the legitimacy of this pathway, promoted by the mild donor-acceptor character of the activated carboxylic acid.



Scheme 2.91 Cyclopropane ring-opening with triethylamine

Encouraged by our promising preliminary results on direct olefination of non-substituted cyclopropanes, we investigated the Heck-type reaction on substrate **II-1g**.[231] Our initial conditions proved to be efficient and water was indeed necessary to achieve high reactivity. Screening of different acrylates showed that only methyl and ethyl acrylate were reactive (Entries 1, 4, 5 and 6). Finally, key improvements were achieved by decreasing the expensive silver acetate amount concomitantly with using an oxygen atmosphere reaction as co-oxidant (Entries 9 and 10, Table 2.11).

Table 2.11 Optimisation of the olefination



Entry	Base (equiv.)	R (equiv.)	atm	Conversion
1	AgOAc (4)	CO_2Me (6)	air	90
2	AgOAc (3)	CO_2Me (3)	air	70
3	AgOAc (2.5)	CO_2Me (3)	air	60
4	AgOAc (4)	CO_2tBu (6)	air	0
5	AgOAc (4)	CN (4)	air	0
6	AgOAc (4)	CO_2Et (4)	air	80
7	AgOAc (2)	CO_2Et (4)	air	75
8	$Cu(OAc)_2$ (1)	CO_2Et (4)	air	10
9	AgOAc (1)	CO_2Et (4)	O_2	50
10	AgOAc (2)	CO_2Et (4)	O_2	85

Based on our previous studies concerning the diastereoselective arylation of cyclopropane (II.4), a catalytic cycle for this diastereoselective olefination may be proposed (Figure 2.36). After metalation of the cyclopropane, ligand exchange between acetate and acrylate allows insertion of the double bond into the σ-Pd-C bond. β-hydride elimination and decoordination of the product delivers **II-18**.

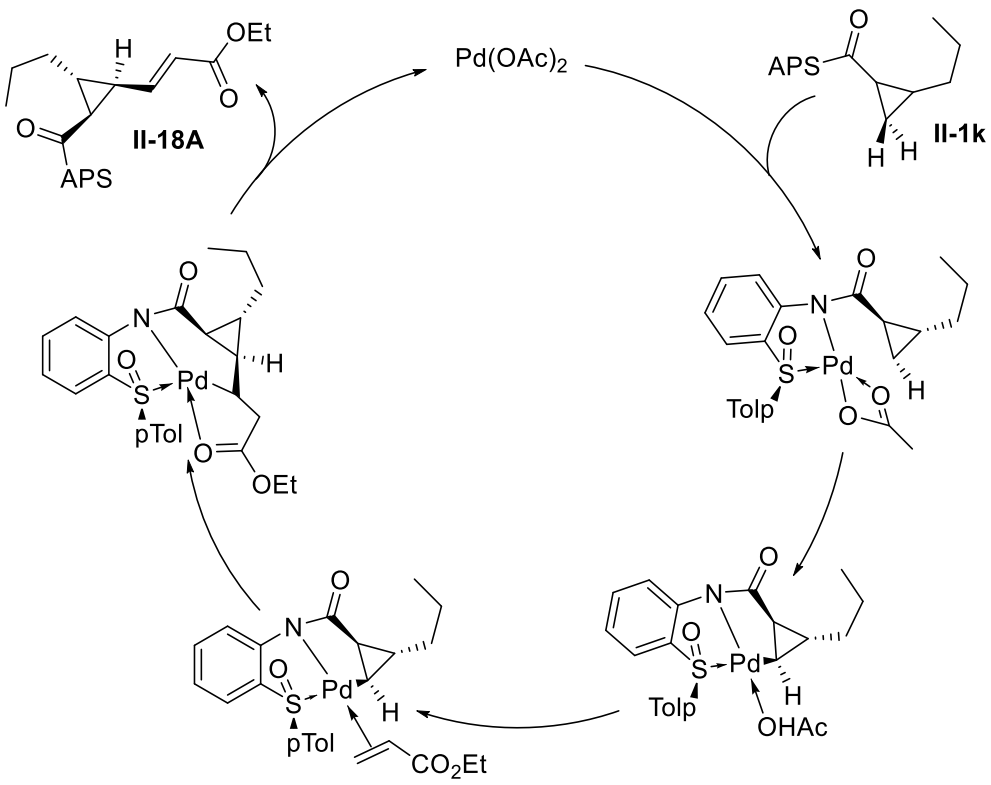
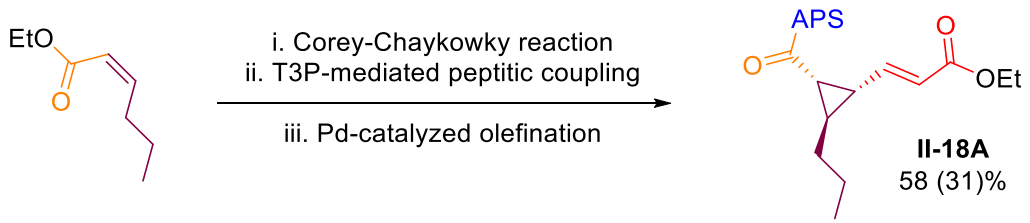


Figure 2.36 Mechanism for APS-directing olefination

With the first steps optimised, we performed a one-pot procedure to convert ethyl 2-(*E*)-hexenoate into the expected interesting diastereomer **II-18A**. A simple purification of the crude mixture after the Heck-type reaction delivered diastereo- and enantio-pure 1,2,3-trisubstituted cyclopropane derivative **II-18A** in 31% yield over three steps (58% for both diastereomers) (Scheme 2.92).

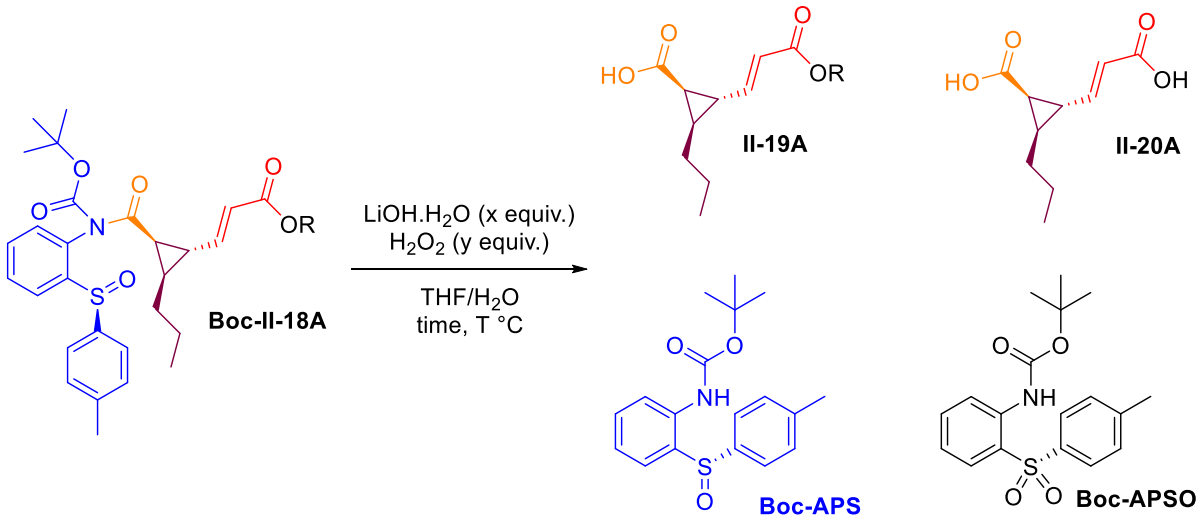


Scheme 2.92 APS-based synthesis of hoshinolactam

Methyl and ethyl acrylate ester derivatives were used for the next challenging step, *i.e.* the selective deprotection of the amide bearing our chiral auxiliary without affecting the ester moiety. Ideally, we would be able to recover our chiral auxiliary with no loss of enantiomeric purity. The first test involved already described basic and acidic conditions to remove the chiral auxiliary.[16,204] However, the acrylate ester did not survive these conditions and furthermore, under acidic conditions, the APS was degraded.

Therefore, based on interesting work of Evans and co-workers, we investigated the mild deprotection of the APS using Boc-protection of the amide prior to lithium peroxide mediated cleavage (Table 2.12 and Figure 2.37).[18,232] Using lithium hydroxide in presence of the methyl acrylate ester, even at low temperature, resulted in partial saponification (Entries 1 and 3, Table 2.12). However, when adding hydrogen peroxide and thus forming in situ lithium peroxide, the methyl ester was totally recovered (Entry 2). This could be explained by the lower basicity of peroxide anions (pk_A(HOOH) = 11.6 vs pk_A(HOH) = 15.8). Higher stability of the ethyl acrylate ester allowed us to remove completely hydrogen peroxide while conserving good reactivity for the amide cleavage and, most importantly, avoiding overoxidation of the sulfoxide functional group (Entry 6).

Table 2.12 Optimisation of the selective APS-deprotection



Entry	R	x	y	T (°C)	Time (min)	Conversion	Ratio II-19A/II-20A	Ratio Boc-APS/Boc-APSO
1	Me	3	5	25	90	100	40/60	10/90
2	Me	3	0	25	120	80	25/75	100/0
3	Me	3	5	0	80	100	100/0	0/100
4	Me	3	0	0	270	50	20/80	100/0
5	Et	3	5	0	90	100	95/5	20/80
6	Et	2	0	0	90	90	>95/5	100/0

In general, ^{1}H NMR of the crude mixture was clean enough to determine both ratios and determine the formation of the different by-products (Figure 2.37).

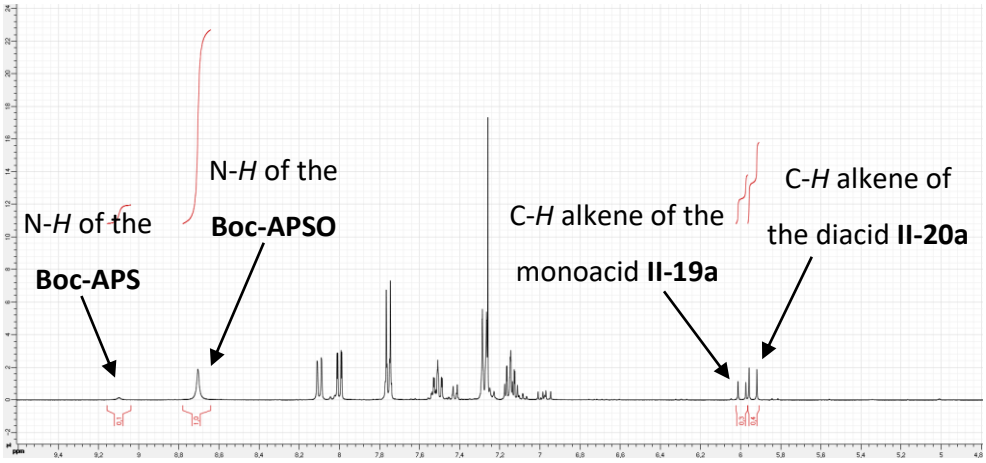
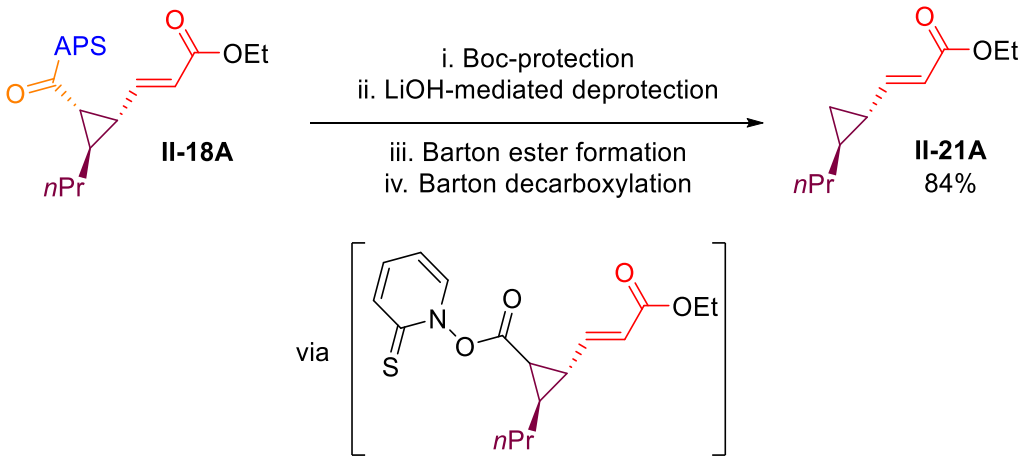


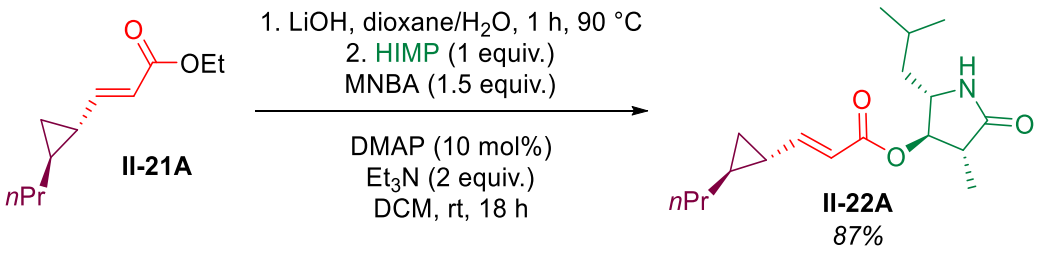
Figure 2.37 Representative ^{1}H NMR of the crude after deprotection of the APS with *in situ* generated LiOOH

With the efficient way of selective deprotection and recovering of the chiral auxiliary in hands, we explored the decarboxylation of the free carboxylic acid to get the key intermediate **II-19A**. Our initial test, using Barton's conditions, gave full conversion to the expected product.[19,233–235] Following this protocol, **II-18A** was thus converted to **II-21A** with an excellent yield of 84% over four steps, with only one column chromatography (Scheme 2.93).



Scheme 2.93 APS-based synthesis of hoshinolactam

As shown previously, **II-21A** is the key intermediate already described by Ogawa and co-workers. Optical rotation showed its full enantiomeric purity and subsequent saponification and esterification with the lactam unit afforded hoshinolactam **II-22A** (Scheme 2.94).



Scheme 2.94 APS-based synthesis of hoshinolactam

Optical rotation of **II-22A** was coherent with the literature data and the proton and carbon NMRs showed good coherence with the extracted compound (Table 2.13). Only small shifts were observed in the HIMP part, probably attributed to the presence of a trace amount of water.

Table 2.13 Comparison of the ^{1}H and ^{13}C NMRs of extracted and synthesized hoshinolactam

Unit	Position	δ_C (Lit.)[1]	δ_C (Exp.)[1]	δ_H (Lit.), couplings[1]	δ_H (Exp.), couplings[1]
HIMP	1	177.8	176.1		
	2	44.1	43.8	2.51, dq (5.2, 7.6)	2.48, dq (5.2, 7.5)
	3	80.8	80.8	4.94, dd (4.6, 5.2)	4.92, dd (4.5, 5.3)
	4	57.3	56.7	3.49, ddd (4.6, 4.7, 9.4)	3.34, ddd (4.5, 4.6, 9.3)
	5a	44.6	44.4	1.21, m	1.34, m
	5b			1.36, m	
	6	25.0	25.1	1.61, m	1.41, m
	7	21.7	21.7	0.74, d (6.2)	0.65, d (6.2)
	8	23.2	23.2	0.76, d 6.3)	0.71, d (6.3)
	9	15.0	14.9	1.33, d (7.6)	1.32, d (7.5)
	NH			7.65, s	6.04, s
PCPA	1	166.0	166.0		
	2	117.4	117.4	5.88, d (15.5)	5.88, d (15.5)
	3	155.0	155.1	6.59, dd (10.3, 15.5)	6.60, dd (15.5, 10.2)
	4	22.4	22.4	0.91, m	0.90, m
	5	23.3	23.2	0.59, m	0.59, m
	6	35.7	35.7	0.96, m	0.96, m
	7	22.5	22.6	1.20, tq (7.1, 7.3)	1.19, m
	8	14.0	14.0	0.78, t (7.3)	0.78, t (7.3)
	9a	16.1	16.1	0.35, ddd (4.5, 6.0, 8.2)	0.35, ddd (8.5, 6.2, 4.4)
	9b			0.42, ddd (4.5, 4.5, 8.8)	0.41, ddd (8.8, 4.4, 4.4)

[1] Proton NMRs were recorded at 500 MHz, carbon NMRs at 125 MHz, in benzene-*d6*. The comparison is done with extracted hoshinolactam, recorded at 400 MHz for proton and 100 MHz for carbon.

II.5.iv. Synthesis of the key intermediates of cascarillic acid and grenadamide

As described previously, many other natural products bear a cyclopropane ring and most of them are *trans*-substituted cyclopropanes (Chart 2.17). Based on our new synthetic approach to access hoshinolactam, we envisaged to apply the strategy to the synthesis of other natural products.

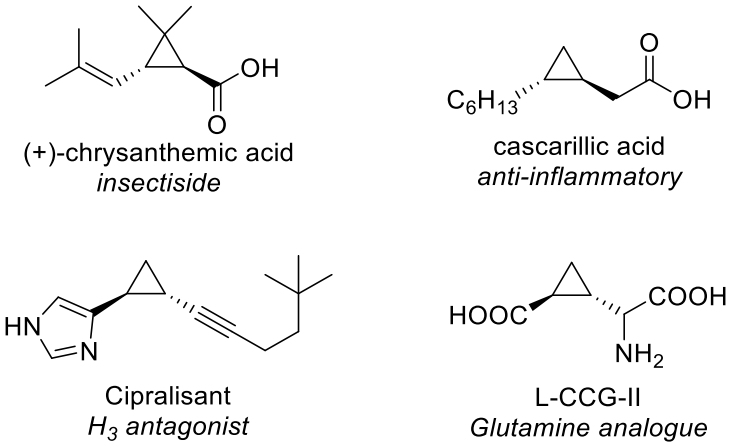
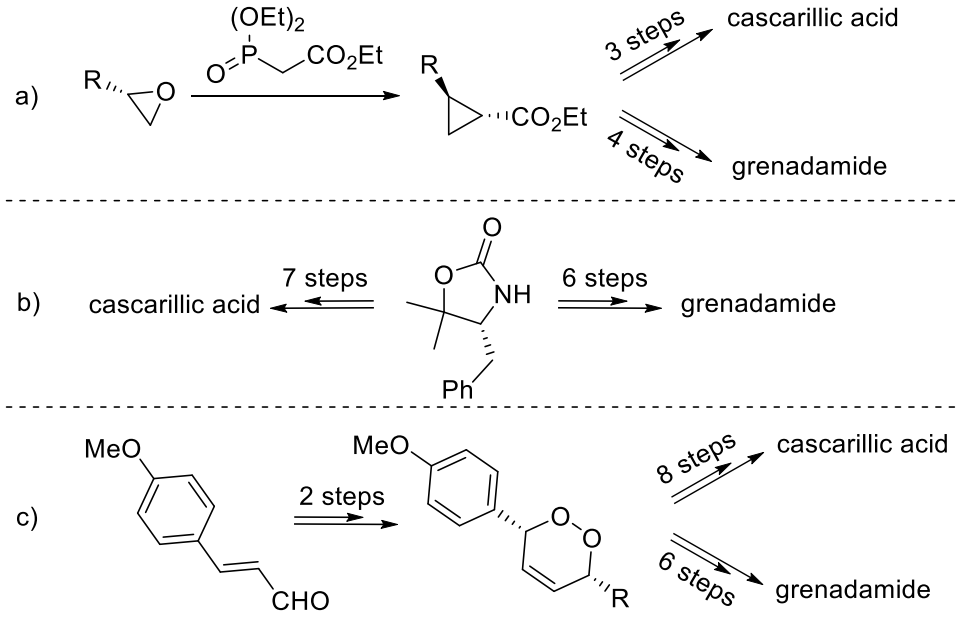


Chart 2.17 Representative cyclopropane-based natural products

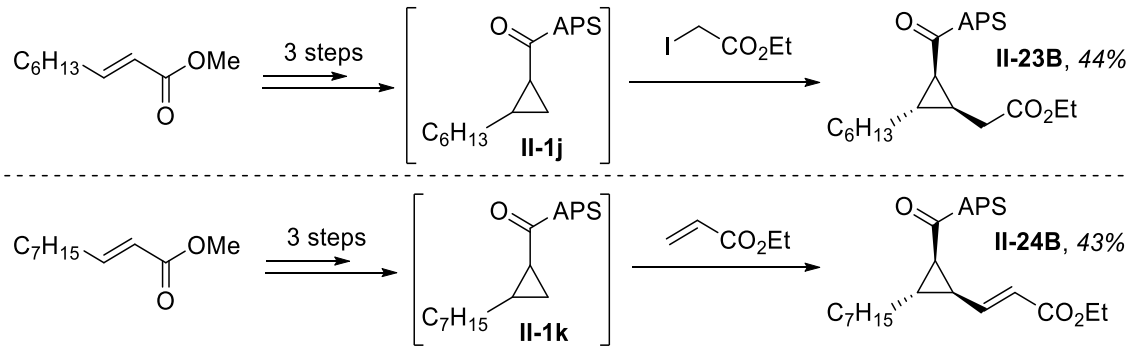
Cascarillic acid was discovered in 1972 by Sedmera and co-workers.[236,237] It is found in cascarilla essential oil and has been used for many years as a symptomatic treatment for various respiratory diseases. Grenadamide, a metabolite isolated from cyanobacterium *Lyngbya majuscula*, shows modest cannabinoid receptor-binding activity and brine shrimp toxicity.[238,239]

Multiple total syntheses of these compounds are described, but only few are enantioselective.[240–244] They are usually multi-steps and require expensive starting materials (Scheme 2.95). Also, and except for the method described in Scheme 2.95.c, only a disubstituted cyclopropane is built, thus limiting the possible diversification of such scaffolds for further medicinal chemistry applications.



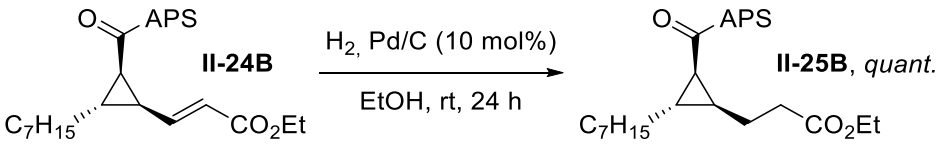
Scheme 2.95 Non-exhaustive syntheses of cascarillic acid and grenadamide

Applying the retrosynthetic analysis disclosed for hoshinolactam (II.5.iii), we endeavoured on preparing the two key intermediates **II-23B** and **II-24B** to access respectively cascarillic acid and grenadamide. Substrates **II-1j** and **II-1k** were obtained thanks to Corey-Chaykovsky cyclopropanation followed by peptidic coupling with APS (Scheme 2.96). Subsequently, C-H bond functionalisation of **II-1j** and **II-1k** was performed. In the case of **II-1j**, challenging C(sp^3)-C(sp^3) coupling occurred.



Scheme 2.96 Cascarillic acid and grenadamide key intermediate synthesis

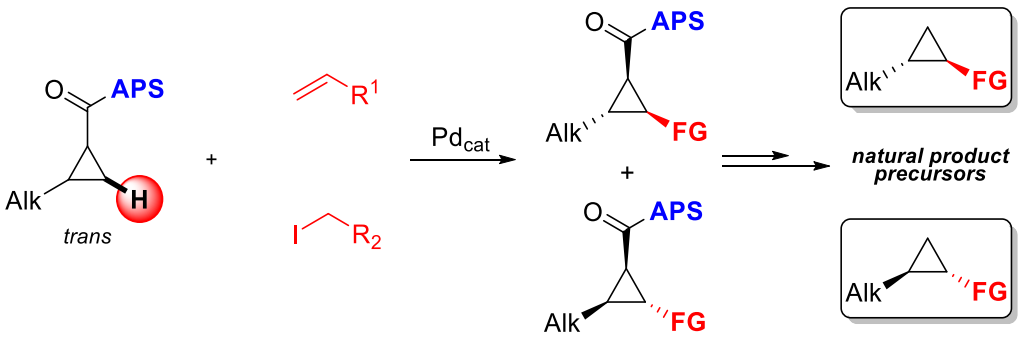
In contrast, olefination of **II-1k** was performed, followed by hydrogenation of **II-24B** to the corresponding alkyl chain. This transformation proceeded smoothly at room temperature without racemization of the cyclopropane chiral skeleton (Scheme 2.97). **II-25B** could also be obtained by direct alkylation of **II-1k** with ethyl β-iodopropionate, however with lower yield and high difficulty to isolate the two diastereomers of the product.



Scheme 2.97 Hydrogenation of I-24B

II.5.v. New methodology for the synthesis of cyclic natural products

Using APS as chiral auxiliary, we managed to perform challenging reactions such as alkylation and olefination to build key 1,2,3-trisubstituted cyclopropane intermediates for the synthesis of three natural products, hoshinolactam, cascarillic acid and grenadamide (Scheme 2.98). Hoshinolactam was synthesized with an overall 25% yield and complete enantiomeric purity while cascarillic acid and grenadamide key intermediates were obtained with approximately 40% yield. Accordingly, our methodology allows access to various cyclopropane-containing natural products, with high variability on: 1) the alkyl chain by changing the starting crotonate; 2) on the functional group by changing the coupling partner used for the C-H bond functionalisation and even 3) on the third carbon of the cyclopropane, initially grafted to a masked carboxylic acid function.



Scheme 2.98 APS-based total synthesis of cyclopropane-containing natural products

II.6. Conclusion

This first project was dedicated to the C(sp^3)-H bond functionalization of cycloalkanes, mainly cyclopropane derivatives. We performed arylation reactions using various coupling partners, affording di- or tri-substituted cyclopropanes with good to excellent yields and moderate to good diastereoselectivity. After the C-H functionalisation step and separation of the diastereomeric product *via* simple column chromatography on silica gel, the chiral auxiliary can be cleaved under basic conditions, delivering on one hand the functionalized carboxylic acid with excellent yield and total enantiomeric purity, and on the other hand our chiral auxiliary APS with no loss of enantiomeric purity. Together with another challenging reaction, alkylation, these results were published in *Chemistry – A European Journal* in 2016 and selected as *Hot Paper*.[16] With these results in hand, we applied this synthetic approach based on C(sp^3)-H bond functionalization of cyclopropane rings to access various key intermediates of natural products. We developed an interesting methodology starting from *trans*-alkenes to access *trans*-disubstituted cyclopropanes in high enantiomeric purity. This new methodology was published in *Organic Chemistry Frontiers* in 2018.

II.7. Experimental section

II.7.i. General considerations

These general considerations are available for all experimental sections in this manuscript.

Anhydrous conditions term denotes reactions conducted under argon in dry glassware using dry solvents. THF was distilled over Na/benzophenone. Anhydrous dichloromethane, diethylether and acetonitrile were purchased from Aldrich (Sure/Seal packaging, kept over 3Å molecular sieves). Molecular sieves were activated by heating at 250°C under vacuum overnight. Palladium(II) acetate, sodium trifluoroacetate and silver(I) acetate were kept in a desiccator prior to use.

Purification on column chromatography either refers to manual column chromatography loaded with silica 60 (40 – 63 µm) or to flash chromatography using Armen Flash Instrument and Biotage SNAP Cartridge KP – Silica 60 µm.

NMR experiments were recorded on a Brucker 500, 400 or 300 MHz, FID treated with NMR Notebook or MestReNova softwares. The chemical shift δ is given relatively to the residual solvent. Fluorine NMR experiments were recorded decoupled from proton, unless otherwise specified. Broad = br, singulet = s, doublet = d, triplet = t, quadruplet = q, multiplet = m.

Melting points were taken on a Buchi M-560 apparatus, with three measures per compound.

Infrared experiments were done on a PerkinElmer UATR Two FT – IR C92778 spectrometer, neat or in solution in dichloromethane or diethylether. Broad = br, weak = w, medium = m, strong = s.

Optical rotations were measured with an Anton Paar Polarimeter MCP 200.

Chiral HPLC measurements were performed on a Shimadzu system with a quaternary low-pressure LC – 20AD pump, an automatic SIL – 20A HT injector, a CTO – 10 AS oven and a SPD – M20 A diode array detector (DAD). The injection volume was 1 µL, the temperature of the oven set to 35°C and the concentration of the sample around 1 g/L.

HMRS measurements were performed by the Service de Spectrométrie de Masse de l'Institut de Chimie at the University of Strasbourg.

X-Ray crystallographic experiments were performed by the Crystallography Service of the University of Strasbourg. The crystals were placed in oil, and a single crystal was selected,

mounted on a glass fibre and placed in a low-temperature N_2 stream. Data collection could be carried out on two instruments:

- A Bruker APEX II DUO Kappa-CCD diffractometer equipped with an Oxford Cryosystem liquid N_2 device, using Cu-Kα radiation (λ = 1.54178 Å). The crystal-detector distance was 40mm. The cell parameters were determined (APEX3 software) from reflections taken from tree sets of 20 frames, each at 10s exposure. The structure was solved using the program SHELXT-2014;
- A Nonius Kappa-CCD diffractometer equipped with an Oxford Cryosystem liquid N_2 device, using Mo-Kα radiation (λ = 0.71073 Å). The crystal-detector distance was 36mm. The cell parameters were determined (Denzo software) from reflections taken from one set of 10 frames (1.0° steps in phi angle), each at 20s exposure. The structure was solved by Direct methods using the program SHELXS-2014.

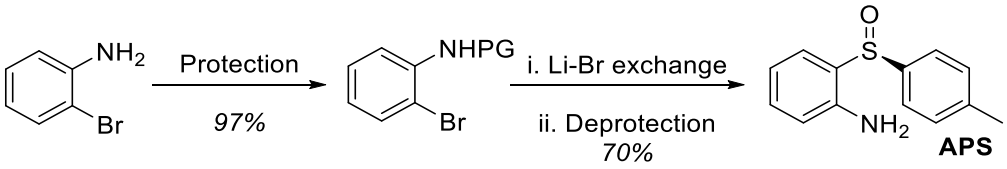
The refinement and all further calculations were carried out using SHELXL-2014. The hydrogen atom of the NH group was located from Fourier difference. The other H-atoms were included in calculated positions and treated as riding atoms using SHELXL default parameters. The non-H atoms were refined anisotropically, using weighted full-matrix least-squares on F^2. A semi-empirical absorption correction was applied using SADABS in APEX3; transmission factors: T_{min}/T_{max} = 0.5751/0.7528.

Computations were performed with methods of the Density Functional Theory, *i.e.* the Perdew-Burke-Ernzerhof (PBE) GGA functional[245] implemented in the Amsterdam Density Functional package[246] (ADF2013 version) and augmented with Grimme's DFT-D3(BJ) implementation of dispersion with a Becke-Johnson (BJ) damping function.[223,224] Within the PBE scheme, electron correlation was treated within the local density approximation (LDA) in the PW92 [247] parametrization. Unless otherwise stated all computations were carried out using scalar relativistic corrections within the Zeroth Order Regular Approximation for relativistic effects[248–250] with ad hoc all-electron (abbr. ae) polarized triple-ζ (TZP) Slater type basis sets. Geometry optimizations by energy gradient minimization were carried out in all cases with grid accuracy comprised between 4.5 and 7.5, an energy gradient convergence criterion of 10^{-3} au and a tight to very tight SCF convergence criterion. Counterpoise correction for basis set superposition error (BSSE) was neglected throughout this study. Vibrational modes were analytically computed to verify that the optimized geometries were related to energy minima: statistical thermodynamic data at 298.15 K were extracted for further determination of enthalpies and variations of Gibbs

free enthalpies by conventional methods. The ground state geometries were computed at the ZORA-PBE-D3(BJ)/ae-TZP level and their minimum energy nature confirmed by the absence of any imaginary frequency above 50 cm^{-1} in their computed vibrational modes. Natural population analyses (NPA) as well as Wiberg indice determination were performed with geometries of models relaxed at the ZORA-PBE-D3(BJ) level using all electron TZP basis sets with the GENNBO 6.0 module of ADF. Representations of molecular structures and isosurfaces were produced with ADFview 2013.

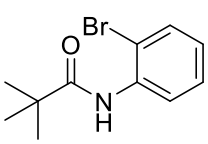
II.7.ii. Optimization of the directing group synthesis

Pathway A to access (S)-2-(*p*-tolylsulfinyl)aniline APS



***N*-pivaloyl-2-bromoaniline**

To a stirred solution of 2-bromoaniline (2.6 mL, 22.9 mmol, 1 equiv.) and triethylamine (3.5 mL, 25.2 mmol, 1.1 equiv.) in 20 mL of anhydrous DCM was added dropwise pivaloyl chloride (3 mL, 24.4 mmol, 1.05 equiv.) while maintaining the internal temperature below 10°C. The mixture was stirred 2h at room temperature. 1M HCl solution (20 mL) was added. The organic layer was extracted, washed with sat. $NaHCO_3$ solution (30 mL), brine (30 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure. Petroleum ether was added and the residue was allowed to crystallize at 0°C. Crystals were filtered off and dried *in vacuo* to afford the title compound (5.67 g, 97%) as white needles.

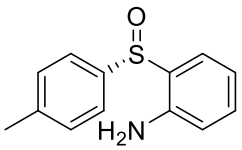


^{1}H NMR (400 MHz, $CDCl_3$): 8.38 (1H, dd, J=8.3, 1.7 Hz), 7.99 (1H, br, N*H*), 7.51 (1H, dd, J=7.9, 1.6 Hz), 7.25-7.32 (1H, m), 6.94 (1H, td, J=7.8, 1.7 Hz), 1.33 (9H, s, C(CH_3)$_3$); other data match the described ones.

(S)-2-(*p*-tolylsulfinyl)aniline APS (from 2'-bromo-pivaloyl-protected aniline)

N-pivaloyl-2-bromoaniline (3.16 g, 12.36 mmol, 1 equiv.) was dissolved in 50 mL of freshly distilled THF and cooled to -78°C. To the resulting solution was added dropwise *n*-BuLi (17 mL, 1.6 M in hexane, 27.2 mmol, 2.2 equiv.) while maintaining the temperature below -65°C. The resulting pale yellow mixture was stirred 1h at -78°C. Then, a solution of compound **2** (4.73 g,

16.06 mmol, 1.3 equiv.) in 20 mL of freshly distilled THF was added slowly to the previous mixture, which was allowed to stir 30 min at -78°C. MeOH (few drops) was added to the mixture. After slow warming to room temperature, saturated NH_4Cl solution (50 mL) was added and the mixture was extracted with EtOAc (30 mL), then washed with brine (20 mL), dried (Na_2SO_4), filtered off and evaporated *in vacuo*. The crude was dissolved in 20 mL of ethanol and NaOH solution (10 M) was added. The mixture was stirred overnight at 80°C. EtOH was evaporated *in vacuo*. Then, Et_2O (40 mL) was added. The organic layer was extracted, washed with brine (20 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure. The crude product can be used as such for the next step or purified by a short column chromatography on silica gel with CyHex/EtOAc (8:2) to afford the title compound (2,01 g, 70%) as a white solid.



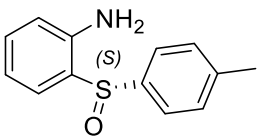
^{1}H NMR (400 MHz, $CDCl_3$): 7.39-7.47 (3H, m), 7.18-7.26 (3H, m), 6.75 (1H, td, J=7.6, 1.1 Hz), 6.57 (1H, d, J=8.2 Hz), 4.89 (2H, br s, N*H*$_2$), 2.35 (3H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 147.69, 140.85, 140.28, 132.99, 129.81, 128.48, 124.94, 124.02, 111.75, 111.42, 21.51; FT-IR (cm^{-1}): 3421 (br, *N*H), 3328 (br, *N*H), 3214 (br, *N*H), 3053 (w), 2921 (w), 1907 (w), 1618 (s), 1593 (s), 1481 (s), 1451 (s), 1318 (m), 1079 (m), 1007 (s), 807 (s), 747 (s), 619 (m), 537 (s); MP: 112°C; HRMS (ESI-TOF): m/z calcd for $C_{13}H_{14}NOS^+$: 232.0791, found: 232.0816; $[\alpha]_D^{20}$= +40.4° (c=1.10, $CHCl_3$); EA: calcd for $C_{13}H_{13}NOS$: C 67.50, H 5.67, N 6.06, found: C 67.55, H 5.70, N 6.06; R_f (CyHex/EtOAc 3:2): 0.40; R_t (min, IC, Hex/IPA 80/20, 0.5 mL/min): 64.58 (99.5%), 79.57 (0.5%).

(S)-2-(*p*-tolylsulfinyl)aniline APS (from 2'-bromoacetanilide)

A stirred solution of 2-bromo-*N*-acetanilide (5g, 23.36 mmol, 1 equiv.) in 100 mL of anhydrous THF was cooled to -78 °C, before dropwise addition of *n*-butyllithium (30 mL, 1.6 M in hexane, 48 mmol, 2.05 equiv.). The resulting yellow mixture was stirred at -78 °C during 1h, before slow addition of a solution of (-)-Menthyl (*S*)-*p*-toluenesulfinate (14g, 47.55 mmol, 2 equiv.) in 50 mL of anhydrous THF. Then, the resulting mixture was further stirred 2h at -78 °C. MeOH (few drops) was added. After warming up to 0°C, sat. ammonium chloride solution (50 mL) and diethyl ether (50 mL) were added. The organic layer was washed with brine, dried (Na_2SO_4), filtered off and evaporated under reduced pressure.

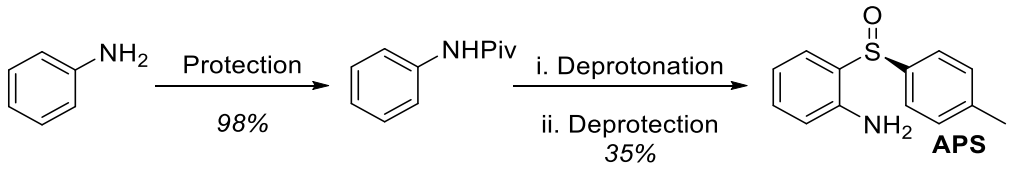
The crude was directly taken up and dissolved in 100 mL of a 1:1 mixture of ethanol and water. Potassium hydroxide (10g, 178.2 mmol, excess) was added. The resulting mixture was stirred at 90 °C during 2h (monitored by GCMS). After cooling down to room temperature, solvents were removed under reduced pressure. Diethyl ether (50 mL) and water (50 mL) were added. The

organic layer was extracted, washed with brine (10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure. Column chromatography on silica gel with CyHex/EtOAc (9:1) afforded the title product as a yellow oil (4.5 g, 83%).



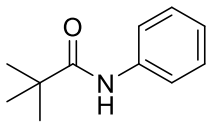
^{1}H NMR (400 MHz, $CDCl_3$): 7.44 (2H, d, J=8.3 Hz), 7.41 (1H, dd, J=7.7, 1.5 Hz), 7.17-7.25 (3H, m), 6.74 (1H, td, =7.4, 1.1 Hz), 6.57 (1H, dd, J=8.2, 1.0 Hz), 4.89 (1H, br s, N*H*), 2.34 (3H, s, PhC*H*$_3$) ; R_t (min, IC, Hex/iPrOH, 80/20, 0.5 mL/min): 64.50 (99%), 79.66 (1%); other data match the reported ones.

Pathway B to access (S)-2-(*p*-tolylsulfinyl)aniline APS



***N*-pivaloylaniline**

To a cold-stirred solution of aniline (5 mL, 54.83 mmol, 1 equiv.) and triethylamine (8 mL, 57.56 mmol, 1.05 equiv.) in 20 mL of anhydrous DCM was added dropwise pivaloyl chloride (7 mL, 56.89 mmol, 1.04 equiv.) while maintaining the internal temperature below 5°C. The mixture was stirred overnight at room temperature. 1M HCl solution (30 mL) was added. The organic layer was extracted, washed with sat. $NaHCO_3$ solution (30 mL), brine (30 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure. Petroleum ether was added and the residue was allowed to crystallize at 0°C. Crystals were filtered off and dried *in vacuo* to afford the title compound (9.48 g, 98%) as pale white needles.

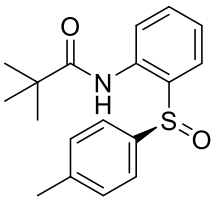


^{1}H NMR (400 MHz, $CDCl_3$): 7.51 (2H, d, J=8.2 Hz), 7.30 (2H, d, J=8.0 Hz), 7.08 (1H, t, J=7.4 Hz), 1.30 (9H, s, C(C*H*$_3$)$_3$); other data match the described ones.

***N*-pivaloyl-(*S*)-2-(*p*-tolylsulfinyl)aniline**

To a stirred solution of *N*-pivaloylaniline (250 mg, 1.41 mmol, 1 equiv.) in 10 mL of anhydrous THF and at 0°C was added dropwise *n*-BuLi (2 mL, 1.6 M in hexane, 3.2 mmol, 2.3 equiv.) . The resulting yellow mixture was stirred at 0°C during 2h and then cooled to -78°C. A solution of compound **2** (550 mg, 1.87 mmol, 1.3 equiv.) in 5 mL of anhydrous THF was then added dropwise to the previous mixture, which was stirred 2h at -78°C. MeOH (few drops) was added.

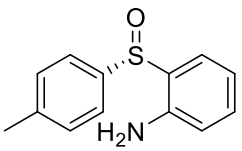
The mixture was allowed to warm to room temperature and NH_4Cl sat. solution (20 mL) and EtOAc (20 mL) were added. The organic layer was extracted, washed with brine (15 mL), dried (Na_2SO_4), filtered off and evaporated in vacuo. The crude was purified by flash chromatography with CyHex/EtOAc (95:5) to get the title compound (174 mg, 39 %) as a white solid.



^{1}H NMR (400 MHz, $CDCl_3$): 10.33 (1H, br, N*H*), 8.52 (1H, d, J=8.3 Hz), 7.44-7.50 (2H, m), 7.33 (2H, d, J=8.2 Hz), 7.21 (2H, d, J=8.0 Hz), 7.13 (1H, td, J=7.6, 1.1 Hz), 2.34 (3H, s, PhC*H*$_3$), 1.17 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 177.72, 141.54, 141.06, 140.16, 133.23, 130.10, 128.21, 127.55, 125.04, 123.02, 123.00, 40.17, 27.57, 21.46; FT-IR (cm^{-1}): 3254 (w), 2965 (m), 2870 (w), 1688 (s), 1584 (s), 1533 (s), 1433 (s), 1300 (s), 1162 (s), 1021 (s), 1010 (s), 818 (s), 760 (s), 534 (s); HRMS (ESI-TOF): m/z calcd for $C_{18}H_{22}NO_2S^+$: 316.1366, found: 316.1399; $[\alpha]_D^{20}$= +25.0° (c=0.5, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.45.

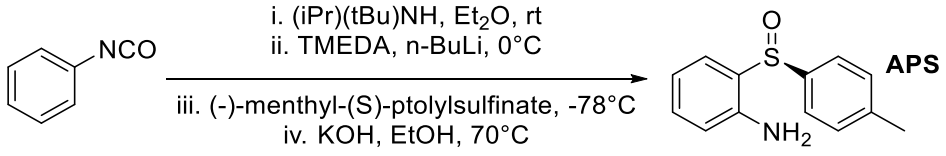
(S)-2-(*p*-tolylsulfinyl)aniline APS

To a stirred solution of *N*-pivaloyl-(*S*)-2-(*p*-tolylsulfinyl)aniline (150 mg, 0.475 mmol, 1 equiv.) in 5 mL of EtOH was added 5 mL of 1M KOH solution. The resulting mixture was stirred at reflux overnight. EtOH was evaporated *in vacuo*. Then, DCM (15 mL) was added. The organic layer was extracted, washed with brine (10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure to get the title compound as a thick white solid (98 mg, 89%).



^{1}H NMR (400 MHz, $CDCl_3$): 7.39-7.47 (3H, m), 7.18-7.26 (3H, m), 6.75 (1H, td, J=7.6, 1.1 Hz), 6.57 (1H, d, J=8.2 Hz), 4.89 (2H, br s, N*H*$_2$), 2.35 (3H, s, PhC*H*$_3$); other data match the described ones; R_t (min, IC, Hex/IPA 80/20, 0.5 mL/min): 64.55 (99.5%), 79.46 (0.5%).

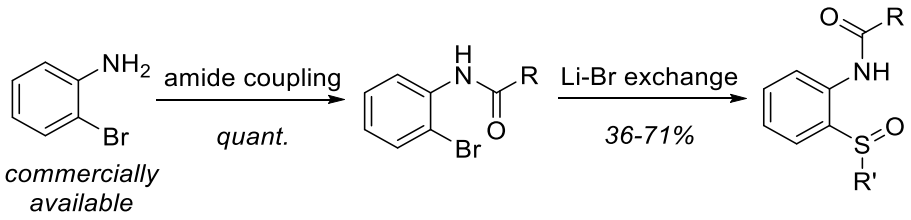
<u>Pathway C to access (*S*)-2-(*p*-tolylsulfinyl)aniline APS</u>[202]



To a stirred solution of phenyl isocyanate (100 µL, 0.92 mmol, 1 equiv.) in 5 mL of anhydrous Et_2O was added *N-tert*-butyl-isopropyl-amine (160 µL, 1.01 mmol, 1.1 equiv.). The resulting clear solution was stirred at room temperature during 3h, until all the starting material was consumed. Then, it was cooled to 0°C, TMEDA (300 µL, 1.99 mmol, 2.2 equiv.) was added,

followed by dropwise addition of *n*-BuLi (1.2 mL, 1.6 M in hexane, 1.92 mmol, 2.1 equiv.). The resulting mixture was stirred at 0°C during 3h. Then, the mixture was cooled to -78°C and a solution of compound **2** (406 mg, 1.38 mmol, 1.5 equiv.) in 2 mL of anhydrous Et_2O was added slowly to the previous mixture, which was allowed to stir at -78°C during 2h. Then, 4 mL of EtOH were added and the mixture was allowed to warm to room temperature and stirred 1h. Solvent were evaporated *in vacuo*. The yellow crude was dissolved in 10 mL of a 1:1 mixture of H_2O/EtOH. KOH (515 mg, 9.19 mmol, 10 equiv.) was added and the mixture was stirred under vigorous stirring at 80°C overnight. LCMS analysis showed aniline and only traces of desired product.

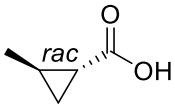
Pathway D to access functionalized sulfinylalkylcarboxamide



Peptidic coupling followed by usual lithium/halogen exchange also allowed efficient access to different substrates.

II.7.iii. Substrate syntheses

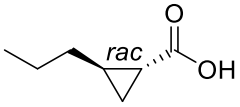
***trans* 2-methylcyclopropane-1-carboxylic acid**



This compound was prepared according to the literature procedure.[47]

^{1}H NMR (400 MHz, $CDCl_3$): 11.5 (1H, br s, CO_2H), 1.38 (1H, m), 1.26 (1H, ddd, J=8.0, 4.8, 4.1 Hz), 1.05 (3H, d, J=6.0 Hz, CH_3), 1.16 (1H, ddd, J=8.5, 4.3, 4.2 Hz), 0.68 (1H, ddd, J=8.1, 6.5, 4.1 Hz); other data match the described ones.

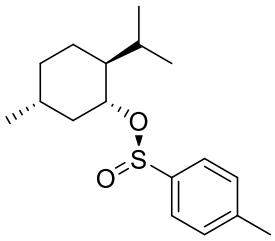
***trans* 2-propylcyclopropane-1-carboxylic acid**



This compound was prepared according to the literature procedure.[251]

^{1}H NMR (400 MHz, $CDCl_3$): 9.17 (1H, br s, CO_2H), 1.13-1.52 (6H, m), 0.69-0.99 (5H, m); other data match the described ones.

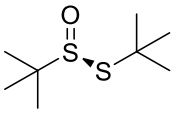
(*S*)-((1*R*,2*S*,5*R*)-5-methyl-2-(propan-2-yl)cyclohexyl 4-methylbenzene-1-sulfinate) S



This compound was prepared according to the literature procedure.[252]

^{1}H NMR (400 MHz, $CDCl_3$): 7.58 (2H, d, J=8.2 Hz), 7.30 (2H, d, J=8.2 Hz), 4.10 (1H, td, J=10.7, 4.6 Hz), 2.39 (3H, s, PhC*H*$_3$), 2.22-2.30 (1H, m), 2.05-2.16 (1H, m), 1.62-1.70 (2H, m), 1.40-1.53 (1H, m), 1.29-1.38 (1H, m), 1.15-1.26 (1H, m), 0.96-1.08 (1H, m), 0.94 (3H, d, J=6.6 Hz), 0.77-0.91 (4H, m), 0.69 (3H, d, J=6.9 Hz); $[\alpha]_D^{20}$= -199.0° (c=1.00, $(CH_3)_2CO$); other data match the described ones.

2-[(S)-tert-butylsulfinyl]sulfanyl-2-methyl-propane T

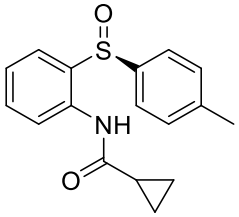


This compound was prepared according to the literature procedure.[105,253]

^{1}H NMR (400 MHz, $CDCl_3$): 1.52 (9H, s, S(O)C(C*H*$_3$)$_3$), 1.34 (9H, s, SC(C*H*$_3$)$_3$); $[\alpha]_D^{20}$= -148.0° (c=0.51, CH_2Cl_2); other data match the described ones.

(*S*)-*N*-(2-(*p*-tolylsulfinyl)phenyl)cyclopropanecarboxamide II-1a

To a stirred solution of *N*-(2-bromophenyl)cyclopropanecarboxamide (3.1 g, 12.91 mmol, 1 equiv.) in 40 mL of freshly distilled THF was added dropwise and at -78°C *n*-BuLi (18 mL, 1.6 M in hexane, 28.6 mmol, 2.2 equiv.). The resulting mixture was stirred at -78°C during 1h, followed by slow addition of a solution of **S** (4.6 g, 15.6 mmol, 1.2 equiv.) in 30 mL of freshly distilled THF. The resulting yellow mixture was stirred 30min at -78°C. Methanol (few drops) was added to the mixture. After slow warming to room temperature, saturated NH_4Cl solution (50 mL) was added and the mixture was extracted with EtOAc (30 mL), then washed with brine (20 mL), dried (Na_2SO_4), filtered off and evaporated *in vacuo*. To the crude was added Et_2O. The precipitate was collected, washed with cold Et_2O and dried to afford the title compound as a white solid (2.73 g, 71%).

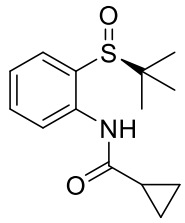


^{1}H NMR (400 MHz, CDCl3): 10.37 (1H, br s, N*H*), 8.30 (1H, d, J=8.4 Hz), 7.50 (1H, d, J=7.7 Hz), 7.37-7.48 (3H, m), 7.23 (2H, d, J=8.1 Hz), 7.12 (1H, t, J=7.5 Hz), 2.35 (3H, s, PhC*H*$_3$), 1.46-1.54 (1H, m), 0.97-1.04 (1H, m), 0.74-0.88 (3H, m); ^{13}C NMR (100 MHz, CDCl3): 172.32 (*C*=O), 141.54, 140.58, 139.79, 133.12, 130.16, 127.82, 124.58, 123.22, 123.19, 21.52 (*C*H_3), 16.22, 8.17, 8.11; FT-IR (cm-1): 3250 (w), 3015 (m), 1690 (s, C=O), 1585 (s), 1525 (s), 1435 (s), 1392 (s), 1298 (s), 1176 (s), 1021 (s), 1011 (s), 954 (s), 809 (s), 758 (s), 547 (s), 531 (s), 493 (m); MP: 151°C;

HRMS (ESI-TOF): m/z calcd for $C_{17}H_{18}NO_2S^+$: 300.1053, found: 300.1051; EA: calcd for $C_{17}H_{17}NO_2S$: C 68.20, H 5.72, N 4.68, found: C 68.12, H 5.73, N 4.73; $[\alpha]_D^{20}$= +59.8° (c=0.98, $CHCl_3$); R_f (CyHex/EtOAc 3:2): 0.47; R_t (min, ODH, Hex/iPrOH 80/20, 0.5 mL/min): 13.19 (<1%), 15.479 min (>99%).

(*S*)-*N*-(2-(*tert*-butylsulfinyl)phenyl)cyclopropanecarboxamide II-1b

To a stirred solution of *N*-(2-bromophenyl)cyclopropanecarboxamide (1.13 g, 4.72 mmol, 1 equiv.) in 15 mL of freshly distilled THF was added dropwise and at -78°C *n*-BuLi (6.5 mL, 1.6 M in hexane, 10.3 mmol, 2.2 equiv.). The resulting mixture was stirred at -78°C during 1h, followed by slow addition of a solution of **T** (1.1 g, 5.66 mmol, 1.2 equiv.) in 15 mL of freshly distilled THF. The resulting yellow mixture was stirred 2h at -78°C. Methanol (few drops) was added to the mixture. After slow warming to room temperature, saturated NH_4Cl solution (50 mL) was added and the mixture was extracted with EtOAc (30 mL), then washed with brine (20 mL), dried (Na_2SO_4), filtered off and evaporated *in vacuo*. To the crude was added Et_2O. The precipitate was collected, washed with cold Et_2O and dried to afford the title compound as a white solid (456 mg, 36%).

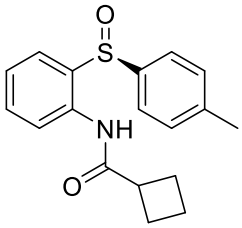


^{1}H NMR (400 MHz, CDCl3): 11.18 (1H, br s, N*H*), 8.47 (1H, dd, J=8.5, 1.0 Hz), 7.42 (1H, ddd, J=8.5, 6.9, 1.7 Hz), 7.01-7.09 (2H, m), 1.52-1.59 (1H, m), 1.27 (9H, s, S(O)C(C*H*$_3$)$_3$), 0.96-1.08 (2H, m), 0.79-0.84 (2H, m); ^{13}C NMR (100 MHz, CDCl3): 172.47 (C=O), 142.76, 132.43, 128.75, 122.79, 121.13, 120.78, 59.19, 23.61, 16.40, 8.10, 8.07; FT-IR (cm-1): 3169 (w), 3101 (w), 3012 (w), 2979 (w), 1688 (s, C=O), 1585 (s), 1521 (br s), 1433 (s), 1390 (s), 1295 (s), 1197 (m), 1173 (s), 1062 (m), 1034 (m, S=O), 1007 (s), 953 (s), 823 (m), 758 (s), 669 (w), 524 (m); MP: 147°C; HRMS (ESI-TOF): m/z calcd for $C_{14}H_{19}NNaO_2S^+$: 288.1029, found: 288.1060; $[\alpha]_D^{20}$= -98.2° (c=0.68, $CHCl_3$); R_f (CyHex/EtOAc 3:2): 0.42; R_t (min, ODH, Hex/iPrOH 80/20, 0.5 mL/min): 9.78 (<1%), 13.18 (>99%).

(*S*)-*N*-(2-(*p*-tolylsulfinyl)phenyl)cyclobutanecarboxamide II-1c

To a stirred solution of *N*-(2-bromophenyl)cyclobutanecarboxamide (1.31 g, 5.14 mmol, 1 equiv.) in 20 mL of freshly distilled THF was added dropwise and at -78°C *n*-BuLi (7.0 mL, 1.6 M in hexane, 11.31 mmol, 2.2 equiv.). The resulting mixture was stirred at -78°C during 1h, followed by slow addition of a solution of **S** (1.97 g, 6.68 mmol, 1.3 equiv.) in 10 mL of freshly distilled THF. The resulting yellow mixture was stirred 1h at -78°C. Methanol (few drops) was added to the mixture. After slow warming to room temperature, saturated NH_4Cl solution (50 mL) was

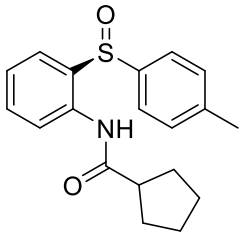
added and the mixture was extracted with EtOAc (30 mL), then washed with brine (20 mL), dried (Na_2SO_4), filtered off and evaporated *in vacuo*. To the crude was added Et_2O. The precipitate was collected, washed with cold Et_2O and dried to afford the title compound as a white solid (1.12 g, 70%).



^{1}H NMR ($CDCl_3$, 400 MHz): 10.06 (1H, br s, N*H*), 8.42 (1H, d, J=8.4 Hz), 7.50 (1H, dd, J=7.8, 1.4 Hz), 7.42-7.47 (1H, m), 7.33 (2H, d, J=8.2 Hz), 7.21 (2H, d, J=8.2 Hz), 7.12 (1H, td, J=7.6, 1.1 Hz), 3.07 (1H, quintd, J=8.6, 1.0 Hz), 2.24-2.36 (4H, m), 2.10-2.21 (3H, m), 1.91-2.02 (1H, m), 1.76-1.96 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): 173.72, 141.50, 140.68, 139.85, 133.21, 130.10, 127.99, 127.92, 124.60, 123.14, 122.93, 41.30, 25.57, 25.18, 21.48, 18.21; FT-IR (cm^{-1}): 3245 (w), 2982 (m), 2864 (w), 1688 (s), 1583 (s), 1525 (br s), 1022 (s), 1011 (s), 727 (s), 550 (s), 461 (m); MP: 108 °C; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{19}NNaO_2S^+$: 336.1029, found: 336.0998; $[\alpha]_D^{20}$= +26.1° (c=0.50, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.55.

(*S*)-*N*-(2-(*p*-tolylsulfinyl)phenyl)cyclopentanecarboxamide II-1d

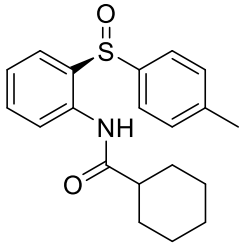
To a stirred solution of cyclopentanecarboxylic acid (275 mg, 2.14 mmol, 1 equiv.), **APS** (500 mg, 2.16 mmol, 1 equiv., prepared according to Pathway **C**) and 4-(dimethylamino)pyridine (660 mg, 5.40 mmol, 2.5 equiv.) in 10 mL of anhydrous DCM was added EDC.HCl (622 mg, 3.24 mmol, 1.5 equiv.) portionwise at room temperature. The resulting mixture was stirred 4 h at room temperature. Water (10 mL) was added. The organic layer was extracted, washed with brine (20 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure. The crude was purified by a short column chromatography on silica gel with CyHex/EtOAc (9:1) to afford the title compound (620 mg, 84%) as a clear oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.13 (1H, br s, NH), 8.37 (1H, d, J=8.4 Hz), 7.30-7.47 (4H, m), 7.19 (2H, d, J=8.2 Hz), 7.04 (1H, td, J=7.5, 1.1 Hz), 2.52-2.59 (1H, m), 2.28 (3H, s, $PhCH_3$), 1.71-1.78 (1H, m), 1.51-1.68 (7H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 174.9, 141.4, 140.6, 139.8, 132.9, 130.1, 127.9, 124.6, 122.9, 122.8, 47.3, 30.4, 30.2, 25.9, 21.3; FT-IR (cm^{-1}): 3240 (w), 2940 (m), 1690 (s), 1024 (s); MP: 147 °C; HRMS (ESI-TOF): m/z calcd for $C_{19}H_{21}NNaO_2S^+$: 350.1191; found: 350.1187; $[\alpha]_D^{20}$= +11.0° (c=1.0, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.6.

(*S*)-*N*-(2-(*p*-tolylsulfinyl)phenyl)cyclohexanecarboxamide II-1e

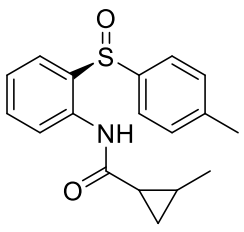
To a stirred solution of cyclohexanecarboxylic acid (277 mg, 2.16 mmol, 1 equiv.), **APS** (500 mg, 2.16 mmol, 1 equiv., prepared according to Pathway **C**) and 4-(dimethylamino)pyridine (660 mg, 5.40 mmol, 2.5 equiv.) in 10 mL of anhydrous DCM was added EDC.HCl (622 mg, 3.24 mmol, 1.5 equiv.) portionwise at room temperature. The resulting mixture was stirred 4 h at room temperature. Water (10 mL) was added. The organic layer was extracted, washed with brine (20 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure. The crude was purified by a short column chromatography on silica gel with CyHex/EtOAc (9:1) to afford the title compound (656 mg, 89%) as a clear oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.11 (1H, br s, NH), 8.43 (1H, dd, J=8.3, 1.1 Hz), 7.42-7.51 (2H, m), 7.35 (2H, d, J=8.3 Hz), 7.21 (2H, d, J=8.3 Hz), 7.12 (1H, td, J=7.6, 1.3 Hz), 2.34 (3H, s, $PhCH_3$), 2.12 (1H, tt, J=11.5, 3.5 Hz), 1.83-1.91 (1H, m), 1.72-1.81 (2H, m), 1.63-1.69 (2H, m), 1.13-1.45 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 174.80, 141.37, 139.80, 133.03, 129.91, 127.90, 127.68, 124.55, 122.94, 122.89, 46.84, 29.38, 29.18, 25.71, 25.64, 25.61, 21.28; FT-IR (cm^{-1}) :3245 (w), 1687 (s), 1033 (s); HRMS (ESI-TOF): m/z calcd for $C_{20}H_{24}NO_2S^+$: 342.1522, found: 342.1525; $[\alpha]_D^{20}$= +76.1° (c=0.80, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.7.

***trans*-2-methyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-1f**

To a stirred solution of *trans* 2-methylcyclopropane-1-carboxylic acid (216 mg, 2.16 mmol, 1 equiv.), **APS** (500 mg, 2.16 mmol, 1 equiv., prepared according to Pathway **C**) and 4-(dimethylamino)pyridine (660 mg, 5.40 mmol, 2.5 equiv.) in 10 mL of anhydrous DCM was added EDC.HCl (622 mg, 3.24 mmol, 1.5 equiv.) portionwise at room temperature. The resulting mixture was stirred 4 h at room temperature. Water (10 mL) was added. The organic layer was extracted, washed with brine (20 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure. The crude was purified by a short column chromatography on silica gel with CyHex/EtOAc (92:8) to afford the title compound (512 mg, 76%) as a thick yellow solid. ^{1}H and ^{13}C NMRs are given for a racemic mixture of ***trans*-(*S*)-II-1f**.

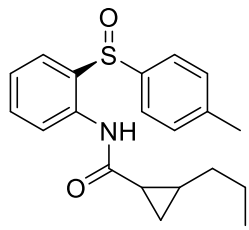


^{1}H NMR (400 MHz, $CDCl_3$): 10.16-10.44 (1H, br m, NH), 8.24-8.32 (1H, m), 7.47-7.53 (1H, m), 7.37-7.45 (3H, m), 7.19-7.24 (2H, m), 7.10 (1H, td, J=7.6, 1.0 Hz), 2.32-2.36 (3H, m), 1.33-1.42 (0.6H, m), 1.15-1.29 (1.8H, m), 1.09-1.13 (3H, m), 0.99-1.06 (0.6H, m), 0.57-0.68 (1H, m); ^{13}C NMR (100 MHz,

$CDCl_3$): 172.06, 171.97, 141.52, 141.50, 140.63, 140.55, 139.77, 133.14, 133.09, 130.13, 130.06, 127.85, 127.79, 124.56, 124.55, 123.14, 123.08, 24.96, 24.78, 21.50, 18.27, 18.08, 17.11, 16.97, 16.66, 16.56; FT-IR (cm^{-1}): 3251 (w), 2956 (w), 1688 (s), 1585 (s), 1529 (br s), 1436 (s), 1181 (s), 1022 (s, S=O), 1011 (s), 809 (m), 759 (s), 547 (m), 532 (m); HRMS (ESI-TOF): m/z calcd for $C_{18}H_{20}NO_2S^+$: 314.1209, found: 314.1217; R_f (CyHex/EtOAc, 3:2): 0.50.

trans-2-propyl-_N_-(2-((_S_)-_p_-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-1g

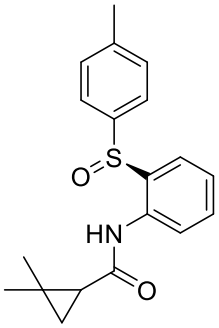
To a stirred solution of *trans* 2-propylcyclopropane-1-carboxylic acid (110 mg, 0.86 mmol, 1 equiv.), **APS** (199 mg, 0.86 mmol, 1 equiv., prepared according to Pathway **C**) and 4-(dimethylamino)pyridine (262 mg, 2.15 mmol, 2.5 equiv.) in 6 mL of anhydrous DCM was added EDC.HCl (247 mg, 1.29 mmol, 1.5 equiv.) portionwise at room temperature. The resulting mixture was stirred 18 h at room temperature. Water (10 mL) was added. The organic layer was extracted, washed with brine (20 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure. The crude was purified by a short column chromatography on silica gel with CyHex/EtOAc (95:5) to afford the title compound (210 mg, 72%, mixed with 5% of impurity resulting of the preparation of the carboxylic acid) as a thick yellow solid. ^1H and ^{13}C NMRs are given for a racemic mixture of ***trans*-(*S*)-II-1g**.



^1H NMR (400 MHz, $CDCl_3$): 10.22-10.50 (1H, m), 8.25-8.39 (1H, m), 7.48-7.51 (1H, m), 7.36-7.46 (3H, m), 7.19-7.23 (2H, m), 7.10 (1H, tt, J=7.6, 1.2 Hz), 2.33-2.37 (3H, m), 0.98-1.46 (7H, m), 0.88-0.94 (3H, m), 0.59-0.71 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 172.17, 172.14, 141.50, 141.44, 140.71, 139.83, 133.14, 133.07, 130.12, 127.84, 127.77, 124.54, 123.17, 123.06, 122.94, 122.79, 35.46, 35.38, 23.78, 23.65, 22.66, 22.54, 22.52, 22.49, 21.48, 15.66, 15.31, 14.11, 14.05; FT-IR (cm^{-1}): 3251 (w), 2925 (m), 1688 (s), 1585 (s), 1530 (br s), 1436 (s), 1288 (s), 1178 (s), 1021 (s), 1011 (s), 808 (s), 757 (s), 546 (s), 531 (s); HRMS (ESI-TOF): m/z calcd for $C_{20}H_{23}NNaO_2S^+$: 364.1342, found: 364.1342; R_f (CyHex/EtOAc, 3:2): 0.55.

2,2-dimethyl-_N_-(2-((_S_)-_p_-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-1h

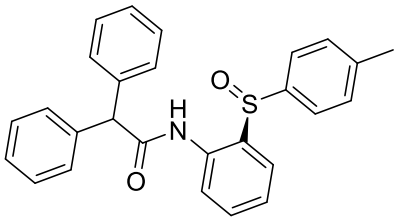
^1H and ^{13}C NMRs are given for a racemic mixture of ***trans*-(*S*)-II-1g**.



^{1}H NMR (400 MHz, $CDCl_3$): 10.18 (1H, m, N*H*), 8.32 (0.5H, d, J=8.2 Hz), 8.25 (0.5H, d, J=8.2 Hz), 7.27-7.76 (6H, m), 6.98-7.18 (2H, m), 2.29 (3H, s, PhC*H*$_3$), 1.32-1.38 (0.5H, m), 1.28 (0.5H, dd, J=7.8, 5.4 Hz), 0.79-1.20 (7H, m), 0.75 (1H, dd, J=7.8, 4.4 Hz), 0.70 (0.5H, dd, J=7.9, 4.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, given for one diastereomer): 171.25, 132.84, 127.74, 127.62, 123.87, 122.91, 122.90, 28.94, 22.32, 24.12, 15.40, 12.32; FT-IR (cm^{-1}): 3248 (br m, N-H), 1637 (s, C-O), 1020 (s, S-O); Rt (min, CHIRALPAK ® IA, Hex/iPrOH 80/20, 0.5 mL/min): 8.61 (0.3%), 9.45 (0.4 %), 14.20 (49.8 %), 15.64 (49.5 %) R_f (CyHex/EtOAc, 3:2): 0.6.

(*S*)-2,2-diphenyl-*N*-(2-(*p*-tolylsulfinyl)phenyl)acetamide II-1i

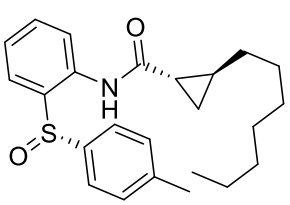
The title compound (169 mg, 13 %) was obtained as a beige solid.



^{1}H NMR (400 MHz, $CDCl_3$): 10.57 (1H, br s, N*H*), 8.49 (1H, d, J=8.4 Hz), 7.45-7.51 (2H, m), 7.24-7.41 (10H, m), 7.12 (2H, d, J=8.1 Hz), 7.02 (1H, td, J=7.6, 1.2 Hz), 4.95 (1H, s), 2.31 (3H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 170.59, 141.21, 139.51, 138.93, 138.85, 132.96, 130.07, 129.12, 129.00, 128.79, 128.77, 128.19, 127.62, 127.46, 127.38, 124.31, 123.55, 122.89, 60.35, 21.42; FT-IR (cm^{-1}): 1674 (s, C-O), 1042 (s, S-O); R_f (CyHex/EtOAc, 3:2): 0.7.

***trans*-2-hexyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-1j**

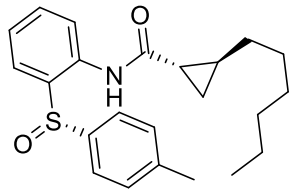
A solution of *trans* 2-hexylcyclopropane-1-carboxylic acid (644 mg, 3.78 mmol, 1.2 equiv.) and **APS** (729 mg, 3.15 mmol, 1 equiv.) were dissolved in 3 mL of anhydrous DMF, followed by addition of pyridine (700 µL, 8.66 mmol, 2.7 equiv.) and propylphosphonic anhydride (2.6 mL, 4.32 mmol, 1.4 equiv., 50% weight solution in DMF). The resulting mixture was stirred 18 h at room temperature. Brine (20 mL) and diethyl ether (20 mL) were added to the mixture and the phases were separated. The organic layer was washed with brine (2x 10 mL), sat. NaHCO3 sol. (3x 10 mL), 1M HCl sol. (3x 10 mL), brine (2x 10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure to give the title compound (1.2 g, 99%, mixed with around 5% of impurity coming from the cyclopropane) as a yellowish oil as an approximate 1:1 mixture of diastereomers.



^{1}H NMR (400 MHz, $CDCl_3$): 10.20-10.45 (1H, m, N*H*), 8.35 and 8.29 (1H, d, J=8.4 Hz), 7.47-7.52 (1H, m), 7.36-7.45 (3H, m), 7.22 (2H, d, J=8.4 Hz), 7.08-7.13 (1H, m), 2.34 (3H, s, PhC*H*$_3$), 0.98-1.39 (13H, m), 0.82-0.92 (3H, m), 0.58-0.70 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 172.18 and 172.15 (1C), 141.49 and 141.45 (1C), 140.73 and 140.62 (1C), 139.81 and 139.76 (1C), 133.11 and 133.08 (1C), 130.13, 127.78, 124.55, 123.21 and 123.07 (1C), 122.95 and 122.80 (1C), 33.45 and 33.30 (1C), 32.07 and 32.00 (1C), 29.35 and 29.33 (1C), 29.31 and 29.22 (1C), 23.80 and 23.70 (1C), 22.91 and 22.87 (1C), 22.83 and 22.73 (1C), 21.48, 15.76 and 15.41 (1C), 14.32 and 14.29 (1C); FT-IR (cm^{-1}): 1694 (s, C=O), 1025 (m, S=O); HRMS (ESI-TOF): m/z calcd for $C_{23}H_{30}NO_2S^+$: 384.1992, found: 384.1979.

trans-2-heptyl-_N_-(2-((_S_)-_p_-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-1k

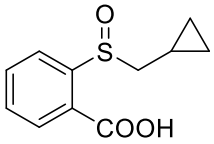
A solution of *trans* 2-heptylcyclopropane-1-carboxylic acid (779 mg, 4.23 mmol, 1.2 equiv.) and **APS** (800 mg, 3.46 mmol, 1 equiv.) were dissolved in 3 mL of anhydrous DMF, followed by addition of pyridine (750 µL, 9.32 mmol, 2.7 equiv.) and propylphosphonic anhydride (2.8 mL, 4.74 mmol, 1.4 equiv., 50% weight solution in DMF). The resulting mixture was stirred 18 h at room temperature. Brine (20 mL) and diethyl ether (20 mL) were added to the mixture and the phases were separated. The organic layer was washed with brine (2x 10 mL), sat. $NaHCO_3$ sol. (3x 10 mL), 1M HCl sol. (3x 10 mL), brine (2x 10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure to give the title compound (1.35 g, 98%) as a brownish oil as an approximate 1:1 mixture of diastereomers.



^{1}H NMR (400 MHz, $CDCl_3$): 10.22-10.46 (1H, m, N*H*), 8.35 and 8.29 (1H, d, J=8.4 Hz), 7.47-7.54 (1H, m), 7.37-7.46 (3H, m), 7.21 (2H, d, J=8.3 Hz), 7.07-7.13 (1H, m), 2.34 (3H, s, PhC*H*$_3$), 0.97-1.38 (15H, m), 0.82-0.92 (3H, m), 0.59-0.71 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 172.21 and 172.19 (1C), 141.52 and 141.49 (1C), 140.73 and 140.71 (1C), 140.63 and 140.61 (1C), 139.82 and 139.77 (1C), 133.13 and 133.10 (1C), 130.14, 127.80 and 127.79 (1C), 124.57, 123.24 and 123.10 (1C), 122.99 and 122.84 (1C), 33.47 and 33.32 (1C), 32.10 and 32.05 (1C), 29.63 and 29.54 (1C), 29.48, 29.41 and 29.39 (1C), 23.81 and 23.71 (1C), 22.94 and 22.92 (1C), 22.88 and 22.76 (1C), 21.50, 15.79 and 15.44 (1C), 14.32; FT-IR (cm^{-1}): 1691 (m, C=O), 1020 (m, S=O); HRMS (ESI-TOF): m/z calcd for $C_{24}H_{32}NO_2S^+$: 398.2148, found: 398.2131.

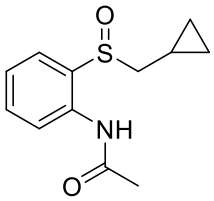
II.7.iv. Other bidentate directing groups

8-((cyclopropylmethyl)sulfinyl)quinoline



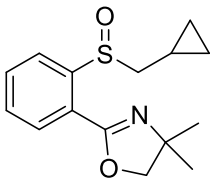
^{1}H NMR (400 MHz, $CDCl_3$): 8.75-8.91 (1H, m), 8.27 (1H, d, J=7.2 Hz), 8.21 (1H, d, J=8.3 Hz), 7.91 (1H, d, J=8.1 Hz), 7.72 (1H, t, J=7.7 Hz), 7.46 (1H, dd, J=8.3, 4.2 Hz), 3.23 (1H, dd, J=13.3, 7.7 Hz), 2.94 (1H, dd, J=13.4, 6.8 Hz), 1.23 (1H, tt, J=13.5, 6.2 Hz), 0.55-0.73 (1H, m), 0.29-0.50 (2H, m), -0.07-0.11 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 150.00, 144.07, 141.86, 136.41, 130.01, 128.05, 126.69, 121.94, 60.40, 5.25, 5.14, 4.11; FT-IR (cm^{-1}): 1024 (s, S-O).

2-((cyclopropylmethyl)sulfinyl)benzoic acid



^{1}H NMR (400 MHz, DMSO-*d6*): 7.92 (1H, d, J=7.8 Hz), 7.86 (1H, d, J=7.7 Hz), 7.71 (1H, t, J=7.1 Hz), 7.47 (1H, t, J=7.5 Hz), 2.71 (1H, dd, J=13.1, 8.3 Hz), 2.44 (1H, dd, J=13.1, 6.5 Hz), 0.88-1.08 (1H, m), 0.42 (1H, tt, J=8.8, 4.8 Hz), 0.33 (1H, tt, J=8.8, 4.9 Hz), 0.14-0.27 (1H, m), -0.04-0.03 (1H, m); ^{13}C NMR (100 MHz, DMSO-*d6*): 170.3, 144.9, 131.2, 131.1, 130.1, 127.4, 127.3, 66.4, 22.3, 7.4, 5.2; FT-IR (cm^{-1}): 3247 (br m, O-H), 1712 (s, C-O), 1034 (s, S-O).

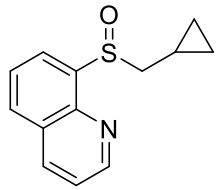
***N*-(2-((cyclopropylmethyl)sulfinyl)phenyl)acetamide**



^{1}H NMR (400 MHz, $CDCl_3$): 10.70 (1H, br s, NH), 8.48 (1H, d, J=8.4 Hz), 7.41-7.51 (1H, m), 7.21-7.31 (1H, m), 7.05-7.14 (1H, m), 3.09 (1H, dd, J=13.1, 7.2 Hz), 2.96 (1H, dd, J=13.1, 7.5 Hz), 2.19 (3H, s, C(O)CH3), 0.74-0.94 (1H, m), 0.51-0.73 (2H, m), 0.26-0.38 (1H, m), 0.14-0.23 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 170.5, 135.3, 133.6, 131.7, 127.2, 125.2, 122.2, 66.3, 24.5, 6.5, 5.1; FT-IR (cm^{-1}): 1684 (s, C-O), 1035 (s, S-O).

2-(2-((cyclopropylmethyl)sulfinyl)phenyl)-4,4-dimethyl-4,5-dihydrooxazole

^{1}H NMR (400 MHz, $CDCl_3$): 8.00 (1H, d, J=7.9 Hz), 7.65 (1H, d, J=7.7 Hz), 7.41-7.51 (1H, m), 7.29 (1H, d, J=7.5 Hz), 3.79-3.89 (2H, m), 2.90 (1H, dd, J=12.9, 8.6 Hz), 2.55 (1H, dd, J=12.9, 6.2 Hz),



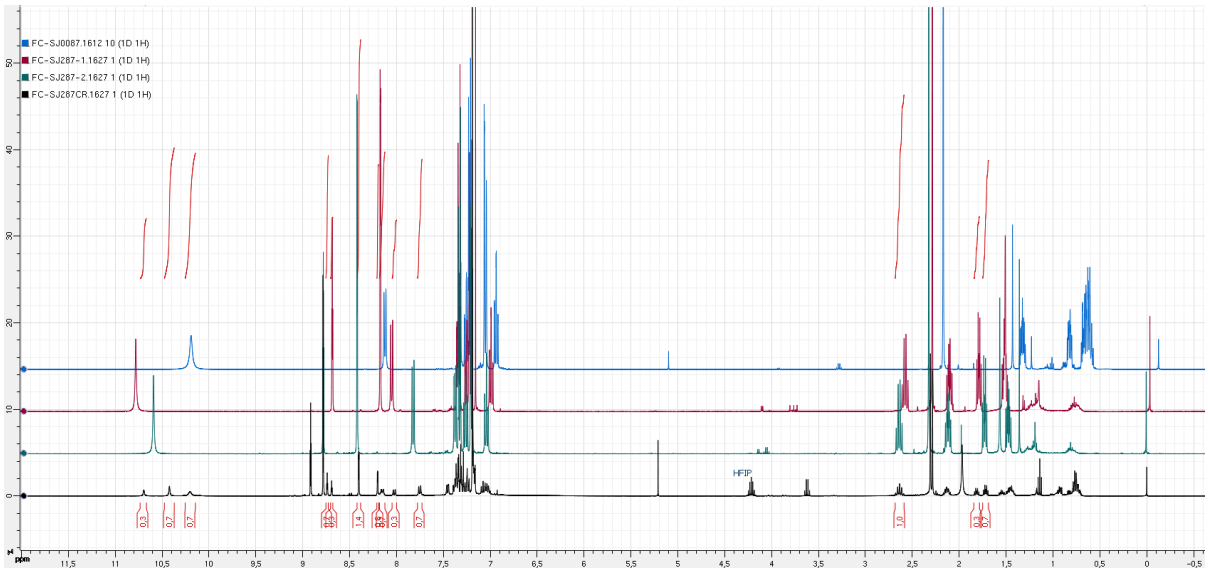
1.15 (6H, app d, J=5.8 Hz), 0.40-0.51 (2H, m), 0.32 (1H, td, J=5.4, 7.5 Hz), -0.02-0.21 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 158.47, 143.23, 131.32, 129.40, 127.49, 126.26, 78.07, 68.07, 66.32, 28.11, 6.21, 5.01; FT-IR (cm^{-1}): 1047 (s, S-O).

II.7.v. Determination of the diastereomeric ratio using crude ^{1}H NMR analysis

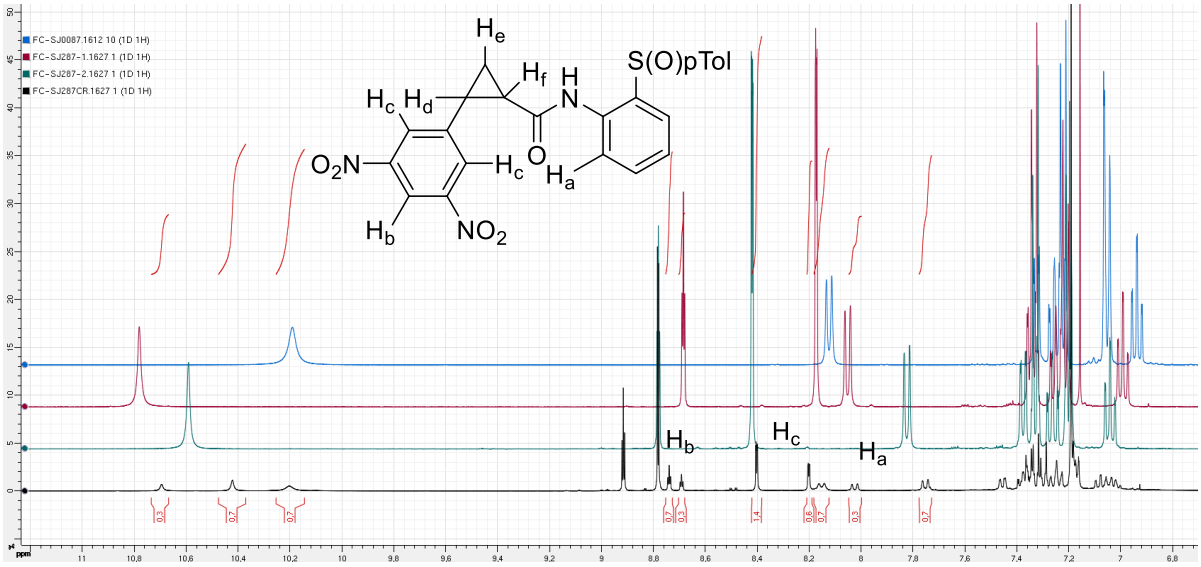
In each experiment, one characteristic proton for the substrate and each diastereomer of the product are distinguishable. This allows the determination of the diastereomeric ratio and conversion using the crude NMR.

Example of the coupling with 3,5-dinitroiodobenzene to afford **II-2lA** and **II-2lB**:

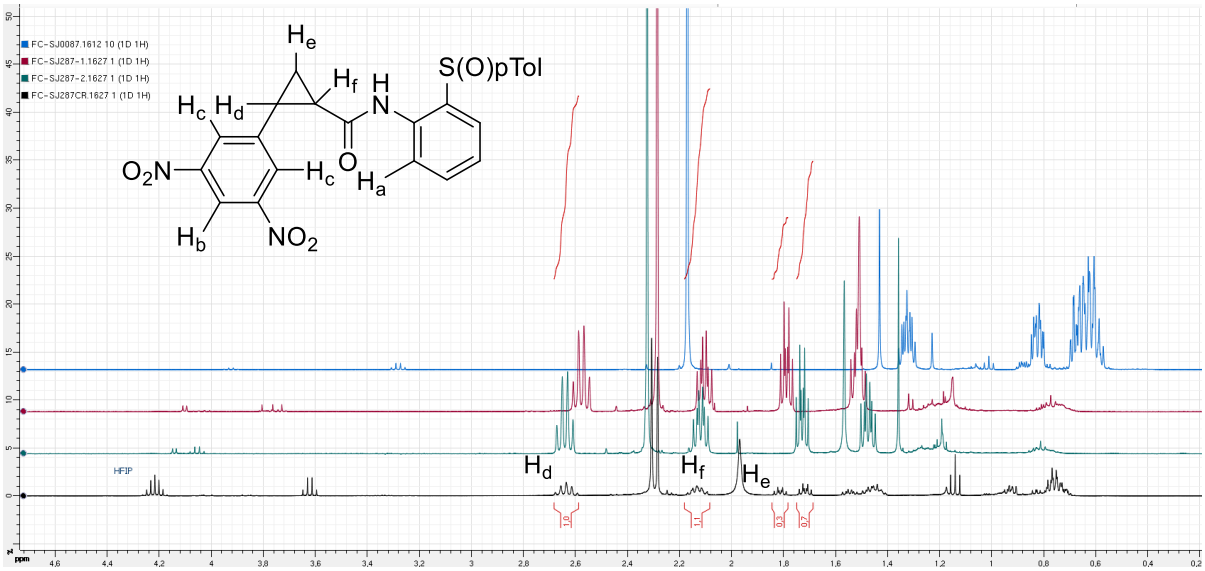
Using 3,5-dinitroiodobenzene as coupling partner afforded for example a crude NMR in which starting material is easily found (FC-SJ0087.1612, in blue in the spectra below) and distinct from the two products (FC-SJ287-1.1612, in red, minor diastereomer and FC-SJ287-2, in green, major diastereomer):



Especially in the aromatic region:



And in the aliphatic region:



According to the ^{1}H crude NMR, there is a 0.7/0.7/0.3 ratio between the starting material, the major diastereomer and the minor diastereomer, corresponding to approximatively 60% conversion and 70/30 diastereomeric ratio.

II.7.vi. Asymmetric C(sp^3)-H bond arylation

General procedure A for the coupling catalysis of unsubstituted cycloalkanes

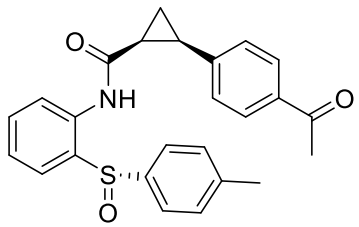
In a Schlenk were added cycloalkanecarboxamides (0.23 mmol, 1 equiv.), coupling partner (0.28 mmol, 1.2 equiv.), silver(I) acetate (86 mg, 0.52 mmol, 2.2 equiv.), sodium trifluoroacetate (17 mg, 0.12 mmol, 50 mol%) and palladium(II) acetate (2.6 mg, 0.012 mmol, 5 mol%). HFIP (2 mL) and water (0.2 mL) were then added and the mixture was stirred at 80°C during the appropriate time (typically between 8 and 18h) under air. The mixture was then allowed to cool to room temperature, diluted with EtOAc, filtered over celite and evaporated *in vacuo*. The crude was purified by column chromatography on silica gel with CyHex/EtOAc to get the two diastereomers of the title compound as pure enantiomers. Only are presented the analysis of pure compounds as in few examples the minor diastereomer comes was isolated as a mixture with remaining starting material. In those cases, the estimation of the yield is based on the ^{1}H NMR of the mixture.

General procedure B for the arylation of substituted cyclopropanes

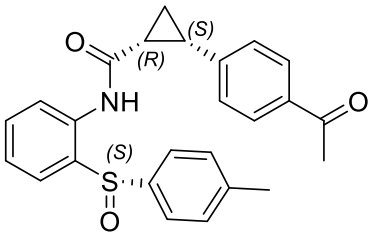
In a Schlenk and under air were added the substituted cyclopropanecarboxamides (0.22 mmol, 1 equiv.), aryliodide (0.87 mmol, 4 equiv.), palladium(II) acetate (4.9 mg, 0.02 mmol, 10 mol%), silver(I) acetate (146 mg, 0.87 mmol, 4 equiv.) and sodium trifluoroacetate (16 mg, 0.12 mmol, 50 mol%). Solids were then dissolved in HFIP (1.8 mL) and water (0.2 mL). The resulting mixture was stirred at 80°C during 24h under air. After cooling to room temperature, the mixture was diluted with EtOAc, filtered through a pad of celite and evaporated in vacuo. The crude was purified by a short column chromatography on silica gel with CyHex/EtOAc to obtain the two diastereomers of the title compound as pure enantiomers. Usually, the minor diastereomer comes first, followed by the major diastereomer.

2-(4-acetylphenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-2a

The general procedure **A** was followed using 4'-iodoacetophenone (70 mg) as coupling partner and with a reaction time of 8h. Column chromatography on silica gel with CyHex/EtOAc (3:2) afforded the minor diastereomer (35 mg, 36%) as a pale yellow solid and the major diastereomer (53 mg, 54%) as a yellow solid. The diastereomeric ratio determined by analysis of the crude 1H NMR is 60/40. For the major diastereomer, suitable crystals for X-Ray diffraction were grown in $CHCl_3$/DCM/Et_2O at 0°C.



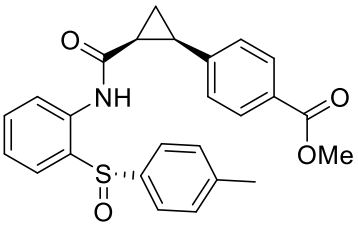
Minor diastereomer **II-2aB**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.53 (1H, br s, N*H*), 8.19 (1H, d, J=8.2 Hz), 7.65 (2H, d, J=7.7 Hz), 7.44 (1H, d, J=7.5 Hz), 7.31-7.41 (3H, m), 7.27 (2H, d, J=7.9 Hz), 6.98-7.10 (3H, m), 2.45-2.56 (4H, m), 2.41 (3H, s, PhC*H*$_3$), 2.02-2.12 (1H, m), 1.73-1.82 (1H, m), 1.36-1.44 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 197.83, 167.81, 142.72, 141.66, 140.54, 140.08, 135.47, 133.21, 130.28, 129.48, 128.15, 127.94, 126.78, 124.76, 122.99, 122.56, 26.68, 25.95, 24.98, 21.58, 11.59; FT-IR (cm^{-1}): 3243 (w), 2923 (w), 1679 (s), 1604 (s), 1585 (s), 1534 (s), 1436 (s), 1295 (s), 1266 (s), 1177 (s), 1021 (m), 1009 (s), 813 (m), 765 (m), 529 (m); MP: 203 °C; HRMS (ESI-TOF): m/z calcd for $C_{25}H_{24}NO_3S^+$: 418.1471, found: 418.1430; $[\alpha]_D^{20}$= -212.0° (c=0.42, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.30; R_t (min, CHIRALPAK ® IA, Hex/iPrOH 80/20, 0.5 mL/min): 26.46 (99.4 %), 54.37 (0.6 %).



Major diastereomer **II-2aA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.41 (1H, br s, N*H*), 7.98 (1H, d, J=8.4 Hz), 7.80 (2H, d, J=8.4 Hz), 7.43 (1H, dd, J=7.7, 1.3 Hz), 7.37 (2H, d, J=8.4 Hz), 7.26-7.34 (3H, m), 7.23 (2H, J=8.1 Hz), 7.05 (1H, dd, J=7.5, 1.1 Hz), 2.50-2.60 (4H, m), 2.35 (3H, s, PhC*H*$_3$), 2.00-2.09 (1H, m), 1.70-1.77 (1H, m), 1.29-1.37 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 198.04, 167.57, 142.69, 141.64, 140.30, 139.88, 135.62, 133.03, 130.23, 129.58, 128.24, 127.72, 127.67, 124.58, 123.23, 123.00, 26.77, 25.89, 25.50, 21.52, 11.01; FT-IR (cm^{-1}): 3250 (w), 3055 (w), 2924 (w), 1678 (s), 1606 (m), 1585 (m), 1522 (br s), 1435 (m), 1297 (m), 1266 (s), 1174 (br s), 1011 (m), 732 (s), 701 (m), 532 (m); MP: 184°C; $[\alpha]_D^{20}$= +28.3° (c=1.05, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.25; R_t (min, CHIRALPAK ® IA, Hex/iPrOH 80/20, 0.5 mL/min): 28.42 (96 %), 38.62 (4 %).

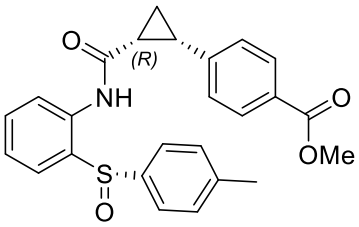
methyl 4-(2-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)benzoate II-2b

The general procedure **A** was followed using methyl 4-iodobenzoate (92 mg) as coupling partner and with a reaction time of 8h. Column chromatography on silica gel with CyHex/EtOAc (7:3) afforded the minor diastereomer (37 mg, 37%) as a white solid and the major diastereomer (55 mg, 54%) as a yellow oil. The diastereomeric ratio determined by analysis of the crude 1H NMR is 60/40.



Minor diastereomer **II-2bB**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.50 (1H, br s, N*H*), 8.14 (1H, d, J=8.4 Hz), 7.67 (2H, d, J=7.9 Hz), 7.35-7.41 (1H, m), 7.25-7.34 (3H, m), 7.21 (2H, d, J=7.9 Hz), 7.06 (1H, t, J=7.5

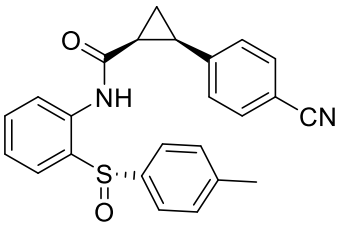
Hz), 6.98 (2H, d, J=7.9 Hz), 3.82 (3H, s, C(O)OC*H*$_3$), 2.46-2.55 (1H, m), 2.40 (3H, s, PhC*H*$_3$), 2.01-2.09 (1H, m), 1.73-1.79 (1H, m), 1.33-1.40 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 167.77, 167.16, 142.44, 141.65, 140.58, 140.09, 133.23, 130.29, 129.34, 129.28, 128.36, 127.94, 126.73, 124.76, 122.94, 122.57, 52.11, 25.96, 24.98, 21.54, 11.50; FT-IR (cm^{-1}): 3245 (w), 2924 (s), 2854 (s), 1714 (s, C=O ester), 1692 (s, C=O amide), 1585 (s), 1293 (s), 1278 (s), 1175 (s), 1104 (s), 1019 (s), 1009 (s), 757 (s), 527 (m); MP: 224°C; HRMS (ESI-TOF): m/z calcd for $C_{25}H_{23}KNO_4S^+$: 472.0979, found: 472.0969; $[\alpha]_D^{20}$= -186.4° (c=0.83, $CHCl_3$); R_f (CyHex/EtOAc 3:2): 0.33.



Major diastereomer **II-2bA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.40 (1H, br s, N*H*), 7.98 (1H, d, J=8.3 Hz), 7.89 (2H, d, J=8.0 Hz), 7.44 (1H, d, J=7.9 Hz), 7.38 (2H, d, J=8.3 Hz), 7.28-7.34 (3H, m), 7.24 (2H, d, J=7.9 Hz), 7.06 (1H, t, J=7.6 Hz), 3.86 (3H, s, C(O)OC*H*$_3$), 2.52-2.60 (1H, m), 2.36 (3H, s, PhC*H*$_3$), 2.04 (1H, ddd, J=9.2, 7.8, 5.7 Hz), 1.74 (1H, ddd, J=7.5, 5.4, 5.2 Hz), 1.29-1.37 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 167.52, 167.27, 142.38, 141.60, 140.31, 139.88, 133.04, 130.21, 129.41, 129.38, 128.50, 127.71, 127.61, 124.57, 123.17, 123.04, 52.13, 25.86, 25.48, 21.50, 10.91; FT-IR (cm^{-1}): 3250 (w), 2922 (m), 2852 (m), 1717 (s, C-O ester), 1692 (s, C-O amide), 1610 (s), 1585 (s), 1435 (s), 1277 (s), 1177 (s), 1110 (s), 1019 (s), 1010 (s), 809 (s), 734 (s), 531 (s); $[\alpha]_D^{20}$= +26.5° (c=1.13, $CHCl_3$); R_f (CyHex/EtOAc 3:2): 0.22.

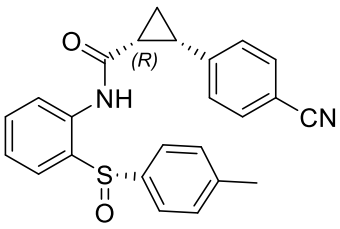
2-(4-cyanophenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-2c

The general procedure **A** was followed using 4-iodobenzonitrile (64 mg) as coupling partner and with a reaction time of 8h. Column chromatography on silica gel with CyHex/EtOAc (7:3) afforded the minor diastereomer (31 mg, 33%) as a pale yellow solid and the major diastereomer (49 mg, 52%) as an off-white solid. The diastereomeric ratio determined by analysis of the crude 1H NMR is 60/40.



Minor diastereomer **II-2cB**: ^{1}H NMR (300 MHz, $CDCl_3$): 10.54 (1H, br s, N*H*), 8.16 (1H, d, J=8.2 Hz), 7.45 (1H, dd, J=7.5, 1.6 Hz), 7.33-7.40 (3H, m), 7.31 (2H, d, J=8.2 Hz), 7.26 (2H, d, J=8.1 Hz), 7.09 (1H, t, J=7.5 Hz), 6.99 (2H, d, J=8.1 Hz), 2.44-2.53 (1H, m), 2.40 (3H, s, PhC*H*$_3$), 2.07 (1H, ddd, J=9.0, 7.8, 5.5 Hz), 1.70-1.77 (1H, m), 1.36-1.45 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): 167.57, 142.75, 141.57, 140.41, 140.13, 133.32, 131.73, 130,20, 130.06, 128.05, 126.78, 124.79, 123.16, 122.59, 119.18, 110.30 (*C*N), 25.81, 24.94, 21.59, 11.68; FT-IR (cm^{-1}): 2924 (s), 2854 (s), 2223 (m, CN), 1729 (m), 1686 (s), 1585 (s), 1535 (s), 1436

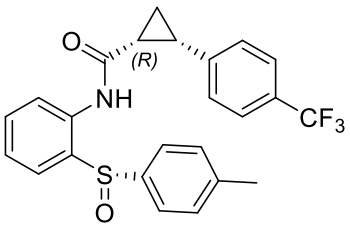
(s), 1294 (s), 1177 (s), 1021 (m), 1009 (s), 743 (s), 560 (m), 470 (m); MP: 225°C; $[\alpha]_D^{20}$= -157.7° (c=0.85, $CHCl_3$); R_f (CyHex/EtOAc 3:2): 0.33.



Major diastereomer **II-2cA**: ^{1}H NMR (300 MHz, $CDCl_3$): 10.47 (1H, br s, N*H*), 7.97 (1H, d, J=8.3 Hz), 7.5 (2H, d, J=8.2 Hz), 7.45 (1H, dd, J=7.7, 1.8 Hz), 7.29-7.42 (5H, m), 7.25 (2H, d, J=8.2 Hz), 7.09 (1H, t, J=7.6 Hz), 2.52-2.60 (1H, m), 2.37 (3H, s, PhC*H*$_3$), 2.08 (1H, ddd, J=9.1, 7.8, 5.6 Hz), 1.69-1.77 (1H, m), 1.33-1.40 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): 167.27, 142.61, 141.66, 140.18, 139.77, 133.05, 131.82, 130.21, 130.14, 127.74, 127.58, 124.54, 123.34, 122.89, 119.26, 110.36 (*C*N), 25.80, 25.54, 21.49, 10.98; FT-IR (cm^{-1}): 3149 (br), 2923 (m), 2854 (m), 2227 (m, CN), 1728 (br), 1673 (m), 1472 (s), 1430 (m), 1180 (m), 1007 (s), 839 (m), 818 (m), 753 (s), 733 (s), 556 (s), 470 (s); MP: 114°C; HRMS (ESI-TOF): m/z calcd for $C_{24}H_{20}KN_2O_2S^+$: 401.1318, found: 401.1290; $[\alpha]_D^{20}$= +36.4° (c=1.02, $CHCl_3$); R_f (CyHex/EtOAc 3:2): 0.10.

***N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)-2-(4-(trifluoromethyl)phenyl)cyclopropane-1-carboxamide II-2d**

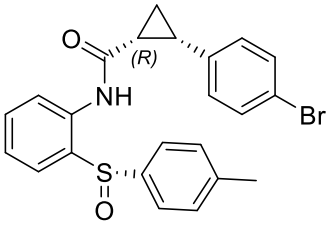
The general procedure **A** was followed using 4-trifluoromethyl-iodobenzene (40 µL) as coupling partner and with a reaction time of 8h. Column chromatography on silica gel with CyHex/EtOAc (8:2) afforded the minor diastereomer (17% estimated, unseparable mixture with the starting material) as a pale yellow oil and the major diastereomer (47 mg, 45%) as a brown oil. The diastereomeric ratio determined by analysis of the crude 1H NMR is 65/35.



Major diastereomer **II-2dA**: ^{1}H NMR ($CDCl_3$, 400 MHz): 10.43 (1H, br s, N*H*), 7.98 (1H, d, J=8.4 Hz), 7.41-7.48 (3H, m), 7.29-7.40 (5H, m), 7.24 (2H, d, J=8.0 Hz), 7.06 (1H, t, J=7.4 Hz), 2.51-2.59 (1H, m), 2.36 (3H, s, PhC*H*$_3$), 2.04 (1H, ddd, J=9.1, 8.0, 5.6 Hz), 1.67-1.77 (1H, m), 1.29-1.38 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): 167.52, 141.65, 141.02, 141.00, 140.32, 139.86, 133.06, 130.23, 129.69, 128.81 (q, J=32 Hz), 127.73, 125.01 (q, J=3.9 Hz), 124.57, 124.50 (q, J=272 Hz), 123.22, 122.98, 25.63, 25.31, 21.50, 10.91; ^{19}F NMR ($CDCl_3$, 377 MHz): -62.35; FT-IR (cm^{-1}): 3246 (w), 3024 (w), 1693 (m), 1586 (m), 1297 (s), 1323 (s), 1113 (s), 1069 (s), 1017 (s), 971 (m), 845 (m), 810 (m), 757 (m), 547 (m, $ArCF_3$), 532 (m, $ArCF_3$), 493 (w); HRMS (ESI-TOF): m/z calcd for $C_{24}H_{21}F_3NO_2S^+$: 444.1240, found: 444.1185; $[\alpha]_D^{20}$= +23.3° (c=0.71, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.38.

2-(4-bromophenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-2e

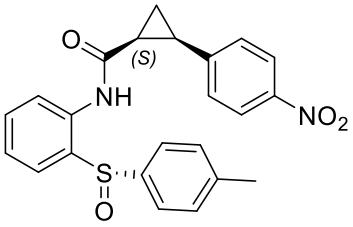
The general procedure **A** was followed using 4-bromo-1-iodobenzene (80 mg) as coupling partner and with a reaction time of 24h. Column chromatography on silica gel with CyHex/EtOAc (8:2) afforded the major diastereomer (27 mg, 26%) as a pale brown oil. The diastereomeric ratio determined by analysis of the crude ^{1}H NMR is 60/40.



Major diastereomer **II-2eA**: ^{1}H NMR (300 MHz, $CDCl_3$): 10.38 (1H, br s, N*H*), 8.02 (1H, d, J=8.5 Hz), 7.44 (1H, dd, J=7.7, 1.1 Hz), 7.37 (2H, d, J=8.2 Hz), 7.32 (2H, d, J=8.3 Hz), 7.22-7.25 (3H, m), 7.12 (2H, d, J=8.4 Hz), 7.07 (1H, td, J=7.6, 1.0 Hz), 2.43-2.51 (1H, m), 2.36 (3H, s, PhC*H*$_3$), 1.93-2.01 (1H, m), 1.61-1.69 (1H, m), 1.25-1.32 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 167.72, 140.64, 140.39, 139.87, 135.86, 133.09, 131.20, 131.14, 130.24, 127.73, 124.60 (2C), 123.14, 123.02, 120.64, 25.42, 25.07, 21.54, 10.78; FT-IR (cm^{-1}): 3248 (w), 2924 (m), 2854 (w), 1693 (m), 1585 (m), 1524 (m), 1490 (m), 1435 (s), 1296 (m), 1173 (br s), 1074 (m), 1021 (m), 1010 (s), 970 (m), 808 (s), 756 (s), 532 (m), 473 (m); HRMS (ESI-TOF): m/z calcd for $C_{23}H_{21}BrNO_2S^+$: 454.0471, found: 454.0474; $[\alpha]_D^{20}$= +10.0° (c=0.50, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.45.

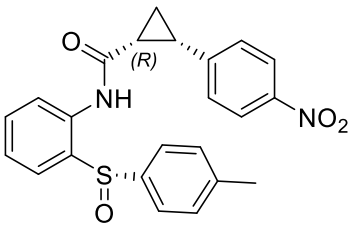
2-(4-nitrophenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-2f

The general procedure **A** was followed using 4-nitroiodobenzene (87 mg) as coupling partner and with a reaction time of 8h. Column chromatography on silica gel with CyHex/EtOAc (4:1 to 7:3) afforded the minor diastereomer (28 mg, 28%) as a pale yellow oil and the major diastereomer (53 mg, 54%) as a yellow solid. The diastereomeric ratio determined by analysis of the crude 1H NMR is 60/40.



Minor diastereomer **II-2fB**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.58 (1H, br s, N*H*), 8.16 (1H, d, J=8.4 Hz), 7.88 (2H, d, J=8.7 Hz), 7.45 (1H, dd, J=7.6, 1.4 Hz), 7.32-7.39 (3H, m), 7.28 (2H, d, J=8.2 Hz), 7.09 (1H, t, J=7.5 Hz), 7.03 (2H, d, J=8.7 Hz), 2.43-2.51 (1H, m), 2.42 (3H, s, PhC*H*$_3$), 2.10 (1H, ddd, J=9.1, 7.9, 5.6 Hz), 1.77 (1H, ddd, J=7.4, 5.5, 5.4 Hz), 1.43 (1H, ddd, J=9.1, 7.4, 5.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 167.47, 146.62, 144.94, 141.68, 140.44, 140.19, 133.34, 130.26, 130.09, 128.10, 126.70, 124.82, 124.81, 123.20, 122.63, 25.61, 25.06, 21.55, 11.83; FT-IR (cm^{-1}): 2924 (w), 1687 (m), 1585 (m), 1514 (s, N-O),

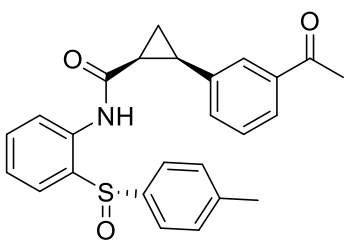
1436 (m), 1389 (w), 1341 (s, N-O), 1295 (m), 1176 (m), 1008 (m, S-O), 755 (m), 735 (m), 473 (w); $[\alpha]_D^{20}$= +32.2° (c=0.29, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.30.



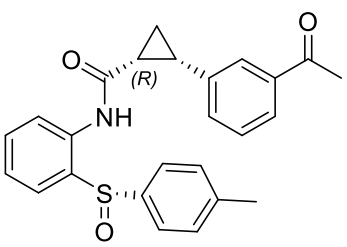
Major diastereomer **II-2fA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.49 (1H, br s, N*H*), 8.06 (2H, d, J=8.8 Hz), 7.97 (1H, d, J=8.5 Hz), 7.43 (1H, dd, J=7.7, 1.4 Hz), 7.34-7.41 (4H, m), 7.31 (1H, td, J=7.8, 1.5 Hz), 7.22-7.26 (2H, m), 7.07 (1H, td, J=7.6, 1.1 Hz), 2.49-2.57 (H, m), 2.36 (3H, s, PhC*H*$_3$), 2.09 (H, ddd, J=8.6, 8.2, 5.6 Hz), 1.70 (H, ddd, J=7.2, 5.5, 5.6 Hz), 1.39 (H, ddd, J=9.0, 7.6, 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 167.23, 146.78, 144.88, 141.70, 140.17, 139.80, 133.06, 130.23, 130.19, 127.75, 127.60, 124.56, 123.39, 123.28, 122.91, 25.72, 25.60, 21.49, 11.34; FT-IR (cm^{-1}): 3249 (w), 1693 (br m), 1598 (m), 1586 (m, C-C aromatic), 1516 (s, N-O), 1436 (m), 1343 (s, N-O), 1298 (m), 1178 (m), 1012 (m), 811 (w), 757 (m), 533 (w), 473 (w); MP: 135°C; HRMS (ESI-TOF): m/z calcd for $C_{23}H_{21}N_2O_4S^+$: 421.1217, found: 421.1194; $[\alpha]_D^{20}$= +45.9° (c=0.47, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.11.

2-(3-acetylphenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-2g

The general procedure **A** was followed using 3'-iodoacetophenone (40 µL, 71 mg) as coupling partner and with a reaction time of 8h. Column chromatography on silica gel with CyHex/EtOAc (6:4) afforded the minor diastereomer (21 mg, 22%) as a yellow solid and the major diastereomer (54 mg, 55%) as an orange oil. The diastereomeric ratio determined by analysis of the crude 1H NMR is 70/30.



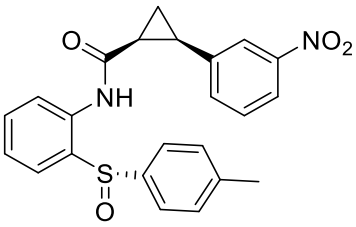
Minor diastereomer **II-2gB**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.57 (1H, br s, N*H*), 8.19 (1H, d, J=8.4 Hz), 7.78 (1H, s), 7.67 (1H, d, J=8.3 Hz), 7.38-7.44 (3H, m), 7.32 (1H, t, J=7.7 Hz), 7.25 (2H, d, J=8.3 Hz), 7.12 (1H, t, J=7.6 Hz), 7.00-7.07 (2H, m), 2.50-2.60 (1H, m), 2.47 (3H, s, C(O)C*H*$_3$), 2.35 (3H, s, PhC*H*$_3$), 2.01 (1H, ddd, J=9.2, 8.1, 5.5 Hz), 1.77 (1H, ddd, J=7.5, 5.4, 5.2 Hz), 1.38-1.46 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 198.28, 168.17, 141.77, 140.57, 139.95, 137.55, 137.03, 133.95, 133.12, 130.31, 129.51, 128.18, 127.73, 126.78, 124.74 (2C), 123.03, 122.42, 26.85, 25.85, 24.85, 21.54, 11.81; FT-IR (cm^{-1}): 3248 (w), 2924 (m), 2854 (m), 1682 (s), 1585 (s), 1533 (br s), 1435 (s), 1398 (s), 1356 (m), 1174 (s), 1021 (s), 1010 (s), 913 (w), 808 (s), 758 (s), 689 (s), 546 (s), 492 (m); $[\alpha]_D^{20}$= -104.5° (c=0.76, $CHCl_3$); R_f (CyHex/EtOAc 3:2): 0.25.



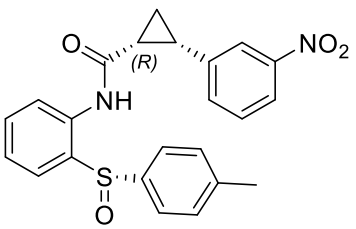
Major diastereomer **II-2gA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.43 (1H, br s, N*H*), 7.97 (1H, d, J=8.4 Hz), 7.88 (1H, s), 7.77 (1H, dd, J=7.7, 1.8 Hz), 7.43-7.49 (2H, m), 7.39 (2H, d, J=8.4 Hz), 7.28-7.35 (2H, m), 7.25 (2H, d, J=7.9 Hz), 7.07 (1H, t, J=7.6 Hz), 2.55-2.63 (1H, m), 2.54 (3H, s, C(O)C*H*$_3$), 2.37 (3H, s, PhC*H*$_3$), 2.03 (1H, ddd, J=8.9, 7.8, 5.6 Hz), 1.69-1.77 (1H, m), 1.32-1.38 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 198.41, 167.76, 141.61, 140.32, 139.85, 137.44, 137.01, 134.11, 132.99, 130.21, 129.72, 128.32, 127.73, 126.71, 124.57, 124.57, 123.17, 122.95, 26.86, 25.74, 24.96, 21.51, 10.96; FT-IR (cm-1): 3248 (w), 2924 (w), 2854 (w), 1681 (s), 1584 (s), 1522 (br s), 1435 (s), 1296 (s), 1263 (s), 1173 (s), 1021 (s), 1010 (s), 807 (s), 757 (s), 733 (s), 589 (m), 492 (m) ; HRMS (ESI-TOF): m/z calcd for $C_{25}H_{23}NNaO_3S^+$: 440.1291, found: 440.1293; $[\alpha]_D^{20}$= +31.5° (c=0.76, $CHCl_3$); R_f (CyHex/EtOAc 3:2): 0.17.

2-(3-nitrophenyl)-*N*-(2-((*S*)-p-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-2h

The general procedure **A** was followed using 3-nitroiodobenzene (87 mg) as coupling partner and with a reaction time of 8h. Column chromatography on silica gel with CyHex/EtOAc (3:1 to 7:3) afforded the minor diastereomer (21 mg, 21%) as a yellow oil and the major diastereomer (69 mg, 70%) as a pale yellow solid. The diastereomeric ratio determined by analysis of the crude 1H NMR is 80/20.



Minor diastereomer **II-2hB**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.65 (1H, br s, N*H*), 8.18 (1H, d, J=8.1 Hz), 7.97 (1H, s), 7.91-7.96 (1H, m), 7.44 (1H, dd, J=7.9, 1.4 Hz), 7.41 (2H, d, J=8.3 Hz), 7.33 (1H, td, J=7.9, 1.4 Hz), 7.28 (2H, d, J=7.9 Hz), 7.2 (2H, d, J=5.2 Hz), 7.06 (1H, td, J=7.6, 0.9 Hz), 2.53-2.60 (1H, m), 2.37 (3H, s, PhC*H*$_3$), 2.09 (1H, ddd, J=9.0, 8.0, 5.7 Hz), 1.79 (1H, ddd, J=7.4, 5.4, 5.3 Hz), 1.46 (1H, ddd, J=8.8, 7.9, 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 167.77, 148.15, 141.96, 140.51, 139.83, 139.12, 135.39, 133.24, 130.31, 128.76, 127.88, 126.93, 124.73, 124.69, 123.20, 122.45, 121.89, 25.51, 24.87, 21.56, 12.00; FT-IR (cm^{-1}): 3247 (m), 3060 (m), 2924 (m), 2854 (m), 1692 (s, C-O), 1586 (s), 1525 (s, N-O), 1436 (s), 1348 (s, N-O), 1298 (s), 1178 (s), 1010 (s), 808 (s), 758 (s), 732 (s), 682 (s), 546 (s), 531 (s); $[\alpha]_D^{20}$= -93.6° (c=0.27, $CHCl_3$); R_f (CyHex/EtOAc 3:2): 0.30.

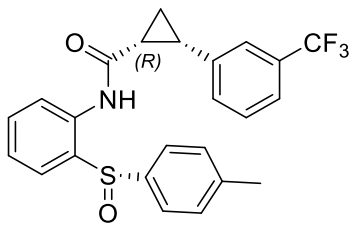


Major diastereomer **II-2hA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.48 (1H, br s, N*H*), 8.14 (1H, s), 8.00 (1H, d, J=8.5 Hz), 7.93 (1H, d, J=8.5 Hz), 7.57 (1H, d, J=8.5 Hz), 7.43 (2H, d, J=8.5 Hz), 7.38 (2H, d, J=7.8 Hz),

7.29 (1H, t, J=8.5 Hz), 7.23 (2H, d, J=7.7 Hz), 7.06 (1H, t, J=7.4 Hz), 2.54-2.63 (1H, m), 2.35 (3H, s, PhC*H*$_3$), 1.99-2.11 (1H, m), 1.69-1.76 (1H, m), 1.33-1.43 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 167.28, 147.98, 141.50, 140.01, 139.64, 138.94, 135.53, 132.83, 130.05, 130.02, 128.66, 127.56, 124.43, 124.40, 123.21, 122.86, 121.70, 25.21, 24.84, 21.34, 11.06; FT-IR (cm^{-1}): 3248 (m), 2924 (m), 1692 (s, C-O), 1585 (s), 1526 (s, N-O), 1436 (s), 1348 (s, N-O), 1298 (s), 1178 (s), 1010 (m), 809 (s), 759 (s), 733 (s), 683 (s), 546 (s), 532 (s); MP: 104°C; HRMS (ESI-TOF): m/z calcd for $C_{23}H_{21}N_2O_4S^+$: 421.1217, found: 421.1215; $[\alpha]_D^{20}$= +16.1° (c=0.59, $CHCl_3$); R_f (CyHex/EtOAc 3:2): 0.17.

_N_-(2-((_S_)-_p_-tolylsulfinyl)phenyl)-2-(3-(trifluoromethyl)phenyl)cyclopropane-1-carboxamide II-2i

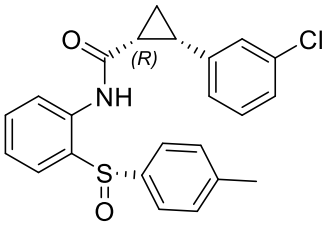
The general procedure **A** was followed using 3-trifluoromethyl-iodobenzene (40 µL) as coupling partner and with a reaction time of 18h. Column chromatography on silica gel with CyHex/EtOAc (5:1 to 4:1) afforded the minor diastereomer (25% estimated, unseparable mixture with the starting material) as a brown oil and the major diastereomer (57 mg, 55%) as an orange oil. The diastereomeric ratio determined by analysis of the crude 1H NMR is 70/30.



Major diastereomer **II-2iA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.41 (1H, br s, NH), 7.94 (1H, d, J=8.4 Hz), 7.52 (1H, s), 7.36-7.47 (5H, m), 7.27-7.35 (2H, m), 7.21-7.26 (2H, m), 7.06 (1H, td, J=7.6, 1.1 Hz), 2.52-2.60 (1H, m), 2.35 (3H, s, PhC*H*$_3$), 2.02 (1H, ddd, J=9.0, 7.8, 5.5 Hz), 1.66-1.72 (1H, m), 1.33 (1H, ddd, J=8.9, 7.7, 5.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 167.54, 141.60, 140.28, 139.85, 137.96, 133.00, 132.76, 130.20, 130.35 (q, J=32 Hz), 128.44, 127.72, 126.39 (q, J=3.6 Hz), 124.56 (2C), 124.35 (q, J=272 Hz), 123.54 (q, J=3.8 Hz), 123.22, 123.13, 25.58, 24.97, 21.49, 10.99; ^{19}F NMR ($CDCl_3$, 377 MHz): -62.51; FT-IR (cm^{-1}): 3248 (w), 2925 (w), 1694 (m), 1586 (m), 1524 (br s), 1325 (s), 1121 (s), 1021 (m), 807 (m), 700 (m), 546 (m, $ArCF_3$), 531 (m, $ArCF_3$), 472 (m); HRMS (ESI-TOF): m/z calcd for $C_{24}H_{21}F_3NO_2S^+$: 444.1240, found: 444.1199; $[\alpha]_D^{20}$= +14.9° (c=1.03, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.42.

2-(3-chlorophenyl)-_N_-(2-((_S_)-p-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-2j

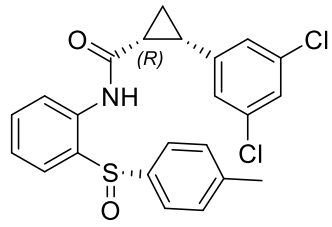
The general procedure **A** was followed using 3-iodo-1-chlorobenzene (35 µL) as coupling partner and with a reaction time of 8h. Column chromatography on silica gel with CyHex/EtOAc (9:1 to 8:2) afforded the minor diastereomer (18% estimated, unseperable mixture with the starting material) as an orange oil and the major diastereomer (54 mg, 56%) as a brownish froth. The diastereomeric ratio determined by analysis of the crude 1H NMR is 80/20.



Major diastereomer **II-2jA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.37 (1H, br, NH), 8.00 (1H, d, J=8.2 Hz), 7.44 (1H, dd, J=7.7, 1.5 Hz), 7.38 (2H, d, J=8.3 Hz), 7.29-7.35 (1H, m), 7.21-7.26 (3H, m), 7.10-7.14 (3H, m), 7.03-7.09 (1H, m), 2.45-2.53 (1H, m), 2.35 (3H, s, PhCH3), 1.95-2.01 (1H, m), 1.63-1.69 (1H, m), 1.24-1.32 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 167.63, 141.61, 140.34, 139.88, 138.97, 133.88, 133.03, 130.22, 129.70, 129.27, 127.72, 127.59, 126.95, 124.59 (2C), 123.19, 123.17, 25.54, 25.00, 21.52, 10.83; FT-IR (cm^{-1}): 3246 (w), 3024 (w), 1693 (s), 1585 (s), 1525 (br s), 1436 (s), 1177 (s), 1022 (s), 1011 (s), 809 (m), 794 (m), 756 (s), 546 (m); MP: 167 °C; HRMS (ESI-TOF): m/z calcd for $C_{23}H_{20}ClNNaO_2S^+$: 432.0795, found: 432.0782; $[\alpha]_D^{20}$= +54.6° (c=0.34, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.44.

2-(3,5-dichlorophenyl)-*N*-(2-((*S*)-p-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-2k

The general procedure **A** was followed using 3-iodo-1,5-dichlorobenzene (109 mg) as coupling partner and with a reaction time of 24h. Column chromatography on silica gel with CyHex/EtOAc (8:2) afforded the minor diastereomer (11% estimated, unseparable mixture with the starting material) as a yellow oil and the major diastereomer (38 mg, 32%) as a salmon froth. The diastereomeric ratio determined by analysis of the crude 1H NMR is 75/25.

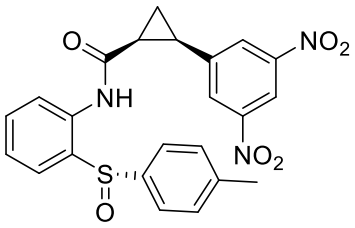


Major diastereomer **II-2kA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.42 (1H, br, N*H*), 8.01 (1H, d, J=8.4 Hz), 7.45 (1H, dd, J=7.7, 1.6 Hz), 7.32-7.40 (3H, m), 7.21-7.27 (2H, m), 7.13-7.15 (3H, m), 7.08 (1H, td, J=7.6, 1.2 Hz), 2.40-2.49 (1H, m), 2.36 (3H, s, PhC*H*$_3$), 1.94-2.03 (1H, m), 1.58-1.65 (1H, m), 1.29 (1H, ddd, J=8.8, 7.8, 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 167.36, 141.64, 140.49, 140.24, 139.83, 134.45, 133.08, 130.22, 128.11, 127.74, 127.05, 124.59, 124.52, 123.37, 123.26, 25.21, 24.93, 21.53, 11.09; FT-IR (cm^{-1}): 3244 (w), 3059 (w), 1694 (m), 1585 (s), 1525 (br m), 1435 (s), 1296 (s), 1176 (s), 1021 (s, S-O), 1011 (s), 799 (s, Ar-Cl), 678 (m), 472 (m); MP: 121°C; HRMS (ESI-TOF): m/z calcd for $C_{23}H_{20}Cl_2NO_2S^+$: 444.0586, found: 444.0557; $[\alpha]_D^{20}$= +46.7° (c=0.76, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.43.

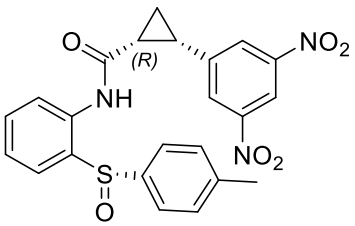
2-(3,5-dinitrophenyl)-*N*-(2-((*S*)-p-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-2l

The general procedure **A** was followed using 3,5-dinitroiodobenzene (82 mg) as coupling partner and with a reaction time of 24h. Column chromatography on silica gel with CyHex/EtOAc (8:2 to 7:3) afforded the minor diastereomer (19 mg, 17%) as a yellow oil and the major diastereomer

(45 mg, 41%) as a yellow froth. The diastereomeric ratio determined by analysis of the crude 1H NMR is 70/30.



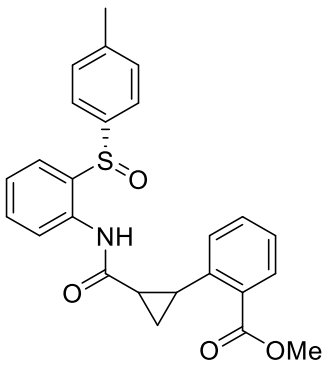
Minor diastereomer **II-2lB**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.86 (1H, br, N*H*), 8.77 (1H, t, J=2.1 Hz), 8.26 (2H, dd, J=2.1, 0.6 Hz), 8.14 (1H, d, J=8.3 Hz), 7.40-7.45 (3H, m), 7.27-7.36 (3H, m), 7.08 (1H, td, J=7.6, 1.2 Hz), 2.62-2.71 (1H, m), 2.37 (3H, s, PhC*H*$_3$), 2.15-2.22 (1H, m), 1.84-1.91 (1H, m), 1.56-1.64 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 167.33, 148.14, 142.36, 141.80, 140.26, 139.37, 133.16, 130.29, 129.75, 127.73, 126.94, 124.56, 123.53, 122.26, 117.30, 25.20, 25.15, 21.47, 12.69; FT-IR (cm^{-1}): 3104 (w), 1691 (w), 1586 (m), 1539 (s, N-O), 1438 (m), 1343 (s, N-O), 1299 (m), 1182 (m), 1011 (m), 729 (s), 663 (m); $[\alpha]_D^{20}$= -125.5° (c=0.82, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.26.



Major diastereomer **II-2lA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.63 (1H, br, N*H*), 8.82 (1H, t, J=2.1 Hz), 8.46 (2H, dd, J=2.1, 0.5 Hz), 7.87 (1H, d, J=8.4 Hz), 7.42 (1H, dd, J=7.6, 1.6 Hz), 7.37 (2H, d, J=8.3 Hz), 7.30 (1H, td, J=7.9, 1.7 Hz), 7.21-7.26 (2H, m), 7.08 (1H, td, J=7.6, 1.2 Hz), 2.63-2.72 (1H, m), 2.37 (3H, s, PhC*H*$_3$), 2.12-2.20 (1H, m), 1.73-1.80 (1H, m), 1.47-1.56 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 167.25, 148.15, 141.87, 141.80, 139.86, 139.74, 133.04, 130.25, 129.97, 128.35, 127.75, 124.60, 123.88, 123.19, 117.26, 25.17, 25.11, 21.54, 12.07; FT-IR (cm^{-1}): 3174 (w), 3104 (w), 1688 (m), 1586 (m), 1537 (s, N-O), 1436 (m), 1342 (s, N-O), 1297 (m), 1180 (m), 1022 (m, S-O), 1011 (m), 729 (s), 662 (m), 472 (m); MP : 192°C; HRMS (ESI-TOF): m/z calcd for $C_{23}H_{20}N_3O_6S^+$: 466.1067, found: 466.1101; $[\alpha]_D^{20}$= -4.6° (c=0.73, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.13.

methyl 2-(2-((2-((*S*)-p-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)benzoate II-2m

The general procedure **A** was followed using methyl 2-iodobenzoate (40 µL) as coupling partner and with a reaction time of 18h. Column chromatography on silica gel with CyHex/EtOAc (3:2) afforded a mixture of the two diastereomers (46 mg, 45%) as a brown oil. The diastereomeric ratio determined by analysis of the crude 1H NMR is 80/20.

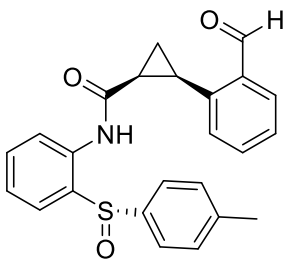


II-2mA and **II-2mB**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.12-10.27 (1H, br s, N*H*), 7.75-8.13 (2H, m), 7.33-7.48 (5H, m), 7.08-7.31 (4H, m), 6.99-7.07 (1H, m), 3.65-3.86 (3H, m, C(O)OC*H*$_3$), 2.84-3.03 (1H, m), 2.32-

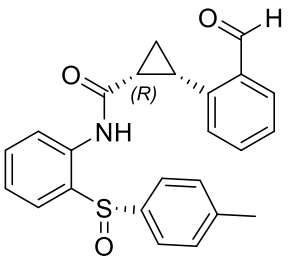
3.38 (3H, m, PhC*H*$_3$), 2.04-2.14 (1H, m), 1.63-1.75 (1H, m), 1.29-1.38 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 168.93, 168.20, 167.95, 167.91, 141.64, 141.19, 139.97, 139.77, 138.14, 138.01, 132.72, 132.49, 131.61, 131.53, 131.35, 130.83, 130.39, 130.14, 130.09, 129.97, 129.93, 127.46, 126.88, 126.62, 126.52, 125.09, 124.35, 123.10, 122.94, 122.40, 52.10, 51.84, 30.95, 29.72, 26.93, 25.87, 25.79, 24.92, 21.38, 21.32, 12.72, 11.60; FT-IR (cm^{-1}): 3250 (w), 2924 (w), 1770 (m), 1720 (s), 1694 (s), 1585 (s), 1528 (br s), 1435 (s), 1295 (s), 1260 (s), 1173 (br s), 1080 (s), 1022 (s), 1011 (s), 757 (s), 547 (m), 472 (m); HRMS (ESI-TOF): m/z calcd for $C_{25}H_{24}NO_4S^+$: 434.1421, found: 434.1370; R_f (CyHex/EtOAc, 3:2): 0.36.

2-(2-formylphenyl)-*N*-(2-((*S*)-p-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-2n

The general procedure **A** was followed using 2-iodobenzaldehyde (65 mg) as coupling partner and with a reaction time of 24h. Column chromatography on silica gel with CyHex/EtOAc (4:1) afforded the minor diastereomer (12 mg, 13%) as a yellow oil and the major diastereomer (38 mg, 40%) as a pale yellow solid. The diastereomeric ratio determined by analysis of the crude 1H NMR is 80/20.



Minor diastereomer **II-2nB**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.38 (1H, s, C*H*O), 10.34 (1H, br, N*H*), 7.84 (1H, dd, J=8.4, 1.4 Hz), 7.75 (1H, dd, J=7.6, 1.5 Hz), 7.32-7.53 (7H, m), 7.20-7.25 (2H, m), 7.05 (1H, td, J=7.5, 1.3 Hz), 2.91-3.00 (1H, m), 2.36 (3H, s, PhC*H*$_3$), 2.17-2.22 (1H, m), 1.69-1.77 (1H, m), 1.38-1.46 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 192.28, 168.02, 141.48, 140.07, 139.99, 139.25, 135.40, 133.64, 132.79, 131.49, 130.88, 130.14, 127.62, 127.37, 127.06, 124.61, 123.29, 123.10, 25.07, 23.80, 21.50, 11.71; FT-IR (cm^{-1}): 2925 (m), 2855 (w), 1751 (m), 1694 (s), 1289 (s), 1194 (s), 1103 (s), 1038 (s), 1012 (s), 757 (s), 472 (w); $[\alpha]_D^{20}$= -77.0° (c=0.66, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.41.

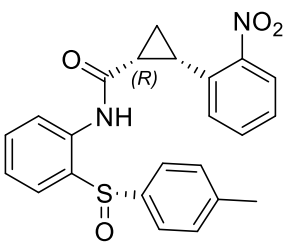


Major diastereomer **II-2nA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.57 (1H, br, N*H*), 10.25 (1H, s, C*H*O), 8.17 (1H, d, J=8.6 Hz), 7.68 (2H, d, J=7.5 Hz), 7.46 (2H, d, J=8.3 Hz), 7.39 (1H, td, J=8.2, 2.2 Hz), 7.25-7.34 (4H, m), 7.21 (1H, d, J=7.8 Hz), 7.03 (1H, t, J=7.2 Hz), 2.88-2.97 (1H, m), 2.38 (3H, s, PhC*H*$_3$), 2.16-2.25 (1H, m), 1.77-1.84 (1H, m), 1.49-1.56 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 191.97, 168.67, 141.89, 140.39, 139.89, 139.26, 135.31, 133.60, 132.84, 131.15, 130.75, 130.43, 127.41, 127.28, 127.09, 124.78, 123.07, 122.21, 25.09, 23.91, 21.60, 13.07; FT-IR (cm^{-1}): 3249 (w), 2925 (w), 1690 (s), 1598 (m), 1585 (m), 1437 (m), 1294 (m), 1021 (m), 1011 (m), 755 (s), 734 (s), 546 (m); MP: 147°C; HRMS (ESI-TOF): m/z

calcd for $C_{24}H_{21}NNaO_3S^+$: 426.1134, found: 426.1086; $[\alpha]_D^{20}$= -41.9° (c=0.64, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.32.

2-(2-nitrophenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-2o

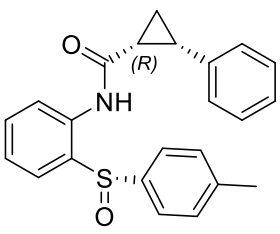
The general procedure **A** was followed using 2-nitro-iodobenzene (88 mg, 0.35 mmol, 1.5 equiv.) as coupling partner and with a reaction time of 48h. Column chromatography on silica gel with CyHex/EtOAc (8:2 to 7:3) afforded the minor diastereomer (12% estimated, unseparable mixture with remaining starting material and biarylation product) as a yellow oil and the major diastereomer (65 mg, 66%) as a bright yellow solid. The diastereomeric ratio determined by analysis of the crude 1H NMR is 70/30.



Major diastereomer **II-2oA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.32 (1H, br, N*H*), 7.80-7.89 (2H, m), 7.41-7.51 (3H, m), 7.26-7.40 (4H, m), 7.22 (2H, d, J=8.2 Hz), 7.07 (1H, td, J=7.6, 1.1 Hz), 2.80-2.90 (1H, m), 2.34 (3H, s, PhC*H*$_3$), 2.10-2.17 (1H, m), 1.53-1.58 (1H, m), 1.38-1.45 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) : 168.08, 150.72, 141.42, 140.04, 140.00, 132.79, 132.68, 132.48, 130.25, 130.11, 128.80, 127.80, 127.61, 124.60, 124.36, 123.55, 123.45, 24.46, 24.21, 21.50, 12.38; FT-IR (cm^{-1}) : 3247 (w), 3059 (w), 2924 (w), 1691 (m, C=O), 1585 (m), 1519 (s, N-O), 1177 (m), 1021 (m, S=O), 757 (m), 547 (m), 472 (m); HRMS (ESI-TOF): m/z calcd for $C_{23}H_{20}KN_2O_4S^+$: 459.0775, found: 459.0775; $[\alpha]_D^{20}$= -116.0° (c=0.13, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.41.

2-phenyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-2p

The general procedure **A** was followed using iodobenzene (80 µL, 0.71 mmol, 3 equiv.) as coupling partner and with a reaction time of 18h. Column chromatography on silica gel with CyHex/EtOAc (4:1) afforded the minor diastereomer (17% estimated, unseparable mixture with the starting material) as a yellow oil and the major diastereomer (27 mg, 31%) as a yellow oil. The diastereomeric ratio determined by analysis of the crude 1H NMR is 60/40.

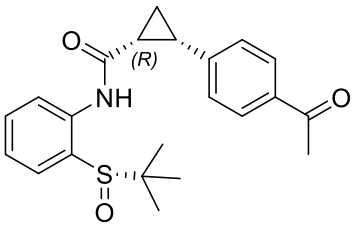


Major diastereomer **II-2pA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.31 (1H, br, N*H*), 7.99 (1H, d, J=8.4 Hz), 7.44 (1H, dd, J=7.5, 1.5 Hz), 7.38 (2H, d, J=8.3 Hz), 7.27-7.32 (1H, m), 7.11-7.27 (7H, m), 7.05 (1H, td, J=7.6, 1.2 Hz), 2.50-2.59 (1H, m), 2.36 (3H, s, PhC*H*$_3$), 1.93-2.02 (1H, m), 1.70 (1H, ddd, J=7.5, 5.3, 5.0 Hz), 1.24-1.31 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 167.97, 141.55, 140.44, 139.88, 136.72, 132.99, 130.19, 129.39, 128.61, 128.10, 127.69, 126.70, 124.58,

123.04, 122.98, 26.01, 25.06, 21.52, 10.57; FT-IR (cm^{-1}): 3252 (w), 3027 (w), 2925 (w), 1697 (s), 1586 (s), 1528 (br s), 1437 (s), 1297 (s), 1173 (s), 1022 (s), 1011 (s), 969 (m), 810 (m), 756 (s), 697 (s), 546 (m), 531 (m), 474 (w); HRMS (ESI-TOF): m/z calcd for $C_{23}H_{22}NO_2S^+$: 376.1366, found: 376.1333; $[\alpha]_D^{20}$= +21.3° (c=0.2, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.42.

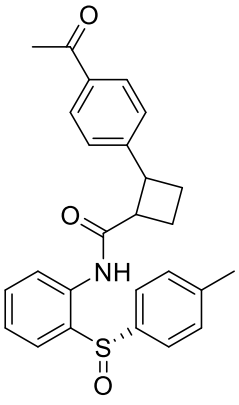
2-(4-acetylphenyl)-*N*-(2-((*S*)-*tert*-butylsulfinyl)phenyl)cyclopropane-1-carboxamide II-3a

The general procedure **A** was followed using compound **II-1b** (200 mg) as substrate, 4-iodoacetophenone (280 mg, 1.14 mmol, 1.5 equiv.) as coupling partner and with a reaction time of 18h, under argon atmosphere. Column chromatography on silica gel with CyHex/EtOAc (7:3) afforded a mixture of two diastereomers (75 mg, 26%) as a clear oil. The diastereomeric ratio determined by analysis of the crude 1H NMR is 90/10.



Major diastereomer **II-3aA**: ^{1}H NMR (400 MHz, $CDCl_3$): 11.20 (1H, br s, N*H*), 8.12 (1H, dd, J=8.4, 1.0 Hz), 7.82 (2H, d, J=8.4 Hz), 7.36 (2H, d, J=8.4 Hz), 7.28 (1H, ddd, J=8.6, 7.2, 1.8 Hz), 6.93-7.06 (2H, m), 2.51-2.60 (4H, m), 2.12 (1H, ddd, J=9.1, 7.8, 5.6 Hz), 1.83 (1H, ddd, J=7.5, 5.3, 5.0 Hz), 1.37 (1H, ddd, J=8.7, 7.8, 5.1 Hz), 1.25 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 198.08, 167.59, 142.82, 142.46, 135.57, 132.32, 129.65, 129.37, 128.57, 128.20, 122.63, 122.13, 59.18, 26.75, 25.89, 25.65, 23.55, 10.99; FT-IR (cm^{-1}): 2958 (m), 2924 (m), 2855 (m), 1680 (s, C=O), 1606 (s), 1585 (s), 1531 (br s), 1458 (m), 1434 (s), 1295 (s), 1267 (s), 1176 (s), 1106 (w), 1007 (s, S=O), 969 (m), 843 (m), 761 (s); HRMS (ESI-TOF): m/z calcd for $C_{22}H_{25}KNO_3S^+$: 422.1187, found: 422.1145; $[\alpha]_D^{20}$= +0.3° (c=0.93, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.35.

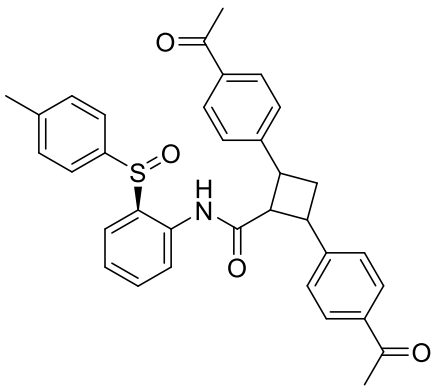
2-(4-acetylphenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclobutane-1-carboxamide II-5a and 2,4-*bis*(4-acetylphenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclobutane-1-carboxamide



The general procedure **A** was followed using compound **II-1c** (70 mg) as substrate and 4-iodoacetophenone (66 mg) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (8:2 to 7:3) afforded the mixture of the two diastereomers (39 mg, 40%) as a clear oil and the product of biarylation (22 mg, 18%) as a yellow oil. The diastereomeric ratio determined by analysis of the crude 1H NMR is 70/30.

II-5aA and **II-5aB**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.22 (0.3H, br s, N*H*), 9.87 (0.7H, br s, N*H*), 8.20 (0.3H, d, J=8.2 Hz), 7.87 (0.7H, dd, J=8.4, 1.2 Hz), 7.76 (1.4H, d, J=8.4 Hz),

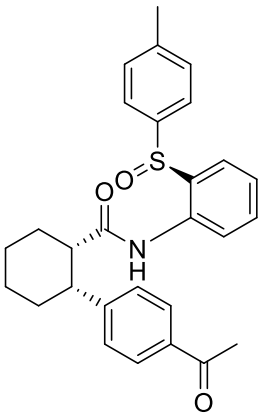
7.63 (0.6H, d, J=8.4 Hz), 7.34-7.40 (1H, m), 7.25-7.33 (4.6H, m), 7.21 (1.4H, d, J=8.4 Hz), 6.99-7.07 (2H, m), 3.87-4.08 (1H, m), 3.40-3.52 (1H, m), 2.52-2.67 (1H, m), 2.47 (3H, s, C(O)C*H*$_3$), 2.29-2.41 (5H, m), 2.13-2.26 (1H, m); ^{13}C NMR (400 MHz, $CDCl_3$): 198.03 (0.7C), 197.89 (0.3C), 171.35 (0.3C), 170.90 (0.7C), 147.26 (0.3C), 146.73 (0.7C), 141.84 (0.3C), 141.56 (0.7C), 140.32 (0.3C), 140.17 (0.3C), 140.02 (0.7C), 139.84 (0.7C), 135.43 (0.7C), 135.15 (0.3C), 133.05 (0.3C), 132.92 (0.7C), 130.33 (0.6C), 130.13 (1.4C), 128.43 (1.4C), 128.39 (0.6C), 127.81 (0.3C), 127.76 (0.7C), 127.72 (1.4C), 127.21 (0.6C), 124.87 (0.6C), 124.58 (1.4C), 123.20 (0.7C), 123.12 (0.3C), 122.80 (0.7C), 122.34 (0.3C), 47.40 (0.3C), 47.20 (0.7C), 43.02 (0.7C), 42.66 (0.3C), 26.72 (2.1C), 26.66 (0.9C), 24.84 (0.3C), 24.68 (0.7C), 21.76 (0.3C), 21.54 (0.9C), 21.48 (2.1C), 20.51 (0.7C); FT-IR (cm^{-1}): 3251 (w), 2948 (w), 1680 (s), 1605 (m), 1585 (m), 1528 (br m), 1435 (m), 1295 (m), 1269 (s), 1182 (m), 1012 (m), 759 (m), 598 (w); HRMS (ESI-TOF): m/z calcd for $C_{26}H_{25}NNaO_3S^+$: 454.1447, found: 454.1490; R_f (CyHex/EtOAc, 1:1): 0.29.



^{1}H NMR (400 MHz, $CDCl_3$): 10.25 (1H, br s, N*H*), 7.81 (2H, d, J=8.3 Hz), 7.69 (1H, dd, J=8.4, 1.2 Hz), 7.61 (2H, d, J=8.3 Hz), 7.32-7.37 (5H, m), 7.29 (2H, d, J=8.5 Hz), 7.16 (1H, td, J=7.8, 1.8 Hz), 6.99 (1H, td, J=7.6, 1.3 Hz), 6.93 (2H, d, J=8.3 Hz), 3.99-4.07 (1H, m), 3.83-3.95 (2H, m), 3.40 (1H, q, J=10.6 Hz), 2.67-2.77 (1H, m), 2.49 (3H, s), 2.47 (3H, s), 2.45 (3H, s);^{13}C NMR (400 MHz, $CDCl_3$): 197.89, 197.59, 168.24, 147.05, 145.57, 141.58, 139.73, 139.65, 135.32, 134.76, 132.84, 130.18, 128.27, 128.19, 127.63, 127.30, 126.73, 126.20, 124.51, 123.09, 122.38, 53.99, 39.22, 37.93, 29.80, 26.59, 26.44, 21.43; FT-IR (cm^{-1}): 3247 (w), 2943 (w), 1678 (s), 1605 (s), 1586 (m), 1435 (m), 1358 (m), 1269 (s), 1176 (m), 1012 (m), 816 (m), 758 (m), 598 (m), 548 (m); HRMS (ESI-TOF): m/z calcd for $C_{34}H_{31}NNaO_4S^+$: 572.1866, found: 572.1843; $[\alpha]_D^{20}$= +44.7° (c=1.1, $CHCl_3$); R_f (CyHex/EtOAc, 1:1): 0.29.

2-(4-acetylphenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclohexane-1-carboxamide II-7a

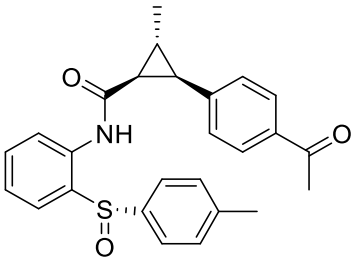
The general procedure **A** was followed using compound **II-1e** (105 mg) as substrate and 4-iodoacetophenone (120 mg) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (8:2 to 7:3) afforded the major cis-diastereomer (23 %) as a clear oil. The diastereomeric ratio determined by analysis of the crude ^{1}H NMR is 70/30 and the *cis-trans* ratio determined by NOESY experiment is 75/25.



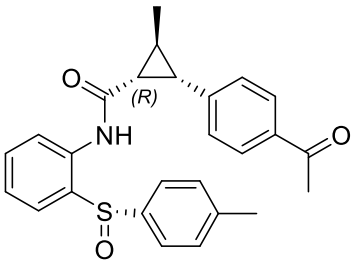
^{1}H NMR (400 MHz, $CDCl_3$): 10.23 (1H, br s, N*H*), 8.26 (1H, d, J=8.3 Hz), 7.74 (2H, d, J=8.4 Hz), 7.24-7.32 (4H, m), 7.13 (2H, d, J=8.3 Hz), 6.95-7.00 (3H, m), 2.80-2.91 (2H, m), 2.52-2.66 (1H, m), 2.47 (3H, s, PhC(O)C*H*$_3$), 2.23 (3H, s, PhC*H*$_3$), 2.06-2.13 (1H, m), 1.79-1.91 (2H, m), 1.60-1.76 (2H, m), 1.53-1.59 (1H, m), 1.32-1.43 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 197.81, 172.42, 150.45, 141.63, 140.40, 139.57, 134.89, 132.56, 130.00, 128.29, 128.04, 127.13, 127.03, 124.31, 122.89, 122.10, 48.07, 44.71, 30.17, 26.98, 26.55, 25.62, 21.85, 21.26; FT-IR (cm^{-1}): 1665 (s), 1032 (s); $[\alpha]_D^{20}$= +89.3° (c=0.54, $CHCl_3$); R_f (CyHex/EtOAc, 1:1): 0.41.

2-(4-acetylphenyl)-3-methyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-8a

The general procedure **B** was followed using compound **II-1f** (70 mg) as substrate and 4'-iodoacetophenone (215 mg) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (4:1) afforded the minor diastereomer (30 mg, 31%) as a yellow oil and the major diastereomer (50 mg, 52%) as an orange oil. The diastereomeric ratio determined by analysis of the crude 1H NMR is 60/40.



Minor diastereomer **II-8aB**: 10.48 (1H, br, N*H*), 8.19 (1H, d, J=8.6 Hz), 7.65 (2H, d, J=8.3 Hz), 7.44 (1H, dd, J=7.6, 1.6 Hz), 7.30-7.40 (3H, m), 7.21-7.26 (2H, m), 7.06 (1H, td, J=7.5, 1.2 Hz), 7.00 (2H, d, J=8.4 Hz), 2.48 (3H, s, C(O)C*H*$_3$), 2.39 (3H, s, PhC*H*$_3$), 2.30 (1H, dd, J=9.0, 6.9 Hz), 2.08-2.17 (1H, m), 1.80 (1H, dd, J=9.0, 5.2 Hz), 1.31 (3H, d, J=6.0 Hz, CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 197.80, 167.77, 143.00, 141.60, 140.54, 140.04, 135.39, 133.30, 130.23, 129.31, 128.13, 127.92, 124.70 (2C), 122.94, 122.58, 34.48, 33.43, 26.64, 21.55, 20.26, 17.87; FT-IR (cm^{-1}): 3248 (w), 2925 (w), 1678 (s), 1604 (m), 1585 (m), 1297 (m), 1266 (s), 1172 (s), 1020 (m, S-O), 1010 (s), 809 (m), 547 (m); $[\alpha]_D^{20}$= -156.2° (c=0.8, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.31.

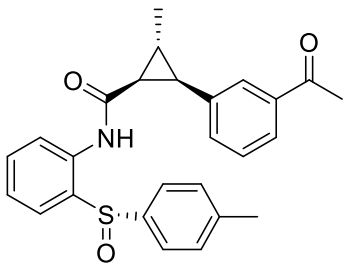


Major diastereomer **II-8aA**: ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$): 10.32 (1H, br, N*H*), 7.99 (1H, d, J=8.5 Hz), 7.80 (2H, d, J=8.3 Hz), 7.43 (1H, dd, J=7.9, 1.6 Hz), 7.35-7.40 (2H, m), 7.27-7.33 (3H, m), 7.21-7.25 (2H, m), 7.05 (1H, td, J=7.6, 1.1 Hz), 2.52 (3H, s, C(O)C*H*$_3$), 2.31-2.39 (4H, m), 2.03-2.12 (1H, m), 1.75 (1H, dd, J=9.0, 5.1 Hz), 1.28 (3H, d, J=6.1 Hz, CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 198.00, 167.58, 142.94, 141.62, 140.25, 139.96, 135.52, 133.01, 130.16, 129.42,

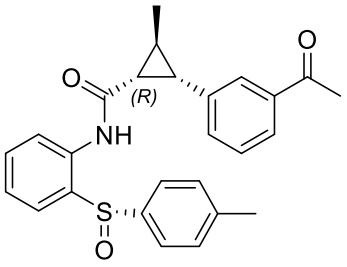
128.21, 127.73, 124.63, 123.18, 123.14, 123.09, 34.58, 33.95, 26.72, 21.50, 19.71, 17.89; FT-IR (cm^{-1}): 3248 (w), 2958 (w), 1678 (s), 1605 (m), 1436 (m), 1266 (s), 1172 (s), 1020 (m), 1011 (s), 809 (m), 733 (s), 598 (m), 532 (m); HRMS (ESI-TOF): m/z calcd for $C_{26}H_{25}NNaO_3S^+$: 454.1447, found: 454.1484; $[\alpha]_D^{20}$= +19.9° (c=1.08, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.15.

2-methyl-3-(3-acetylphenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-8g

The general procedure **B** was followed using compound **II-1f** (70 mg) as substrate and 3'-iodoacetophenone (193 mg) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (8:2 to 7:3) afforded the minor diastereomer (31 mg, 36%) as a yellow oil and the major diastereomer (49 mg, 56%) as an orange oil. The diastereomeric ratio determined by analysis of the crude ^{1}H NMR is 60/40.



Minor diastereomer **II-8gB**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.52 (1H, br s, N*H*), 8.19 (1H, d, J=8.4 Hz), 7.75 (1H, s), 7.63-7.67 (1H, m), 7.38-7.44 (3H, m), 7.29-7.34 (1H, m), 7.20-7.24 (2H, m), 7.11 (1H, t, J=7.7 Hz), 6.99-7.07 (2H, m), 2.46 (3H, s, C(O)C*H*$_3$), 2.28-2.37 (4H, m), 2.07-2.15 (1H, m), 1.79 (1H, dd, J=9.0, 5.2 Hz), 1.32 (3H, d, J=6.1 Hz) ; ^{13}C NMR (400 MHz, $CDCl_3$): 198.31, 168.11, 141.70, 140.54, 139.85, 137.75, 136.97, 133.80, 133.11, 130.24, 129.29, 128.13, 127.73, 126.96, 126.68, 124.66,, 122.95, 122.41, 34.40, 33.19, 26.82, 21.49, 20.44, 18.01; FT-IR (cm^{-1}): 3249 (w), 2971 (w), 2868 (w), 1682 (s), 1585 (s), 1532 (br s), 1435 (s), 1297 (s), 1172 (s), 1021 (s, S=O), 1010 (s), 757 (s), 691 (s), 546 (s), 530 (s); $[\alpha]_D^{20}$= -131.2° (c=0.5, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.37; R_t (min, CHIRALPAK ® IA, Hex/iPrOH 80/20, 0.5 mL/min): 21.37 min (99 %), 30.37 (1 %).

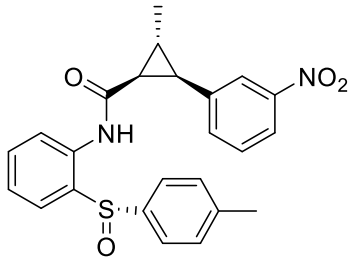


Major diastereomer **II-8gA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.32 (1H, br s, N*H*), 7.96 (1H, d, J=8.2 Hz), 7.83 (1H, s), 7.74 (1H, dt, J=7.6, 1.7 Hz), 7.36-7.46 (4H, m), 7.31 (2H, d, J=7.8 Hz), 7.21-7.26 (2H, m), 7.05 (1H, td, J=7.6, 1.1 Hz), 2.53 (3H, s, C(O)C*H*$_3$), 2.33-2.39 (4H, m), 2.02-2.10 (1H, m), 1.71 (1H, dd, J=9.0, 5.1 Hz), 1.28 (3H, d, J=6.0 Hz); ^{13}C NMR (400 MHz, $CDCl_3$): 198.51, 167.83, 141.63, 140.30, 139.92, 137.67, 137.00, 134.04, 133.03, 130.18, 129.54, 128.30, 127.78, 127.74, 126.66, 124.63, 123.15, 123.06, 34.51, 33.39, 26.89, 21.54, 19.71, 17.96; FT-IR (cm^{-1}): 3248 (w), 2960 (w), 2926 (w), 1682 (s), 1584 (s), 1435 (s), 1173 (s), 1021 (s, S=O), 810 (m), 758 (m), 692 (m), 547 (m); HRMS (ESI-TOF): m/z calcd for $C_{26}H_{26}NO_3S^+$: 432.1628, found: 432.1598; $[\alpha]_D^{20}$=

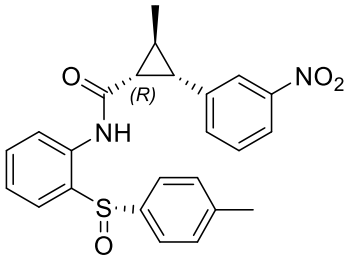
+23.7° (c=0.8, $CHCl_3$);R_f (CyHex/EtOAc, 3:2): 0.28; 7; R_t (min, CHIRALPAK ® IA, Hex/iPrOH 80/20, 0.5 mL/min): 20.37 min (99 %), 26.39 (1 %).

2-methyl-3-(3-nitrophenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-8h

The general procedure **B** was followed using compound **II-1f** (70 mg) as substrate and 3-nitro-iodobenzene (217 mg) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (4:1 to 7:3) afforded the minor diastereomer (30 mg, 31%) as an orange oil and the major diastereomer (52 mg, 54%) as a pale yellow oil. The diastereomeric ratio determined by analysis of the crude ^{1}H NMR is 60/40.



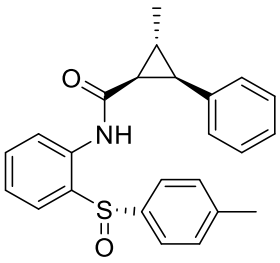
Minor diastereomer **II-8hB**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.60 (1H, br s, NH), 8.17 (1H, d, J=8.3 Hz), 7.89-7.97 (2H, m), 7.45 (1H, dd, J=7.7, 1.3 Hz), 7.40 (2H, d, J=8.3 Hz), 7.33 (1H, td, J=8.1, 1.7 Hz), 7.27 (2H, d, J=8.2 Hz), 7.15-7.22 (2H, m), 7.06 (1H, td, J=7.5, 1.1 Hz), 2.31-2.39 (4H, m), 2.13 (1H, dqd, J=6.8, 6.1, 5.0 Hz), 1.82 (1H, dd, J=8.9, 5.1 Hz), 1.34 (3H, d, J=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 167.66, 148.09, 141.87, 140.47, 139.76, 139.27, 135.21, 133.18, 130.22, 128.67, 127.83, 126.94, 124.64, 124.47, 123.09, 122.42, 121.71, 33.86, 33.18, 21.47, 20.65, 17.82; FT-IR (cm^{-1}): 3247 (w), 1690 (m), 1585 (m), 1525 (s, N-O), 1436 (m), 1348 (s, N-O), 1179 (m), 1021 (m, S-O), 1010 (m), 757 (m), 547 (m); $[\alpha]_D^{20}$= - 90.9° (c=1.07, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.24.



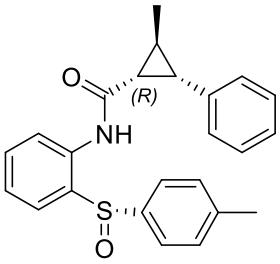
Major diastereomer **II-8hA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.40 (1H, br s, NH), 8.11 (1H, s), 7.98-8.03 (1H, m), 7.95 (1H, d, J=8.3 Hz), 7.54 (1H, dt, J=7.6, 1.1 Hz), 7.44 (1H, dd, J=7.8, 1.4 Hz), 7.36-7.41 (3H, m), 7.28-7.33 (1H, m), 7.24 (2H, d, J=8.2 Hz), 7.06 (1H, td, J=7.5, 1.1 Hz), 2.34-2.41 (4H, m), 2.03-2.10 (1H, m), 1.76 (1H, dd, J=8.8, 5.1 Hz), 1.30 (3H, d, J=6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 167.46, 148.14, 141.66, 140.16, 139.90, 139.29, 135.56, 133.02, 130.23, 130.16, 128.79, 127.76, 124.62, 124.46, 123.31, 123.10, 121.75, 33.93, 33.39, 21.50, 20.01, 17.78; FT-IR (cm^{-1}): 3243 (w), 2955 (w), 1690 (m, C-O), 1585 (m, C-C aromatic), 1526 (s, N-O), 1348 (s, N-O), 1022 (m, S-O), 1012 (m); HRMS (ESI-TOF): m/z calcd for $C_{24}H_{22}KN_2O_4S^+$: 473.0932, found: 473.0880; $[\alpha]_D^{20}$= +18.0° (c=1.12, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.15.

2-methyl-3-phenyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-8p

The general procedure **B** was followed using compound **II-1f** (70 mg) as substrate and iodobenzene (90 µL) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (9:1) afforded the minor diastereomer (28 mg, 36%) and the major diastereomer (39 mg, 50%) as clear oils. The diastereomeric ratio determined by analysis of the crude 1H NMR is 60/40.



Minor diastereomer **II-8pB**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.38 (1H, br, N*H*), 8.21 (1H, d, J=8.6 Hz), 7.44 (1H, dd, J=7.7, 1.4 Hz), 7.39 (2H, d, J=8.4 Hz), 7.30-7.36 (1H, m), 7.21-7.26 (2H, m), 7.02-7.08 (4H, m), 6.90-6.96 (2H, m), 2.37 (3H, s, PhC*H*$_3$), 2.29 (1H, dd, J=9.2, 6.8 Hz), 2.08 (1H, dqd, J=6.9, 6.1, 5.1 Hz), 1.73 (1H, dd, J=9.2, 5.1 Hz), 1.29 (3H, d, J=6.1 Hz, CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.26, 141.50, 140.68, 140.04, 137.05, 133.18, 130.24, 129.17, 128.01, 127.86, 126.51, 124.72 (2C), 122.75, 122.60, 34.83, 33.10, 21.56, 20.00, 18.06; FT-IR (cm^{-1}): 3252 (w), 2924 (m), 1694 (s), 1585 (s), 1530 (br s), 1437 (s), 1296 (s), 1170 (s), 1021 (s, S-O), 1011 (s), 756 (s), 697 (s), 532 (m), 474 (w); $[\alpha]_D^{20}$= -89.4° (c=0.53, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.73.

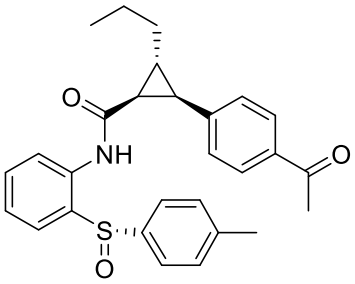


Major diastereomer **II-8pA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.23 (1H, br, N*H*), 8.01 (1H, d, J=8.3 Hz), 7.44 (1H, dd, J=8.0, 1.5 Hz), 7.39 (2H, d, J=8.3 Hz), 7.26-7.33 (1H, m), 7.18-7.25 (6H, m), 7.10-7.17 (1H, m), 7.04 (1H, td, J=7.5, 1.2 Hz), 2.30-2.37 (4H, m), 2.00-2.09 (1H, m), 1.68 (1H, dd, J=9.0, 5.3 Hz), 1.26 (3H, d, J=6.1 Hz, CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 167.98, 141.54, 140.40, 140.00, 136.96, 132.97, 130.15, 129.24, 128.08, 127.69, 126.59, 125.06, 124.63, 123.10, 122.93, 34.89, 33.56, 21.51, 19.24, 18.01; FT-IR (cm^{-1}): 3250 (w), 2956 (w), 2888 (w), 1693 (s), 1436 (s), 1375 (m), 1295 (s), 1170 (s), 1021 (s, S-O), 1010 (s), 696 (s), 531 (s); HRMS (ESI-TOF): m/z calcd for $C_{24}H_{23}NNaO_2S^+$: 412.1342, found: 412.1320; $[\alpha]_D^{20}$= +45.9° (c=1.0, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.70.

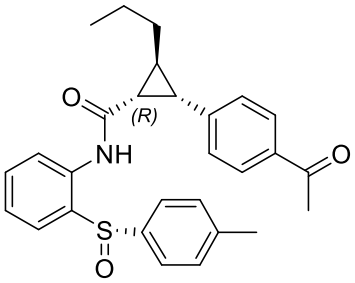
2-(4-acetylphenyl)-3-propyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-9a

The general procedure **B** was followed using compound **II-1g** (75 mg) as substrate and 4'-iodoacetophenone (217 mg) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (8:2 to 7:3) afforded the minor diastereomer (34 mg, 34%) as a yellow oil and the

major diastereomer (57 mg, 56%) as a pale yellow oil. The diastereomeric ratio determined by analysis of the crude 1H NMR is 60/40.



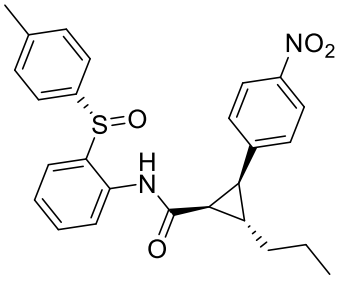
Minor diastereomer **II-9aB**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.47 (1H, br, N*H*), 8.18 (1H, d, J=8.3 Hz), 7.65 (2H, d, J=8.3 Hz), 7.45 (1H, dd, J=7.7, 1.6 Hz), 7.31-7.40 (3H, m), 7.23-7.37 (2H, m), 7.06 (1H, td, J=7.6, 1.3 Hz), 6.99 (2H, d, J=8.2 Hz), 2.48 (3H, s, C(O)C*H*$_3$), 2.39 (3H, s, PhC*H*$_3$), 2.31 (1H, dd, J=9.3, 7.0 Hz), 2.06-2.14 (1H, m), 1.82 (1H, dd, J=9.1, 5.1 Hz), 1.47-1.61 (3H, m), 1.35-1.45 (1H, m), 0.98 (3H, t, J=7.0 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 197.75, 167.81, 143.06, 141.56, 140.52, 140.02, 135.35, 133.17, 130.19, 129.32, 128.11, 127.90, 124.67 (2C), 122.89, 122.58, 35.04, 33.42, 32.17, 26.60, 25.76, 22.39, 21.52, 14.05; FT-IR (cm^{-1}): 3249 (w), 2959 (w), 2925 (w), 2871 (w), 1679 (s), 1606 (m), 1585 (m), 1532 (br m), 1435 (m), 1266 (s), 1020 (m, S-O), 808 (m), 548 (m), 531 (m); $[\alpha]_D^{20}$= -98.0° (c=0.65, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.41.



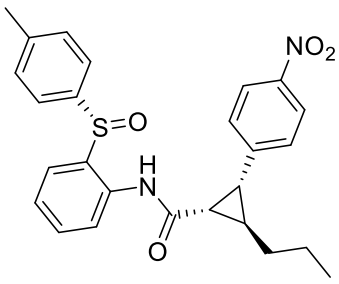
Major diastereomer **II-9aA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.35 (1H, br, N*H*), 8.01 (1H, d, J=8.4 Hz), 7.80 (2H, d, J=8.3 Hz), 7.44 (1H, dd, J=7.8, 1.5 Hz), 7.37 (2H, d, J=8.2 Hz), 7.28-7.34 (3H, m), 7.19-7.24 (2H, m), 78.05 (1H, t, J=7.6 Hz), 2.52 (3H, s, C(O)C*H*$_3$), 2.31-2.38 (4H, m), 2.01-2.10 (1H, m), 1.76 (1H, dd, J=9.1, 5.2 Hz), 1.38-1.55 (4H, m, $CH_2CH_2CH_3$), 0.96 (3H, t, J=7.0 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 197.94, 167.57, 143.00, 141.51, 140.27, 139.90, 135.47, 132.99, 130.12, 129.44, 128.18, 127.74, 124.53 (2C), 123.07, 122.95, 35.03, 33.55, 32.66, 26.69, 25.24, 22.30, 21.43, 14.06; FT-IR (cm^{-1}): 3253 (w), 2958 (w), 2925 (w), 2871 (w), 1679 (s), 1605 (m), 1585 (m), 1524 (br m), 1435 (m), 1296 (m), 1267 (s), 1170 (br m), 1020 (s), 809 (m), 757 (m), 598 (m); HRMS (ESI-TOF): m/z calcd for $C_{28}H_{30}NO_3S^+$: 460.1941, found: 460.1947; $[\alpha]_D^{20}$= +31.5° (c=0.65, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.30.

2-(4-nitrophenyl)-3-propyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-9f

The general procedure **B** was followed using compound **II-1f** (75 mg) as substrate and 4-nitro-iodobenzene (219 mg) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (9:1 to 8:2) afforded the minor diastereomer (41 mg, 40%) as a yellow oil and the major diastereomer (48 mg, 47%) as a clear oil. The diastereomeric ratio determined by analysis of the crude 1H NMR is 60/40.



Minor diastereomer **II-9fB**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.51 (1H, br, N*H*), 8.16 (1H, d, J=8.5 Hz), 7.88 (2H, d, J=8.7 Hz), 7.46 (1H, dd, J=7.7, 1.6 Hz), 7.32-7.40 (3H, m), 7.26 (2H, d, J=8.3 Hz), 7.08 (1H, td, J=7.6, 1.2 Hz), 7.00 (2H, d, J=8.6 Hz), 2.40 (3H, s, PhC*H*$_3$), 2.31 (1H, dd, J=9.3, 7.2 Hz), 2.05-2.14 (1H, m), 1.85 (1H, dd, J=9.1, 5.1 Hz), 1.41-1.60 (4H, m, C*H*$_2$*CH*$_2$CH$_3$), 0.98 (3H, t, J=7.0 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 167.53, 146.54, 145.33, 141.63, 140.45, 140.13, 133.36, 130.22, 129.96, 128.12, 126.78, 124.78, 123.22, 123.14, 122.70, 34.92, 32.99, 32.28, 26.12, 22.41, 21.55, 14.08; FT-IR (cm^{-1}): 3250 (w), 2958 (w), 2871 (w), 1691 (m, C-O), 1514 (s, N-O), 1435 (m), 1341 (s, N-O), 1021 (m, S-O), 1010 (m), 854 (m), 757 (m), 548 (m), 472 (w); $[\alpha]_D^{20}$= -167.7° (c=0.70, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.29.

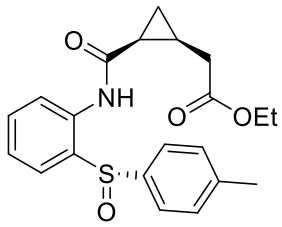


Major diastereomer **II-9fA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.43 (1H, br, N*H*), 8.06 (2H, d, J=8.6 Hz), 8.01 (1H, d, J=8.4 Hz), 7.45 (1H, dd, J=7.6, 1.5 Hz), 7.30-7.40 (5H, m), 7.20-7.25 (2H, m), 7.07 (1H, td, J=7.6, 1.2 Hz), 2.34-2.41 (4H, m), 2.02-2.11 (1H, m), 1.81 (1H, dd, J=9.1, 5.2 Hz), 1.41-1.54 (4H, m, C*H*$_2$C*H*$_2$CH$_3$), 0.96 (3H, t, J=7.1 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 167.33, 146.72, 145.29, 141.66, 140.25, 139.89, 133.13, 130.21, 130.12, 127.85, 127.52, 124.59, 123.32, 122.93, 34.95, 33.22, 32.97, 25.71, 22.33, 21.50, 14.09; FT-IR (cm^{-1}): 3249 (w), 2958 (w), 2872 (w), 1691 (m), 1596 (m), 1514 (s, N-O), 1342 (s, N-O), 1296 (m), 1169 (m), 1021 (m, S-O), 854 (m), 533 (m); HRMS (ESI-TOF): m/z calcd for $C_{26}H_{27}N_2O_4S^+$: 463.1686, found: 464.1640; $[\alpha]_D^{20}$= +53.8° (c=0.80, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.14.

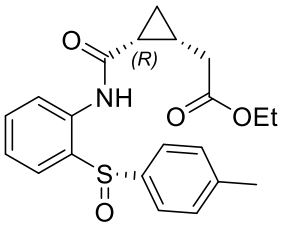
II.7.vii. Asymmetric C(sp^3)-H bond alkylation and olefination

ethyl 2-(2-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acetate II-11a

The general procedure **A** was followed using iodo ethylacetate (100 µL, 3.6 equiv.) as coupling partner and with a reaction time of 24h. Column chromatography on silica gel with CyHex/EtOAc (8:2) afforded the minor diastereomer (22 mg, 24%) and the major diastereomer (31 mg, 34%) as clear oils. The diastereomeric ratio determined by analysis of the crude NMR is 60/40.



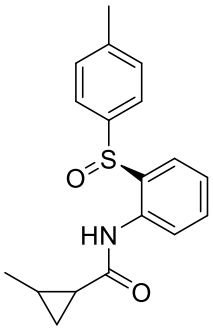
Minor diastereomer **II-11aB**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.42 (1H, br s, N*H*), 8.28 (1H, d, J=8.5 Hz), 7.50 (1H, dd, J=7.7 Hz, 1.4 Hz), 7.40-7.46 (3H, m), 7.25 (2H, d, J=8.3 Hz), 7.12 (1H, td, J=7.6 Hz, 1.1 Hz), 3.96-4.12 (2H, m, C*H*$_2$CH$_3$), 2.12-2.39 (5H, m), 1.64-1.72 (1H, m), 1.47-1.57 (1H, m), 1.15 (3H, t, J=7.2 Hz, CH$_2$C*H*$_3$), 1.03-1.13 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 172.93 (*C*=O ester), 169.83 (*C*=O amide), 141.41, 140.21, 139.82, 132.92, 130.06, 127.97, 127.70, 124.55, 123.12, 122.84, 60.26, 31.90, 21.26, 20.61, 16.80, 14.22, 12.75; FTIR (cm^{-1}): 3248 (w), 2981 (m), 2925 (m), 1732 (s, C=O ester), 1687 (s, C=O amide), 1585 (s), 1524 (br s), 1436 (s), 1397 (s), 1296 (s), 1171 (br s), 1034 (s), 1021 (s), 1010 (s), 809 (s), 758 (s), 547 (m), 531 (m), 473 (m); $[\alpha]_D^{20}$= -1.27° (c=0.87, $CHCl_3$); R$_f$ (CyHex/EtOAc, 3:2): 0.44.



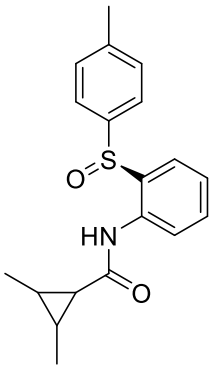
Major diastereomer **II-11aA**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.39 (1H, br s, N*H*), 8.29 (1H, d, J=8.5 Hz), 7.50 (1H, dd, J=7.7, 1.3 Hz), 7.35-7.46 (3H, m), 7.22 (2H, d, J=8.3 Hz), 7.12 (1H, t, J=7.7 Hz), 4.07 (2H, q, J=7.1 Hz, C*H*$_2$CH$_3$), 2.56-2.70 (2H, m), 2.34 (3H, s, PhC*H*$_3$), 1.49-1.69 (2H, m), 1.16 (3H, t, J=7.2 Hz, CH$_2$C*H*$_3$), 1.01-1.09 (1H, m), 0.93-0.99 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 173.08 (*C*=O ester), 169.99 (*C*=O amide), 141.54, 140.49, 139.86, 133.05, 130.17, 128.04, 128.02, 127.83, 124.56, 123.21, 60.60, 32.29, 21.51, 20.98, 17.31, 14.38, 12.48; FTIR (cm^{-1}): 3250 (w), 2924 (m), 2854 (m), 1732 (s, C=O ester), 1688 (s, C=O amide), 1585 (s), 1525 (br s), 1436 (s), 1398 (s), 1297 (s), 1174 (br s), 1022 (s), 1011 (s), 855 (w), 809 (s), 758 (s), 731 (m), 547 (m), 532 (m), 472 (m); HRMS (ESI-TOF): m/z calcd for $C_{21}H_{24}NO_4S^+$: 386.1421, found: 386.1418; $[\alpha]_D^{20}$= +15.2° (c=0.73, $CHCl_3$); R$_f$ (CyHex/EtOAc, 3:2): 0.40.

2-methyl-N-(2-((S)-p-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-11b and 2,3-dimethyl-N-(2-((S)-p-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide

The general procedure A was followed using iodomethane (100 µL, 3.4 equiv.) as coupling partner, silver(I) acetate (184 mg, 1.10 mmol, 2.2 equiv.), sodium trifluoroacetate (36 mg, 0.26 mmol, 50 mol%), palladium(II) acetate (11 mg, 0.05 mmol, 10 mol%) in 4,5 mL of HFIP and 500 µL of water, and with a reaction time of 24h. Column chromatography on silica gel with CyHex/EtOAc (9:1) afforded the bi alkylated product (47 mg, 29%) and the mono alkylated product as a mixture of diastereomers (53 mg, 34%) as clear oils. The diastereomeric ratio determined by analysis of the crude NMR is 60/40.



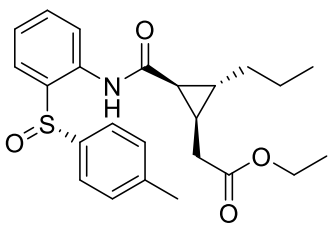
^{1}H NMR (400 MHz, $CDCl_3$): 10.28 (1H, br, NH), 8.39 (0.6H, d, J=8.4 Hz), 8.29 (0.4H, d, J=8.4 Hz), 7.46-7.54 (1H, m), 7.36-7.45 (3H, m), 7.20-7.29 (2H, m), 7.07-7.13 (1H, m), 2.32-2.36 (3H, m), 1.49-1.61 (1H, m), 1.20-1.30 (1H, m), 1.14 (1.9H, d, J=6.1 Hz), 0.90-1.08 (2H, m), 0.87 (1.1H, d, J=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 170.33, 170.24, 141.53, 141.41, 140.63, 140.52, 139.86, 139.82, 133.20, 133.10, 130.16, 130.06, 129.11, 127.99, 127.84, 124.57, 123.03, 122.95, 22.16, 21.94, 21.49, 21.44, 16.24, 16.05, 13.37, 13.17, 12.16, 11.97; FTIR (cm^{-1}): 3256 (w), 2926 (m), 1691 (s), 1585 (s), 1529 (br s), 1436 (s), 1394 (m), 1298 (s), 1182 (m), 1165 (s), 1079 (m), 1022 (s), 1012 (s), 810 (m), 757 (m), 547 (m), 532 (m); HRMS (ESI-TOF): m/z calcd for $C_{18}H_{19}NNaO_2S^+$: 336.1029, found: 336.1021; R_f (CyHex/EtOAc, 3:2): 0.50.



^{1}H NMR (400 MHz, $CDCl_3$): 10.12 (1H, br, NH), 8.26 (1H, d, J=8.4 Hz), 7.51 (1H, dd, J=7.7, 1.6 Hz), 7.36-7.46 (3H, m), 7.20-7.24 (2H, m), 7.09 (1H, td, J=7.6, 1.2 Hz), 2.35 (3H, s, $PhCH_3$), 1.29-1.43 (3H, m), 1.22 (3H, d, J=5.8 Hz), 1.00 (3H, d, J=6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 170.37, 141.37, 140.56, 139.91, 133.09, 130.06, 127.95, 124.60, 123.26, 122.84, 23.63, 21.48, 19.28, 19.08, 7.12, 7.03; FTIR (cm^{-1}): 3250 (w), 2926 (m), 1691 (s), 1585 (s), 1524 (s), 1435 (s), 1296 (s), 1088 (s), 1022 (s), 1012 (s), 804 (m), 758 (s), 548 (m), 533 (m), 492 (m), 471 (m); HRMS (ESI-TOF): m/z calcd for $C_{19}H_{21}NNaO_2S^+$: 350.1185, found: 350.1162; R_f (CyHex/EtOAc, 3:2): 0.56.

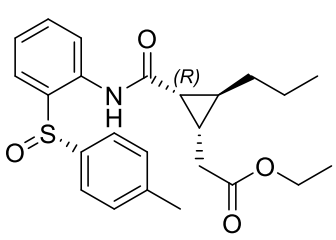
ethyl 2-(2-propyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acetate II-12

The general procedure **B** was followed using compound **II-1g** (75 mg) as substrate and ethyl iodoacetate (105 µL) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (95:5 to 9:1) afforded the minor diastereomer (21 mg, 22%) and the major diastereomer (38 mg, 40%) as clear oils. The diastereomeric ratio determined by analysis of the crude NMR is 60/40.



Minor diastereomer **II-12B**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.35 (1H, br, N*H*), 8.27 (1H, dd, J=8.6, 1.6 Hz), 7.5 (1H, d, J=8.1 Hz), 7.35-7.46 (3H, m), 7.22-7.27 (2H, m), 7.11 (1H, t, J=7.3 Hz), 3.96-4.11 (2H, m, C(O)OC*H*$_2$CH$_3$), 2.29-2.44 (4H, m), 2.11-2.20 (1H, m), 1.26-1.46 (7H, m), 1.16 (3H, t, J=7.2 Hz, C(O)OCH$_2$C*H*$_3$), 0.90 (3H, t, J=7.1 Hz, CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 173.15, 170.03, 141.57, 140.40, 139.90, 133.11, 130.20, 127.89, 124.68, 123.23, 123.07, 123.03, 60.39, 35.18, 31.99, 27.91, 27.30, 24.47, 22.42, 21.43,

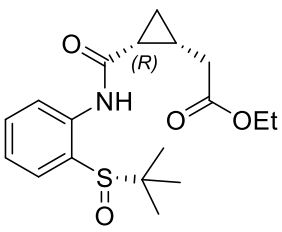
14.40, 14.07; FTIR (cm^{-1}): 3251 (w), 2958 (w), 1733 (s, C-O ester), 1688 (s, C-O amide), 1585 (s), 1436 (s), 1295 (s), 1022 (s, S-O), 809 (s), 547 (s); $[\alpha]_D^{20}$= -11.7° (c=0.3, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.53.



Major diastereomer **II-12A**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.34 (1H, br, N*H*), 8.31 (1H, d, J=8.0 Hz), 7.50 (1H, dd, J=7.6, 1.8 Hz), 7.40-7.46 (1H, m), 7.34-7.40 (2H, m), 7.21 (2H, d, J=8.0 Hz), 7.11 (1H, td, J=7.6, 1.2 Hz), 4.07 (2H, q, J=7.2 Hz, C(O)OC*H*$_2$CH$_3$), 2.57-2.74 (2H, C*H*$_2$CO$_2$Et), 2.34 (3H, s, PhC*H*$_3$), 1.28-1.43 (6H, m), 1.20-1.27 (1H, m), 1.17 (3H, t, J=7.1 Hz, C(O)OCH$_2$C*H*$_3$), 0.89 (3H, t, J=7.1 Hz, CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 173.15, 170.03, 141.46, 140.54, 139.92, 133.11, 130.13, 127.92, 127.81, 124.55, 123.06, 123.03, 60.55, 35.18, 32.08, 28.19, 27.08, 25.01, 22.24, 21.49, 14.40, 14.10; FTIR (cm^{-1}): 3251 (w), 2959 (w), 2926 (w), 2872 (w), 1733 (s, C-O ester), 1687 (s, C-O amide), 1585 (s), 1436 (s), 1022 (s, S-O), 809 (m), 533 (m), 493 (w); HRMS (ESI-TOF): m/z calcd for $C_{24}H_{29}NNaO_4S^+$: 450.1710, found: 450.1712; $[\alpha]_D^{20}$= +5.7° (c=0.5, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.50.

ethyl 2-(2-((2-((*S*)-*tert*-butylsulfinyl)phenyl)carbamoyl)cyclopropyl)acetate II-13

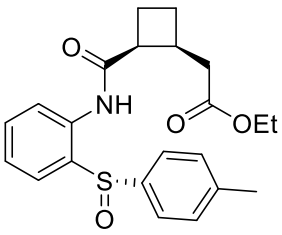
The general procedure **A** was followed using compound **II-1b** (240 mg) as substrate and iodo ethylacetate (400 µL, 3.6 equiv.) as coupling partner and with a reaction time of 24h. Column chromatography on silica gel with CyHex/EtOAc (7:3) afforded a mixture of two diastereomers (42 mg, 13%) as a yellow oil. The diastereomeric ratio determined by analysis of the crude NMR is 90/10.



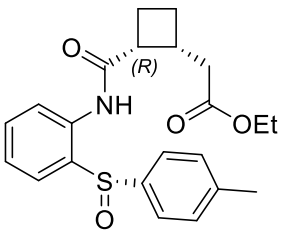
Major diastereomer **II-13**: ^{1}H NMR (400 MHz, $CDCl_3$): 11.20 (1H, br s, N*H*), 8.44 (1H, dd, J=8.5, 1.1 Hz), 7.37-7.43 (1H, m), 7.00-7.10 (2H, m), 4.06 (2H, qd, J=7.1, 0.9 Hz, C*H*$_2$CH$_3$), 2.67 (2H, dd, J=7.2, 3.8 Hz), 1.67-1.77 (1H, m), 1.49-1.60 (1H, m), 1.25 (9H, s, C(C*H*$_3$)$_3$), 1.15 (3H, t, J=7.1 Hz, CH$_2$C*H*$_3$), 1.03-1.11 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 173.14, 170.07, 142.64, 132.36, 128.74, 122.81, 122.18, 120.82, 60.55, 59.17, 32.31, 23.59, 21.17, 17.25, 14.36, 12.48; FTIR (cm^{-1}): 3169 (w), 2980 (m), 1732 (s, C=O ester), 1687 (s, C=O), 1585 (m), 1526 (br m), 1435 (s), 1295 (s), 1174 (s), 1033 (m, S=O), 1007 (s), 761 (m), 526 (w); HRMS (ESI-TOF): m/z calcd for $C_{18}H_{25}NNaO_4S^+$: 374.1397, found: 374.1350; $[\alpha]_D^{20}$= -58.4° (c=1.1, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.44.

ethyl 2-(2-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclobutyl)acetate II-14

The general procedure **A** was followed using compound **II-1c** (70 mg) as substrate and ethyl iodoacetate (60 µL, 0.49 mmol, 2 equiv.) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (9:1 to 8:2) afforded the minor diastereomer (20 mg, 21%) and the major diastereomer (45 mg, 46%) as clear oils. The diastereomeric ratio determined by analysis of the crude NMR is 70/30.



Minor diastereomer **II-14B**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.06 (1H, br, N*H*), 8.47 (1H, d, J=8.4 Hz), 7.43-7.52 (2H, m), 7.33 (2H, d, J=8.2 Hz), 7.20-7.25 (2H, m), 7.14 (1H, td, J=7.6, 1.1 Hz), 3.96-4.10 (2H, m, C*H*$_2$CH$_3$), 3.15-3.23 (1H, m), 2.89-3.00 (1H, m), 2.32-2.45 (2H, m), 2.30 (3H, s, PhC*H*$_3$), 2.17-2.25 (1H, m), 2.01-2.12 (1H, m), 1.87 (1H, dd, J=16.1, 5.0 Hz), 1.68-1.77 (1H, m), 1.17 (3H, t, J=7.1 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 172.55, 171.56, 141.58, 140.34, 139.91, 133.28, 130.23, 128.12, 127.78, 124.60, 123.28, 122.71, 60.36, 43.54, 35.40, 34.12, 24.71, 21.39, 20.88, 14.40; FTIR (cm^{-1}): 3250 (w), 2941 (m), 1730 (s, C=O ester), 1692 (s, C=O amide), 1584 (s), 1529 (br s), 1435 (s), 1294 (s), 1179 (s), 1022 (s), 1011 (s), 808 (s), 757 (s), 493 (m); $[\alpha]_D^{20}$= -20.8° (c=0.58, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.52.

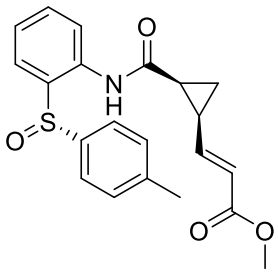


Major diastereomer **II-14A**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.01 (1H, br, NH), 8.36 (1H, d, J=8.3 Hz), 7.43-7.53 (2H, m), 7.33 (2H, d, J=8.3 Hz), 7.21 (2H, d, J=8.3 Hz), 7.14 (1H, td, J=7.6, 1.2 Hz), 4.02 (2H, q, J=7.2 Hz, CH_2CH_3), 3.02-3.20 (2H, m), 2.60 (1H, dd, J=16.2, 6.8 Hz), 2.29-2.38 (4H, m), 2.11-2.23 (2H, m), 1.99-2.08 (1H, m), 1.75-1.85 (1H, m), 1.14 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 172.54, 171.83, 141.54, 140.26, 139.91, 133.12, 130.15, 128.36, 128.04, 124.61, 123.41, 123.32, 60.48, 43.68, 36.06, 34.25, 25.04, 21.47, 20.90, 14.36; FTIR (cm^{-1}): 3249 (w), 2929 (m), 1730 (s, C=O ester), 1690 (s, C=O amide), 1585 (s), 1526 (br s), 1294 (s), 1179 (s), 1022 (s), 1012 (s), 809 (m), 759 (s), 473 (m); HRMS (ESI-TOF): m/z calcd for $C_{22}H_{25}NNaO_4S^+$: 422.1397, found: 422.1386; $[\alpha]_D^{20}$= +22.4° (c=0.53, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.48.

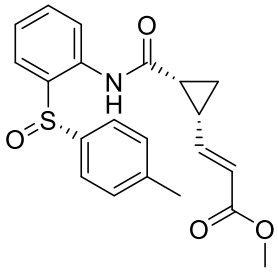
methyl (E)-3-(2-((2-((S)-p-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acrylate II-16

The general procedure **A** was followed using compound methyl acrylate (22 µL) as coupling partner and with a reaction time of 24h. Column chromatography on silica gel with CyHex/EtOAc

(8:2) afforded the minor diastereomer (9 mg, 14%) and the major diastereomer (28 mg, 44%) as clear oils. The diastereomeric ratio determined by analysis of the crude NMR is 75/25.



Minor diastereomer **II-16B**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.56 (1H, br, N*H*), 8.23 (1H, d, J=8.3 Hz), 7.36-7.45 (2H, m), 7.32 (2H, d, J=8.2 Hz), 7.12 (2H, d, J=8.2 Hz), 7.07 (1H, td, J=7.6, 1.1 Hz), 6.71 (1H, ddd, J=15.6, 8.3, 1.9 Hz), 5.88 (1H, d, J=15.6 Hz), 3.58 (3H, s, C(O)OC*H*$_3$), 2.24 (3H, s, PhC*H*$_3$), 1.93-2.02 (2H, m), 1.43-1.50 (1H, m), 1.28-1.35 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 167.96, 166.43, 146.87, 141.74, 140.31, 139.46, 133.06, 130.23, 128.00, 127.66, 124.45, 123.47, 123.11, 121.76, 51.50, 25.36, 23.98, 21.36, 14.79; FTIR (cm^{-1}): 3251 (w), 2951 (w), 1716 (s), 1693 (s), 1649 (s), 1585 (s), 1529 (br s), 1436 (s), 1174 (s), 1021 (s), 1011 (s), 758 (m), 548 (m); $[\alpha]_D^{20}$= -5.2° (c=0.82, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.33.



Major diastereomer **II-16A**: ^{1}H NMR (400 MHz, $CDCl_3$): 10.47 (1H, br, N*H*), 8.32 (1H, d, J=8.4 Hz), 7.36-7.45 (2H, m), 7.33 (2H, d, J=8.4 Hz), 7.16-7.20 (2H, m), 7.08 (1H, td, J=7.5, 1.2 Hz), 6.93 (1H, dd, J=15.6, 10.0 Hz), 5.93 (1H, d, J=15.6 Hz), 3.63 (3H, s, C(O)OC*H*$_3$), 2.30 (3H, s, PhC*H*$_3$), 1.86-2.01 (2H, m), 1.35-1.41 (1H, m), 1.22-1.28 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 167.91, 166.51, 146.65, 141.48, 140.18, 139.67, 132.95, 130.03, 127.56, 124.38 (2C), 123.24, 123.10, 121.79, 51.38, 26.92, 25.27, 23.89, 21.32, 14.49; FTIR (cm^{-1}): 3250 (w), 2951 (w), 1716 (s), 1693 (s), 1435 (s), 1297 (s), 1147 (s), 1020 (s), 1011 (s), 808 (m), 758 (s), 548 (m), 473 (m); HRMS (ESI-TOF): m/z calcd for $C_{21}H_{22}NO_4S^+$: 384.1264, found: 384.1256; $[\alpha]_D^{20}$= +32.0° (c=0.59, $CHCl_3$); R_f (CyHex/EtOAc, 3:2): 0.27.

II.7.viii. Gram-scale and deprotection experiments

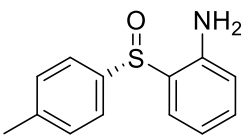
Gram-scale experiment to get II-2a

In a Schlenk were added compound **3** (1.0 g, 3.34 mmol, 1 equiv.), 4'-iodoacetophenone (1.0 g, 4.06 mmol, 1.2 equiv.), silver(I) acetate (1.23 g, 7.39 mmol, 2.2 equiv.), sodium trifluoroacetate (240 mg, 1.77 mmol, 0.5 equiv.) and palladium(II) acetate (37.1 mg, 0.165 mmol, 5 mol %). HFIP (27 mL) and water (3 mL) were then added and the mixture was stirred at 80°C during 10h under air. The mixture was then allowed to cool to room temperature, diluted with EtOAc, filtered over celite and evaporated *in vacuo*. The crude was purified by column chromatography on silica gel

with CyHex/EtOAc (8:2 to 6:4) to get the remaining starting material (56 mg, 6%) as a white solid, **II-2aB** (504 mg, 36%) as an off-white solid and **II-2aA** (754 mg, 54%) as a yellow solid.

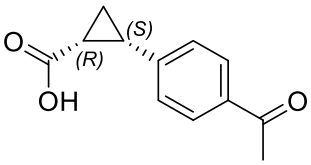
(*S*)-2-(*p*-tolylsulfinyl)aniline APS and (1*R*,2*S*)-2-(4-acetylphenyl)cyclopropanecarboxylic acid II-4A

To a stirred solution of compound **II-2aA** (100 mg, 0.24 mmol, 1 equiv.) in 5 mL of ethanol was added 5 mL of KOH (1M in water). The resulting mixture was stirred overnight at 80°C. The mixture was cooled to room temperature and solvent were evaporated *in vacuo*. Diethylether (5 mL) and water (5 mL) were added. The organic layer was extracted, washed with brine (10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure to afford the free aniline **APS** (54 mg, 97%) as a yellow powder.



^{1}H NMR (400 MHz, $CDCl_3$): 7.39-7.47 (3H, m), 7.18-7.26 (3H, m), 6.75 (1H, td, J=7.6, 1.1 Hz), 6.57 (1H, d, J=8.2 Hz), 4.89 (2H, br s, N*H*$_2$), 2.35 (3H, s, PhC*H*$_3$); other data match the described ones; R_t (min, CHIRALPAK ® IC, Hex/iPrOH 80/20, 0.5 mL/min): 64.902 min (99.5 %), 79.84 (0.5 %).

The previous aqueous layer was carefully acidified with HCl (1M in water). Diethylether (10 mL) was added. The organic layer was extracted, washed with brine (10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure to afford the free carboxylic acid **II-4A** (42 mg, 86%) as an off-white solid.



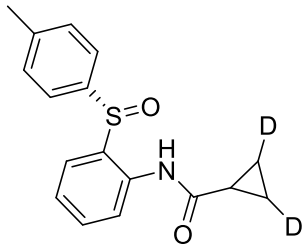
^{1}H NMR (400 MHz, $CDCl_3$): 9.21 (1H, br s, COO*H*), 7.83 (2H, d, J=8.4 Hz), 7.31 (2H, d, J=8.0 Hz), 2.58-2.67 (1H, m), 2.55 (3H, s, C(O)C*H*$_3$), 2.10 (1H, ddd, J=9.4, 7.8, 5.7 Hz), 1.66-1.74 (1H, m), 1.36-1.47 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 198.25, 176.67, 141.91, 135.81, 129.69, 128.24, 26.77, 26.53, 22.04, 12.50; FT-IR (cm^{-1}): 3100 (br w, COOH), 2922 (w), 1679 (s, C-O), 1606 (s), 1268 (s), 1180 (m), 843 (m); HRMS (ESI-TOF): m/z calcd for $C_{12}H_{11}O_3^+$: 203.0714, found: 203.0741; $[\alpha]_D^{20}$= -60.2° (c=0.8, $CHCl_3$);[245] R_f (CyHex/EtOAc, 3:2): 0.12.

II.7.ix. Kinetic isotopic effects and intermediate isolation

***N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-2,3-*d*$_2$-1-carboxamide II-1a-*d*$_2$**

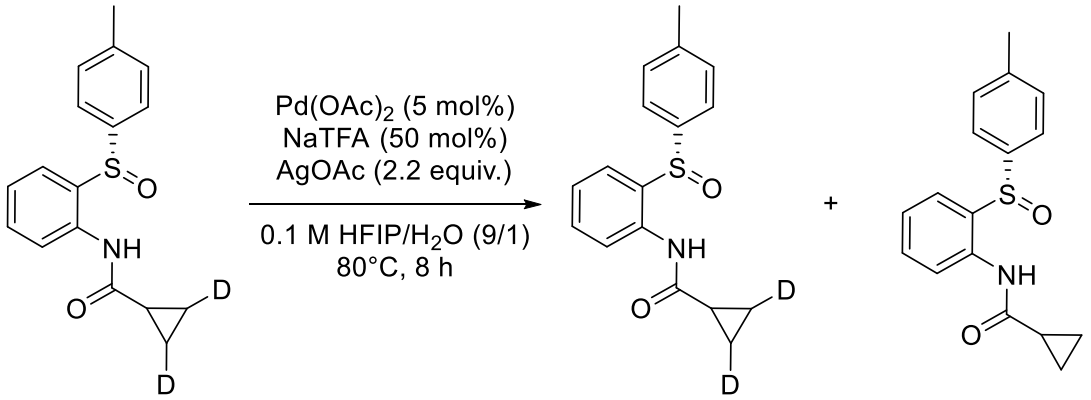
Compound **3** (100 mg, 0.33 mmol, 1 equiv.), palladium(II) acetate (3.75 mg, 0.017 mmol, 5 mol%) were dissolved in acetic acid-*d* (400 µL) and 2 mL of anhydrous acetonitrile. The resulting orange mixture was stirred at 80°C during 8h. After cooling to room temperature, the mixture was filtered and evaporated *in vacuo*. ^{1}H NMR of the crude mixture showed approximatively 75% to

80% deuteration. The reaction was launched a second time on the crude and in the same conditions to achieve full deuteration. Then, solvents were evaporated under reduced pressure and the residue was purified by a short column chromatography on silica gel with CyHex/EtOAc (4:1) to afford the title compound (89 mg, 88%, >99% *cis*-D) as a white solid.



^{1}H NMR (400 MHz, $CDCl_3$): 10.36 (1H, br s, N*H*), 8.29 (1H, d, J=8.4 Hz), 7.49 (1H, dd, J=7.7, 1.6 Hz), 7.36-7.45 (3H, m), 7.19-7.24 (2H, m), 7.11 (1H, td, J=7.6, 1.2 Hz), 2.34 (3H, s, PhC*H*$_3$), 1.49 (1H, t, J=7.9 Hz), 0.73-0.83 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 172.33, 141.54, 140.49, 139.77, 133.11, 130.16, 127.82, 124.58, 123.22, 123.20, 21.51, 16.04, 7.82 (t, J=25.3 Hz), 7.75(t, J=25.5 Hz); HRMS (ESI-TOF): m/z calcd for $C_{17}H_{16}D_2NO_2S^+$: 302.1178, found: 302.1149.

Kinetic study: stability of II-1a-*d*$_2$ in the reaction conditions



In a Schlenk and under air were added compound **II-1a-*d*$_2$** (25 mg, 0.08 mmol, 1 equiv.), silver(I) acetate (31 mg, 0.18 mmol, 2.2 equiv.), sodium trifluoroacetate (5.6 mg, 0.04 mmol, 50 mol%) and palladium(II) acetate (0.93 mg, 0.004 mmol, 5 mol%). The solids were dissolved in 840 µL of a 9:1 mixture of HFIP and water and heated at 80°C during 8h. The mixture was cooled to room temperature, diluted with EtOAc, filtered over celite and evaporated under reduced pressure. Analysis of the crude by ^{1}H NMR experiment showed no more deuterated product.

Kinetic study: conversion between 0 and 25 min

In a microwave tube and under air were added compound **II-1a** (60 mg, 0.20 mmol, 1 equiv.), 4'-iodoacetophenone (60 mg, 0.24 mmol, 1.2 equiv.), sodium trifluoroacetate (14 mg, 0.10 mmol, 50 mol%), silver(I) acetate (74 mg, 0.44 mmol, 2.2 equiv.), palladium(II) acetate (2.2 mg, 0.009 mmol, 5 mol%) and mesitylene (one drop) as internal standard. The compounds were dissolved

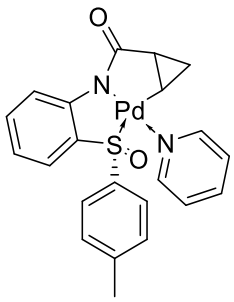
in 1 mL of a 9:1 mixture of HFIP/H_2O. The tube was sealed and after 1 minute of stirring, a sample was taken from the reaction mixture, diluted with DCM and filtered through a small pad of celite. The sample was evaporated under reduced pressure and analyzed by ^1H NMR. The tube was then stirred at 80°C during 20 min and samples were taken every 3 to 5 min, following the same procedure, to get the K_H. The same procedure as above was repeated using compound **II-1a-*d*$_2$** (60 mg, 0.20 mmol, 1 equiv.) as substrate, to get the K_D. All the results are reported in the tables below.

t (min) H	int substrat (H or D)	int dia 1 H	int dia 2 H	Conversion H
0	1	0	0	0,00
3	1	0,03	0,06	0,08
7	1	0,07	0,12	0,16
11	1	0,09	0,19	0,22
16	1	0,14	0,26	0,29
20	1	0,17	0,35	0,34

t(min) D	int dia 1 D	int dia 2 D	Conversion D
0	0	0	0
3	0,03	0,06	1,00
6	0,05	0,09	1,00
10	0,07	0,14	1,00
16	0,11	0,21	1,00
20	0,13	0,26	1,00

Palladacycle II-17

To a degassed and argon-purged Schlenk, compound **3** (50 mg, 0.17 mmol, 1 equiv.) was dissolved in 5 mL of anhydrous acetonitrile. Pyridine (30 µL, 0.37 mmol, 2.2 equiv.) and palladium(II) acetate (38 mg, 0.17 mmol, 1 equiv.) were added and the resulting orange mixture, which turned slowly to bright yellow, was stirred 4h at 60°C. The reaction mixture was cooled to room temperature and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel with CyHex/EtOAc (20:80) to afford the mixture of the two diastereomers of the palladacycle (41 mg, 51%) as a yellow oil. The diastereomeric ratio determined by analysis of the crude ^1H NMR is 60/40. Single crystals suitable for X-Ray diffraction were grown in benzene.

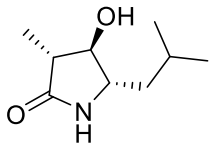


^{1}H NMR (Benzene-d_6, 400 MHz): 9.92 (0.6H, d, J=8.7 Hz), 9.79 (0.4H, dd, J=8.7, 0.9 Hz), 8.21-8.44 (2H, m), 7.69-7.88 (2H, m), 7.49 (0.4H, dd, J=7.9, 1.6 Hz), 7.46 (0.6H, dd, J=7.9, 1.6 Hz), 7.03-7.11 (1H, m), 6.66-6.76 (2H, m), 6.55-6.61 (1H, m), 6.50-6.54 (1H, m), 6.19-6.28 (2H, m), 2.29-2.40 (1H, m, C*H*Pd), 1.82 (1.2H, s, PhCH_3), 1.77 (1.8H, s, PhCH_3), 1.21-1.50 (1H, m), 0.94-0.99 (1H, m), 0.63-0.85 (1H, m); ^{13}C NMR (Benzene-d_6, 100 MHz): 188.39 and 187.94 (*C*=O), 152.83, 152.71, 152.08, 152.05, 142.87, 142.66, 142.15, 142.00, 137.86, 137.81, 136.80, 136.56, 134.50, 134.44, 130.66, 130.55, 126.58, 126.39, 125.605, 125.20, 125.04, 124.22, 124.19, 121.56, 121.51, 28.65 and 27.77 (*C*-Pd), 21.34 and 21.27 (CH_3), 18.39, 17.64, 15.76, 11.49; FT-IR (cm^{-1}): 2976 (w), 1617 (s, C=O), 1581 (m), 1487 (w), 1457 (s), 1341 (s), 1294 (s), 1261 (s), 1099 (m), 1069 (m, S=O), 809 (m), 756 (m), 696 (m), 553 (m), 499 (m); HRMS (ESI-TOF): m/z calcd for $C_{22}H_{21}N_2O_2PdS^+$: 481.0359, found: 481.0166; R_f (CyHex/EtOAc, 3:2): 0.10.

II.7.x. Total synthesis of cyclopropane bearing natural products

(3*R*,4*R*,5*S*)-4-hydroxy-5-isobutyl-3-methylpyrrolidin-2-one

This compound was synthesized according to the literature procedure.[1]



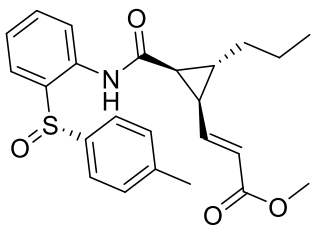
^{1}H NMR (400 MHz, MeOD): 3.50 (1H, dd, J=7.9, 6.1 Hz), 3.37 (1H, ddd, J=8.4, 6.1, 5.2 Hz), 2.30 (1H, dq, J=7.4, 7.3 Hz), 1.74-1.85 (1H, m), 1.50 (1H, ddd, J=13.7, 8.5, 5.1 Hz), 1.38 (1H, ddd, J=13.6, 8.3, 6.0 Hz), 1.19 (3H, d, J=7.2 Hz), 0.97 (3H, d, J=6.7 Hz), 0.95 (3H, d, J=6.6 Hz); ^{13}C NMR (100 MHz, MeOD): 179.68, 82.04, 59.89, 46.80, 45.19, 26.30, 23.88, 22.60, 13.88; $[\alpha]_D^{25} - 21.0°$ ($c = 0.9$, $CHCl_3$);[2] other data match the reported ones.

methyl (*E*)-2-propyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acrylate II-18

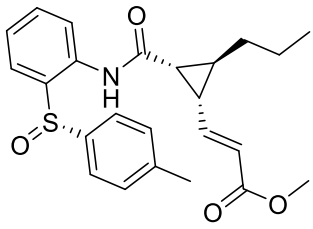
***trans*-II-1g** (500 mg, 1.5 mmol, 1 equiv.), methyl acrylate (750 µL, 8.3 mmol, 5.6 equiv.), silver acetate (489 mg, 2.9 mmol, 2 equiv.), palladium(II) acetate (33 mg, 0.15 mmol, 10 mol%) and sodium trifluoroacetate (100 mg, 0.73 mmol, 50 mol%) were dissolved in 10 mL of HFIP/H_2O (4:1). The resulting mixture was flushed with oxygen and then stirred 24 h at 80 °C under oxygen atmosphere. After cooling down to room temperature, the mixture was diluted with DCM, filtered over celite and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel with CyHex/EtOAc (95:5 to 85:5) to afford the two

[2] Litt. $[\alpha]_D^{27.9} - 21°$ ($c = 1.0$, $CHCl_3$).

diastereoisomers **methyl II-18A** (262 mg, 42%) as a clear oil and **methyl II-18B** (300 mg, 48%) as a yellow solid.



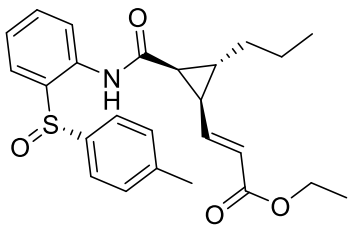
^{1}H NMR (400 MHz, $CDCl_3$): 10.56 (1H, s, N*H*), 8.28 (1H, d, J=8.4 Hz), 7.42-7.52 (2H, m), 7.37 (2H, d, J=8.4 Hz), 7.18 (2H,d, J=8.4 Hz), 7.13 (1H, td, J=7.6, 0.8 Hz), 6.82 (1H, dd, J=15.6, 9 Hz, C*H*=CH-CO_2Me), 5.90 (1H, d, J=15.6 Hz, CH=C*H*-CO_2Me), 3.64 (3H, s, C(O)OC*H*$_3$), 2.30 (3H, s, PhC*H*$_3$), 1.78-1.89 (3H, m), 1.23-1.53 (4H, m), 0.92 (3H, t, J=7.2 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 167.97, 166.49, 146.77, 141.66, 140.28, 139.35, 133.01, 130.16, 127.95, 127.61, 124.36, 123.34, 123.09, 120.98, 51.41, 34.60, 32.44, 31.64, 29.00, 22.10, 21.29, 13.90; HRMS (ESI-TOF): m/z calcd for $C_{24}H_{27}NNaO_4S^+$: 448.1553, found: 448.1495; $[\alpha]_D^{20} - 16.5°$ $(c = 0.7,\ CHCl_3)$; R_t (min, IC, Hex/IPA 80/20, 0.5 mL/min): 49.21 (99%), 63.37 (1%).



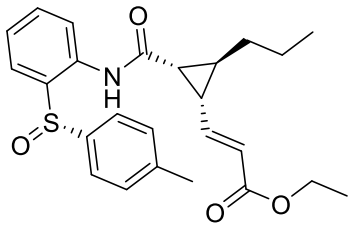
^{1}H NMR (400 MHz, $CDCl_3$): 10.46 (1H, s, N*H*), 8.39 (1H, d, J=8.8 Hz), 7.42-7.53 (2H, m), 7.39 (2H, d, J=8 Hz), 7.23 (2H, d, J=8.4 Hz), 7.13 (1H, td, J=7.6, 1.2 Hz), 7.06 (1H, dd, J=16, 8.2 Hz, C*H*=CH-CO_2Me), 5.95 (1H, d, J=16 Hz, CH=C*H*-CO_2Me), 3.69 (3H, s, C(O)OC*H*$_3$), 2.36 (3H, s, PhC*H*$_3$), 1.66-1.90 (3H, m), 1.22-1.46 (4H, m), 0.91 (3H, t, J=7 Hz, $CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.08, 166.75, 146.70, 141.52, 140.34, 139.88, 133.10, 130.11, 127.75, 127.53, 124.51, 123.23, 123.11, 121.21, 51.47, 34.66, 32.65, 31.91, 29.04, 22.08, 21.41, 13.93; mp: 76 °C $[\alpha]_D^{20} + 23.3°$ $(c = 0.8,\ CHCl_3)$; R_t (min, IA, Hex/IPA 80/20, 0.5 mL/min): 16.02 (99%), 31.72 (1%).

ethyl (*E*)-3-(2-propyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acrylate II-18A

***trans*-4** (1 g, 2.9 mmol, 1 equiv.), ethyl acrylate (1 mL, 9.2 mmol, 3.1 equiv.), silver acetate (1 g, 6.0 mmol, 2 equiv.), palladium(II) acetate (35 mg, 0.16 mmol, 5 mol%) and sodium trifluoroacetate (200 mg, 1.47 mmol, 50 mol%) were dissolved in 20 mL of HFIP/H_2O (4:1). The resulting mixture was flushed with oxygen and then stirred 24 h at 80 °C under oxygen atmosphere. After cooling down to room temperature, the mixture was diluted with DCM, filtered over celite and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel with CyHex/EtOAc (95:5 to 85:5) to afford the two diastereoisomers **ethyl II-18A** (564 mg, 44%) and **ethyl II-18B** (597 mg, 46%) as yellow oils.



^{1}H NMR (400 MHz, $CDCl_3$): 10.53 (1H, br s, N*H*), 8.28 (1H, d, J=8.4 Hz), 7.41-7.50 (2H, m), 7.36 (2H, d, J=8.2 Hz), 7.17 (2H, d, J=8.4 Hz), 7.11 (1H, td, J=7.6, 0.8 Hz), 6.80 (1H, dd, J=15.6, 9.4 Hz), 5.88 (1H, d, J=15.6 Hz), 4.03-4.16 (2H, m, C(O)OC*H*$_2$CH$_3$), 2.29 (3H, s, PhC*H*$_3$), 1.74-1.86 (3H, m), 1.29-1.49 (4H, m), 1.21 (3H, t, J=7.2 Hz, C(O)OCH$_2$C*H*$_3$), 0.91 (3H, t, J=7.1 Hz, CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.07, 166.21, 146.51, 141.75, 140.37, 139.47, 133.09, 130.25, 127.99, 127.69, 124.48, 123.40, 123.15, 121.50, 60.26, 34.71, 32.54, 31.75, 29.07, 22.18, 21.40, 14.50, 13.98; FT-IR (cm^{-1}): 1716 (s, C=O ester), 1689 (s, C=O amide), 1021 (s, S=O); HRMS (ESI-TOF): m/z calcd for $C_{25}H_{30}NO_4S^+$: 440.1890, found: 440.1871; $[\alpha]_D^{20} - 18.6°$ $(c = 0.9,\ CHCl_3)$.



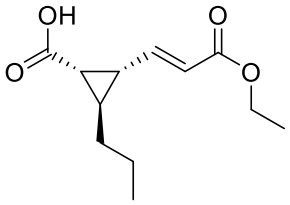
^{1}H NMR (400 MHz, $CDCl_3$): 10.43 (1H, br s, N*H*), 8.37 (1H, d, J=8.4 Hz), 7.48 (1H, dd, J=7.8, 1.1 Hz), 7.44 (1H, ddd, J=8.6, 7.3, 1.8 Hz), 7.37 (2H, d, J=8.2 Hz), 7.21 (2H, d, J=8.3 Hz), 7.12 (1H, td, J=7.5, 0.7 Hz), 7.04 (1H, dd, J=15.6, 10.2 Hz), 5.93 (1H, d, J=15.6 Hz), 4.07-4.19 (2H, m, C(O)OC*H*$_2$CH$_3$), 2.34 (3H, s, PhC*H*$_3$), 1.83 (1H, ddd, J=10.2, 8.3, 6.3 Hz), 1.72-1.79 (1H, m), 1.68 (1H, dd, J=8.2, 5.6 Hz), 1.27-1.39 (4H, m), 1.24 (3H, t, J=7.2 Hz, C(O)OCH$_2$C*H*$_3$), 0.89 (3H, t, J=7.1 Hz, CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.17, 166.47, 146.46, 141.59, 140.43, 139.92, 133.21, 130.19, 127.85, 127.59, 124.58, 123.30, 123.21, 121.73, 60.30, 34.75, 32.69, 32.02, 29.05, 22.17, 21.50, 14.52, 14.02; FT-IR (cm^{-1}): 1711 (s, C=O ester), 1687 (s, C=O amide), 1025 (s, S=O); $[\alpha]_D^{20} + 36.5$ $(c = 1.1,\ CHCl_3)$.

tert-butyl (2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamate Boc-APS and (1*S*,2*R*,3*R*)-2-((*E*)-3-ethoxy-3-oxoprop-1-en-1-yl)-3-propylcyclopropane-1-carboxylic acid II-19A

To a stirred solution of **ethyl II-18A** (500 mg, 1.14 mmol, 1 equiv.) in 1 mL of anhydrous THF was added 4-(dimethylamino)-pyridine (12.5 mg, 0.102 mmol, 10 mol%), followed by di-tert-butyl dicarbonate (248 mg, 1.14 mmol, 1 equiv.). The resulting orange mixture was stirred 10 min at room temperature. The previous mixture was cooled to 0 °C with an ice-bath, followed by slow addition of a solution of lithium hydroxide monohydrate (100 mg, 2.391 mmol, 2.1 equiv.) in 1 mL of water. The resulting yellow mixture was stirred at 0 °C during 2 h.

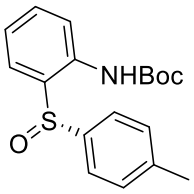
1M HCl sol. (10 mL) was added to reach pH 1-2, followed by diethyl ether (10 mL). The organic layer was extracted and washed with 1M HCl sol. (10 mL). Then, sat. $NaHCO_3$ solution (10 mL) was added to the organic layer, which was stirred 5 min at room temperature. It was extracted twice with sat. $NaHCO_3$ solution (5 mL). The organic layer was washed with water, dried

(Na_2SO_4), filtered off and evaporated under reduced pressure to afford *tert*-butyl (2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamate (345 mg, 92 %) as a yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): 9.11 (1H, br s, N*H*), 8.02 (1H, d, J=8.4 Hz), 7.51 (1H, dd, J=7.6, 1.6 Hz), 7.37-7.44 (3H, m), 7.22 (2H, d, J=8.3 Hz), 7.06 (1H, td, J=7.6, 1.2 Hz), 2.34 (3H, s, PhC*H*$_3$), 1.42 (9H, s, NH*Boc*); ^{13}C NMR (100 MHz, $CDCl_3$): 152.76, 141.31, 140.66, 139.80, 133.05, 129.99, 128.92, 127.87, 124.65, 122.49, 122.09, 80.71, 28.50, 21.50; FT-IR (cm^{-1}): 1033 (m, S=O); HRMS (ESI-TOF): m/z calcd for $C_{18}H_{22}NO_3S^+$: 332.1315, found: 332.1312; $[\alpha]_D^{20} + 74.2°$ ($c = 1.0$, $CHCl_3$); R_t (min, IA, Hex/iPrOH 98/2, 0.5 mL/min): 35.84 (99%), 38.34 (1%).

The combined aqueous layers were carefully acidified with 1M HCl sol. to pH *ca.* 1. Diethyl ether (20 mL) was added. The organic layer was extracted, and the aqueous layer back-extracted with diethyl ether (2 x 10mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure to get the crude carboxylic acid (255 mg) as a yellow oil.



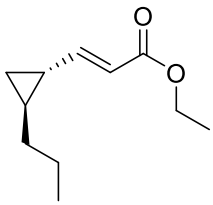
^{1}H NMR (400 MHz, $CDCl_3$): 9.10 (1H, br s, COO*H*), 6.95 (1H, dd, J=15.5, 9.9 Hz), 5.96 (1H, d, J=15.6 Hz), 4.15 (2H, qd, J=7.1, 0.6 Hz, C(O)OC*H*$_2$CH$_3$), 1.72-1.93 (3H, m), 1.31-1.48 (4H, m), 1.25 (3H, t, J=7.1 Hz, C(O)OCH$_2$C*H*$_3$), 0.90 (3H, t, J=7.1 Hz, CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 177.58, 166.40, 145.78, 122.32, 60.47, 34.67, 32.13, 30.70, 29.02, 22.06, 14.46, 13.88; FT-IR (cm^{-1}): 3143 (br w, OH acid), 1694 (s, C=O); HRMS (ESI-TOF): m/z calcd for $C_{12}H_{19}O_4^+$: 227.1278, found: 227.1274; $[\alpha]_D^{20} + 41.0°$ ($c = 0.9$, $CHCl_3$).[3]

ethyl (*E*)-3-((1*S*,2*S*)-2-propylcyclopropyl)acrylate II-21A

Under dark, 2-mercaptopyridine-N-oxide (144 mg, 1.14 mmol, 1 equiv.) and DCC (234 mg, 1.14 mmol, 1 equiv.) were added to a solution of the crude acid **II-18A** (255 mg, 1.14 mmol, 1 equiv.) in 20 mL of anhydrous DCM. The resulting mixture was stirred under argon atmosphere at room temperature during 3 h. The previous mixture was then evaporated under reduced pressure under dark and then redissolved in 20 mL of benzene. 2-methyl-2-propanethiol (205 mg, 0.256 mL, 2.27 mmol, 2 equiv.) was added and the solution was degassed under dark, before being lightened with two sun lamps (distance around 20 - 30 cm) during 3 h.

[3] For the other enantiomer, $[\alpha]_D^{20} - 40.8°$ ($c = 1.0$, $CHCl_3$).

The mixture was evaporated *in vacuo*. Diethyl ether (20 mL) and 1M HCl sol. (10 mL) were added. The organic layer was extracted, washed with 1M HCl sol. (2x 5 mL), sat. $NaHCO_3$ sol. (2x 5 mL), brine (10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure. The crude was purified by a short column chromatography on silica gel with CyHex/EtOAc (95:5) to afford the title compound (174 mg, 84% over four steps) as a clear oil.



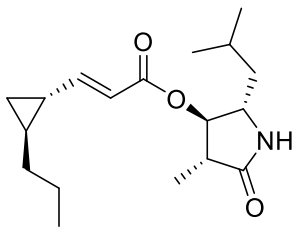
^{1}H NMR (400 MHz, $CDCl_3$): 6.45 (1H, dd, J=15.4, 10.1 Hz), 5.80 (1H, d, J=15.4 Hz), 4.14 (2H, q, J=7.2 Hz), 1.32-1.43 (2H, m), 1.21-1.30 (5H, m), 0.93-1.02 (1H, m), 0.89 (3H, t, J=7.3 Hz), 0.79 (1H, ddd, J=8.3, 4.6, 4.6 Hz), 0.73 (1H, ddd, J=8.1, 6.1, 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 167.13, 154.03, 117.68, 60.20, 35.87, 23.31, 22.57, 22.33, 16.19, 14.56, 14.08; $[\alpha]_D^{25} + 65.9°$ $(c = 1.0, CHCl_3)$;[4] other data match the reported ones.

(2*S*,3*R*,4*R*)-2-isobutyl-4-methyl-5-oxopyrrolidin-3-yl (*E*)-3-((1*S*,2*S*)-2-propylcyclopropyl)acrylate II-22A

II-21A (10 mg, 54.9 µmol, 1 equiv.) was dissolved in 1 mL of a 1:1 mixture of 1,4-dioxane/H_2O. Lithium hydroxide monohydrate (10 mg, 238 µmol, 4.3 equiv.) was added and the mixture was stirred 3 h at 90 °C. After cooling to room temperature, the mixture was carefully acidified with 1M HCl sol. to reach pH *ca* 1-2. Ethyl acetate (10 mL) was added. The organic layer was extracted, washed with brine (2x 10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure.

The crude acid (8.4 mg, 54 µmol, 1 equiv.), **(3*R*,4*R*,5*S*)-4-hydroxy-5-isobutyl-3-methylpyrrolidin-2-one** (10 mg, 58.4 µmol, 1.1 equiv.) and 2-methyl-6-nitrobenzoic anhydride (60 mg, 174 µmol, 3.2 equiv.) were dissolved in 1 mL of anhydrous DCM. Triethylamine (50 µL, 360 µmol, 6.5 equiv.) and 4-(dimethylamino)-pyridine (1 mg, 8.2 µmol, 15 mol%) were added and the mixture was stirred 2 h at room temperature. Sat. $NaHCO_3$ sol. (5 mL) was added. The organic layer was extracted, washed with brine (5 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure. The crude was purified by preparative thin layer chromatography with CyHex/EtOAc (1:1) to afford the title compound (11 mg, 87% over two steps) as a clear oil.

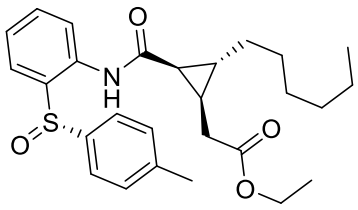
[4] Litt. $[\alpha]_D^{29.6} + 64°$ $(c = 1.0, CHCl_3)$.



^{1}H NMR (500 MHz, C_6D_6): 6.60 (1H, dd, J=15.5, 10.2 Hz), 6.04 (1H, br s, N*H*), 5.88 (1H, d, J=15.5 Hz), 4.92 (1H, dd, J=5.3, 4.5 Hz), 3.34 (1H, ddd, J=9.3, 4.6, 4.5 Hz), 2.48 (1H, dq, J=7.5, 5.2 Hz), 1.39-1.45 (1H, m), 1.32 (3H, d, J=7.5 Hz), 1.25-1.42 (2H, m), 1.16-1.21 (2H, m), 0.93-1.01 (2H, m), 0.89-0.92 (1H, m), 0.78 (3H, t, J=J=7.3 Hz), 0.71 (3H, d, J= 6.3 Hz), 0.65 (3H, d, J=6.2 Hz), 0.55-0.61 (1H, m), 0.41 (1H, ddd, J=8.8, 4.4, 4.4 Hz), 0.35 (1H, ddd, J=8.5, 6.2, 4.4 Hz); ^{13}C NMR (125 MHz, C_6D_6): 176.07, 166.02, 155.11, 117.41, 80.79, 56.66, 44.43, 43.78, 35.68, 25.12, 23.22, 23.18, 22.58, 22.41, 21.71, 16.14, 14.94, 14.00; $[\alpha]_D^{25} + 63.7°$ ($c = 0.4,\ CHCl_3$);[5] other data match the reported ones.

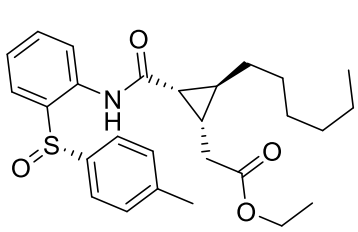
ethyl 2-(2-hexyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acetate II-23

***trans*-11** (200 mg, 0.52 mmol, 1 equiv.), ethyl iodoacetate (186 µL, 1.6 mmol, 3 equiv.), silver acetate (180 mg, 1.1 mmol, 2 equiv.), palladium(II) acetate (12 mg, 0.05 mmol, 10 mol%) and sodium trifluoroacetate (35 mg, 0.26 mmol, 50 mol%) were dissolved in 2 mL of HFIP/H_2O (4:1). The resulting mixture was stirred 24 h at 80 °C. After cooling down to room temperature, the mixture was diluted with DCM, filtered over celite and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel with CyHex/EtOAc (95:5 to 90:10) to afford **II-23A** (116 mg, 47%) as a yellow oil and the key intermediate diastereoisomer **II-23B** (107 mg, 44%) as a clear oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.36 (1H, br s, N*H*), 8.27 (1H, d, J=8.5 Hz), 7.50 (1H, dd, J=7.7, 1.6 Hz), 7.37-7.45 (3H, m), 7.25 (2H, d, J=7.2 Hz), 7.11 (1H, td, J=7.6, 0.8 Hz), 4.04 (2H, qq, J=10.8, 7.2 Hz, C(O)OC*H*$_2$CH$_3$), 2.38 (1H, dd, J=16.5, 8.2 Hz), 2.33 (3H, s, PhC*H*$_3$), 2.15 (1H, dd, J=16.8, 5.1 Hz), 1.20-1.42 (13H, m), 1.16 (3H, t, J=7.2 Hz, C(O)OCH$_2$C*H*$_3$), 0.85 (3H, t, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 173.13, 170.04, 141.57, 140.43, 139.94, 133.10, 130.22, 130.17, 127.89, 124.69, 123.22, 123.07, 60.39, 33.12, 32.02, 31.99, 29.23, 29.02, 27.95, 27.56, 24.53, 22.83, 21.43, 14.42, 14.30; FT-IR (cm^{-1}): 1736 (s, C=O ester), 1688 (m, C=O amide), 1023 (m, S=O); $[\alpha]_D^{20} - 1.8°$ ($c = 0.7,\ CHCl_3$).

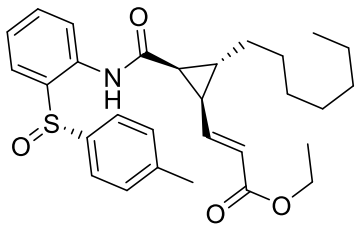
[5] Litt. $[\alpha]_D^{27.5} + 66°$ ($c = 0.25,\ CHCl_3$)



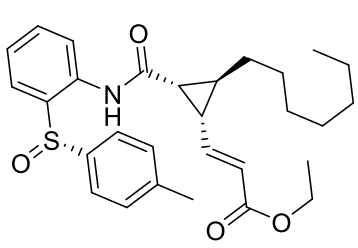
^{1}H NMR (400 MHz, $CDCl_3$): 10.32 (1H, br s, N*H*), 8.26 (1H, d, J=8.6 Hz), 7.45 (1H, dd, J=7.5, 1.3 Hz), 7.31-7.40 (3H, m), 7.17 (2H, d, J=8.1 Hz), 7.06 (1H, td, J=7.6, 1.1 Hz), 4.02 (2H, q, J=7.1 Hz, C(O)OC*H*$_2$CH$_3$), 2.51-2.70 (2H, m), 2.23-2.36 (4H, m), 1.16-1.37 (12H, m), 1.12 (3H, t, J=7.2 Hz, C(O)OCH$_2$C*H*$_3$), 0.83 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 172.93, 169.84, 141.27, 140.35, 139.65, 132.88, 129.94, 127.68, 127.63, 124.34, 122.87, 122.80, 60.34, 32.95, 31.92, 31.86, 29.07, 28.81, 27.98, 27.08, 24.91, 22.66, 21.30, 14.20, 14.13; FT-IR (cm^{-1}): 1736 (s, C=O ester), 1688 (m, C=O amide), 1023 (m, S=O); HRMS (ESI-TOF): m/z calcd for $C_{27}H_{36}NO_4S^+$: 470.2360, found: 470.2338; $[\alpha]_D^{20} + 35.0°$ ($c = 0.6$, $CHCl_3$).

ethyl (*E*)-3-(2-heptyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acrylate II-24

***trans*-8** (100 mg, 0.25 mmol, 1 equiv.), ethyl acrylate (100 µL, 0.92 mmol, 3.6 equiv.), silver acetate (85 mg, 0.51 mmol, 2 equiv.), palladium(II) acetate (5.6 mg, 0.03 mmol, 10 mol%) and sodium trifluoroacetate (17 mg, 0.13 mmol, 50 mol%) were dissolved in 1 mL of HFIP/H_2O (4:1). The resulting mixture was flushed with oxygen and then stirred 24 h at 80 °C under oxygen atmosphere. After cooling down to room temperature, the mixture was diluted with DCM, filtered over celite and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel with CyHex/EtOAc (95:5 to 9:1) to afford **II-24A** (57 mg, 46%) and the key diastereomer **II-24B** (52 mg, 43%) as clear oils.



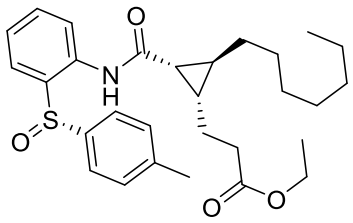
^{1}H NMR (400 MHz, $CDCl_3$): 10.52 (1H, br s, N*H*), 8.27 (1H, d, J=8.3 Hz), 7.40-7.49 (2H, m), 7.36 (2H, d, J=8.3 Hz), 7.16 (2H, d, J=8.2 Hz), 7.10 (1H, td, J=7.6, 1.0 Hz), 6.79 (1H, dd, J=15.6, 9.1 Hz), 5.88 (1H, d, J=15.6 Hz), 3.99-4.19 (2H, m, C(O)OC*H*$_2$CH$_3$), 2.28 (3H, s, PhC*H*$_3$), 1.76-1.87 (3H, m), 1.15-1.50 (15H, m), 0.85 (3H, t, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 168.06, 166.20, 146.53, 147.74, 140.34, 139.44, 133.08, 130.22, 128.01, 127.68, 124.46, 123.39, 123.16, 121.46, 60.24, 32.69, 32.59, 31.95, 31.78, 29.39, 29.37, 29.31, 28.96, 22.83, 21.38, 14.49, 14.28; FT-IR (cm^{-1}): 1722 (s, C=O ester), 1687 (s, C=O amide), 1027 (m, S=O); $[\alpha]_D^{20} - 5.4°$ ($c = 0.5$, $CHCl_3$).



^{1}H NMR (400 MHz, $CDCl_3$): 10.45 (1H, br s, N*H*), 8.34 (1H, d, J=8.4 Hz), 7.46 (1H, dd, J=7.6, 1.3 Hz), 7.35-7.43 (3H, m), 7.20 (2H, d, J=8.1 Hz), 7.10 (1H, td, J=7.6, 1.1 Hz), 7.03 (1H, dd, J=15.6, 10.1 Hz), 5.92 (1H, d, J=15.6 Hz), 4.06-4.18 (2H, m, C(O)OC*H*$_2$CH$_3$), 2.33 (3H, s, PhC*H*$_3$), 1.83 (1H, ddd, J=8.3, 6.2, 2.4 Hz), 1.72-1.78 (1H, m), 1.65-1.71 (1H, m), 1.14-1.41 (14H, m), 0.85 (3H, t, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 168.13, 166.41, 146.45, 141.55, 140.39, 139.86, 133.12, 130.15, 127.71, 127.62, 124.54, 123.27, 123.14, 121.66, 60.25, 32.75, 32.68, 32.07, 31.97, 29.42, 29.41, 29.25, 28.93, 2.85, 21.47, 14.50, 14.27; FT-IR (cm^{-1}): 1717 (s, C=O ester), 1687 (m, C=O amide), 1021 (m, S=O); $[\alpha]_D^{20} + 51.5°$ ($c = 1.0$, $CHCl_3$).

ethyl 3-((1*S*,2*S*,3*R*)-2-heptyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)propanoate II-25B

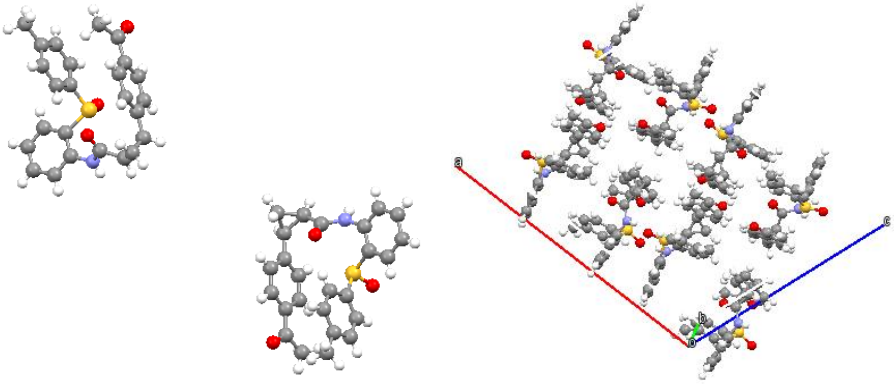
II-24B (54 mg, 0.11 mmol, 1 equiv.) was dissolved in 5 mL of EtOH. The solution was flushed with argon and vacuum few times, before addition of Pd/C (10 wt. % loading, matrix activated carbon support, 20 mg). The resulting mixture was flushed with argon and vacuum before being put under hydrogen atmosphere and stirred 24 h at room temperature. The mixture was carefully filtered over celite, washed with EtOH and evaporated under reduced pressure to yield the title compound (54%, 99%) as a clear oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.35 (1H, br s, N*H*), 8.31 (1H, d, J=8.5 Hz), 7.51 (1H, dd, J=7.6, 1.6 Hz), 7.37-7.46 (3H, m), 7.26 (2H, d, J=8.2 Hz), 7.10 (1H, td, J=7.6, 1.1 Hz), 4.09 (2H, q, J=7.1 Hz), 2.34 (3H, s), 2.03-2.19 (2H, m), 1.50-1.72 (2H, m), 1.19-1.39 (17H, m), 1.03-1.13 (1H, m), 0.86 (3H, t, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 173.43, 170.15, 141.60, 140.62, 139.77, 133.18, 130.22, 127.96, 127.81, 124.52, 123.00, 122.83, 60.39, 34.25, 33.29, 32.02, 29.53, 29.46, 29.29, 29.17, 28.75, 27.46, 22.86, 22.07, 21.43, 14.51, 14.31; FT-IR (cm^{-1}): 1732 (C=O ester), 1690 (C=O amide), 1022 (S=O); HRMS (ESI-TOF): m/z calcd for $C_{29}H_{39}NNaO_4S^+$: 520.2492, found: 520.2510; $[\alpha]_D^{20} + 8.5°$ ($c = 0.5$, $CHCl_3$).

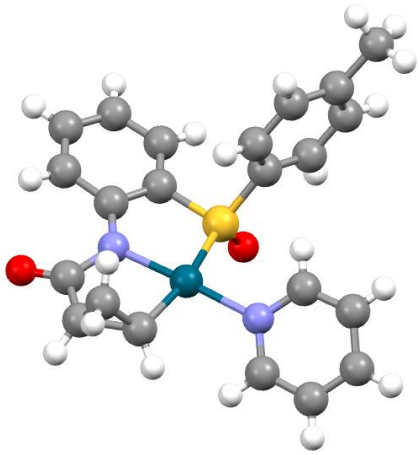
II.7.xi. X-Ray Data

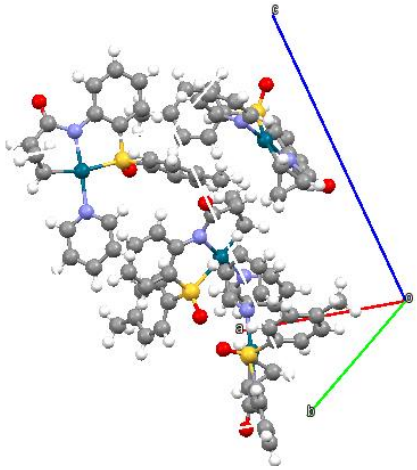
(*1R*,*2S*)-2-(4-acetylphenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)cyclopropane-1-carboxamide II-2aA



Compound	**II-2aA**
Structure identifier	**fcsj160718**
CCDC identifier	**1495369**
Formula	$C_{25}H_{23}NO_3S$
Space group	C_2
Cell lengths	**a** 23.0809(9) **b** 10.7934(4) **c** 18.1795(7)
Cell angles	**α** 90 **β** 109.6230(10) **γ** 90
Cell volume	4265.88
Z, Z'	Z: 8 Z':0
Symmetry cell setting	Monoclinic
Flack parameter	0.00 (3)
R_1	4.4%

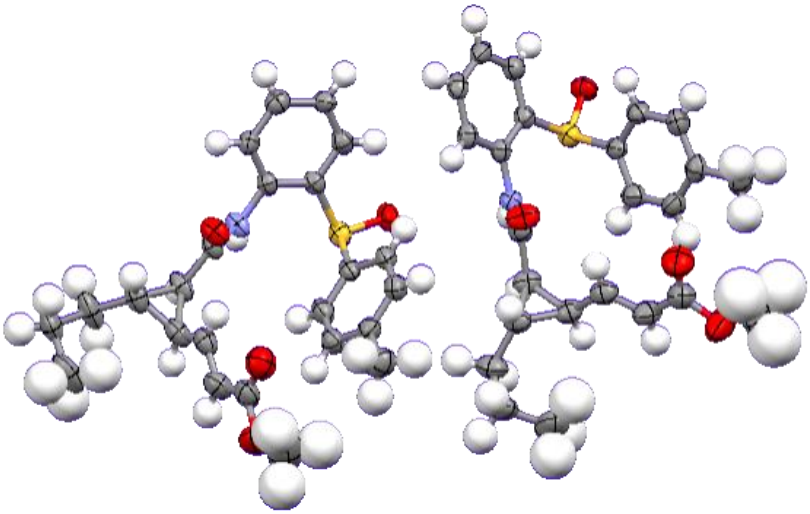
Palladacycle II-17A





Compound	**II-17A**
Structure identifier	**fcsj160526**
CCDC identifier	**1495368**
Formula	$C_{22}H_{20}N_2O_2PdS$
Space group	P 2_1 2_1 2_1
Cell lengths	**a** 10.4585(3) **b** 11.3232(4) **c** 16.8119(5)
Cell angles	**α** 90 **β** 90 **γ** 90
Cell volume	1990.93
Z, Z'	Z: 4 Z':0
Symmetry cell setting	Orthorhombic
Flack parameter	-0.012 (10)
R_1	4.7%

methyl (*E*)-3-((1*S*,2*S*,3*R*)-2-propyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)carbamoyl)cyclopropyl)acrylate II-18B



Compound	**methyl II-18B**
Structure identifier	**fcsj170918**
CCDC identifier	**Not submitted**
Formula	$C_{24}H_{27}NO_4S$
Space group	P 2_1
Cell lengths	**a** 22.1340(6) **b** 4.95080(10) **c** 24.5460(6)
Cell angles	α 90 β 115.741(2) γ 90
Cell volume	2422.86
Z, Z'	**Z**: 4 **Z'**: 0
Symmetry cell setting	Monoclinic
R_1	5.79

II.8. Bibliographic references

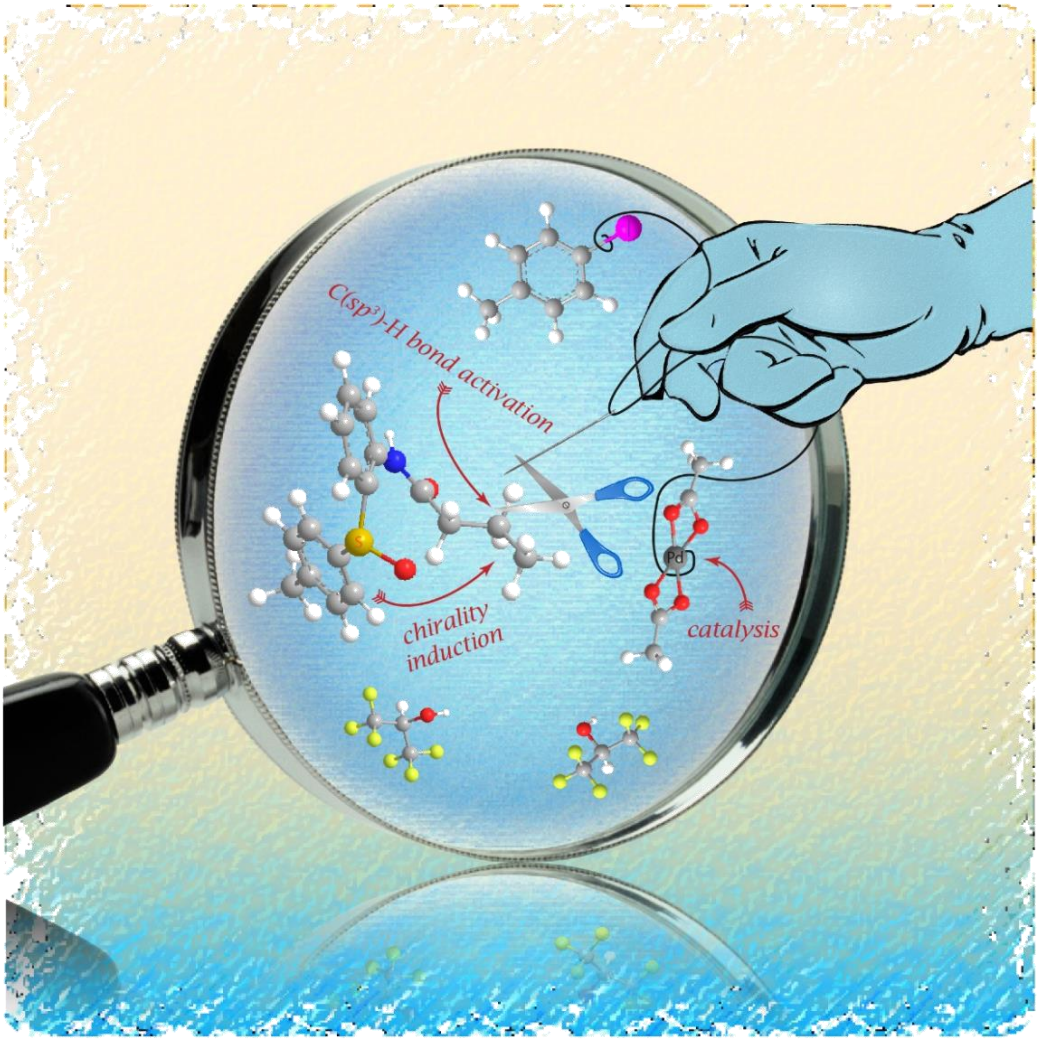
[161] D. Y.-K. Chen, R. H. Pouwer, J.-A. Richard, *Chem. Soc. Rev.* **2012**, *41*, 4631.
[162] L. Pauling, *J. Am. Chem. Soc.* **1931**, *53*, 1367–1400.
[163] C. A. Coulson, H. C. Longuet-Higgins, *Proc. R. Soc. Math. Phys. Eng. Sci.* **1947**, *192*, 16–32.
[164] H. N. C. Wong, M. Y. Hon, C. W. Tse, Y. C. Yip, J. Tanko, T. Hudlicky, *Chem. Rev.* **1989**, *89*, 165–198.
[165] L. A. Wessjohann, W. Brandt, T. Thiemann, *Chem. Rev.* **2003**, *103*, 1625–1648.
[166] A. D. Walsh, *Nature* **1947**, *159*, 712–713.
[167] W. Wu, B. Ma, J. I-Chia Wu, P. von R. Schleyer, Y. Mo, *Chem. - Eur. J.* **2009**, *15*, 9730–9736.
[168] E. Vogel, *Angew. Chem.* **1960**, *72*, 4–26.
[169] C. G. Overberger, A. E. Borchert, *J. Am. Chem. Soc.* **1960**, *82*, 1007–1008.
[170] J. E. Baldwin, *Chem. Rev.* **2003**, *103*, 1197–1212.
[171] C. G. Overberger, A. E. Borchert, *J. Am. Chem. Soc.* **1960**, *82*, 4896–4899.
[172] S. Nozoe, J. Furukawa, U. Sankawa, S. Shibata, *Tetrahedron Lett.* **1976**, *17*, 195–198.
[173] T. Hudlicky, T. M. Kutchan, S. R. Wilson, D. T. Mao, *J. Am. Chem. Soc.* **1980**, *102*, 6351–6353.
[174] M. Yu, B. L. Pagenkopf, *Tetrahedron* **2005**, *61*, 321–347.
[175] T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed.* **2014**, *53*, 5504–5523.
[176] G. Bartoli, G. Bencivenni, R. Dalpozzo, *Synthesis* **2014**, *46*, 979–1029.
[177] H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1958**, *80*, 5323–5324.
[178] A. W. Johnson, R. B. LaCount, *J. Am. Chem. Soc.* **1961**, *83*, 417–423.
[179] E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364.
[180] J. M. Vega-Pérez, I. Periñán, M. Vega, F. Iglesias-Guerra, *Tetrahedron Asymmetry* **2008**, *19*, 1720–1729.
[181] J. M. Vega-Pérez, I. Periñán, F. Iglesias-Guerra, *Tetrahedron Asymmetry* **2009**, *20*, 1065–1072.
[182] J. M. Vega-Pérez, I. Periñán, C. Palo-Nieto, M. Vega-Holm, F. Iglesias-Guerra, *Tetrahedron Asymmetry* **2010**, *21*, 81–95.
[183] Z. Song, T. Lu, R. P. Hsung, Z. F. Al-Rashid, C. Ko, Y. Tang, *Angew. Chem. Int. Ed.* **2007**, *46*, 4069–4072.
[184] M. Cheeseman, I. R. Davies, P. Axe, A. L. Johnson, S. D. Bull, *Org. Biomol. Chem.* **2009**, *7*, 3537.
[185] K.-Y. Ko, H.-S. Yun, *Bull. Korean Chem. Soc.* **2012**, *33*, 2415–2418.
[186] A. B. Charette, H. Juteau, *J. Am. Chem. Soc.* **1994**, *116*, 2651–2652.
[187] H. Y. Kim, L. Salvi, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2009**, *131*, 954–962.
[188] S. Xiao-hua, L. Cun, J. Zhao, Z. Cai-rong, J. Deng-gao, *J. Chem. Res.* **2011**, *35*, 582–584.
[189] W. A. Nugent, *Chem. Commun.* **1999**, 1369–1370.
[190] J. Kallemeyn, M. Mulhern, Y.-Y. Ku, *Synlett* **2011**, *2011*, 535–538.
[191] E. Nadeau, D. L. Ventura, J. A. Brekan, H. M. L. Davies, *J. Org. Chem.* **2010**, *75*, 1927–1939.
[192] C. Mazet, V. Köhler, A. Pfaltz, *Angew. Chem. Int. Ed.* **2005**, *44*, 4888–4891.
[193] J. V. Ruppel, T. J. Gauthier, N. L. Snyder, J. A. Perman, X. P. Zhang, *Org. Lett.* **2009**, *11*, 2273–2276.
[194] S. Zhu, X. Xu, J. A. Perman, X. P. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 12796–12799.
[195] N. Hoshiya, T. Kobayashi, M. Arisawa, S. Shuto, *Org. Lett.* **2013**, *15*, 6202–6205.
[196] L. M. Chapman, J. C. Beck, L. Wu, S. E. Reisman, *J. Am. Chem. Soc.* **2016**, *138*, 9803–9806.
[197] W. R. Gutekunst, R. Gianatassio, P. S. Baran, *Angew. Chem. Int. Ed.* **2012**, *51*, 7507–7510.
[198] C. Reddy, N. Bisht, R. Parella, S. A. Babu, *J. Org. Chem.* **2016**, *81*, 12143–12168.

[199] J. Kim, M. Sim, N. Kim, S. Hong, *Chem Sci* **2015**, *6*, 3611–3616.
[200] D. E. Applequist, D. F. O'Brien, *J. Am. Chem. Soc.* **1963**, *85*, 743–748.
[201] M. Hutchby, C. E. Houlden, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem. Int. Ed.* **2009**, *48*, 8721–8724.
[202] C. E. Houlden, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Org. Lett.* **2010**, *12*, 3090–3092.
[203] J. W. Lockman, B. R. Murphy, D. F. Zigar, W. R. Judd, P. M. Slattum, Z.-H. Gao, K. Ostanin, J. Green, R. McKinnon, R. T. Terry-Lorenzo, et al., *J. Med. Chem.* **2010**, *53*, 8734–8746.
[204] D. Mu, F. Gao, G. Chen, G. He, *ACS Catal.* **2017**, *7*, 1880–1885.
[205] L. Alcaraz, A. Bailey, N. Kindon, *Spirocyclic Amide Derivatives*, **2011**, WO/2011/012896.
[206] S. S. Kim, K. Nehru, S. S. Kim, D. W. Kim, H. C. Jung, *Synthesis* **2002**, 2484–2486.
[207] F. Pan, P.-X. Shen, L.-S. Zhang, X. Wang, Z.-J. Shi, *Org. Lett.* **2013**, *15*, 4758–4761.
[208] S. M. Ennaceur, J. M. Sanderson, *Langmuir* **2005**, *21*, 552–561.
[209] J. Ammer, H. Mayr, *J. Phys. Org. Chem.* **2013**, *26*, 59–63.
[210] C. Janiak, *J. Chem. Soc. Dalton Trans.* **2000**, 3885–3896.
[211] X. Yang, T.-Y. Sun, Y. Rao, *Chem. - Eur. J.* **2016**, *22*, 3273–3277.
[212] J. J. MacKetta, Ed. , *Encyclopedia of Chemical Processing and Design. 34: Pentachlorophenol to Petroleum Fractions, Liquid Densities*, Dekker, New York, **1990**.
[213] R. Kumar, M. Tao, *Biochim. Biophys. Acta* **1975**, *410*, 87–98.
[214] Y. Nishii, N. Maruyama, K. Wakasugi, Y. Tanabe, *Bioorg. Med. Chem.* **2001**, *9*, 33–39.
[215] S. F. Martin, R. E. Austin, C. J. Oalmann, W. R. Baker, S. L. Condon, E. DeLara, S. H. Rosenberg, K. P. Spina, H. H. Stein, *J. Med. Chem.* **1992**, *35*, 1710–1721.
[216] T. D. Avery, G. Fallon, B. W. Greatrex, S. M. Pyke, D. K. Taylor, E. R. T. Tiekink, *J. Org. Chem.* **2001**, *66*, 7955–7966.
[217] H.-Y. Wang, F. Yang, X.-L. Li, X.-M. Yan, Z.-Z. Huang, *Chem. - Eur. J.* **2009**, *15*, 3784–3789.
[218] H. M. Key, P. Dydio, D. S. Clark, J. F. Hartwig, *Nature* **2016**, *534*, 534–537.
[219] X. Chen, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 12634–12635.
[220] K. J. Stowers, K. C. Fortner, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 6541–6544.
[221] H. Jiang, J. He, T. Liu, J.-Q. Yu, *J. Am. Chem. Soc.* **2016**, *138*, 2055–2059.
[222] M. Wasa, K. M. Engle, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3680–3681.
[223] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104.
[224] S. Grimme, S. Ehrlich, L. Goerigk, *J. Comput. Chem.* **2011**, *32*, 1456–1465.
[225] F. Weinhold, in *Encycl. Comput. Chem.* (Eds.: P. von Ragué Schleyer, N.L. Allinger, T. Clark, J. Gasteiger, P.A. Kollman, H.F. Schaefer, P.R. Schreiner), John Wiley & Sons, Ltd, Chichester, UK, **2002**.
[226] J. W. Blunt, B. R. Copp, R. A. Keyzers, M. H. G. Munro, M. R. Prinsep, *Nat Prod Rep* **2016**, *33*, 382–431.
[227] P. Jouin, B. Castro, D. Nisato, *J. Chem. Soc. Perkin 1* **1987**, 1177.
[228] Y. Nagai, T. Kusumi, *Tetrahedron Lett.* **1995**, *36*, 1853–1856.
[229] M. T. Crimmins, B. W. King, E. A. Tabet, *J. Am. Chem. Soc.* **1997**, *119*, 7883–7884.
[230] V. Theodorou, M. Gogou, M. Philippidou, V. Ragoussis, G. Paraskevopoulos, K. Skobridis, *Tetrahedron* **2011**, *67*, 5630–5634.
[231] R. F. Heck, J. P. Nolley, *J. Org. Chem.* **1972**, *37*, 2320–2322.
[232] B. Mondal, B. Roy, U. Kazmaier, *J. Org. Chem.* **2016**, *81*, 11646–11655.
[233] D. H. R. Barton, D. Crich, W. B. Motherwell, *Tetrahedron Lett.* **1983**, *24*, 4979–4982.
[234] D. H. R. Barton, D. Crich, W. B. Motherwell, *Tetrahedron* **1985**, *41*, 3901–3924.
[235] D. H. R. Barton, D. Bridon, I. Fernandaz-Picot, S. Z. Zard, *Tetrahedron* **1987**, *43*, 2733–2740.
[236] O. Motl, M. Amin, P. Sedmera, *Phytochemistry* **1972**, *11*, 407–408.
[237] I. O. Roberts, M. S. Baird, Y. Liu, *Tetrahedron Lett.* **2004**, *45*, 8685–8686.

[238] N. Sitachitta, W. H. Gerwick, *J. Nat. Prod.* **1998**, *61*, 681–684.
[239] J. R. Al Dulayymi, M. S. Baird, K. Jones, *Tetrahedron* **2004**, *60*, 341–345.
[240] M. Cheeseman, S. Bull, *Synlett* **2006**, *2006*, 1119–1121.
[241] R. Green, M. Cheeseman, S. Duffill, A. Merritt, S. D. Bull, *Tetrahedron Lett.* **2005**, *46*, 7931–7934.
[242] T. D. Avery, J. A. Culbert, D. K. Taylor, *Org Biomol Chem* **2006**, *4*, 323–330.
[243] H. Salim, O. Piva, *Tetrahedron Lett.* **2007**, *48*, 2059–2062.
[244] P. Kumar, A. Dubey, A. Harbindu, *Org Biomol Chem* **2012**, *10*, 6987–6994.
[245] J. P. Perdew, K. Burke, M. Ernzerhof, *Phys. Rev. Lett.* **1996**, *77*, 3865–3868.
[246] G. te Velde, F. M. Bickelhaupt, E. J. Baerends, C. Fonseca Guerra, S. J. A. van Gisbergen, J. G. Snijders, T. Ziegler, *J. Comput. Chem.* **2001**, *22*, 931–967.
[247] J. P. Perdew, Y. Wang, *Phys. Rev. B* **1992**, *45*, 13244–13249.
[248] E. van Lenthe, E. J. Baerends, J. G. Snijders, *J. Chem. Phys.* **1993**, *99*, 4597.
[249] E. van Lenthe, E. J. Baerends, J. G. Snijders, *J. Chem. Phys.* **1994**, *101*, 9783.
[250] E. van Lenthe, A. Ehlers, E.-J. Baerends, *J. Chem. Phys.* **1999**, *110*, 8943.
[251] L. Delhaye, C. Stevens, A. Merschaert, P. Delbeke, W. Briône, U. Tilstam, A. Borghese, G. Geldhof, K. Diker, A. Dubois, et al., *Org. Process Res. Dev.* **2007**, *11*, 1104–1111.
[252] G. Solladié, F. Colobert, in *Encycl. Reag. Org. Synth.*, John Wiley & Sons, Ltd, **2001**.
[253] S. A. Blum, R. G. Bergman, J. A. Ellman, *J. Org. Chem.* **2003**, *68*, 150–155.

Chapter 3

Diastereoselective sulfoxide-enabled activation of aliphatic C(sp^3)-H bonds



Chapter 3 – Table of contents

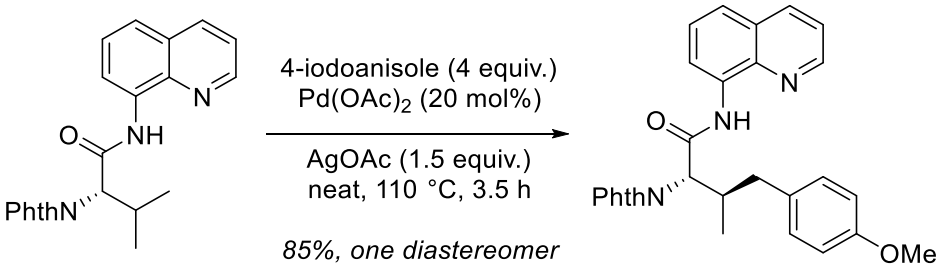
III.1. Introduction

III.1.i. Summary of this work

When we developed and applied the methodology for diastereoselective C(sp^3)-H bond activation on cycloalkane derivatives, one of the main limitations was the total lack of reactivity using linear alkyl chains (II.3.iii). Accordingly, the goal of this work was to extend the previous methodology using our (*S*)-2-(*p*-tolylsulfinyl)aniline (APS) directing group for the C(sp^3)-H bond activation of linear, acyclic alkanes. We performed not only arylation but also challenging diastereoselective acetoxylation.

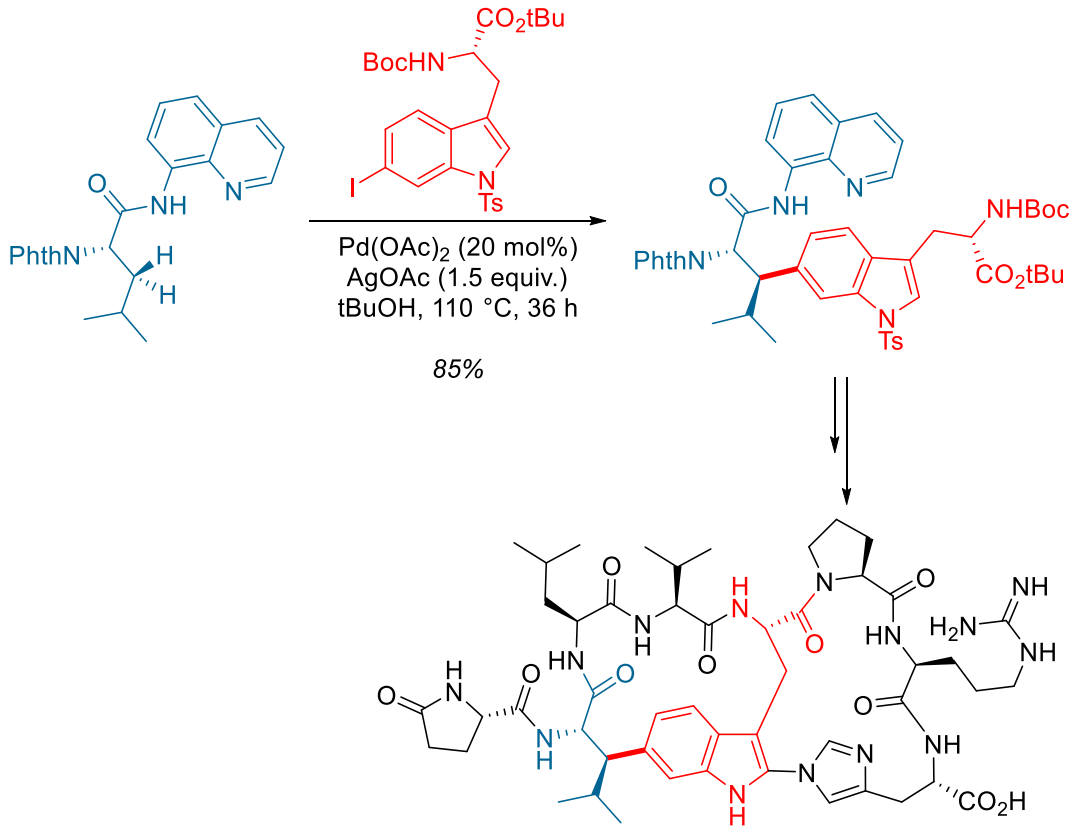
III.1.ii. Diastereoselective C(sp^3)-H bond arylation

As mentioned before, the early development in 2005 of chiral oxazoline directing groups (I.4.v) suffered from an important limitation in terms of scope and no arylation was possible using this auxiliary.[89] Following this pioneering study and in order to access more complex structures, Corey and co-workers published their work on diastereoselective β- and γ- acetoxylation and arylation of aminoquinoline-protected amino-acids.[254] The stereochemistry of the newly formed stereocentre was induced by the existing proximal chiral centre on the amino acid. Diastereomeric ratios varied between 5:1 and > 20:1 depending on the substrate (Scheme 3.99).



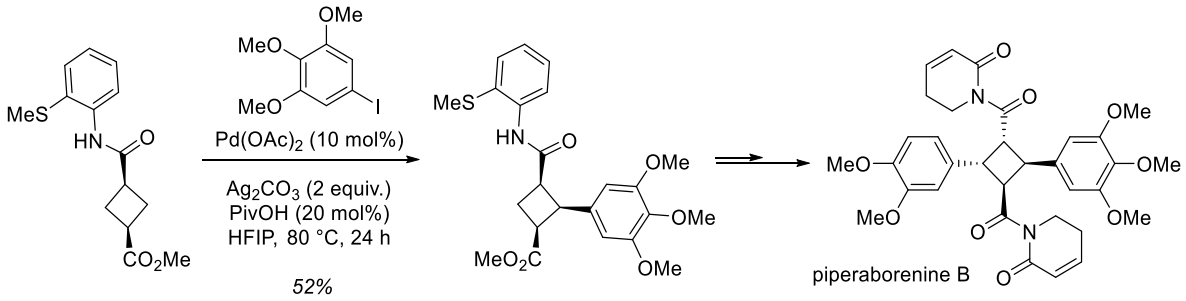
Scheme 3.99 Corey γ-functionalisation of amino acid derivatives

Using this methodology, Chen and co-workers reported the elegant total synthesis of celogentin C, a bicyclic peptide with rare architecture, bearing two unusual Trp C6 to Leu Cβ and Trp C2 to His N1 linkages.[255] The C-C bond between the indole and the lateral chain of leucine was constructed thanks to C-H functionalization (Scheme 3.100).



Scheme 3.100 Chen's total synthesis of celogentin C

In the same manner, Baran and co-workers used the 2-(methylthio)aniline auxiliary originally developed by Daugulis and Babu to promote twice *cis*-arylation on a cyclobutane ring, thus affording the key intermediate for the total synthesis of piperaborenine B (Scheme 3.101).[3,4,256] The predefined absolute stereochemistry on the cyclobutane ring and the higher stability of the *cis*-five-membered palladacyclic intermediate allowed total diastereoselectivity for the arylation. Complete epimerization of the amide using potassium *tert*-butoxide permitted a second *cis*-arylation and subsequently the obtention of the key skeleton of the molecule.



Scheme 3.101 Baran's total synthesis of piperaborenine B

In 2014, a breakthroughing work was published by Yu and co-workers, disclosing the use of a chiral amino acid derivative as directing group and stereoinductor (I.4.iii).[64] As presented in chapter 2, Hong and co-workers extended this strategy and published the first diastereoselective synthesis of *cis*-cyclopropanes (Chart 3.18).[199] High level of diastereomeric induction were obtained (up to 70:1), however the two diastereomers were not separable by simple column chromatography.

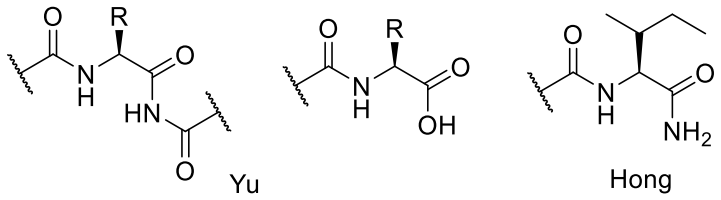
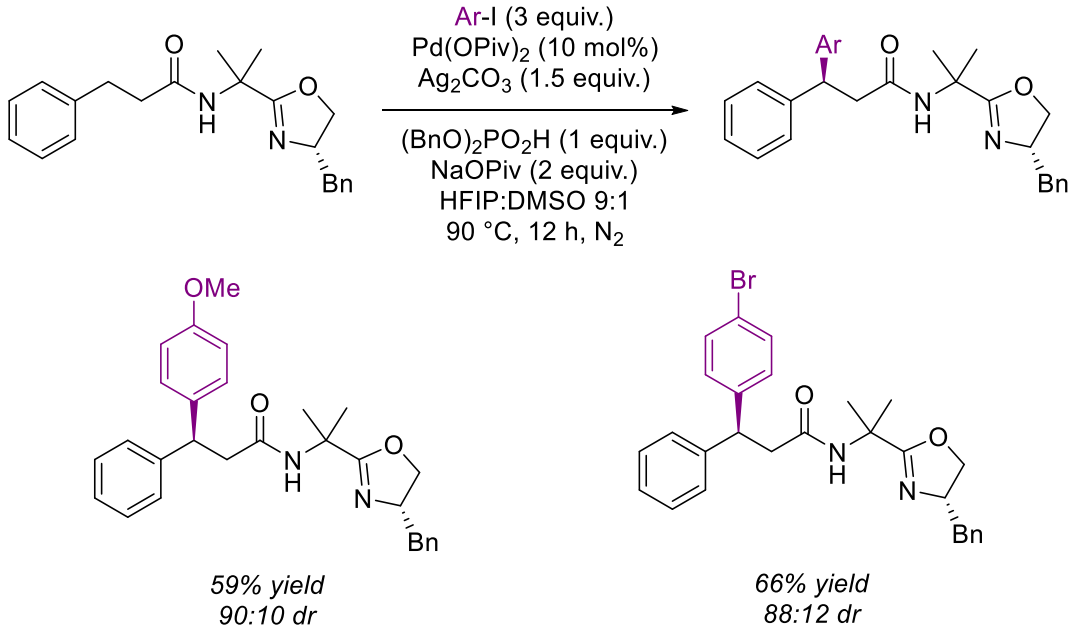


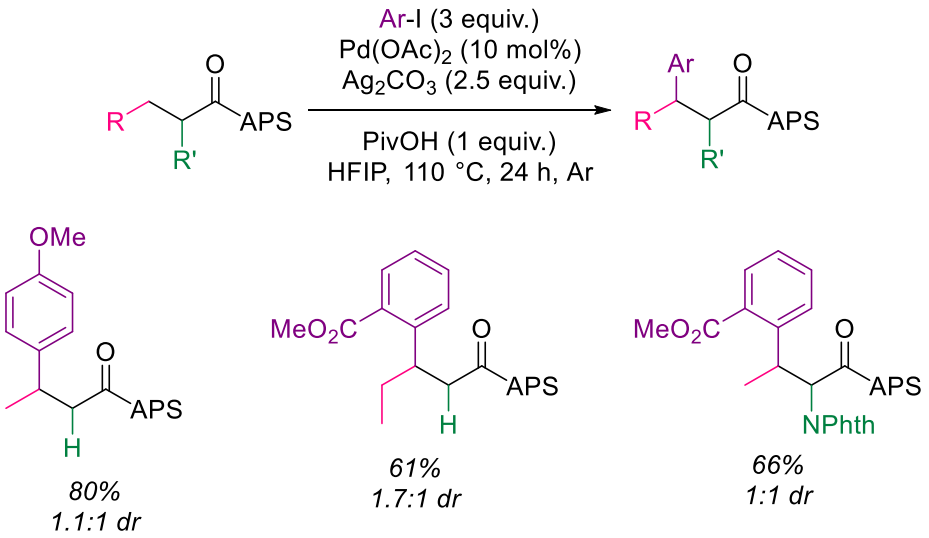
Chart 3.18 Chiral amino acid directing groups for the asymmetric C-H bond activation

The same year, an amino-oxazoline directing group was developed by Shi for the functionalisation of alkyl chains.[257] Initially, the authors demonstrated that their auxiliary is an efficient tool to control regioselectivity. Besides, they also disclosed few diastereoselective examples, obtaining the chiral compounds with good diastereomeric ratios (Scheme 3.102).



Scheme 3.102 Shi's diastereoselective C-H bond functionalisation

Finally, in 2017, when we were developing the herein presented project, He and co-workers disclosed the use of APS-directing group for the functionalisation of aliphatic chains with a large panel of iodoarenes including sterically hindered ones. However, the majority of examples concerned used of a racemic chiral auxiliary and low diastereomeric excesses were observed.[204]



Scheme 3.103 He's diastereoselective C-H activation using APS directing group

Accordingly, considering the scarcity of catalytic systems allowing diastereoselective C-H bond activation and in the continuity of our recent work on the asymmetric functionalisation of cycloalkane rings, we embarked on the diastereoselective C-H bond functionalisation of aliphatic acyclic substrates.

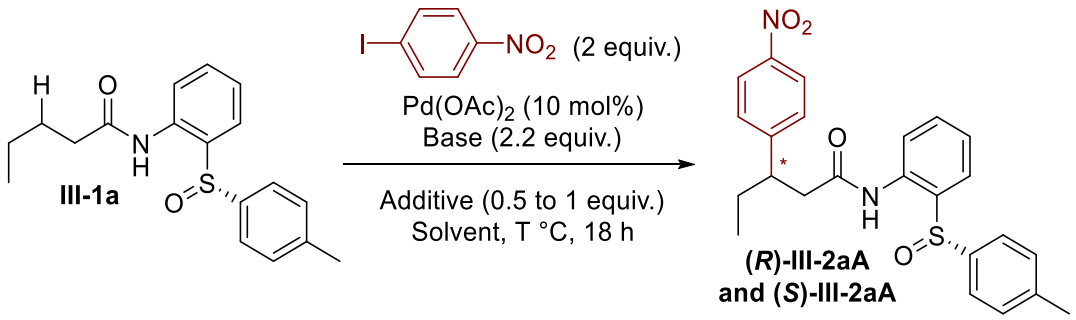
III.2. Reaction condition optimization

III.2.i. From cycloalkanes to linear alkyl chains

In our optimisation of diastereoselective C(sp^3)-H bond functionalisation using the APS as chiral directing group, we faced some difficulties to activate the linear alkyl chains under the previously optimised protocol.

We chose as model substrate **III-1a** to optimise the β-arylation (Table 3.14). This substrate was obtained by a standard peptidic coupling (II.2.i.4) between the APS and valeroyl chloride and indeed showed no reactivity under our previously developed conditions (Entry 1). However, omitting water in the reaction mixture allowed partial conversion to the desired diastereomers **(*R*)-III-2aA** and **(*S*)-III-2aA** with 60:40 ratio between the two diastereomers (Entry 2). Change of a silver salt from acetate to carbonate counterion did not allow to improve the efficiency of the reaction as shown in Entry 3.

Table 3.14 Optimisation of the β-C-H arylation of alkyl chains

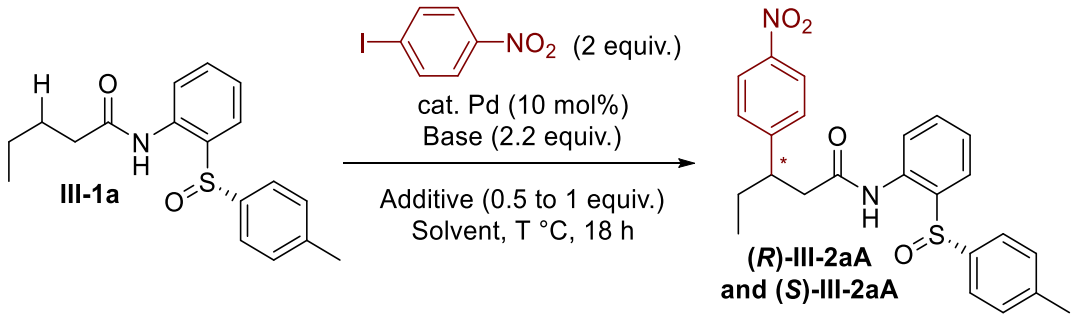


Entry	Cat.	Base	Additive	Solvent	T °C	Conversion	*dr*
1	$Pd(OAc)_2$	AgOAc	NaTFA	HFIP/H_2O (4:1)	80	0	-
2	$Pd(OAc)_2$	AgOAc	-	HFIP	80	30	3:2
3	$Pd(OAc)_2$	Ag_2CO_3	-	HFIP	80	25	1:1

Following these preliminary results, solvent screening showed that toluene was crucial to achieve good reactivity (Entry 1, Table 3.15). When performing the reaction in 1,2-dichloroethane using potassium bases, a low conversion of 30 and 40% was observed (Entries 2 and 3). Addition of a small amount of HFIP in the reaction mixture improved both conversion and diastereomeric ratio (Entry 4). This could be explained by the hydrogen-bonding between the solvent and the sulfoxide, thus enhancing its properties and permitting better coordination and

chiral induction.[15] Other polar protic solvents like acetic acid or trifluoroacetic acid did not give better results (Entries 6 and 7). Surprisingly, although we found that direct functionalisation of cycloalkanes might be enhanced adding sodium trifluoroacetate, this additive seriously decreased the reactivity of the system in this case as the conversion dropped to 30 % (Entry 14). Likewise, using the optimal solvent system, no other base than silver acetate was well tolerated, and conversions dropped below 20% (Entries 10 to 13).

Table 3.15 Optimisation of the β-C-H arylation of alkyl chains



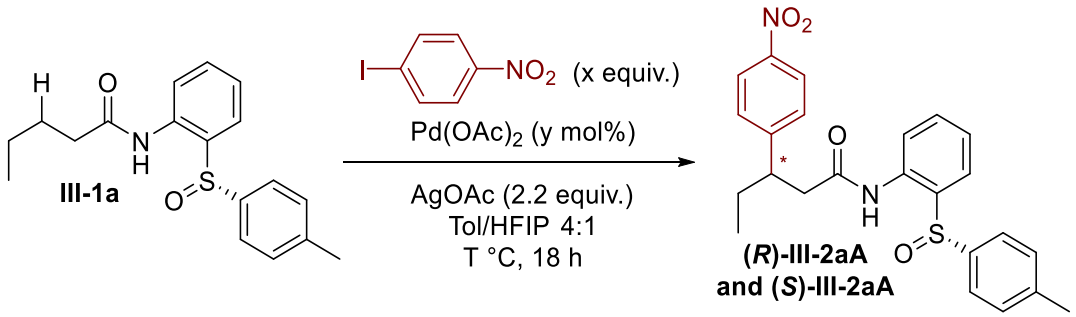
Entry	Cat.	Base	Additive	Solvent	T °C	Conversion	*dr*
1	$Pd(OAc)_2$	AgOAc	-	Toluene	100	60	1:1
2	$Pd(OAc)_2$	K_2CO_3	-	DCE	120	30	3:2
3	$Pd(OAc)_2$	K_3PO_4	-	DCE	120	40	3:2
4	$Pd(OAc)_2$	AgOAc	-	Toluene/HFIP (4:1)	100	65	3:2
5	$Pd(OAc)_2$	AgOAc	-	Xylene	130	55	1:1
6	$Pd(OAc)_2$	AgOAc	-	Toluene/TFA (4:1)	100	50	3:2
7	$Pd(OAc)_2$	AgOAc	-	Toluene/AcOH (4:1)	100	<5	-
8	$Pd(OAc)_2$	Ag_2CO_3	KF[6]	HFIP	110	65	1:1
9	$Pd(OAc)_2$	AgOAc	PivOH	Toluene/HFIP (4:1)	110	20	3:2
10	$Pd(OAc)_2$	AgTFA	-	Toluene/HFIP (4:1)	110	0	-
11	$Pd(OAc)_2$	K_2CO_3	-	Toluene/HFIP (4:1)	110	0	-
12	$Pd(OAc)_2$	Cs_2CO_3	-	Toluene/HFIP (4:1)	110	0	-
13	$Pd(OAc)_2$	Ag_3PO_4	-	Toluene/HFIP (4:1)	110	15	1:1
14	$Pd(OAc)_2$	AgOAc	NaTFA	HFIP	80	30	3:2

[6] 3 equiv. were used.

Then, we studied the stoichiometry of the reaction's partners as well as the reaction time and the temperature.

Using 3 equivalents of the coupling iodide allowed to increase the yield up to 80 % (Entries 1 and 2, Table 3.16). Interestingly, the coupling works better under air atmosphere and thus does not require strictly anhydrous conditions (Entries 3 and 4). Final optimisation rewardingly showed that increasing the reaction time to 36 h concomitantly with adding more equivalents of iodoarene coupling partner allowed us to get 85 % conversion to the desired product (Entry 5). The two diastereomers were separated by column chromatography on silica gel. It is important to precise that the same conditions were applied with the (*S*)-2-(*tert*-butylsulfinyl)aniline ATS chiral auxiliary and only gave less than 10 % conversion, thus the diastereomeric excess could not be exactly determined, but assumed to 9:1 (Entry 8). Moreover, further increase of the reaction temperature was detrimental to both, efficiency and stereoselectivity (Entry 6), and arylbromides were not tolerated as we assumed that they did not undergo oxidative addition (Entry 7).

Table 3.16 Optimisation of the β-C-H arylation of alkyl chains



Entry	x	y	T °C	Variations from standard conditions	Conversion	*dr*
1	2	10	100	-	65	3:2
2	3	10	110	-	80	3:2
3	3	10	110	Ar atm.	55	3:2
4	3	10	110	Ar atm. and 4 Å mol. sieves.	50	3:2
5	3	5	110	36 h reaction time	85	3:2
6	3	5	130	-	70	1:1
7	3	5	110	ArBr as coupling partner	0	-
8	3	5	110	ATS chiral auxiliary	10	9:1

III.2.ii. Rationalization of the solvent role

Optimisation of the conditions for the asymmetric C(sp^3)-H activation of simple alkyl chains revealed that presence of water poisoned the reaction. Also, polar protic solvents other than HFIP were inadequate (Table 3.14 and Table 3.15). However, setting up an argon atmosphere and/or using molecular sieves in the reaction mixture was deleterious and the yield dropped from 80 to 50 %.

Interestingly, when carrying out the reaction with toluene/HFIP/water (64:16:1), the reaction proceeded well, showing the tolerance of small amount of water.

The high lipophilicity of the alkyl chain used for the optimisation may not be compatible with high amounts of water. Indeed, HFIP and water can form micelles and substrate **III-1a** is not likely to enter these micelles for the C-H activation, while a homogenous mixture of toluene and HFIP will 1) better solubilize this hydrophobic substrate and 2) improve the properties of the sulfoxide by creating hydrogen bonds and an HFIP sphere around the sulfoxide.

Another argument is related to the pK_A of the species: indeed, cyclopropane rings have a pK_A around 46 while aliphatic chains are around 50. Thus, the pH of the reaction mixture may be crucial for the reactivity and the buffer created by either HFIP, water and toluene may tune the reactivity of the system.

III.3. C(sp^3)-H arylation and application to the synthesis of biologically active molecules

III.3.i. Arylation of simple alkyl chains

With the optimised reaction conditions in hand, we explored the scope of this transformation regarding both, the influence of the aliphatic substituent of the C-H substrate and the nature of the iodoarenes. The mono-arylation of **III-1a** occurred smoothly using electron-rich and -poor iodoarenes, delivering the expected products with high yields. However, the diastereoselectivity remained low. Remarkably, this catalytic system tolerates well the steric hindrance on the iodoarene and with *ortho*-substitued coupling partners slight increase of the diastereomeric excess was observed. However, further improvement was achieved by rising the steric hindrance on the aliphatic chain. Rewardingly, the stereoinduction went up to 4:1 with **III-2f** and the only deceiving example was **III-2g** which showed poor reactivity, assumed to the high steric hindrance of the *tert*-butyl group (Figure 4.38).

In most cases, the major diastereomer could be isolated from the other one, delivering enantiopure valuable compounds in interesting yields. Indeed, not only a large variety of iodoarenes was tolerated, but also a panel of substrates, bearing sensitive moieties such as methyl ester in **III-2i** and phthalimide in **III-2j** on the aliphatic chain. This last compound may be seen as a precursor for derivatives of γ-amino butyric acid (GABA), the main inhibitory neurotransmitter in the mammalian central nervous system, like Baclofen[258] or Phenibut.[259]

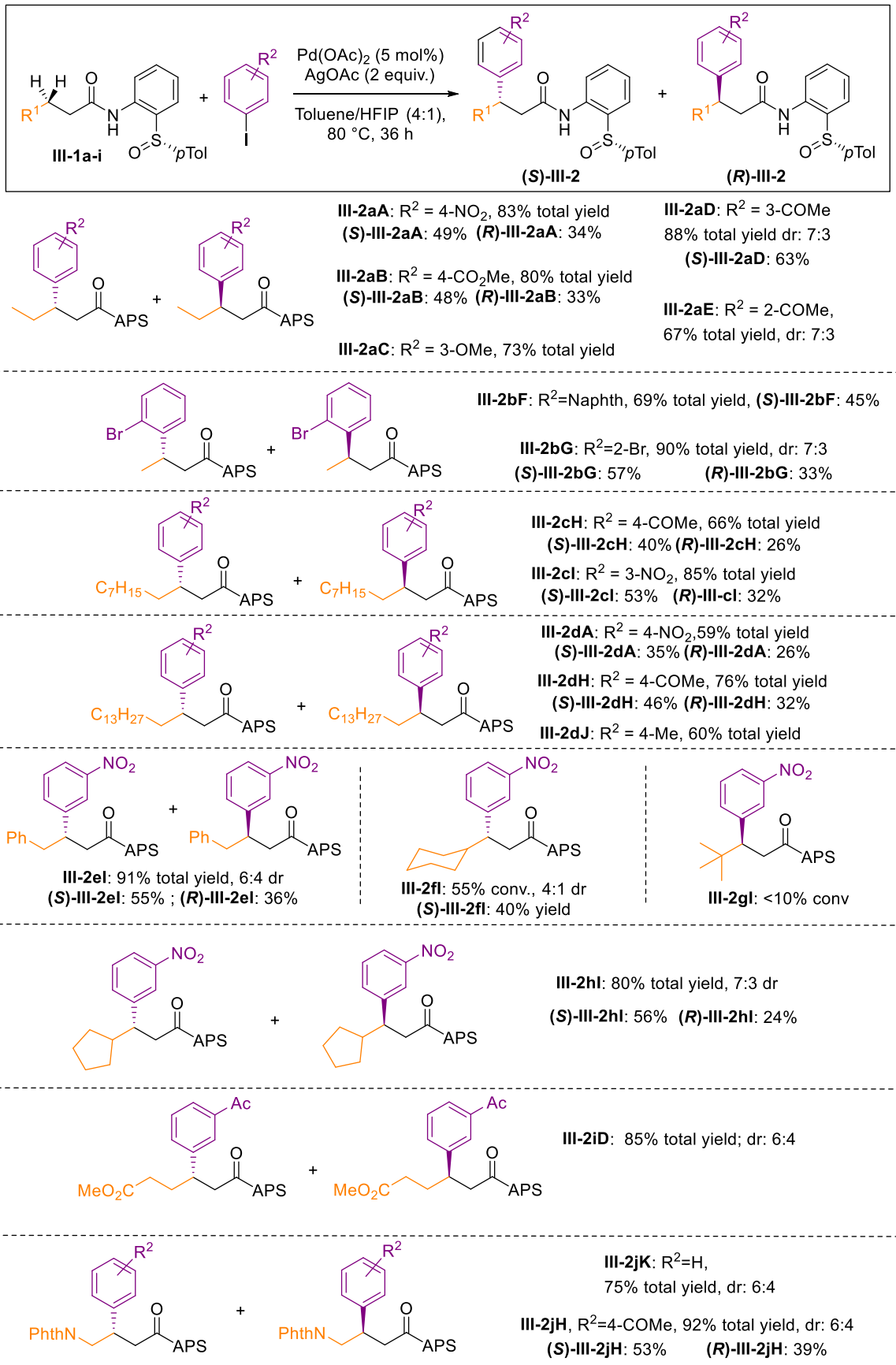


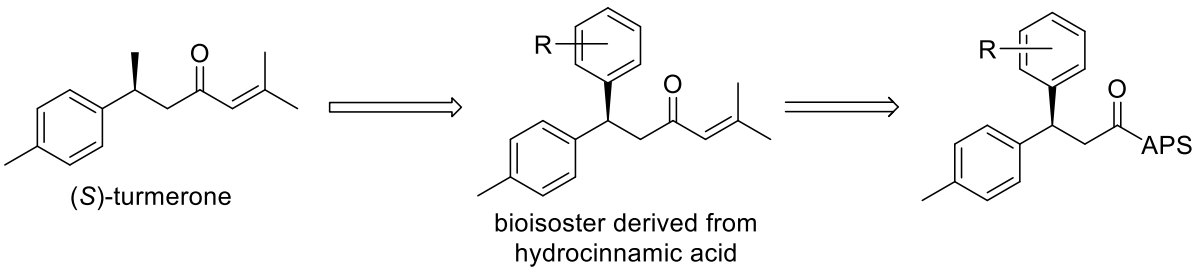
Figure 4.38 Scope of arylation on acyclic aliphatic chains

In order to further delimitate the potential of our catalytic system, we focused on the direct arylation of benzylic positions of substrates **III-1k**, **III-1l** and **III-1m**. Due to the better reactivity of these C-H bonds, the reaction temperature could be lowered to 80 °C as well as the reaction time to 16 h (Figure 4.39).

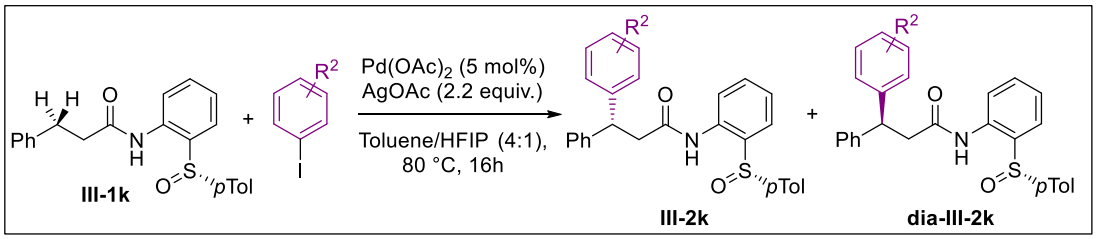
Coupling with hydrocinnamic acid derivative **III-1k** was highly efficient and the diastereomeric ratio went up to 9:1 using electron-rich coupling partners such as iodoanisole. Many iodoarene coupling partners were tolerated, such as a sensitive nitro for **III-2kA** and **III-2kI** or halogen groups in **III-2kL** and **III-2kN**. Starting from other commercial derivatives such as **III-1l** and **III-1m**, the arylation proceeded smoothly and allowed obtention of complex compounds with an average yield of 84 % and good diastereomeric ratio.

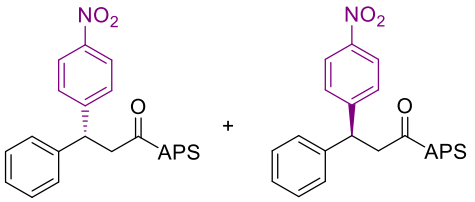
Interestingly, no δ-C-H activation on the aryl moiety was observed. Despite fairly good diastereomeric ratios, none of the coupling products except **III-2kA** was obtained as a single diastereomer. Multiple elution systems on column chromatography and recrystallisation solvents were attempted without success. Moreover, the methodology was poorly tolerant with *ortho*-substituted coupling partners, arguably due to high steric hindrance of the palladacycle, resulting in a difficult oxidative addition.

However, this easy access to various complex 3-aryl-hydrocinnamic acid derivatives could for example allow concise synthesis of turmerone bioisosters (Scheme 3.104).[260]

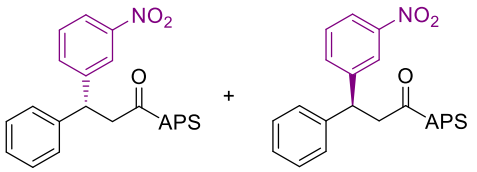


Scheme 3.104 Access to turmerone bioisosters

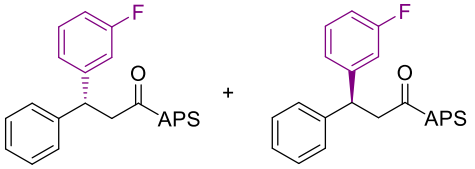




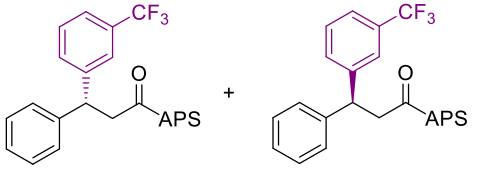
III-2kA: 80% total yield; 3:1 dr
(***S***)-**III-2kA**: 50% (***R***)-**III-2kA**: *nd*



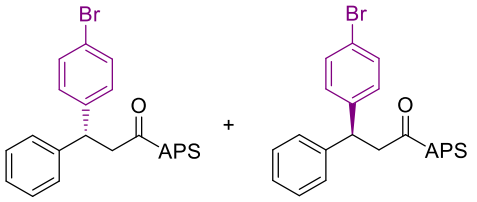
III-2kI: 84% total yield; 3:1 dr



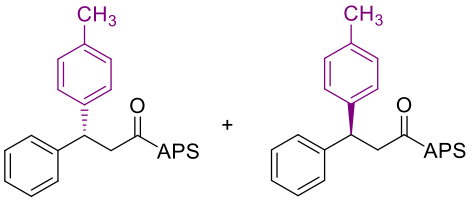
III-2kL: 87% total yield; 4:1 dr



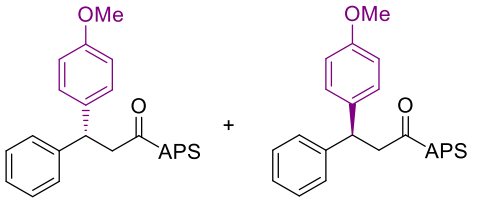
III-2kM: 87% total yield; 4:1 dr



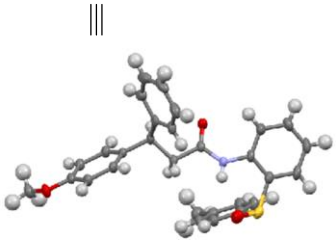
III-2kN: 92% total yield; 9:1 dr

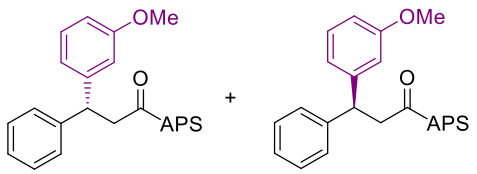


III-2kH: 87% total yield; 5.7:1 dr

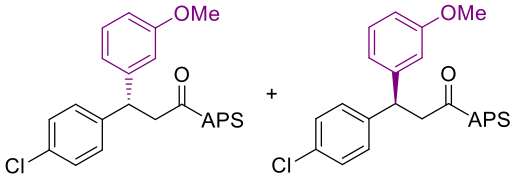


III-2kO: 84% total yield; 9:1 dr

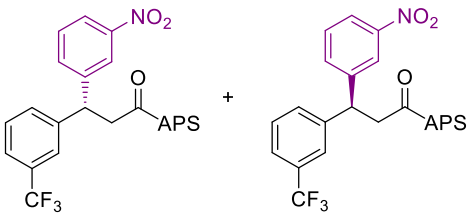




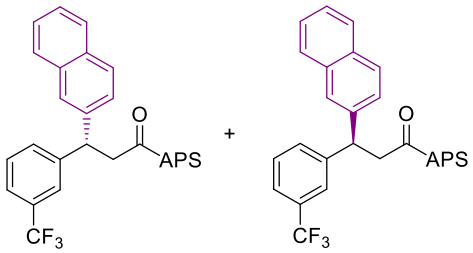
III-2kC: 78% total yield; 9:1 dr



III-2lC: 92% total yield, 85:15 dr



III-2ml: 88% total yield, 9:1 dr



III-2mF: 72% total yield, 9:1 dr

Figure 4.39 Scope of arylation on hydrocinnamic acid derivatives

Rewardingly, the major diastereomer of racemic **III-2kO** afforded mono-crystals suitable for X-Ray diffraction analysis by slow evaporation of a mixture of dichloromethane and chloroform. This crystallographic data allows unambigously the determination of the absolute configuration of the newly formed stereocentre with respect to the known (*S*) configuration of the sulfoxide and the absolute configuration of all products was attributed accordingly (Figure 3.40).

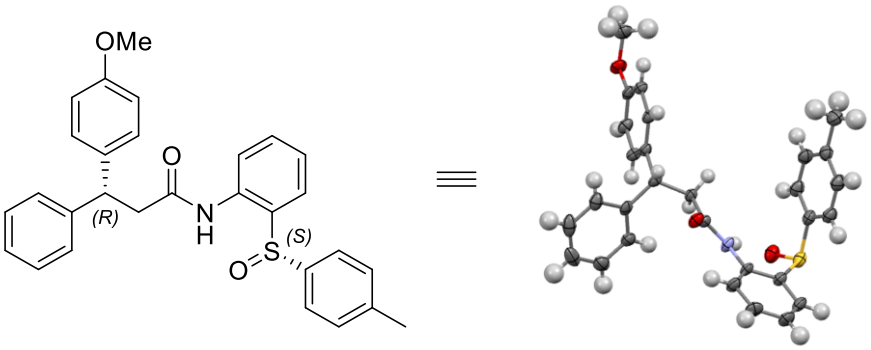


Figure 3.40 ORTEP view of III-2kO

III.3.ii. Efficient synthesis of enantioenriched 2,2-dimethylcyclopropane bioisosters

In order to highlight the synthetic value of our methodology, we next focused on the diastereoselective arylation of substrate **III-1n**, a 2,2-dimethylcyclopropane bioisoster (Figure 3.41). During the past few years, the expanding use of pyrethroids as insecticides was concomitantly accompanied with growing resistance in the insect populations. Therefore, new derivatives are urgently needed and hence structures have been designed, some of them showing good activity against insects.[261]

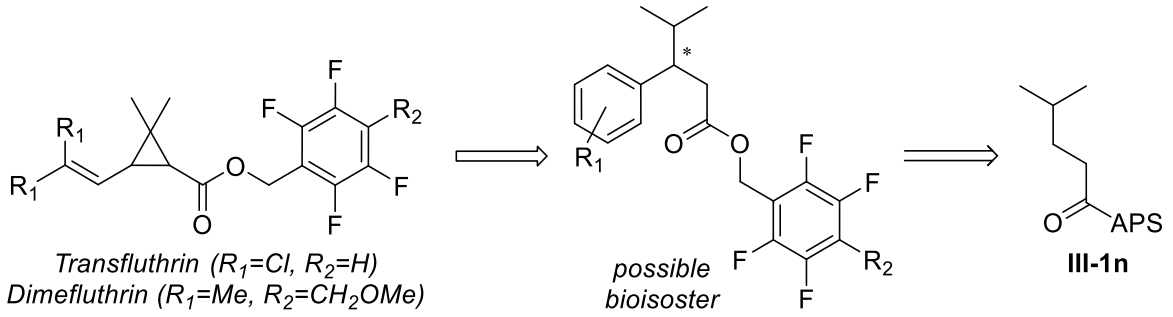


Figure 3.41 Design of novel chiral esters derived from fluthrin derivatives

Using substrate **III-1n**, diastereoselective arylation afforded various functionalised product **III-2n** which are key intermediate for pyrethroid analogues (Figure 3.42).

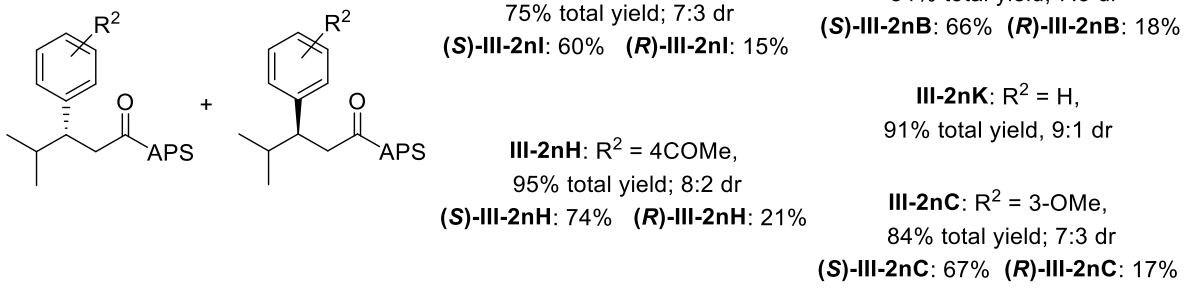
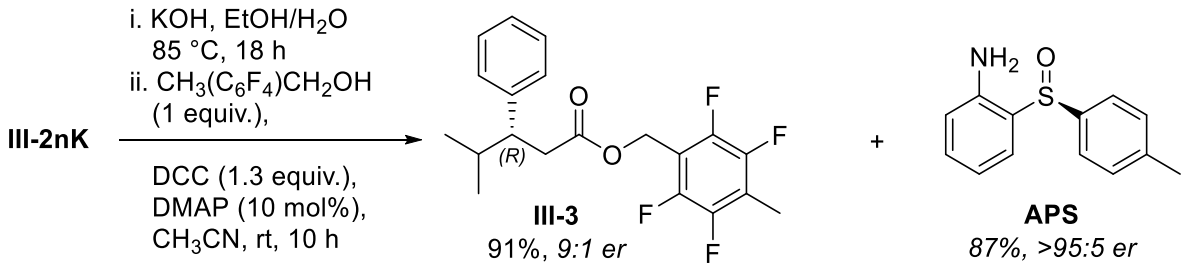


Figure 3.42 Diastereoselective β-C-H arylation of III-1n

Particularly, we focused on the expedient synthesis of **III-3**, compound known in the literature and showing a promising insecticide activity. Following our general protocol, the arylated compound was generated with excellent yield and high diastereomeric ratio of 9:1. Subsequent removal of the chiral auxiliary followed by esterification afforded the desired compound with a remarkable 81% yield and conserved 9:1 enantiomeric ratio. Moreover, the chiral auxiliary was cleaved and recovered without loss of optical purity (Scheme 3.105). **III-3** is the only example in which both enantiomers exhibit excellent insecticidal activity even at low doses (between 70 and

90% mortality at 11.1 mg/L), nevertheless in all other compounds only the (*R*)-enantiomer demonstrated good activity, showcasing the interest of a diastereoselective pathway.[261] This new route opens interesting perspectives for the synthesis of pyrethroid bioisosters.

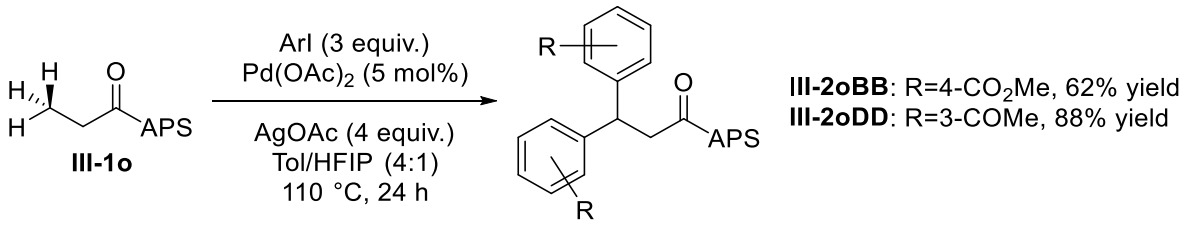


Scheme 3.105 Synthesis of insecticide derivative III-3

III.4. One-pot double functionalisation of propionic acid derivatives

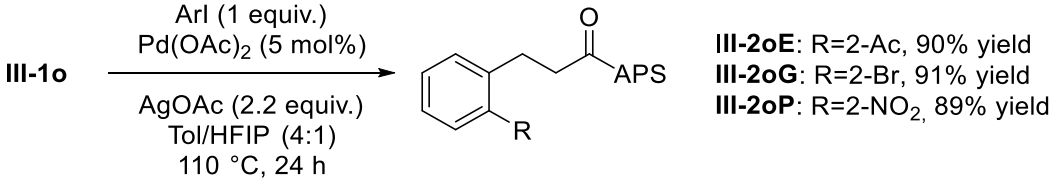
Regarding the high activity of our catalytic system, we hypothesized that a sequential functionalisation could be performed on a simple propionic acid substrate. Such two-step C-H activation would be particularly appealing as it allows in situ construction of a variety of 3,3-disubstituted propionic acid derived scaffolds that are difficult to access via other synthetic routes.

We estimated the feasibility of such double functionalisation by reacting an excess of aryliodide coupling partners with **III-1o**, accordingly yielding non-chiral 3,3-diaryl moieties. Interestingly, the reaction worked well even with more sterically hindered *meta*-substituted coupling partner (Scheme 3.106).



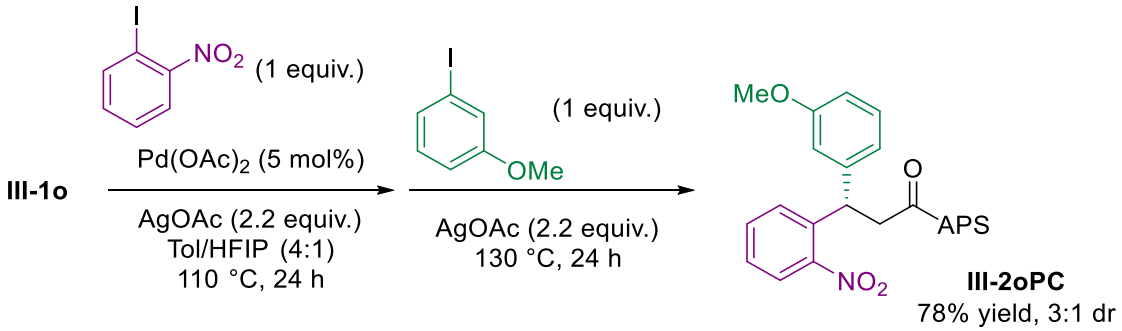
Scheme 3.106 Non-chiral double-arylation of III-1o

Subsequently, we explored the mono-arylation of propionic acid substrate to access uncommercial hydrocinnamic acid derivatives. Using one equivalent of a coupling partner, the reaction furnished a variety of non-chiral coupling products with excellent yields (Scheme 3.107). It is important to highlight the exceptional tolerance towards hindered iodoarenes such as in **III-2oG**.



Scheme 3.107 Non-chiral mono-arylation of III-1o

Regarding the efficiency of these transformations, a one-pot, two-step difunctionalisation of **III-1o** was thus explored. Rewardingly, after initial total conversion of the starting material into the desired mono-arylated product **III-2oP**, 3-iodoanisole was added to the reaction mixture alongside with an additional portion of silver acetate and the temperature was raised to 130 °C, affording the asymmetric diarylated propionic acid derivative **III-2oPC** in 78% isolated yield and encouraging 3:1 diastereomeric ratio (Scheme 3.108). Using chloro- or bromo-coupling partners, this strategy could offer an original synthetic pathway to chiral ligands for asymmetric synthesis.



Scheme 3.108 Asymmetric one-pot double-arylation of III-1o

Besides, this interesting methodology could allow easy access to natural product key intermediates from ubiquitous propionic acid, like the podophyllotoxin intermediate drawn in Chart 3.19, as described by Peng and co-workers in 2018.[262] Indeed, arylation of propionic acid derivative with sterically hindered 5-bromo-6-iodobenzo[*d*][1,3]dioxole followed by 3,4,5-trimethoxyiodobenzene should afford the key amide.

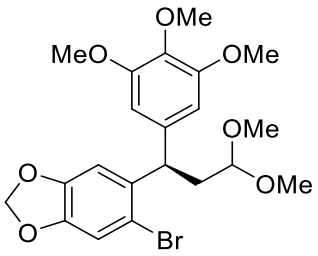


Chart 3.19 A key intermediate in the total synthesis of podophyllotoxin

III.5. Diasteroselective acetoxylation

III.5.i. Inter- and intramolecular acetoxylation

Alkoxylation and acetoxylation were widely investigated with monodentate directing groups. However, diastereoselective C-O bond formation by means of C(sp^3)-H bond activation remains elusive and only one procedure has been reported by Yu and co-workers in 2005 (Figure 3.43).[89]

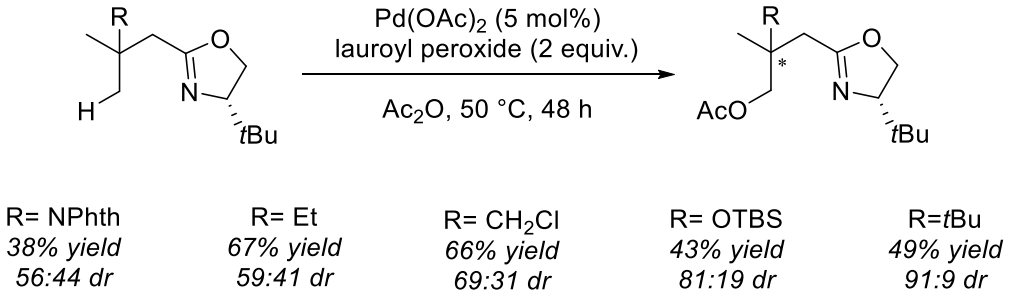
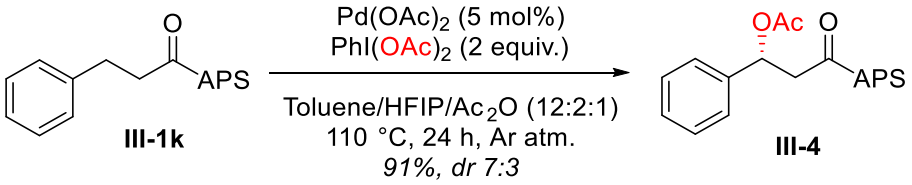


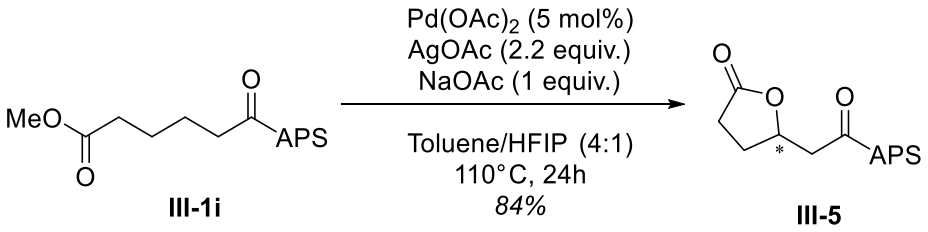
Figure 3.43 Diastereoselective acetoxylation using a chiral oxazoline directing group

Following Yu's condition, but using toluene/HFIP/Ac_2O (12:2:1) as solvent mixture, the desired acetoxylated product **III-4** was isolated in 32 % yield. Encouragingly, when using (diacetoxyiodo)benzene as acetate source in presence of acetic anhydride, **III-4** was obtained with excellent yield of 91% starting from hydrocinnamic acid derivatives (Scheme 3.109). Despite low diastereoselectivity, this reaction can still be considered as a proof a concept showcasing the potential of the C-H bond activation concept to generate stereoselectively C-O bonds.



Scheme 3.109 Acetoxylation of hydrocinnamic acid derivative

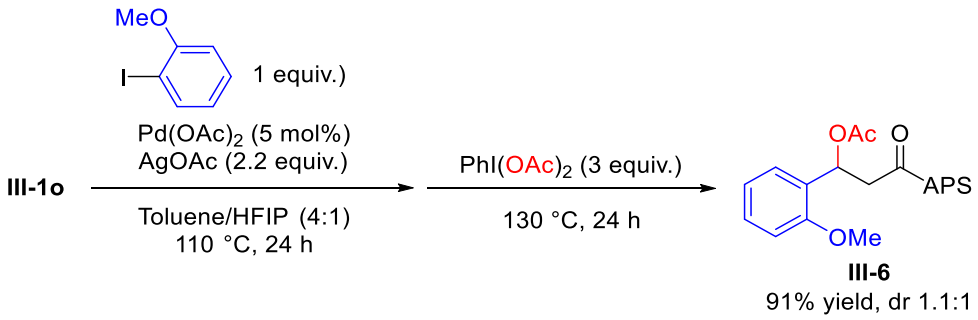
Interestingly, applying the very same reaction conditions to **III-1i**, bearing a methyl ester in the side chain, the desired product was not observed. In contrast, deprotection of the methyl ester occurred, followed by intramolecular acetoxylation. Addition of silver acetate and sodium acetate promoted both deprotection and lactonization, delivering **III-5** in 84% yield (Scheme 3.110). The ^{1}H and ^{13}C NMRs seem to indicate only one diastereomer but we failed in separating the diastereomers in chiral HPLC to prove it. No cyclization product was observed using *tert*-butyl ester, suggesting that the deprotection occurs first, followed by directed C-H bond activation.



Scheme 3.110 Lactonisation of III-1i

III.5.ii. One-pot arylation and acetoxylation

The same one-pot procedure as mentioned before (III.4) was followed to access other type of acetoxylated hydrocinnamic acid derivatives. However, the diastereomeric ratio was deceivingly low, thus limiting the potential of this methodology (Scheme 3.111). This drop in diastereoselectivity may be explained by the elevated temperature during the second step.

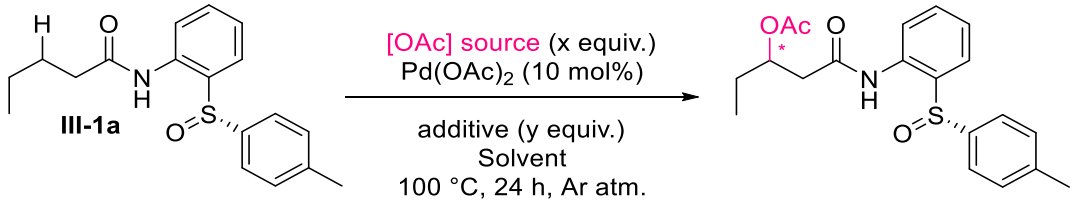


Scheme 3.111 Asymmetric one-pot arylation and acetoxylation of III-1o

III.5.iii. Limitation of the scope

The scope of this reaction was unfortunately limited to hydrocinnamic and adipic acid analogues and attempts on other substrates were ineffective (Table 3.17). The reaction conditions adapted from Yu and co-workers did not work (Entry 2),[64] and other modification of the catalytic system either resulted in the lack of conversion or decomposition of the substrate (Entry 5).

Table 3.17 Attemps of acetoxylation of III-1a



Entry	[OAc] (x)	Additive (y)	Solvent	Conversion (%)
1	$PhI(OAc)_2$ (2)	-	Toluene/HFIP/Ac_2O (12:2:1)	0
2	$PhI(OAc)_2$ (4)	Under air	Ac_2O	0
3	$PhI(OAc)_2$ (2)	-	Toluene/Ac_2O (30:1)	0
4	$PhI(OAc)_2$ (2)	AcOH (10)	HFIP/Ac_2O (5:1)	0
5	$PhI(OAc)_2$ (2)	HCl (10)	HFIP/Ac_2O (5:1)	0

III.6. Conclusion

This second main project was dedicated to the C(sp^3)-H bond functionalisation of acyclic substrates. Thanks to the fine tuning of the reaction conditions, we succeeded in designing a catalytic system allowing excellent reactivity by changing the solvent system from HFIP/H_2O to toluene/HFIP and performed arylation using various coupling partners, bearing electron-donating or -withdrawing groups. Rewardingly, our catalytic system was powerful enough to promote acetoxylation and lactonization with excellent yield and moderate diastereomeric ratio. These results were published in *Chemistry – A European Journal* in 2017 and selected as *Hot Paper*.[21] With our expertise in diastereoselective C-H bond functionalisation in hand, knowing that sulfinylaniline directing group could promote various reactions such as arylation, alkylation and acetoxylation, we consequently endeavoured on designing an enantioselective system for the C-H bond functionalisation.

III.7. Experimental section

III.7.i. Substrate synthesis

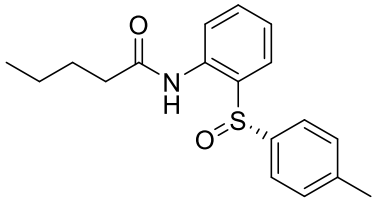
General procedure for the substrate synthesis

To a stirred solution of enantioenriched APS (250 mg, 1.08 mmol, 1 equiv.), carboxylic acid (1.08 mmol, 1 equiv.), triethylamine (300 µL, 2.16 mmol, 2 equiv.) and 4-(dimethylamino)-pyridine (one or two crystals) in 5 mL of anhydrous DMF was added propylphosphonic anhydride (700 µL, 1.19 mmol, ≥50% wt. in DMF, 1.1 equiv.). The resulting mixture was stirred 16h at room temperature, before addition of water (10 mL) and diethyl ether (10 mL). The organic layer was extracted, washed with brine (3x 10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel to get the corresponding amide.

When available, the amide coupling was done using enantioenriched APS (250 mg, 1.08 mmol, 1 equiv.), acyl chloride (1.08 mmol, 1 equiv.) and triethylamine (200 µL, 1.44 mmol, 1.5 equiv.) in 5 mL of DCM. When the solution became colorless (generally after 1h), water (10 mL) was added. The organic layer was extracted, washed with brine (10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure, before purification.

(*S*)-*N*-(2-(*p*-tolylsulfinyl)phenyl)pentanamide III-1a

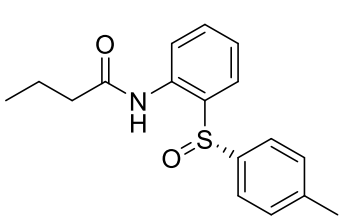
Reaction was carried out using valeryl chloride (125 µL) as coupling partner. Purification with CyHex/EtOAc (4:1) afforded the title compound (252 mg, 81%) as a yellow solid.



^{1}H NMR (400 MHz, $CDCl_3$): 10.10 (1H, br s, N*H*), 8.39 (1H, d, J=8.5 Hz), 7.42-7.53 (2H, m), 7.34 (2H, d, J=8.4 Hz), 7.22 (2H, J=8.2 Hz), 7.13 (1H, td, J=7.5, 1.1 Hz), 2.34 (3H, s, PhC*H*$_3$), 2.14-2.30 (2H, m), 1.50-1.61 (2H, m), 1.22-1.33 (2H, m), 0.88 (3H, t, J=7.3 Hz); R_t (min, ODH, Hex/iPrOH, 98/2, 0.5 mL/min): 36.20 (99%), 43.22 (1%); other data match the reported ones.

(*S*)-*N*-(2-(*p*-tolylsulfinyl)phenyl)butyramide III-1b

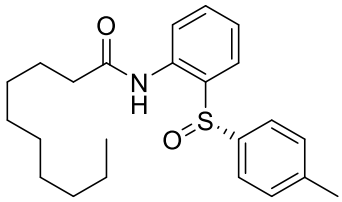
Reaction was carried out using propionic acid (80 µL) as coupling partner. Purification with CyHex/EtOAc (4:1) afforded the title compound (297 mg, 96%) as a white solid.



^{1}H NMR (400 MHz, $CDCl_3$): 10.12 (1H, br s, N*H*), 8.39 (1H, d, J=8.2 Hz), 7.51 (1H, dd, J=7.9, 1.5 Hz), 7.43-7.47 (1H, m), 7.35 (2H, d, J=8.2 Hz), 7.22 (2H, d, J=8.3 Hz), 7.13 (1H, td, J=7.5, 1.2 Hz), 2.34 (3H, s, PhC*H*$_3$), 2.13-2.31 (2H, m), 1.58-1.65 (2H, m), 0.89 (3H, t, J=7.0 Hz); other data match the reported ones.

(*S*)-*N*-(2-(*p*-tolylsulfinyl)phenyl)decanamide III-1c

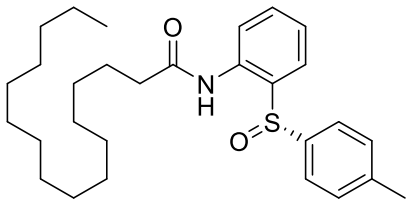
Reaction was carried out using decanoyl chloride (250 µL) as coupling partner. Purification with CyHex/EtOAc (9:1) afforded the title compound (362 mg, 87%) as a clear oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.06 (1H, br s, N*H*), 8.33 (1H, d, J=8.3 Hz), 7.46 (1H, dd, J=7.6, 1.7 Hz), 7.37-7.41 (1H, m), 7.30 (2H, d, J=8.4 Hz), 7.17 (2H, d, J=8.3 Hz), 7.08 (1H, td, J=7.7, 1.1 Hz), 2.29 (3H, s, PhC*H*$_3$), 2.07-2.26 (2H, m), 1.44-1.62 (2H, m), 1.20 (12H, app s), 0.81 (3H, t, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 171.97, 141.52, 140.53, 139.90, 133.23, 130.16, 128.05, 124.59, 123.22, 123.10, 38.29, 32.11, 29.68, 29.61, 29.53, 29.45, 25.53, 22.90, 21.50, 14.34; FT-IR (cm^{-1}): 1698 (s, C=O), 1022 (s, S=O); HRMS (ESI-TOF): m/z calcd for $C_{23}H_{31}KNO_2S^+$: 424.1707, found: 424.1694; $[\alpha]_D^{20}$= +5.4° (c=0.35, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.45.

(*S*)-*N*-(2-(*p*-tolylsulfinyl)phenyl)palmitamide III-1d

Reaction was carried out using palmitoyl chloride (330 µL) as coupling partner. Purification with CyHex/EtOAc (95:5) afforded the title compound (408 mg, 80%) as a white solid.

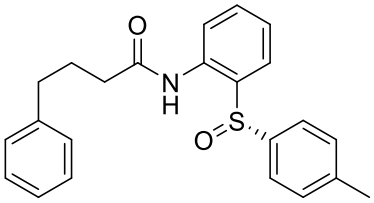


^{1}H NMR (400 MHz, $CDCl_3$): 10.11 (1H, br s, N*H*), 8.38 (1H, d, J=8.2 Hz), 7.50 (1H, dd, J=7.6, 1.5 Hz), 7.46 (1H, ddd, J=8.4, 7.4, 1.6 Hz), 7.35 (2H, d, J=8.3 Hz), 7.22 (2H, d, J=8.3 Hz), 7.13 (1H, td, J=7.6, 1.2 Hz), 2.34 (3H, s, PhC*H*$_3$), 2.14-2.31 (2H, m), 1.51-1.63 (2H, m), 1.24 (24H, app s), 0.86 (3H, t, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 171.94, 141.49, 140.53, 139.90, 133.21, 130.15, 128.03, 124.57, 123.02, 123.07, 38.27, 32.13, 29.91, 29.87, 29.72, 29.60, 29.57, 29.44, 25.51, 22.90, 21.48, 14.34; HRMS (ESI-TOF): m/z calcd for

$C_{29}H_{43}KNO_2S^+$: 508.2646, found: 508.2631; FT-IR (cm-1): 1698 (s, C=O), 1023 (s, S=O); mp (°C): 74; $[\alpha]_D^{20}$= +2.1° (c=0.50, $CHCl_3$); R_f (CyHex/EtOAc, 4/1): 0.39.

4-phenyl-(*S*)-*N*-(2-(*p*-tolylsulfinyl)phenyl)butyramide III-1e

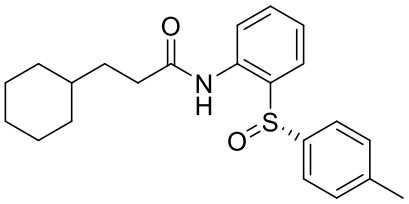
Reaction was carried out using 4-phenylbutyric acid (178 mg) as coupling partner. Purification with CyHex/EtOAc (9:1) afforded the title compound (297 mg, 70%) as a clear oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.09 (1H, br s, N*H*), 8.36 (1H, d, J=8.2 Hz), 7.43-7.56 (2H, m), 7.25-7.33 (4H, m), 7.11-7.19 (6H, m), 2.54-2.61 (2H, m), 2.17-2.32 (5H, m), 1.85-1.94 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 171.46, 141.69, 141.55, 140.43, 139.84, 133.27, 130.17, 128.70, 128.62, 128.15, 126.19, 124.55, 123.33, 123.22, 37.50, 35.41, 27.05, 21.45; HRMS (ESI-TOF): m/z calcd for $C_{23}H_{23}NNaO_2S^+$: 400.1342, found: 400.1322; FT-IR (cm^{-1}): 1695 (s, C=O), 1022 (s, S=O); $[\alpha]_D^{20}$= +23.7° (c=0.50, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.65.

3-cyclohexyl-(*S*)-*N*-(2-(*p*-tolylsulfinyl)phenyl)propionamide III-1f

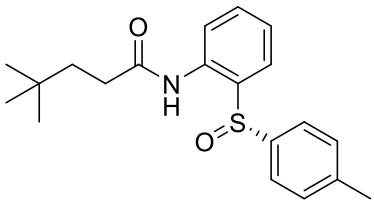
Reaction was carried out using 3-cyclohexylpropionic acid (170 µL) as coupling partner. Purification with CyHex/EtOAc (9:1) afforded the title compound (317 mg, 79%) as a brown oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.09 (1H, br s, N*H*), 8.38 (1H, d, J=8.4 Hz), 7.43-7.52 (2H, m), 7.35 (2H, d, J=8.2 Hz), 7.22 (2H, d, J=8.2 Hz), 7.13 (1H, td, J=7.6, 1.1 Hz), 2.35 (3H, s, PhC*H*$_3$), 2.16-2.31 (2H, m), 1.58-1.73 (5H, m), 1.42-1.49 (2H, m), 1.09-1.28 (4H, m), 0.83-0.91 (2H, m) ; ^{13}C NMR (100 MHz, $CDCl_3$): 172.23, 141.53, 140.59, 139.92, 133.26, 130.20, 128.08, 126.53, 124.60, 123.20, 123.07, 37.44, 35.73, 33.24, 32.83, 26.78, 26.72, 26.46, 26.43, 21.52; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{27}NNaO_2S^+$: 392.1655, found: 392.1674; FT-IR (cm^{-1}): 1697 (s, C=O), 1022 (m, S=O); $[\alpha]_D^{20}$= +2.4° (c=0.50, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.6.

4,4-dimethyl-(*S*)-*N*-(2-(*p*-tolylsulfinyl)phenyl)pentanamide III-1g

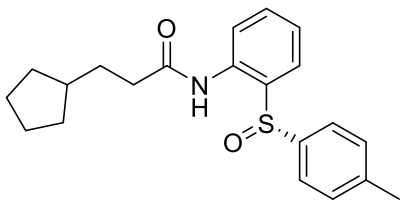
Reaction was carried out using 4,4-dimethyl-pentanoic acid (141 mg) as coupling partner. Purification with CyHex/EtOAc (9:1) afforded the title compound (274 mg, 74%) as a brownish oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.05 (1H, br s, N*H*), 8.36 (1H, d, J=8.4 Hz), 7.52 (1H, dd, J=7.7, 1.6 Hz), 7.46 (1H, ddd, J=8.3, 7.5, 1.6 Hz), 7.34 (2H, d, J=8.4 Hz), 7.22 (2H, d, J=8.4 Hz), 7.13 (1H, td, J=7.5, 1.1 Hz), 2.34 (3H, s, PhC*H*$_3$), 2.09-2.26 (2H, m), 1.36-1.51 (2H, m), 0.88 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 172.39, 141.47, 140.52, 139.96, 133.27, 130.17, 128.17, 124.58, 123.20, 123.16, 39.10, 33.89, 30.32, 29.26, 21.47; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{25}NNaO_2S^+$: 366.1498, found: 366.1494; FT-IR (cm^{-1}): 1698 (s, C=O), 1022 (s, S=O); $[\alpha]_D^{20}$= +5.6° (c=0.22, $CHCl_3$); R_f (CyHex/EtOAc, 4/1): 0.45.

3-cyclopentyl-(*S*)-*N*-(2-(*p*-tolylsulfinyl)phenyl)propionamide III-1h

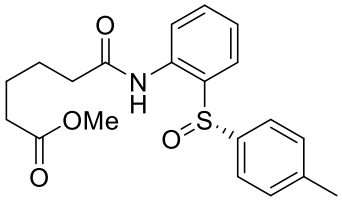
Reaction was carried out using 3-cyclopentylpropionic acid (150 µL) as coupling partner. Purification with CyHex/EtOAc (9:1) afforded the title compound (281 mg, 73%) as a yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.04 (1H, br s, N*H*), 8.34 (1H, d, J=8.1 Hz), 7.46 (1H, dd, J=7.7, 1.4 Hz), 7.39-7.44 (1H, m), 7.30 (2H, d, J=8.3 Hz), 7.17 (2H, d, J=8.3 Hz), 7.06 (1H, td, J=7.6, 1.1 Hz), 2.30 (3H, s, PhC*H*$_3$), 2.10-2.27 (2H, m), 1.62-1.72 (3H, m), 1.37-1.59 (6H, m), 0.97-1.08 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 171.87, 141.32, 140.36, 139.72, 133.06, 129.97, 127.90, 124.42, 123.00, 122.89, 39.67, 37.34, 32.48, 31.49, 25.17, 21.29; HRMS (ESI-TOF): m/z calcd for $C_{21}H_{25}KNO_2S^+$: 394.1238, found: 394.1235; FT-IR (cm^{-1}): 1698 (s, C=O), 1022 (s, S=O); $[\alpha]_D^{20}$= +10.5° (c=0.70, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.5.

methyl (*S*)-6-oxo-6-((2-(*p*-tolylsulfinyl)phenyl)amino)hexanoate III-1i

Reaction was carried out using methyl adipoyl chloride (150 µL) as coupling partner. Purification with CyHex/EtOAc (7:3) afforded the title compound (347 mg, 92%) as a white solid.

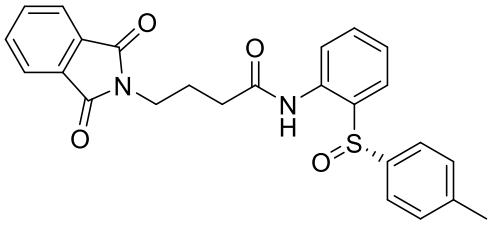


^{1}H NMR (400 MHz, $CDCl_3$): 10.14 (1H, br s, N*H*), 8.31 (1H, d, *J*=8.3 Hz), 7.46 (1H, dd, *J*=7.7, 1.5 Hz), 7.41 (1H, td, *J*=8.0, 1.5 Hz), 7.29 (2H, d, *J*=8.4 Hz), 7.20-7.24 (2H, m), 7.09 (1H, td, *J*=7.6, 1.0 Hz), 3.65 (3H, s, C(O)OC*H*$_3$), 2.34 (3H, s, PhC*H*$_3$), 2.26-2.32 (3H, m), 2.16-2.25 (1H, m), 1.57-1.65 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 173.72, 171.01, 141.34, 140.21, 139.66, 133.02, 130.00, 127.84, 127.78, 124.34, 123.14, 122.91, 51.56, 37.43, 33.75, 24.63, 24.43, 21.28; HRMS (ESI-TOF): m/z calcd for $C_{20}H_{24}NO_4S^+$: 374.1421, found: 374.1411; FT-IR (cm^{-1}): 1732 (s, C-O

ester), 1695 (s, C-O amide), 1021 (s, S-O); mp (°C): 74; $[\alpha]_D^{20}$= -24.7° (c=0.50, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.2.

(*S*)-4-(1,3-dioxoisoindolin-2-yl)-*N*-(2-(*p*-tolylsulfinyl)phenyl)butanamide III-1j

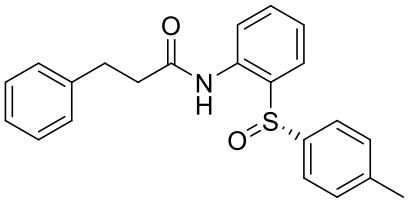
Reaction was carried out using 4-phthalimidobutyric acid (250 mg) as coupling partner. Purification with CyHex/EtOAc (3:1) afforded the title compound (357 mg, 75%) as a white solid.



^{1}H NMR (400 MHz, $CDCl_3$): 10.07 (1H, br s, N*H*), 8.26 (1H, d, *J*=8.4 Hz), 7.79-7.85 (2H, m), 7.66-7.73 (2H, m), 7.49 (1H, dd, *J*=7.7, 1.8 Hz), 7.43 (1H, ddd, *J*=8.6, 7.6, 1.7 Hz), 7.33 (2H, d, *J*=8.1 Hz), 7.21 (2H, d, *J*=8.2 Hz), 7.13 (1H, td, *J*=7.6, 1.3 Hz), 3.70 (2H, t, *J*=7.2 Hz), 2.19-2.40 (5H, m), 1.87-2.05 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 170.33, 168.48 (2C), 141.58, 140. 15, 139.80, 134.16, 133.14, 132.28, 130.21, 128.41, 127.98, 124.53, 123.47 (2C), 123.35, 37.51, 35.07, 24.37, 21.45; FT-IR (cm^{-1}): 2961 (m), 1770 (w, C-O amide), 1709 (s, C-O phthalimide), 1032 (m, S-O); HRMS (ESI-TOF): m/z calcd for $C_{25}H_{22}N_2NaO_4S^+$: 469.1192, found: 469.1202; $[\alpha]_D^{20}$= +41.7° (c=1.0, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.22.

(*S*)-3-phenyl-*N*-(2-(*p*-tolylsulfinyl)phenyl)propanamide III-1k

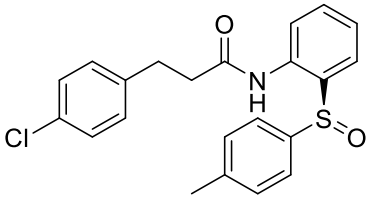
Reaction was carried out using hydrocinnamic acid (150 µL) as coupling partner. Purification with CyHex/EtOAc (9:1) afforded the title compound (357 mg, 91%) as a yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.20 (1H, br s, N*H*), 8.37 (1H, d, *J*=8.4 Hz), 7.51 (1H, dd, J=7.7, 1.9 Hz), 7.44-7.49 (1H, m), 7.33 (2H, d, *J*=8.4 Hz), 7.25-7.30 (2H, m), 7.17-7.22 (5H, m), 7.14 (1H, td, *J*=7.5, 1.2 Hz), 2.84-2.99 (2H, m), 2.47-2.67 (2H, m), 2.34 (3H, s, PhC*H*$_3$); R_t (min, ODH, Hex/iPrOH, 80/20, 0.5 mL/min): 19.13 (1%), 24.60 (99%); other data match the reported ones.

(*S*)-3-(4-chlorophenyl)-*N*-(2-(*p*-tolylsulfinyl)phenyl)propanamide III-1l

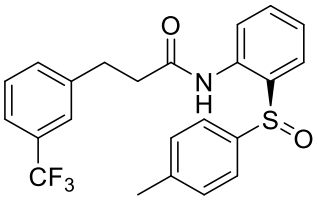
Reaction was carried out using 3-(4-chlorophenyl)propionic acid (188 mg) as coupling partner. Purification with CyHex/EtOAc (9:1) afforded the title compound (363 mg, 90%) as a yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.26 (1H, br s, N*H*), 8.36 (1H, d, *J*=8.1 Hz), 7.43-7.52 (2H, m), 7.30 (2H, d, J=8.2 Hz), 7.22 (2H, d, *J*=8.3 Hz), 7.08-7.19 (5H, m), 2.88 (2H, t, *J*=7.5 Hz), 2.60 (1H, td, *J*=15.2, 7.6 Hz), 2.48 (1H, td, *J*=15.2, 7.6 Hz), 2.34 (3H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 170.10, 140.17, 139.60, 139.08, 132.99, 131.98, 130.00, 129.74, 128.63, 127.74, 127.69, 124.29 (2C), 123.25, 122.85, 39.15, 30.29, 21.31; FT-IR (cm^{-1}): 1670 (s, C-O), 1036 (s, S-O), 931 (s, C-Cl); HRMS (ESI-TOF): m/z calcd for $C_{22}H_{20}ClNNaO_2S^+$: 420.0795, found: 420.0800; $[\alpha]_D^{20}$= +21.7° (c=0.5, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.43.

(*S*)-3-(3-trifluoromethylphenyl)-*N*-(2-(*p*-tolylsulfinyl)phenyl)propanamide III-1m

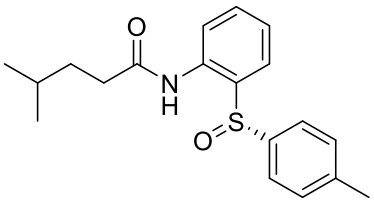
Reaction was carried out using 3-(3-trifluoromethylphenyl)propionic acid (235 mg) as coupling partner. Purification with CyHex/EtOAc (95:5) afforded the title compound (402 mg, 86%) as a clear oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.24 (1H, br s, N*H*), 8.36 (1H, d, *J*=7.8 Hz), 7.41-7.54 (4H, m), 7.35-7.42 (2H, m), 7.32 (2H, d, *J*=8.3 Hz), 7.19 (2H, d, *J*=8.3 Hz), 7.15 (1H, td, J=7.6, 0.9 Hz), 2.89-3.02 (2H, m), 2.63 (1H, ddd, *J*=15.3, 8.6, 6.9 Hz), 2.51 (1H, ddd, *J*= 15.4, 8.9, 6.6 Hz), 2.33 (3H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.90, 141.53, 141.47, 140.11, 139.63, 133.04, 131.78, 130.82 (q, *J*=33.2 Hz), 129.99, 128.97, 127.84, 125.11 (q, *J*=3.8 Hz), 124.76 (q, *J*=272.0 Hz), 124.32, 123.32, 123.17 (q, *J*=3.8 Hz), 122.95, 122.80, 38.95, 30.79, 21.27; ^{19}F NMR (377 MHz, $CDCl_3$): -62.56; FT-IR (cm^{-1}): 1697 (m, C-O), 1328 (s, C-F), 1120 (s, C-F), 1022 (s, S-O); HRMS (ESI-TOF): m/z calcd for $C_{23}H_{21}F_3NO_2S^+$: 432.1240, found: 432.1220; $[\alpha]_D^{20}$= +25.2° (c=0.5, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.42.

4-methyl-(*S*)-*N*-(2-(*p*-tolylsulfinyl)phenyl)pentanamide III-1n

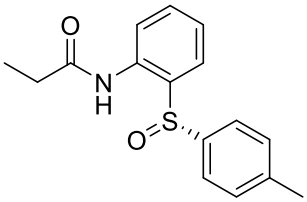
Reaction was carried out using 4-methylvaleric acid (140 µL) as coupling partner. Purification with CyHex/EtOAc (9:1) afforded the title compound (315 mg, 88%) as a clear oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.10 (1H, br s, N*H*), 8.37 (1H, d, J=8.4 Hz), 7.50 (1H, dd, J=7.4, 1.1 Hz), 7.41-7.47 (1H, m), 7.35 (2H, d, J=8.3 Hz), 7.21 (2H, d, J=8.3 Hz), 7.12 (1H, td, J=7.5, 1.2 Hz), 2.33 (3H, s, PhC*H*$_3$), 2.14-2.30 (2H, m), 1.39-1.58 (3H, m), 0.84-0.91 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 171.89, 141.34, 140.34, 139.82, 133.05, 130.01, 127.93, 124.45, 123.11, 122.95, 36.04, 34.13, 27.76, 22.38, 21.33; HRMS (ESI-TOF): m/z calcd for $C_{19}H_{23}NNaO_2S^+$: 352.1342, found: 352.1307; FT-IR (cm-1): 1684 (s, C=O), 1025 (s, S=O); R_t (min, ODH, Hex/iPrOH, 98/2, 0.5 mL/min): 30.25 (99%), 36.17 (1%); $[\alpha]_D^{20}$= +28.6° (c=1.1, $CHCl_3$); R_f (CyHex/EtOAc, 4/1): 0.50.

(*S*)-*N*-(2-(*p*-tolylsulfinyl)phenyl)propionamide III-1o

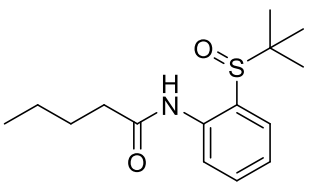
Reaction was carried out using propionic acid (80 µL) as coupling partner. Purification with CyHex/EtOAc (4:1) afforded the title compound (297 mg, 96%) as a white solid.



^{1}H NMR (400 MHz, $CDCl_3$): 10.15 (1H, br s, N*H*), 8.41 (1H, d, J=8.3 Hz), 7.53 (1H, d, J=7.6 Hz), 7.47 (1H, t, J=7.8 Hz), 7.39 (2H, d, J=8.2 Hz), 7.26 (2H, d, *J* = 8.4 Hz), 7.18 (1H, t, J=7.5 Hz), 2.35 (3H, s, PhC*H*$_3$), 2.20-2.37 (2H, m), 1.16 (3H, t, *J* = 7.6 Hz); R_t (min, ODH, Hex/iPrOH, 98/2, 0.5 mL/min): 51.81 (98%), 60.55 (2%); other data match the reported ones.

***N*-(2-*tert*-butylsulfinyl)phenyl)pentanamide III-1a'**

Reaction was carried out using racemic 2-(*tert*-butylsulfinyl)aniline (660 mg)[7] as substrate and valeryl chloride (400 µL) as coupling partner. Purification with CyHex/EtOAc (9:1) afforded the title compound (814 mg, 88%) as a clear oil.

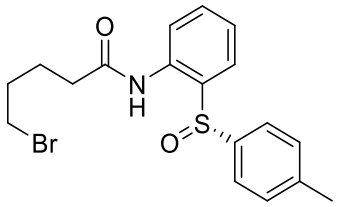


^{1}H NMR (400 MHz, $CDCl_3$): 10.97 (1H, br s, N*H*), 8.55 (1H, dd, J=8.5, 0.8 Hz), 7.43 (1H, ddd, J=8.5, 7.3, 2.0 Hz), 7.01-7.10 (2H, m), 2.30-2.37 (2H, m), 1.63-1.72 (2H, m), 1.33-1.40 (2H, m), 1.25 (9H, s, C(C*H*$_3$)$_3$), 0.92 (3H, t, J=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 171.87, 142.54, 132.25, 128.54, 122.42, 122.02, 120.59, 58.60, 38.06, 27.41, 23.39, 22.37, 13.82; LC-MS: m/z calcd for $C_{15}H_{23}NO_2S^+$: 281.14, found: 281.15; FT-IR (cm^{-1}): 1697 (s, C=O), 1028 (s, S=O); R_f (CyHex/EtOAc, 7/3): 0.60.

[7] Prepared by oxidation of 2-(*tert*-butylthio)aniline with *m*-CPBA.

5-bromo-(*S*)-*N*-(2-(*p*-tolylsulfinyl)phenyl)pentanamide III-1p

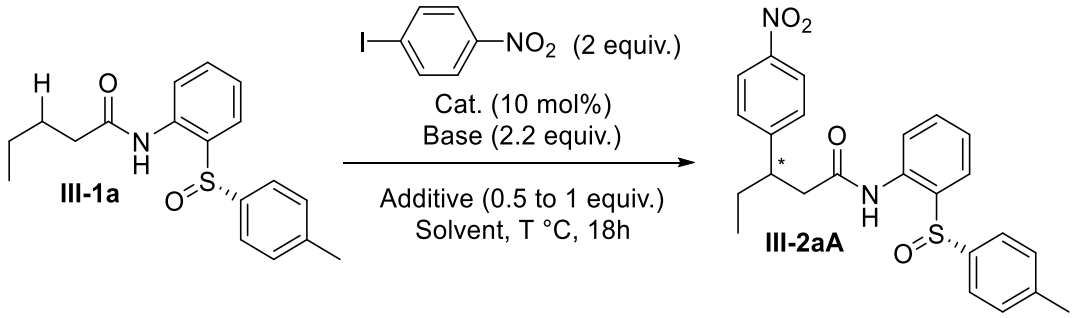
Reaction was carried out using 5-bromovaleric acid (196 mg) as coupling partner. Purification with CyHex/EtOAc (4:1) afforded the title compound (384 mg, 90%) as a yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.16 (1H, br s, N*H*), 8.33 (1H, d, J=8.4 Hz), 7.49 (1H, dd, J=7.7, 1.5 Hz), 7.40-7.46 (1H, m), 7.33 (2H, d, J=8.3 Hz), 7.21 (2H, d, J=8.2 Hz), 7.12 (1H, td, J=7.5, 1.1 Hz), 3.28-3.337 (2H, m), 2.15-2.37 (5H, m), 1.64-1.84 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 170.74, 141.40, 140.12, 139.67, 133.01, 130.02, 127.88, 127.85, 124.34, 123.24, 122.91, 36.72, 33.08, 32.00, 23.73, 21.32; HRMS (ESI-TOF): m/z calcd for $C_{18}H_{20}BrNNaO_2S^+$: 416.0290, found: 416.0268; FT-IR (cm^{-1}): 1696 (s, C=O), 1021 (s, S=O), 757 (s, C-Br); $[\alpha]_D^{20}$= -3.2° (c=0.10, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.32.

III.7.ii. Optimization of the coupling reaction conditions

III-1a (15 mg, 48 µmol, 1 equiv.), 4-iodonitrobenzene (24 mg, 96 µmol, 2 equiv.), catalyst (10 mol%), base (2.2 equiv.) and additive (1 equiv.) were weighted in a pressure tube. 500 µL of solvent were added, the tube was then closed, stirred 10 min at room temperature and 18h at the appropriate temperature. After cooling to room temperature, the mixture was filtered through PTFE 45 µm filter with a syringe, evaporated under reduced pressure and analyzed by ^{1}H NMR and LC-MS. Diastereomeric ratios are based on the integration of the terminal CH_3.



General optimization of the base, solvent and temperature

Entry	Cat.	Base	Additive	Solvent	T °C	Conversion	dr
1	$Pd(OAc)_2$	AgOAc	-	Toluene/HFIP (4:1)	100	65	3:2
2	$Pd(OAc)_2$	AgOAc	-	HFIP	80	30	3:2
3	$Pd(OAc)_2$	Ag_2CO_3	-	HFIP	80	25	1:1
4	$Pd(OAc)_2$	AgOAc	NaTFA	HFIP/H_2O (4:1)	80	0	-
5	$Pd(OAc)_2$	AgOAc	-	Toluene	100	60	1:1
6	$Pd(OAc)_2$	AgOAc	-	Xylene	130	55	1:1
7	$Pd(TFA)_2$	AgTFA	-	Toluene/HFIP (4:1)	100	0	-
8	$Pd(OAc)_2$	AgOAc	-	Toluene/TFA (4:1)	100	50	3:2
9	$Pd(OAc)_2$	AgOAc	-	Toluene/AcOH (4:1)	100	<5	-
10	$Pd(OAc)_2$	Ag_2CO_3	KF[8]	HFIP	110	65	1:1
11	$Pd(OAc)_2$	AgOAc	PivOH	Toluene/HFIP (4:1)	110	20	3:2
12	$Pd(OAc)_2$	K_2CO_3	-	Toluene/HFIP (4:1)	110	0	-
13	$Pd(OAc)_2$	Cs_2CO_3	-	Toluene/HFIP (4:1)	110	0	-
14	$Pd(OAc)_2$	Ag_3PO_4	-	Toluene/HFIP (4:1)	110	15	1:1
15	$Pd(OAc)_2$	AgOAc	NaTFA	HFIP	80	30	3:2

[8] 3 equiv. were used.

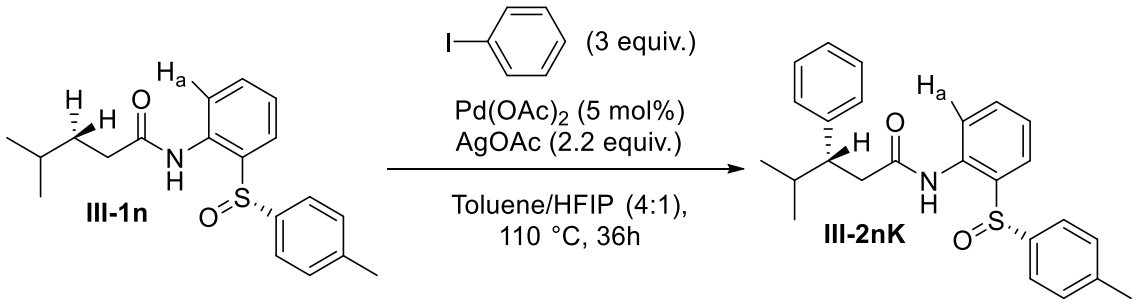
Final optimization of the reaction conditions

Entry	Cat.	Base	Additive	Solvent	T °C	Conversion	dr
1	$Pd(OAc)_2$	AgOAc	-	Toluene/HFIP (4:1)	100	65	3:2
2[9]	$Pd(OAc)_2$	AgOAc	-	Toluene/HFIP (4:1)	110	80	3:2
3[10]	$Pd(OAc)_2$	AgOAc	-	Toluene/HFIP (4:1)	110	55	3:2
4[4,11]	$Pd(OAc)_2$	AgOAc	-	Toluene/HFIP (4:1)	110	50	3:2
5[12]	**$Pd(OAc)_2$**	**AgOAc**	**-**	**Toluene/HFIP (4:1)**	**110**	**85**	**3:2**
6[6]	$Pd(OAc)_2$	AgOAc	-	Toluene/HFIP (4:1)	130	70	1:1
7[6,13]	$Pd(OAc)_2$	AgOAc	-	Toluene/HFIP (4:1)	110	0	-

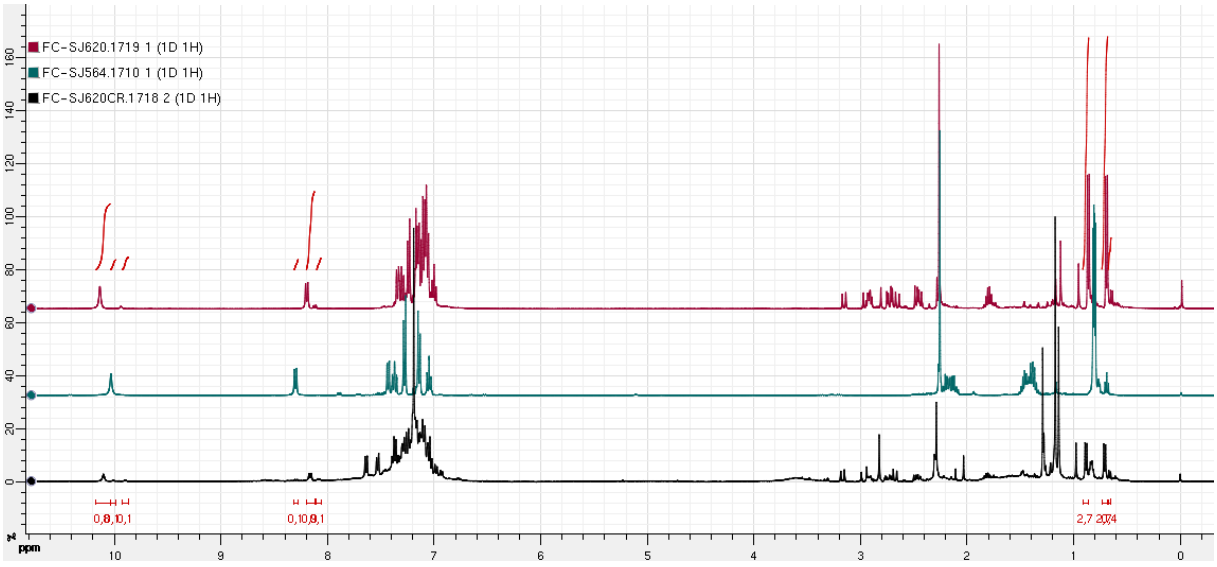
[9] 3 equiv. of coupling partner were used.
[10] Performed under argon atmosphere.
[11] Performed with an excess of 4Å molecular sieves.
[12] 5 mol% of catalyst was used with a reaction time of 36h.
[13] In this case, the corresponding aryl bromide was used as coupling partner.

III.7.iii. ^{1}H NMR determination of the conversion and diastereomeric ratio

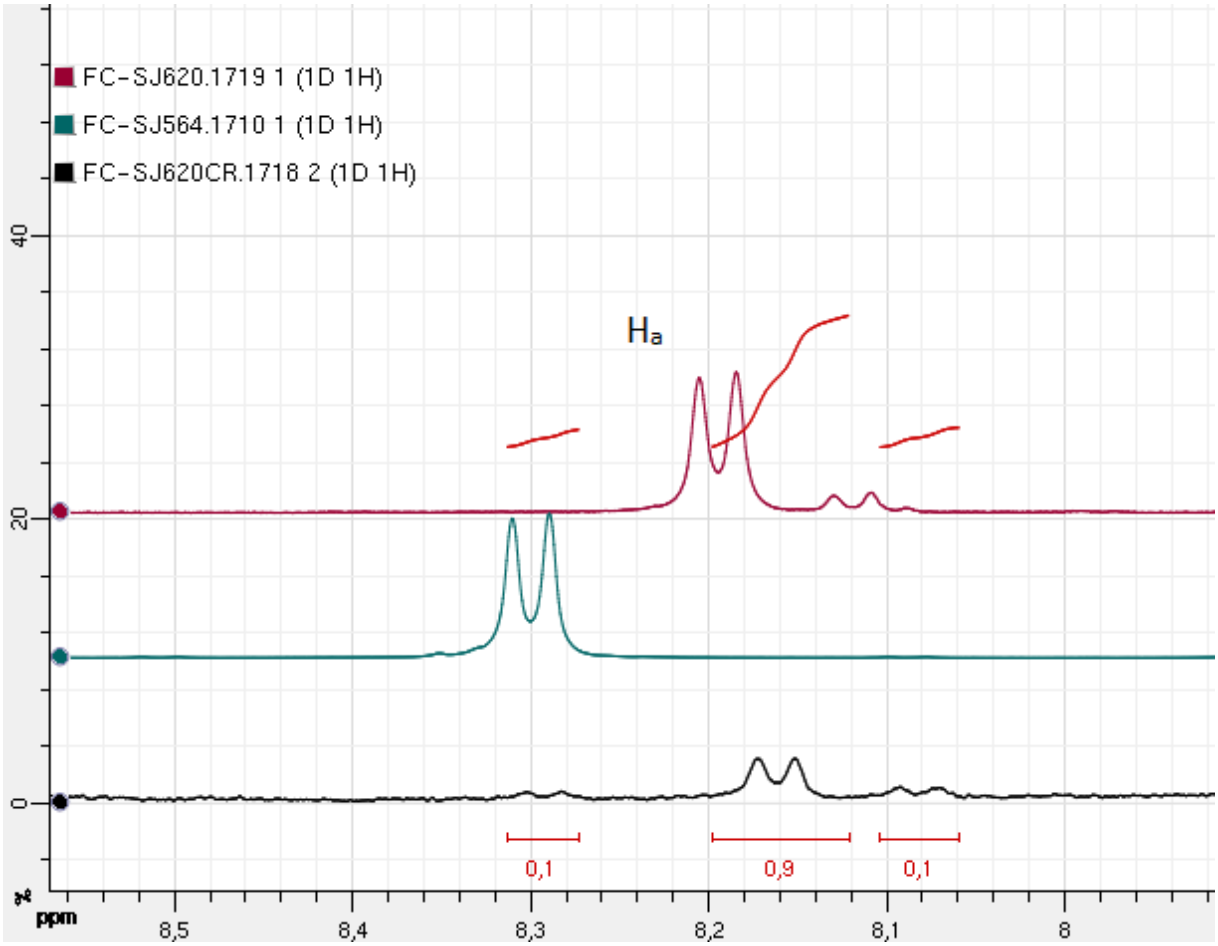
The conversion and diastereomeric ratio were determined by ^{1}H NMR analysis of the crude mixture, after filtration and evaporation.



For example, for the reaction of **III-1n** with iodobenzene, as shown above, the crude ^{1}H NMR was the following (in dark: crude mixture, in green: starting material, in red: purified product obtained as a mixture of diastereomers):



More specifically, in the aromatic part here (still in dark: crude mixture, in green: starting material, in red: purified product):



The diastereomeric ratio for this reaction was around 90/10 and the conversion around 91%. The same interpretation can be done with the terminal CH_3, and other protons for some molecules.

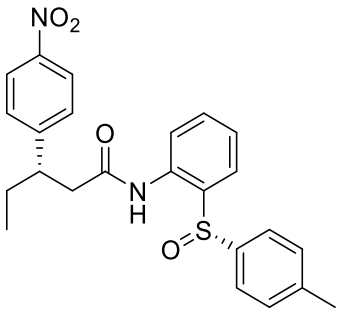
III.7.iv. Arylation of alkyl chains

General procedure for the coupling reactions

To a pressure tube were added the appropriate substrate (1 equiv.), coupling partner (2.5 - 3 equiv.), silver acetate (2.2 equiv.) and palladium(II) acetate (5 mol%). The mixture was then dissolved in a 0.1 M of a 4:1 mixture of toluene and 1,1,1,3,3,3-hexafluoroisopropanol. The mixture was then stirred 10 min at room temperature, then at 110 °C during 36h. After cooling down to room temperature, the mixture was diluted with DCM, filtered through PTFE 45 µm filter with a syringe and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel.

3-(4-nitrophenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)pentanamide III-2aA

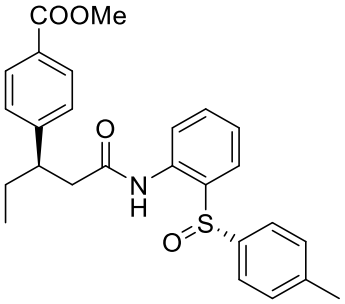
Reaction was carried out using **III-1a** (100 mg) as substrate and 4-iodonitrobenzene (200 mg, 2.3 equiv.) as coupling partner. Purification with CyHex/EtOAc (7:3) afforded the major diastereomer (74 mg, 49%) as a yellow oil and the minor diastereomer as a mixture with some impurities (assumed 34%). ^{1}H NMR of the crude showed a 6:4 diastereomeric ratio.



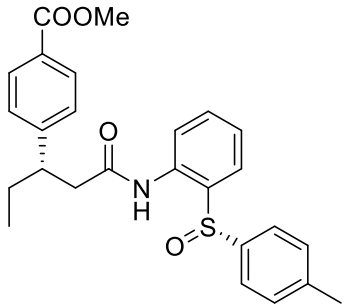
Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.42 (1H, br s, N*H*), 8.32 (1H, d, J=8.9 Hz), 8.07 (2H, d, J=8.7 Hz), 7.38-7.44 (2H, m), 7.25-7.33 (4H, m), 7.16 (2H, d, J=8.2 Hz), 7.10 (1H, td, J=7.6, 1.1 Hz), 3.16-3.26 (1H, m), 2.71 (1H, dd, J=15.3, 6.3 Hz), 2.50 (1H, dd, J=15.3, 8.8 Hz), 2.33 (3H, s, PhC*H*$_3$), 1.69-1.79 (1H, m), 1.57-1.68 (1H, m), 0.78 (3H, t, J=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 169.37, 152.22, 146.74, 141.90, 140.37, 139.80, 133.10, 130.22, 128.58, 127.80, 127.04, 124.60, 123.88, 123.44, 122.66, 44.22, 43.59, 29.18, 21.42, 12.01; HRMS (ESI-TOF): m/z calcd for $C_{24}H_{24}N_2NaO_4S^+$: 459.1349, found: 459.1353; FT-IR (cm^{-1}): 1694 (m, C=O), 1516 (s, N-O), 1344 (s, N-O), 1021 (m, S=O); $[\alpha]_D^{20}$= +22.3° (c=0.10, $CHCl_3$); R_f (CyHex/EtOAc): 0.34.

methyl 4-(1-oxo-1-((2-((S)-p-tolylsulfinyl)phenyl)amino)pentan-3-yl)benzoate III-2aB

Reaction was carried out using **III-1a** (100 mg) as substrate and methyl 4-iodobenzoate (200 mg, 2.4 equiv.) as coupling partner. Purification with CyHex/EtOAc (7:3) afforded the major diastereomer (72 mg, 51%) as a yellow oil and the minor diastereomer (45 mg, 32%) as a clear oil. ^{1}H NMR of the crude showed a 6:4 diastereomeric ratio.



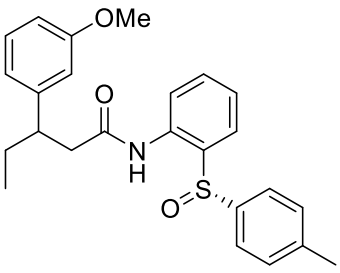
Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.34 (1H, br s, N*H*), 8.33 (1H, d, J=8.1 Hz), 7.92 (2H, d, J=8.2 Hz), 7.38-7.45 (2H, m), 7.28 (2H, d, J=8.2 Hz), 7.23 (2H, d, J=8.3 Hz), 7.15 (2H, d, J=8.2 Hz), 7.09 (1H, td, J=7.7, 1.2 Hz), 3.88 (3H, s, C(O)OC*H*$_3$), 3.14 (1H, dddd, J= 9.1, 8.1, 6.9, 6.1 Hz), 2.66 (1H, dd, J=15.2, 6.9 Hz), 2.50 (1H, dd, J=15.1, 8.1 Hz), 2.32 (3H, s, PhC*H*$_3$), 1.56-1.77 (2H, m), 0.75 (3H, t, J=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 169.86, 167.22, 149.86, 141.72, 140.41, 139.82, 133.07, 130.24, 130.03, 128.49, 127.82, 127.73, 127.44, 124.51, 123.33, 122.77, 52.17, 44.61, 43.72, 29.12, 21.43, 12.05; HRMS (ESI-TOF): m/z calcd for $C_{26}H_{28}NO_4S^+$: 450.1734, found: 450.1746; FT-IR (cm^{-1}): 1719 (s, C=O ester), 1694 (s, C=O amide), 1020 (s, S=O); R_t (min, IA, Hex/iPrOH, 80/20, 0.5 mL/min): 25.79 (1%), 31.55 (99%); $[\alpha]_D^{20}$= +105.9° (c=0.12, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.25.



Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.15 (1H, br s, N*H*), 8.26 (1H, d, J=8.0 Hz), 7.93 (2H, d, J=8.2 Hz), 7.39-7.48 (2H, m), 7.34 (2H, d, J=8.3 Hz), 7.20-7.25 (4H, m), 7.12 (1H, td, J=7.6, 1.3 Hz), 3.87 (3H, s, C(O)OC*H*$_3$), 3.01-3.11 (1H, m), 2.45-2.57 (2H, m), 2.35 (3H, s, PhC*H*$_3$), 1.46-1.58 (2H, m), 0.69 (3H, t, J=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 169.93, 167.25, 149.54, 141.65, 140.27, 140.03, 133.18, 130.22, 130.04, 129.65, 128.63, 128.02, 127.82, 124.70, 123.44, 123.15, 52.19, 44.93, 44.09, 29.06, 21.49, 12.06; FT-IR (cm^{-1}): 1719 (s, C=O ester), 1694 (s, C=O amide), 1020 (m, S=O); R_t (min, IA, Hex/iPrOH, 90/10, 0.5 mL/min): 63.62 (98%), 66.96 (2%); $[\alpha]_D^{20}$= -58.7° (c=0.22, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.21.

3-(3-methoxyphenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)pentanamide III-2aC

Reaction was carried out using **III-1a** (100 mg) as substrate and 3-iodoanisole (90 µL, 2.4 equiv.) as coupling partner. Purification with CyHex/EtOAc (9:1) afforded a mixture of diastereomers (97 mg, 73%) as a brownish oil. ^{1}H NMR of the crude showed a 6:4 diastereomeric ratio.

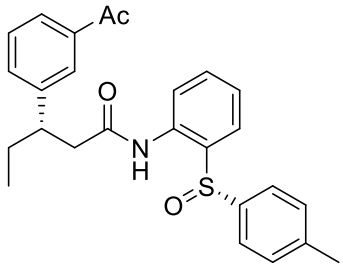


^{1}H NMR (400 MHz, $CDCl_3$): 10.14 (0.6H, br s, N*H*), 10.00 (0.4H, br s, N*H*), 8.35 (0.6H, d, J=8.2 Hz), 8.29 (0.4H, d, J=8.2 Hz), 7.42-7.50 (1H, m), 7.37-7.42 (1H, m), 7.32-7.37 (2H, m), 7.02-7.23 (5H, m), 6.80-6.92 (2H, m), 3.81-3.87 (3H, m, OC*H*$_3$), 3.45-3.53 (1H, m), 2.41-2.68 (2H, m), 2.30-2.40 (3H, m, PhC*H*$_3$), 1.50-1.72 (2H, m), 0.67-0.79 (3H, m, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 169.82 (0.6C), 169.80 (0.4C), 156.53 (0.6C), 156.48

(0.4C), 140.27 (0.6C), 140.23 (0.4C), 139.22 (0.6C), 139.07 (0.4C), 138.75 (0.6C), 138.73 (0.4C), 131.87, 131.79, 130.95 (0.4C), 130.67 (0.6C), 128.96 (0.6C), 128.92 (0.4C), 127.23 (0.4C), 126.90 (0.6C), 126.71 (0.4C), 126.45 (0.6C), 126.26 (0.4C), 126.15 (0.6C), 123.38, 122.08 (0.4C), 122.03 (0.6C), 122.00 (0.6C), 121.74 (0.4C), 119.47, 54.35, 42.69 (0.4C), 42.59 (0.6C), 37.20, 36.32, 25.95 (0.4C), 25.91 (0.6C), 20.27, 10.99 (0.4C), 10.84 (0.6C); HRMS (ESI-TOF): m/z calcd for $C_{25}H_{28}NO_3S^+$: 422.1784, found: 422.1800; FT-IR (cm^{-1}): 1687 (s, C=O), 1298 (s, C-O ether), 1023 (m, S=O); R_f (CyHex/EtOAc, 8/2): 0.40.

3-(3-acetylphenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)pentanamide III-2aD

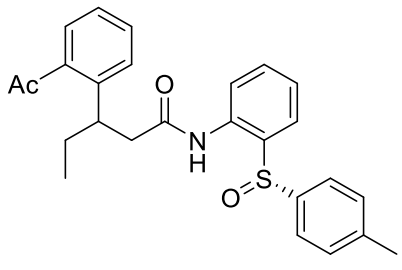
Reaction was carried out using **III-1a** (100 mg) as substrate and 3'-iodoacetophenone (100 µL, 2.5 equiv.) as coupling partner. Purification with CyHex/EtOAc (9:1) afforded the major diastereomer (44 mg, 63%) as a yellow oil. ^{1}H NMR of the crude showed a 7:3 diastereomeric ratio.



Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.30 (1H, br s, N*H*), 8.33 (1H, d, J=8.2 Hz), 7.74-7.80 (2H, m), 7.43 (2H, d, J=8.4 Hz), 7.25-7.41 (4H, m), 7.06-7.19 (3H, m), 3.05-3.18 (1H, m), 2.44-2.68 (5H, m), 2.31 (3H, s, PhC*H*$_3$), 1.57-1.81 (2H, m), 0.75 (3H, t, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 198.21, 169.82, 144.75, 141.51, 140.20, 139.63, 132.87, 132.43, 130.04, 128.70, 127.56, 127.48, 127.38, 127.32, 126.54, 124.40, 123.20, 122.66, 44.74, 43.61, 28.85, 26.73, 21.30, 11.91; HRMS (ESI-TOF): m/z calcd for $C_{26}H_{27}NNaO_3S^+$: 456.1604, found: 456.1652; FT-IR (cm^{-1}): 1684 (s, C=O), 1022 (s, S=O); $[\alpha]_D^{20}$= +23.1° (c=0.10, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.23.

3-(2-acetylphenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)pentanamide III-2aE

Reaction was carried out using **III-1a** (100 mg) as substrate and 3-iodoanisole (90 µL, 2.4 equiv.) as coupling partner. Purification with CyHex/EtOAc (9:1) afforded a mixture of diastereomers (92 mg, 67%) as an orange oil. ^{1}H NMR of the crude showed a 7:3 diastereomeric ratio.

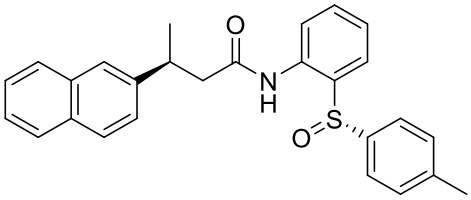


^{1}H NMR (400 MHz, $CDCl_3$): 10.09 (0.3H, br s, N*H*), 9.97 (0.7H, br s, N*H*), 8.22 (0.3H, d, J=8.2 Hz), 8.14 (0.7H, d, J=8.2 Hz), 7.26-7.49 (7H, m), 7.07-7.23 (4H, m), 3.52-3.68 (1H, m), 2.58-2.65 (1.4H, m), 2.55-2.58 (3H, m, PhC(O)C*H*$_3$), 2.40-2.48 (0.6H, m), 2.33 (2.1H, s, PhC*H*$_3$), 2.32 (0.9H, s, PhC*H*$_3$), 1.54-1.75 (2H, m), 0.77 (1.1H, t, J=7.0 Hz), 0.72 (1.9H, t, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 203.91, 170.03,

142.75 (0.3C), 142.53 (0.7C), 141.34, 140.75 (0.7C), 140.56 (0.3C), 139.91 (0.3C), 139.83 (0.7C), 139.73 (0.7C), 139.70 (0.3C), 132.82 (0.7C), 132.68 (0.3C), 130.98 (0.7C), 130.88 (0.3C), 130.00 (0.3C), 129.96 (0.7C), 127.65 (0.7C), 127.62 (0.3C), 127.45 (0.7C), 127.27 (0.3C), 127.06 (0.7C), 127.00 (0.3C), 125.99 (0.3C), 125.93, 125.86 (0.7C), 124.49 (0.3C), 124.46 (0.7C), 123.45 (0.3C), 123.41 (0.7C), 123.21 (0.7C), 122.99 (0.3C), 44.87 (0.7C), 44.57 (0.3C), 38.41 (0.7C), 38.23 (0.3C), 30.72 (0.7C), 30.69 (0.3C), 28.86 (0.3C), 28.80 (0.7C), 21.33 (0.3C), 21.31 (0.7C), 11.88; HRMS (ESI-TOF): m/z calcd for $C_{26}H_{27}NNaO_3S^+$: 456.1604, found: 456.1593; FT-IR (cm^{-1}): 1688 (s, C=O), 1021 (m, S=O); R_f (CyHex/EtOAc, 7/3): 0.20.

3-(naphthalen-2-yl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)butanamide III-2bF

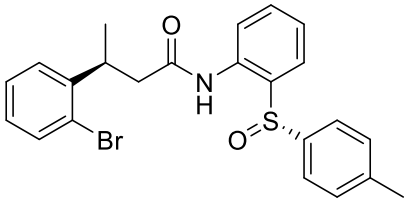
Reaction was carried out using **III-1b** (20 mg) as substrate and 2-iodonaphthalene (50 mg, 3 equiv.) as coupling partner. Purification by preparative thin layer chromatography with CyHex/EtOAc (9:1) afforded the major diastereomer (13 mg, 45%) as a clear oil and the minor diastereomer (4 mg, assumed 14%, mixed with some starting material). ^{1}H NMR of the crude showed a 70:30 diastereomeric ratio.



Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.21 (1H, br s, N*H*), 8.32 (1H, d, *J*=8.5 Hz), 7.69-7.81 (3H, m), 7.64 (1H, d, *J*=1.4 Hz), 7.32-7.48 (7H, m), 7.21 (2H, d, *J*=8.4 Hz), 7.12 (1H, td, *J*=7.5, 1.0 Hz), 3.40-3.51 (1H, m, C*H*CH_3), 2.72 (1H, dd, *J*=14.6, 6.4 Hz), 2.48 (1H, dd, *J*=14.7, 8.7 Hz), 2.33 (3H, s, PhC*H*$_3$), 1.24 (3H, d, *J*=6.9 Hz, CHC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): 169.08, 142.19, 140.44, 139.12, 138.78, 132.58, 131.94, 131.32, 129.01, 127.30, 127.21, 126.74, 126.70, 126.57, 124.95, 124.54, 124.36, 123.89, 123.45, 122.18, 121.96, 45.33, 35.53, 20.69, 20.27; HRMS (ESI-TOF): m/z calcd for $C_{27}H_{25}NNaO_2S^+$: 450.1498, found: 450.1519; FT-IR (cm^{-1}): 1709 (m, C-O), 1038 (m, S-O); $[\alpha]_D^{20}$= +74.5° (c=0.1, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.48.

3-(2-bromophenyl)-N-(2-((S)-p-tolylsulfinyl)phenyl)butyramide III-2bG

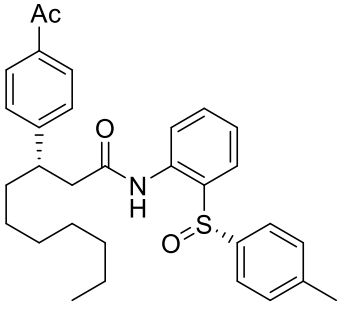
Reaction was carried out using **III-1b** (100 mg) as substrate and 2-bromoiodobenzene (100 µL, 2.3 equiv.) as coupling partner. Purification with CyHex/EtOAc (9:1) afforded the major diastereomer (86 mg, 57%) as a brown oil. ^{1}H NMR of the crude showed a 6:4 diastereomeric ratio.



Major diastereomer : ^{1}H NMR (400 MHz, $CDCl_3$): 10.17 (1H, br s, N*H*), 8.35 (1H, d, J=8.4 Hz), 7.42-7.57 (4H, m), 7.37 (2H, d, J=8.3 Hz), 7.19-7.26 (3H, m), 7.14 (1H, t, J=7.6 Hz), 7.08-7.08 (1H, m), 3.71-3.82 (1H, m), 2.72 (1H, dd, J=15.2, 5.2 Hz), 2.26-2.43 (4H, m), 1.16 (3H, d, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 169.70, 144.44, 141.43, 137.53, 133.11, 133.00, 131.56, 130.02, 128.18, 127.86, 127.76, 127.16, 127.13, 126.14, 124.47, 123.27, 123.10, 43.81, 35.23, 21.30, 20.06; HRMS (ESI-TOF): m/z calcd for $C_{23}H_{23}BrNO_2S^+$: 456.0627, found: 456.0646; FT-IR (cm^{-1}): 1699 (s, C=O), 1023 (s, S=O), 754 (s, C-Br); $[\alpha]_D^{20}$= -3.2° (c=0.20, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.6.

3-(4-acetylphenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)decanamide III-2cH

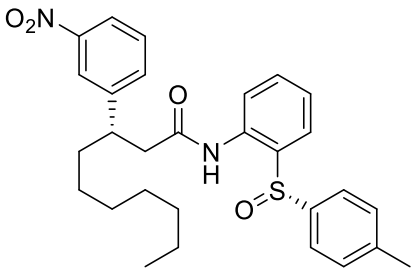
Reaction was carried out using **III-1c** (100 mg) as substrate and 4'-iodoacetophenone (150 mg, 2.4 equiv.) as coupling partner. Purification with CyHex/EtOAc (7:3) afforded the major diastereomer (52 mg, 40%) as an orange oil and the minor diastereomer (34 mg, 26%) as a clear oil. ^{1}H NMR of the crude showed a 6:4 diastereomeric ratio.



Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.18 (1H, br s, N*H*), 8.25 (1H, d, J=8.4 Hz), 7.86 (2H, d, J=8.3 Hz), 7.45 (1H, dd, J=7.7, 1.4 Hz), 7.41 (1H, td, J=7.9, 1.5 Hz), 7.35 (2H, d, J=8.3 Hz), 7.21-7.28 (4H, m), 7.11 (1H, td, J=7.7, 1.1 Hz), 3.12-3.20 (1H, m), 2.49-2.57 (5H, m), 2.35 (3H, s, PhC*H*$_3$), 1.46-1.57 (2H, m), 1.08-1.20 (10H, m), 0.82 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 198.02, 169.86, 150.15, 141.64, 140.26, 139.93, 135.77, 133.15, 130.23, 128.88, 127.95, 127.92, 127.78, 124.64, 123.44, 123.07, 45.24, 42.44, 36.18, 31.98, 29.73, 29.38, 27.61, 26.77, 22.81, 21.51, 14.27; HRMS (ESI-TOF): m/z calcd for $C_{31}H_{38}NO_3S^+$: 504.2567, found: 504.2605; FT-IR (cm^{-1}): 1682 (s, C=O), 1022 (m, S=O); $[\alpha]_D^{20}$= +2.8° (c=0.10, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.35.

3-(3-nitrophenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)decanamide III-2cI

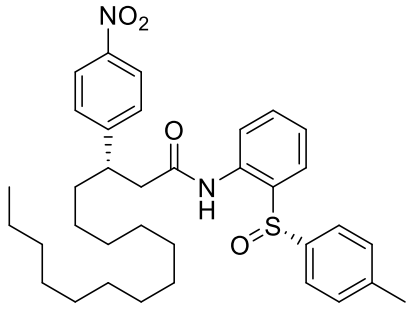
Reaction was carried out using **III-1c** (100 mg) as substrate and 3-iodonitrobenzene (150 mg, 2.3 equiv.) as coupling partner. Purification with CyHex/EtOAc (7:3) afforded the major diastereomer (70 mg, 53%) as a yellow oil and the minor diastereomer (42 mg, 32%) as an orange oil. ^{1}H NMR of the crude showed a 6:4 diastereomeric ratio.



Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.34 (1H, br s, N*H*), 8.32 (1H, d, J=8.2 Hz), 7.99-8.07 (2H, m), 7.47-7.54 (1H, m), 7.34-7.45 (3H, m), 7.28 (2H, d, J=8.4 Hz), 7.07-7.17 (3H, m), 3.26 (1H, dddd, J=9.1, 7.8, 6.8, 5.7 Hz), 2.68 (1H, dd, J=15.3, 6.8 Hz), 2.50 (1H, dd, J=15.3, 8.1 Hz), 1.52-1.73 (2H, m), 1.11-1.23 (10H, m), 0.83 (3H, t, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 169.26, 148.42, 146.74, 141.56, 140.17, 139.53, 134.19, 132.92, 130.00, 129.29, 127.64, 127.19, 124.37, 123.24, 122.61, 122.16, 121.51, 44.60, 41.69, 35.97, 31.75, 29.72, 29.40, 29.10, 27.31, 22.61, 21.27, 14.07; HRMS (ESI-TOF): m/z calcd for $C_{29}H_{35}N_2O_4S^+$: 507.231, found: 507.232; FT-IR (cm^{-1}): 1695 (m, C=O), 1528 (s, N-O), 1344 (s, N-O), 1025 (w, S=O); $[\alpha]_D^{20}$= +10.7° (c=0.10, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.21.

3-(4-nitrophenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)palmitamide III-2dA

Reaction was carried out using **III-1d** (100 mg) as substrate and 4-iodonitrobenzene (160 mg, 3 equiv.) as coupling partner. Purification with CyHex/EtOAc (4:1) afforded the major diastereomer (44 mg, 35%) as a clear oil and the minor diastereomer (30 mg, 24%) as a yellow oil. ^{1}H NMR of the crude showed a 6:4 diastereomeric ratio.

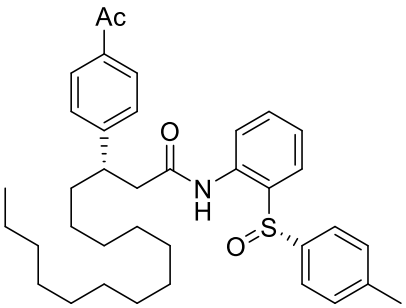


Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.36 (1H, br s, N*H*), 8.27 (1H, dd, J=8.6, 1.0 Hz), 8.02 (2H, d, J=8.6 Hz), 7.33-7.40 (2H, m), 7.25 (2H, d, J=8.6 Hz), 7.22 (2H, d, J=8.3 Hz), 7.11 (2H, d, J=8.3 Hz), 7.05 (1H, td, J=7.7, 1.1 Hz), 3.18-3.30 (1H, m), 2.65 (1H, dd, J=15.4, 6.3 Hz), 2.44 (1H, dd, J=15.4, 8.8 Hz), 2.28 (3H, s, PhC*H*$_3$), 1.46-1.66 (2H, m), 1.06-1.26 (24H, m), 0.80 (3H, t, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 169.38, 152.59, 146.72, 141.92, 140.41, 139.81, 133.13, 130.23, 128.53, 127.80, 127.04, 124.61, 123.92, 123.43, 122.68, 44.60, 41.98, 36.30, 32.13, 29.88, 29.84, 29.81, 29.74, 29.63, 29.55, 27.50, 22.90, 21.44, 14.33; HRMS (ESI-TOF): m/z calcd for $C_{35}H_{46}N_2NaO_4S^+$: 613.3070,

found: 613.3084; FT-IR (cm^{-1}) : 1698 (s, C=O), 1522 (s, N-O), 1345 (s, N-O), 1028 (m, S=O); $[\alpha]_D^{20}$= +1.2° (c=0.32, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.45.

3-(4-acetylphenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)palmitamide III-2dH

Reaction was carried out using **III-1d** (100 mg) as substrate and 4'-iodoacetophenone (100 mg, 2 equiv.) as coupling partner. Purification with CyHex/EtOAc (4:1) afforded the major diastereomer (58 mg, 46%) as an orange oil and the minor diastereomer (38 mg, 30%) as a yellow oil. ^{1}H NMR of the crude showed a 6:4 diastereomeric ratio.



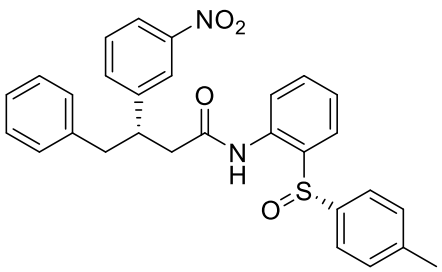
Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.18 (1H, br s, N*H*), 8.25 (1H, d, J=8.2 Hz), 7.86 (2H, d, J=8.4 Hz), 7.46 (1H, dd, J=7.7, 1.4 Hz), 7.37-7.42 (1H, m), 7.35 (2H, d, J=8.3 Hz), 7.19-7.30 (4H, m), 7.11 (1H, td, J=7.6, 1.1 Hz), 3.10-3.21 (1H, m),2.55 (3H, s, PhC(O)C*H*$_3$), 2.51 (2H, dd, J= 7.3, 4.7 Hz), 2.35 (3H, s, PhC*H*$_3$), 1.48-1.54 (2H, m), 1.06-1.30 (22H, m), 0.85 (3H, t, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 198.02, 169.85, 150.15, 141.63, 140.26, 139.93, 135.76, 133.15, 130.24, 128.87, 127.95, 127.92, 127.78, 124.63, 123.44, 123.06, 45.24, 42.43, 36.18, 32.12, 29.88, 29.84, 29.79, 29.77, 29.73, 29.55, 27.61, 26.77, 22.89, 21.51, 14.33; HRMS (ESI-TOF): m/z calcd for $C_{37}H_{50}NO_3S^+$: 588.3506, found: 588.3516; FT-IR (cm^{-1}): 1683 (s, C=O), 1022 (m, S=O); $[\alpha]_D^{20}$= +6.1° (c=0.13, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.47.

3-tolyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)palmitamide III-2dJ

Reaction was carried out using **III-1d** (100 mg) as substrate and 4-iodotoluene (100 mg, 2 equiv.) as coupling partner. Purification with CyHex/EtOAc (4:1) afforded a mixture of starting material and diastereomers (assumed 50% conversion) as an orange oil. ^{1}H NMR of the crude showed a 6:4 diastereomeric ratio. HRMS (ESI-TOF): m/z calcd for $C_{36}H_{50}NO_2S^+$: 560.3557, found: 560.3582.

3-(3-nitrophenyl)-4-phenyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)butanamide III-2eI

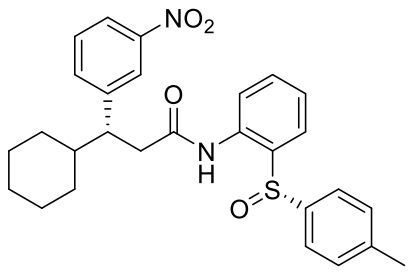
Reaction was carried out using **III-1e** (100 mg) as substrate and 3-iodonitrobenzene (132 mg, 2 equiv.) as coupling partner. Purification with CyHex/EtOAc (9:1 to 7:3) afforded the major diastereomer (73 mg, 55%) and the minor diastereomer (48 mg, 36%) as clear oils. ^{1}H NMR of the crude showed a 6:4 diastereomeric ratio.



Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.33 (1H, br s, N*H*), 8.26 (1H, d, J=8.6 Hz), 8.03 (1H, t, J=1.9 Hz), 7.99 (1H, ddd, J=8.1, 2.3, 1.1 Hz), 7.37-7.44 (3H, m), 7.28-7.35 (1H, m), 7.07-7.22 (8H, m), 7.05 (2H, d, J=8.2 Hz), 3.58-3.68 (1H, m), 2.98 (1H, dd, J=13.7, 7.5 Hz), 2.90 (1H, dd, J=13.3, 7.8 Hz), 2.74 (1H, dd, J=15.6, 6.0 Hz), 2.55 (1H, dd, J=15.5, 8.8 Hz), 2.30 (3H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.98, 148.30, 145.75, 141.52, 140.09, 139.46, 138.52, 134.27, 132.92, 129.99, 129.22, 129.21, 128.48, 127.63, 127.22, 126.55, 124.31, 123.26, 122.58, 122.19, 121.66, 43.37, 42.91, 42.62, 21.27; HRMS (ESI-TOF): m/z calcd for $C_{29}H_{27}N_2O_4S^+$: 499.1686, found: 499.1697; FT-IR (cm^{-1}): 1694 (m, C=O), 1526 (s, N-O), 1347 (s, N-O), 1022 (m, S=O); $[\alpha]_D^{20}$= +67.1° (c=0.45, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.54.

3-cyclohexyl-3-(3-nitrophenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)propenamide III-2fI

Reaction was carried out using **III-1f** (100 mg) as substrate and 3-iodonitrobenzene (132 mg, 2 equiv.) as coupling partner. Purification with CyHex/EtOAc (95:5) afforded the major diastereomer (54 mg, 40%) as a brownish oil. ^{1}H NMR of the crude showed a 4:1 diastereomeric ratio.

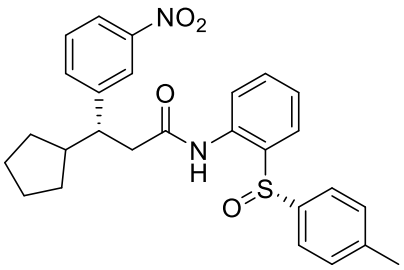


Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.36 (1H, br s, N*H*), 8.26 (1H, d, J=8.4 Hz), 7.96-8.01 (2H, m), 7.31-7.47 (4H, m), 7.28 (2H, d, J=8.3 Hz), 7.16 (2H, d, J=8.4 Hz), 7.08 (1H, td, J=7.6, 1.0 Hz), 3.13 (1H, ddd, J=9.8, 7.6, 5.1 Hz), 2.90 (1H, dd, J=15.7, 5.2 Hz), 2.52 (1H, dd, J=15.7, 9.6 Hz), 2.33 (3H, s, PhC*H*$_3$), 1.79-1.86 (1H, m), 1.69-1.77 (1H, m), 1.50-1.60 (2H, m), 1.37-1.44 (1H, m), 1.02-1.24 (4H, m), 0.89-1.00 (1H, m), 0.75-0.86 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 169.67, 148.18, 145.60, 141.62, 139.59, 134.89, 132.90, 130.04, 129.66, 128.91, 127.58, 124.79, 124.45, 123.13, 122.75, 122.43, 121.38, 47.33, 42.69, 40.92, 30.93, 30.66, 26.33, 26.22, 21.28; HRMS (ESI-TOF): m/z calcd for $C_{28}H_{31}N_2O_4S^+$: 491.1999, found: 491.1986; FT-IR (cm^{-1}): 1697 (m, C=O), 1528 (s, N-O), 1348 (s, N-O), 1022 (m, S=O); $[\alpha]_D^{20}$= -4.9° (c=0.20, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.31.

3-cyclopentyl-3-(3-nitrophenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)propenamide III-2hI

Reaction was carried out using **III-1h** (100 mg) as substrate and 3-iodonitrobenzene (132 mg, 2 equiv.) as coupling partner. Purification with CyHex/EtOAc (9:1 to 7:3) afforded the major

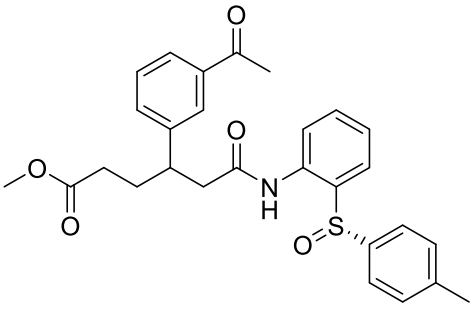
diastereomer (81 mg, 56%) and the minor diastereomer (35 mg, 24%) as clear oils. ^{1}H NMR of the crude showed a 7:3 diastereomeric ratio.



Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.09 (1H, br s, N*H*), 8.18 (1H, d, J=8.4 Hz), 8.00 (1H, ddd, J=7.9, 2.2, 1.3 Hz), 7.96 (1H, t, J=2.0 Hz), 7.36-7.48 (4H, m), 7.34 (2H, d, J=8.2 Hz), 7.26 (2H, d, J=8.2 Hz), 7.10 (1H, td, J=7.6, 1.2 Hz), 2.94 (1H, ddd, J=10.2, 9.9, 4.7 Hz), 2.70 (1H, dd, J=14.9, 4.8 Hz), 2.51 (1H, dd, J=14.8, 9.9 Hz), 2.26-2.41 (4H, m), 1.98-2.09 (1H, m), 1.76-1.85 (1H, m), 1.59-1.69 (1H, m), 1.40-1.53 (2H, m), 1.25-1.37 (2H, m), 0.90-1.01 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 169.40, 148.26, 146.35, 141.56, 140.03, 139.88, 134.08, 133.00, 130.07, 129.18, 127.85, 127.39, 124.53, 123.21, 122.81, 122.78, 121.55, 47.91, 45.92, 43.86, 31.54, 31.28, 25.25, 24.93, 21.32; HRMS (ESI-TOF): m/z calcd for $C_{27}H_{29}N_2O_4S^+$: 477.1843, found 477.1841; FT-IR (cm^{-1}): 1695 (w, C=O), 1528 (s, N-O), 1348 (s, N-O), 1022 (w, S=O); $[\alpha]_D^{20}$= -21.8° (c=0.15, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.25.

methyl 4-(3-acetylphenyl)-6-oxo-6-((2-((*S*)-*p*-tolylsulfinyl)phenyl)amino)hexanoate III-2iD

Reaction was carried out using **III-1i** (100 mg) as substrate and 3'-iodoacetophenone (170 mg, 2.6 equiv.) as coupling partner. Purification using CyHex/EtOAc (3:2) afforded a mixture of diastereomers (112 mg, 85%) as a yellow oil. ^{1}H NMR of the crude mixture showed a 60:40 diastereomeric ratio.

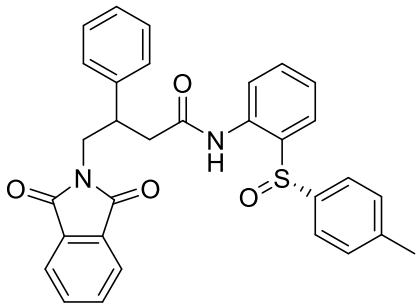


^{1}H NMR (400 MHz, $CDCl_3$): 10.30 (0.4H, br s, N*H*), 10.15 (0.6H, br s, N*H*), 8.29 (0.4H, d, J=8.4 Hz), 8.21 (0.6H, d, J=8.4 Hz), 7.74-7.81 (2H, m), 7.32-7.47 (5H, m), 7.24-7.29 (2H, m), 7.07-7.17 (2H, m), 3.54-3.58 (3H, m, C(O)OC*H*$_3$), 3.16-3.29 (1.4H, m), 2.52-2.82 (4.6H, m), 2.35 (1.8H, s, PhC*H*$_3$), 2.30 (1.2H, s, PhC*H*$_3$), 2.04-2.19 (2H, m), 1.80-2.01 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 198.14 (0.6C), 198.07 (0.4C), 173.37 (0.6C), 137.34 (0.4C), 169.21, 143.63 (0.4C), 143.36 (0.6C), 141.60 (0.6C), 141.55 (0.4C), 137.71 (0.4C), 137.53 (0.6C), 137.49 (0.6C), 137.02 (0.4C), 135.01, 132.90 (0.6C), 132.87 (0.4C), 132.41 (0.6C), 132.35 (0.4C), 130.12 (0.6C), 130.06 (0.4C), 128.99 (0.6C), 128.97 (0.6C), 128.44, 127.70 (0.6C), 127.57 (0.4C), 127.46 (0.4C), 127.36 (0.6C), 127.05 (0.6C), 126.91 (0.4C), 124.41 (0.4C), 124.38 (0.6C), 123.40 (0.6C), 123.37 (0.4C), 122.94 (0.6C), 122.79 (0.4C), 51.60 (0.4C), 51.55 (0.6C), 45.52, 44.80 (0.6C), 44.60 (0.4C), 41.51 (0.6C), 41.32

(0.4C), 32.03 (0.4C), 30.90 (0.6C), 26.74 (0.6C), 26.65 (0.4C), 21.30 (0.6C), 21.29 (0.4C); HRMS (ESI-TOF): m/z calcd for $C_{28}H_{29}NNaO_5S^+$: 514.1659, found: 514.1676; FT-IR (cm^{-1}): 1734 (C=O ester), 1683 (C=O amide and ketone), 1022 (S=O); R_f (CyHex/EtOAc, 7/3): 0.19.

3-phenyl-4-(1,3-dioxoisoindolin-2-yl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)butanamide III-2jK

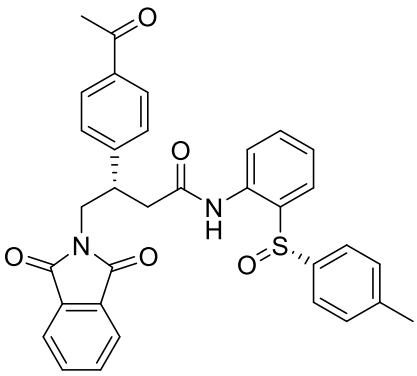
Reaction was carried out using **III-1k** (120 mg) as substrate and iodobenzene (100 µL, 3.3 equiv.) as coupling partner. Purification with CyHex/EtOAc (4:1) afforded a mixture of diastereomers (105 mg, 75%) as a yellow oil. ^{1}H NMR of the crude showed a 60:40 diastereomeric ratio.



^{1}H NMR (400 MHz, $CDCl_3$): 10.21 (0.6H, br s, N*H*), 10.05 (0.4H, br s, N*H*), 8.11 (0.4H, d, *J*=8.4 Hz), 8.01 (0.6H, d, *J*=8.4 Hz), 7.70-7.79 (2H, m), 7.58-7.66 (2H, m), 7.39-7.45 (1H, m), 7.00-7.36 (11H, m), 3.79-3.97 (2H, m), 3.66-3.77 (1H, m), 2.53-2.79 (2H, m), 2.28 (1.8H, s, PhC*H*$_3$), 2.24 (1.2H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.95, 168.13 (0.6C), 168.05 (0.4C), 141.31, 140.80 (0.6C), 140.22 (0.4C), 139.91 (0.6C), 139.78 (0.4C), 139.76 (0.4C), 139.67 (0.6C), 133.92 (0.4C), 133.85 (0.6C), 132.80 (0.4C), 132.65 (0.6C), 131.92 (0.6C), 131.87 (0.4C), 130.04 (0.4C), 130.01 (0.6C), 128.67 (0.6C), 128.65 (0.4C), 127.80 (0.4C), 127.71, 127.63 (0.6C), 127.43 (0.6C), 127.26 (0.4C), 127.13, 124.44 (0.4C), 124.29 (0.6C), 123.29 (0.4C), 123.24 (0.6C), 123.23 (0.6C), 123.14 (0.4C), 123.05 (0.4C), 122.61 (0.6C), 43.26 (0.6C), 42.97 (0.4C), 41.83 (0.4C), 41.46 (0.6C), 40.94 (0.4C), 40.28 (0.6C), 21.30 (0.6C), 21.24 (0.4C); FT-IR (cm-1): 1711 (s, C-O), 1022 (m, S-O); HRMS (ESI-TOF): m/z calcd for $C_{31}H_{26}N_2NaO_4S^+$: 545.1505, found: 545.1508; R_f (CyHex/EtOAc, 7/3): 0.25.

3-(4-acetylphenyl)-4-(1,3-dioxoisoindolin-2-yl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)butanamide III-2jH

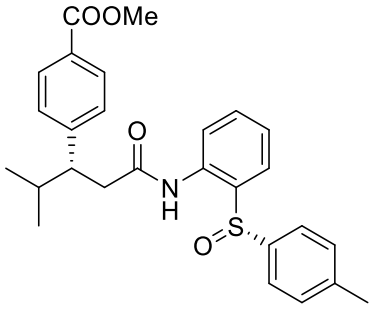
Reaction was carried out using **III-1j** (120 mg) as substrate and 4'-iodoacetophenone (200 mg, 3 equiv.) as coupling partner. Purification with CyHex/EtOAc (6:4) afforded the major diastereomer (80 mg, 53%) as a yellow oil and the minor diastereomer (59 mg, 39%) as a brownish oil. ^{1}H NMR of the crude showed a 60:40 diastereomeric ratio.



Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.33 (1H, br s, N*H*), 8.08 (1H, d, *J*=8.4 Hz), 7.81 (2H, d, *J*=8.5 Hz), 7.76 (2H, dd, *J*=5.5, 3.0 Hz), 7.64 (2H, dd, *J*=5.5, 3.1 Hz), 7.40 (1H, dd, *J*=7.4, 1.6 Hz), 7.34 (2H, d, *J*=8.4 Hz), 7.25-7.31 (3H, m), 7.13 (2H, d, *J*=8.3 Hz), 7.05 (1H, td, *J*=7.7, 1.1 Hz), 3.80-4.02 (3H, m), 2.74-2.86 (1H, m), 2.59-2.69 (1H, m), 2.51 (3H, s, PhC(O)C*H*$_3$), 2.31 (3H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 196.58, 167.39, 167.00, 145.25, 140.49, 138.91, 138.60, 135.00, 132.97, 131.70, 130.76, 129.01, 127.74, 127.30, 126.98, 126.45, 123.29, 122.34, 122.18, 121.52, 41.79, 40.02, 39.32, 25.55, 20.25; FT-IR (cm^{-1}): 1713 (s, C-O), 1682 (s, C-O), 1022 (m, S-O); HRMS (ESI-TOF): m/z calcd for $C_{33}H_{29}N_2O_5S^+$: 565.1792, found: 565.1788; mp (°C): 187; $[\alpha]_D^{20}$= -35.0° (c=0.1, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.17.

methyl 4-(4-methyl-1-oxo-1-((2-(*S*)-(*p*-tolylsulfinyl)phenyl)amino)pentan-3-yl)benzoate III-2nB

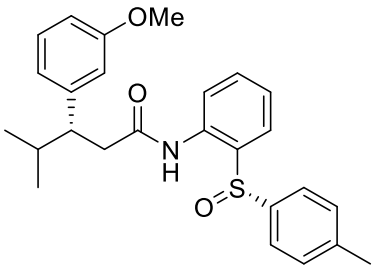
Reaction was carried out using **III-1n** (100 mg) as substrate and methyl 4-iodobenzoate (180 mg, 2.3 equiv.) as coupling partner. Purification using CyHex/EtOAc (7:3) afforded the major diastereomer (93 mg, 66%) as a clear oil and the minor diastereomer (26 mg, 18%). ^{1}H NMR of the crude mixture showed a 75:25 diastereomeric ratio.



Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.34 (1H, br s, N*H*), 8.28 (1H, d, J=8.4 Hz), 7.88 (2H, d, J=8.1 Hz), 7.35-7.43 (2H, m), 7.30 (2H, d, J=8.1 Hz), 7.15-7.21 (4H, m), 7.07 (1H, t, J=7.5 Hz), 3.88 (3H, s, C(O)OC*H*$_3$), 3.02-3.10 (1H, m), 2.85 (1H, dd, J=15.3, 5.2 Hz), 2.54 (1H, dd, J=15.4, 9.8 Hz), 2.35 (3H, s, PhC*H*$_3$), 1.83-1.92 (1H, m), 0.95 (3H, d, J=6.7 Hz), 0.76 (3H, d, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 169.95, 167.05, 148.72, 141.59, 140.26, 139.73, 132.86, 130.10, 129.51, 128.25, 128.13, 127.51, 124.39, 124.37, 123.03, 122.45, 51.95, 48.26, 41.23, 33.11, 21.26, 20.57, 20.32; HRMS (ESI-TOF): m/z calcd for $C_{27}H_{29}NNaO_4S^+$: 486.1710, found: 186.1713; FT-IR (cm^{-1}): 1720 (s, C=O), 1020 (m, S=O); $[\alpha]_D^{20}$= +78.2° (c=0.20, $CHCl_3$); R_f (CyHex/EtOAc): 0.32.

4-methyl-3-(3-methoxyphenyl)-*N*-(2-(*S*)-(para-tolylsulfinyl)phenyl)valeramide III-2nC

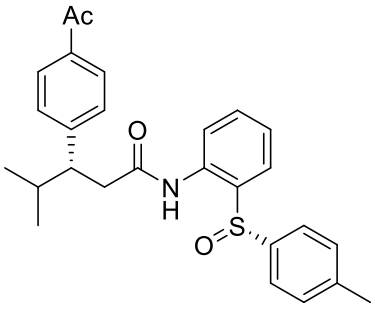
Reaction was carried out using **III-1n** (100 mg) as substrate and 3-iodoanisole (100 µL, 2.8 equiv.) as coupling partner. Purification with CyHex/EtOAc (4:1) afforded the major diastereomer (89 mg, 67%) and the minor diastereomer (22 mg, 17%) as clear oils. ^{1}H NMR of the crude showed a 7:3 diastereomeric ratio.



Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.23 (1H, br s, N*H*), 8.28 (1H, d, J=8.4 Hz), 7.35-7.47 (2H, m), 7.31 (2H, d, J=8.2 Hz), 7.04-7.18 (4H, m), 6.68-6.77 (3H, m), 3.75 (3H, s, COC*H*$_3$), 2.96 (1H, ddd, J=9.1, 7.3, 5.7 Hz), 2.78 (1H, dd, J=15.2, 5.6 Hz), 2.52 (1H, dd, J=15.3, 8.9 Hz), 2.32 (3H, s, PhC*H*$_3$), 1.80-1.90 (1H, m), 0.94 (3H, d, J=6.7 Hz), 0.77 (3H, d, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 170.46, 159.36, 144.79, 141.45, 140.25, 139.76, 132.76, 130.06, 129.02, 127.38, 124.79, 124.42, 123.04, 122.60, 120.62, 114.11, 111.57, 55.09, 48.40, 41.75, 33.14, 21.32, 20.72, 20.28; HRMS (ESI-TOF): m/z calcd for $C_{26}H_{29}NNaO_3S^+$: 458.1760, found: 458.1768; FT-IR (cm^{-1}): 1694 (m, C=O); 1159 (m, C-O ether), 1021 (m, S=O); $[\alpha]_D^{20}$= -55.2° (c=0.10, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.41.

4-methyl-3-(4-acetylphenyl)-*N*-(2-(*S*)-(para-tolylsulfinyl)phenyl)valeramide III-2nH

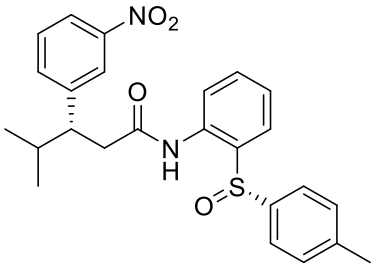
Reaction was carried out using **III-1n** (100 mg) as substrate and 4'-iodoacetophenone (150 mg, 2 equiv.) as coupling partner. Purification with CyHex/EtOAc (4:1) afforded the major diastereomer (100 mg, 74%) and the minor diastereomer (28 mg, 21%) as orange oils. ^{1}H NMR of the crude showed a 7:3 diastereomeric ratio.



Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.34 (1H, br s, N*H*), 8.26 (1H, d, J=8.4 Hz), 7.80 (2H, d, J=8.2 Hz), 7.33-7.41 (2H, m), 7.29 (2H, d, J=8.4 Hz), 7.14-7.22 (4H, m), 7.07 (1H, t, J=7.6 Hz), 3.07 (1H, ddd, J=9.7, 7.4, 5.0 Hz), 2.84 (1H, dd, J=15.3, 4.7 Hz), 2.52 (3H, s, PhC(O)C*H*$_3$), 2.28-2.40 (4H, m), 1.82-1.95 (1H, m), 0.95 (3H, d, J=6.8 Hz), 0.75 (3H, d, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 197.78, 169.98, 148.97, 141.67, 135.61, 135.32, 132.86, 130.45, 130.11, 128.43, 128.33, 128.16, 127.54, 124.45, 123.10, 122.48, 48.32, 41.16, 33.13, 26.53, 21.31, 20.57, 20.32; HRMS (ESI-TOF): m/z calcd for $C_{27}H_{30}NO_3S^+$: 448.1941, found: 448.1964; FT-IR (cm^{-1}): 1683 (s, C=O), 1022 (m, S=O); $[\alpha]_D^{20}$= +172.1° (c=0.30, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.27.

4-methyl-3-(3-nitrophenyl)-*N*-(2-(*S*)-(para-tolylsulfinyl)phenyl)valeramide III-2nI

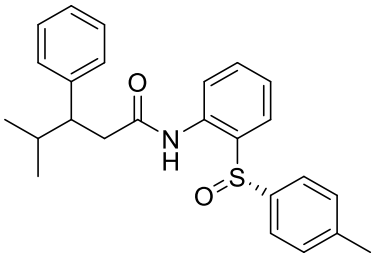
Reaction was carried out using **III-1n** (100 mg) as substrate and 3-iodonitrobenzene (151 mg, 2 equiv.) as coupling partner. Purification using CyHex/EtOAc (4:1) afforded the major diastereomer (82 mg, 60%) as a yellow solid and the minor diastereomer (21 mg, 15%) as an orange oil. ^{1}H NMR of the crude mixture showed a 75:25 diastereomeric ratio.



Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.17 (1H, br s, NH), 8.18 (1H, d, J=8.2 Hz), 8.02 (1H, ddd, J=7.9, 2.2, 1.2 Hz), 7.95 (1H, t, J=2.2 Hz), 7.36-7.48 (4H, m), 7.34 (2H, d, J=8.4 Hz), 7.24-7.27 (2H, m), 7.10 (1H, td, J=7.6, 1.1 Hz), 2.99 (1H, ddd, J=9.5, 7.7, 1.5 Hz), 2.71 (1H, dd, J=15.0, 5.3 Hz), 2.54 (1H, dd, J=15.0, 9.6 Hz), 1.81-1.91 (1H, m), 0.92 (3H, d, J=6.8 Hz), 0.72 (3H, d, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 169.80, 148.41, 145.32, 145.31, 141.79, 140.27, 140.09, 134.60, 133.19, 130.29, 129.26, 128.02, 124.75, 123.46, 123.42, 123.00, 121.80, 48.75, 41.61, 33.17, 21.52, 20.75, 20.43; HRMS (ESI-TOF): m/z calcd for $C_{25}H_{26}KN_2O_4S^+$: 489.1245, found: 489.1281; FT-IR (cm^{-1}): 1694 (m, C=O), 1528 (s, N-O), 1348 (s, N-O), 1022 (w, S=O); mp (°C): 145; $[\alpha]_D^{20}$= +125.2° (c=0.10, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.37.

4-methyl-3-phenyl-*N*-(2-(*S*)-(para-tolylsulfinyl)phenyl)valeramide III-2nK

Reaction was carried out using **III-1n** (100 mg) as substrate and iodobenzene (100 µL) as coupling partner. Purification using CyHex/EtOAc (95:5) afforded a mixture of diastereomers (112 mg, 91%) as a clear oil. ^{1}H NMR of the crude showed a 90:10 diastereomeric ratio.



^{1}H NMR (400 MHz, $CDCl_3$): 10.21 (0.9H, br s, NH), 10.01 (0.1H, br s, N*H*), 8.26 (0.9H, d, J=8.2 Hz), 8.19 (0.1H, d, J=8.4 Hz), 7.28-7.43 (4H, m), 7.11-7.23 (7H, m), 7.07 (1H, t, J=7.6 Hz); 2.89-3.03 (1H, m), 2.80 (0.9H, dd, J=15.5, 6.0 Hz), 2.67 (0.1H, dd, J=15.6, 5.8 Hz), 2.47-2.57 (1H, m), 1.79-1.92 (1H, m), 0.93 (2.7H, d, J=6.7 Hz), 0.88 (0.3H, d, J=6.7 Hz), 0.76 (2.7H, d, J=6.7 Hz), 0.72 (0.3H, d, J=6.8 Hz); ^{13}C NMR (100MHz, $CDCl_3$): 170.53, 142.96 (0.9C), 142.73 (0.1C), 141.43, 140.22, 139.72, 132.83, 130.42 (0.9C), 130.30 (0.1C), 130.07 (0.9C), 130.02 (0.1C), 128.27, 128.11 (0.9C), 128.05 (0.1C), 127.54 (0.1C), 127.48 (0.9C), 126.17, 124.52 (0.1C), 124.44 (0.9C), 123.05, 122.65, 48.30 (0.9C), 45.92 (0.1C), 41.64, 33.14, 21.33, 20.74 (0.1C), 20.68 (0.9C), 20.19 (0.9C), 19.75

(0.1C); HRMS (ESI-TOF): m/z calcd for $C_{25}H_{28}NO_2S^+$: 406.1835, found: 406.1846; FT-IR (cm^{-1}): 1697 (s, C=O), 1022 (s, S=O); R_f (CyHex/EtOAc, 4/1): 0.50.

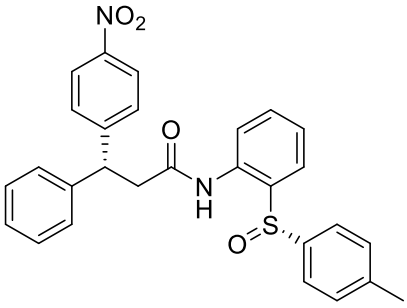
III.7.v. Arylation of hydrocinnamic acid derivatives

General procedure for the coupling reactions of hydrocinnamic acid derivatives

To a pressure tube were added **1l** (50 mg, 0.138 mmol, 1 equiv.), coupling partner (0.276 mmol, 2 equiv.), silver acetate (50 mg, 0.304 mmol, 2.2 equiv.) and palladium(II) acetate (1.5 mg, 0.7 µmol, 5 mol%). The mixture was then dissolved in a 0.1 M of a 4:1 mixture of toluene and 1,1,3,3-hexafluoroisopropanol. The mixture was then stirred 10 min at room temperature, then at 80 °C during 16h. After cooling down to room temperature, the mixture was diluted with DCM, filtered through PTFE 45 µm filter with a syringe and evaporated under reduced pressure. The crude mixture was purified by column chromatography on silica gel.

(*R*)-3-(4-nitrophenyl)-3-phenyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)propenamide III-2kA

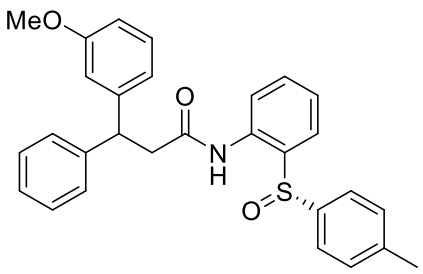
Reaction was carried out using 4-iodonitrobenzene (70 mg) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (9:1 to 7:3) afforded the major diastereomer (33 mg, 50%) as a yellow oil.



Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): 10.48 (1H, br s, N*H*), 8.24 (1H, d, J=8.4 Hz), 7.96 (2H, d, J=8.8 Hz), 7.29-7.39 (2H, m), 7.20-7.28 (6H, m), 7.10-7.17 (5H, m), 7.06 (1H, td, J=7.6, 1.1 Hz), 4.69 (1H, dd, J=9.3, 6.5 Hz), 3.04 (1H, dd, J=15.6, 6.3 Hz), 2.92 (1H, dd, J=15.6, 9.2 Hz), 2.32 (3H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.46, 151.19, 146.49, 142.03, 141.81, 140.16, 139.71, 132.98, 130.14, 128.98, 128.59, 127.68, 127.18, 124.51, 123.81, 123.40, 122.65, 46.36, 43.35, 21.30; HRMS (ESI-TOF): m/z calcd for $C_{28}H_{25}N_2O_4S^+$: 485.1530, found: 485.1540; FT-IR (cm^{-1}) 1694 (m, C=O), 1518 (s, N-O), 1345 (s, N-O), 1020 (m, S=O); $[\alpha]_D^{20}$= -14.5° (c=0.21, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.35.

3-(3-methoxyphenyl)-3-phenyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)propenamide III-2kC

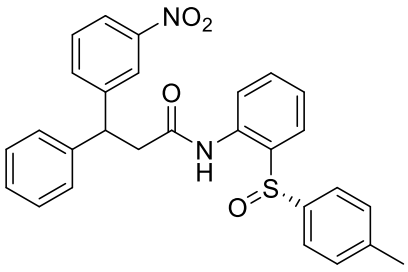
Reaction was carried out using 3-iodoanisole (approx. 35 µL) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (9:1 to 7:3) afforded the title compound (50 mg, 78%) as an orange oil as a 9:1 mixture of diastereomers.



^{1}H NMR (400 MHz, $CDCl_3$): 10.34 (1H, br s, N*H*), 8.27 (1H, d, J=8.4 Hz), 7.42 (1H, dd, J=7.7, 1.3 Hz), 7.36-7.40 (1H, m), 7.31-7.35 (2H, m), 7.12-7.26 (8H, m), 7.07 (1H, td, J=7.5, 1.3 Hz), 6.79-6.83 (1H, m), 6.76-6.79 (1H, m), 6.67-6.73 (1H, m), 4.60 (1H, t, J=7.8 Hz), 3.73 (0.3H, s, OC*H*$_3$), 3.72 (2.7H, s, OC*H*$_3$), 3.05 (1H, dd, J=15.5, 8.1 Hz), 2.96 (1H, dd, J=15.2, 7.4 Hz), 2.33 (3H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.38, 159.82, 145.55, 143.43, 141.58, 140.25, 139.90, 132.94, 130.21, 129.64, 128.74, 127.65, 127.57, 126.68, 124.52, 123.34, 122.93, 120.07, 113.95, 111.79, 55.27, 46.90, 44.05, 21.46; HRMS (ESI-TOF): m/z calcd for $C_{29}H_{27}KNO_3S^+$: 508.1343, found: 508.1398; FT-IR (cm^{-1}): 1694 (m, C=O), 1259 (s, C-O), 1037 (m, C-O), 1022 (s, S=O); R_f (CyHex/EtOAc, 7/3): 0.28.

3-(3-nitrophenyl)-3-phenyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)propenamide III-2kH

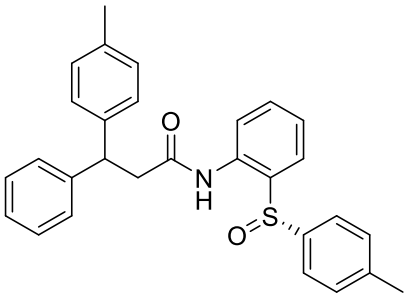
Reaction was carried out using 3-iodo-nitrobenzene (100 mg) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (7:3) afforded the title compound (78 mg, 84%) as a yellow oil as a 75:25 mixture of diastereomers.



^{1}H NMR (400 MHz, $CDCl_3$): 10.46 (1H, br s, N*H*), 8.27 (1H, d, J=8.4 Hz), 8.08 (1H, t, J=2.1 Hz), 7.98-8.03 (1H, m), 7.50-7.54 (1H, m), 7.28-7.46 (7H, m), 7.17-7.24 (4H, m), 7.11 (1H, t, J=7.6, 1.1 Hz), 4.65-4.77 (1H, m), 3.04-3.15 (1H, m), 2.94-3.02 (1H, m), 2.35 (0.8H, s, PhC*H*$_3$), 2.34 (2.2H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.47, 148.42, 145.97, 142.02, 141.65, 140.11, 139.65, 134.09, 132.90, 130.09, 129.43, 128.99, 127.68, 127.61, 127.25, 127.17, 124.45, 123.37, 122.73, 122.59, 121.61; HRMS (ESI-TOF): m/z calcd for $C_{28}H_{25}N_2O_4S^+$: 485.1530, found: 485.1503; FT-IR (cm^{-1}): 1694 (m, C=O), 1528 (s, N-O), 1347 (s, N-O), 1022 (m, S=O); R_f (CyHex/EtOAc, 7/3): 0.2.

3-(*p*-tolyl)-3-phenyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)propenamide III-2kI

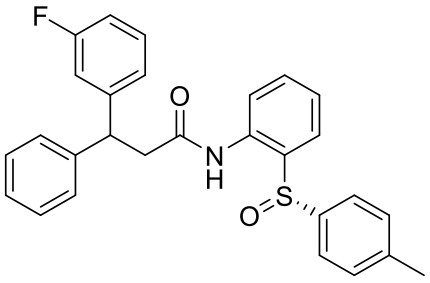
Reaction was carried out using 4-iodotoluene (60 mg) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (9:1 to 8:2) afforded the title compound (54 mg, 87%) as a clear oil as a 85:15 mixture of diastereomers.



^{1}H NMR (400 MHz, $CDCl_3$): 10.33 (1H, br s, N*H*), 8.28 (1H, d, J=8.3 Hz), 7.42 (1H, dd, J=7.7, 1.5 Hz), 7.31-7.39 (3H, m), 7.06-7.27 (11H, m), 7.03 (2H, d, J=8.1 Hz), 4.58 (1H, t, J=7.9 Hz), 3.04 (1H, dd, J=15.3, 7.9 Hz), 2.95 (1H, dd, J=15.3, 7.9 Hz), 2.34 (3H, s, PhC*H*$_3$), 2.27 (2.6H, s, PhC*H*$_3$), 2.25 (0.4H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.51, 143.92, 141.54, 140.89, 140.33, 139.95, 135.99, 132.97, 130.23, 129.44, 128.74, 127.85, 127.81, 127.75, 127.72, 127.63, 126.59, 124.56, 123.30, 122.94, 46.48, 44.19, 21.50, 21.20; HRMS (ESI-TOF): m/z calcd for $C_{29}H_{27}KNO_2S^+$: 492.1394, found: 492.1391; FT-IR (cm^{-1}): 1695 (s, C=O), 1021 (s, S=O); R_f (CyHex/EtOAc, 7/3): 0.6.

3-(3-fluorophenyl)-3-phenyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)propenamide III-2kL

Reaction was carried out using 3-fluoroiodobenzene (40 µL) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (95:5) afforded the title compound (77 mg, 87%) as a clear oil as a 4:1 mixture of diastereomers.

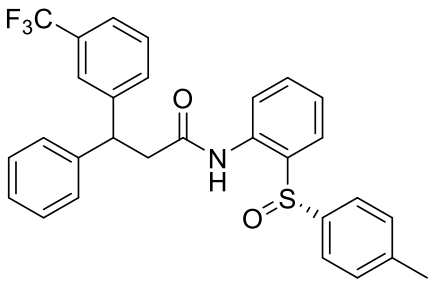


^{1}H NMR (400 MHz, $CDCl_3$): 10.37 (1H, br s, N*H*), 8.29 (1H, d, J=8.2 Hz), 7.37-7.46 (2H, m), 7.33 (2H, d, J=8.2 Hz), 7.24-7.29 (2H, m), 7.13-7.23 (6H, m), 7.10 (1H, td, J=7.7, 1.1 Hz), 7.02 (0.2H, d, J=7.7 Hz), 6.98 (0.8H, d, J=7.8 Hz), 6.81-6.91 (2H, m), 4.57-4.66 (1H, m), 2.99-3.08 (1H, m), 2.93 (1H, dd, J=15.5, 8.1 Hz), 2.35 (3H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.93 (0.2C), 168.90 (0.8C), 162.88 (d, J=246 Hz), 146.40 (0.8C), 146.33 (0.2C), 143.07 (0.2C), 142.87 (0.8C), 141.56 (0.8C), 141.51 (0.2C), 140.15, 139.65, 132.89, 130.10 (0.8C), 130.01 (0.2C), 129.93, 128.73 (0.8C), 128.70 (0.2C), 127.70 (0.8C), 127.66 (0.2C), 127.57 (0.8C), 127.43 (0.2C), 126.78 (0.8C), 126.67 (0.2C), 124.43 (0.2C), 124.36 (0.8C), 123.48, 123.45, 123.24, 122.75, 114.88 (0.2C, d, J=21.4 Hz), 114.60 (0.8C, d, J=21.4 Hz), 113.47 (0.2C, d, J=20.2 Hz), 113.34 (0.8C, d, J=20.2 Hz), 46.38 (0.2C), 46.30 (0.8C), 43.73 (0.2C), 43.66 (0.8C), 21.34 (0.2C), 21.31 (0.8C); ^{19}F NMR (376 MHz, $CDCl_3$): -112.73 (0.8F), -112.86 (0.2F); HRMS (ESI-TOF): m/z calcd for

$C_{28}H_{24}FKNO_2S^+$: 496.1143, found: 496.1199; FT-IR (cm^{-1}): 1697 (s, C=O), 1025 (s, S=O); R_f (CyHex/EtOAc, 7/3): 0.45.

3-(3-trifluorophenyl)-3-phenyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)propenamide III-2kM

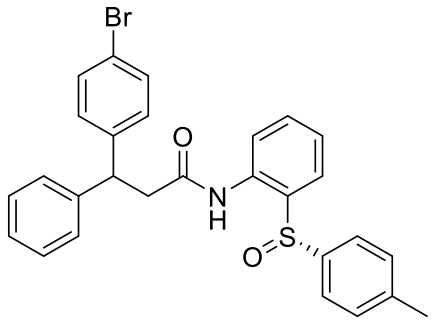
Reaction was carried out using 3-iodobenzotrifluoride (50 µL) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (9:1 to 7:3) afforded the title compound (97 mg, 87%) as a yellow oil as a 4:1 mixture of diastereomers.



^{1}H NMR (400 MHz, $CDCl_3$): 10.39 (1H, br s, N*H*), 8.27 (1H, d, J=8.4 Hz), 7.48 (1H, s), 7.35-7.45 (4H, m), 7.29-7.34 (3H, m), 7.27 (2H, d, J=8.2 Hz), 7.16-7.23 (5H, m), 7.10 (1H, td, J=7.5, 1.3 Hz), 4.69 (1H, t, J=7.7 Hz), 3.02-3.12 (1H, m), 2.91-3.00 (1H, m), 2.35 (0.6H, s, PhC*H*$_3$), 2.34 (2.4H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.76, 144.84 (0.8C), 144.57 (0.2C), 142.76 (0.2C), 142.49 (0.8C), 141.57 (0.8C), 141.53 (0.2C), 140.11, 139.76 (0.2C), 139.71 (0.8C), 132.87, 131.07, 130.12 (0.2C), 130.07 (0.8C), 129.06 (0.2C), 129.00 (0.8C), 128.83 (0.8C), 128.79 (0.2C), 127.73 (0.8C), 127.69 (0.2C), 127.57 (0.8C), 127.46 (0.2C), 126.92 (0.8C), 126.79 (0.2C), 124.58 (q, J=3.8 Hz), 124.42, 124.10 (q, J=271.7 Hz), 123.39 (q, J=3.0 Hz), 122.82, 46.51, 43.69, 26.94, 21.29; ^{19}F NMR (376 MHz, $CDCl_3$): -62.44 (0.8F), -62.46 (0.2F); HRMS (ESI-TOF): m/z calcd for $C_{29}H_{25}F_3NO_2S^+$: 508.1553, found: 508.1599; FT-IR (cm^{-1}): 1693 (s, C=O), 1327 (s, C-F), 1022 (m, S=O); R_f (CyHex/EtOAc, 7/3): 0.32.

3-(4-bromophenyl)-3-phenyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)propenamide III-2kN

Reaction was carried out using 4-iodobromobenzene (120 mg) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (95:5) afforded the title compound (92 mg, 92%) as a brown oil as a 9:1 mixture of diastereomers.

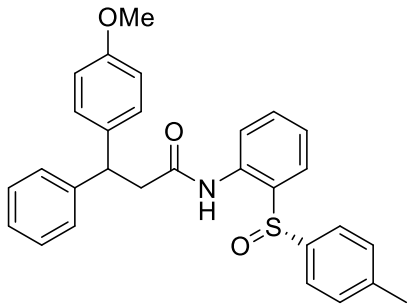


^{1}H NMR (400 MHz, $CDCl_3$): 10.46 (0.9H, br s, N*H*), 10.40 (0.1H, br s, N*H*), 8.26-8.37 (1H, m), 7.36-7.44 (2H, m), 7.24-7.33 (6H, m), 7.15-7.23 (5H, m), 7.08-7.12 (1H, m), 7.06 (2H, d, J=8.4 Hz), 4.53-4.63 (1H, m), 2.99-3.08 (1H, m), 2.92 (1H, dd, J=15.3, 8.7 Hz), 2.38 (2.6H, s, PhC*H*$_3$), 2.35 (0.4H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.97, 143.03, 142.73, 141.65, 140.21, 139.75, 132.87, 131.67 (0.1C), 131.63 (0.9C), 130.15 (0.9C), 130.11 (0.1C), 129.53, 128.73 (0.9C), 128.70 (0.1C), 127.65 (0.9C), 127.62

(0.1C), 127.54 (0.1C), 127.51 (0.9C), 127.20, 126.74, 124.44, 123.25, 122.67, 120.27, 46.00, 43.78, 21.40; HRMS (ESI-TOF): m/z calcd for $C_{28}H_{25}BrNO_2S^+$: 518.0784, found: 518.0753; FT-IR (cm-1): 1694 (s, C=O), 1021 (m, S=O), 757 (s, C-Br); R_f (CyHex/EtOAc, 8/2): 0.47.

3-(4-methoxyphenyl)-3-phenyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)propenamide III-2kO

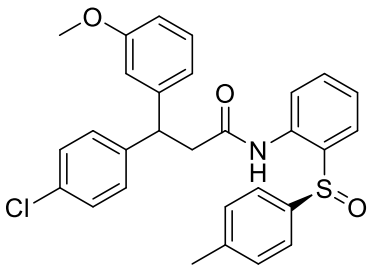
Reaction was carried out using 4-iodoanisole (65 mg) as coupling partner. Column chromatography on silica gel with CyHex/EtOAc (9:1 to 8:2) afforded the title compound (61 mg, 94%) as a yellow oil as a 9:1 mixture of diastereomers. Suitable single crystals for X-Ray analysis were grown by slow evaporation method in a mixture of DCM and chloroform.



^{1}H NMR (400 MHz, $CDCl_3$): 10.35 (1H, br s, N*H*), 8.28 (1h, d, J=8.3 Hz), 7.34-7.43 (2H, m), 7.32 (2H, d, J=8.4 Hz), 7.13-7.27 (8H, m), 7.11 (2H, d, J=8.4 Hz), 7.06 (1H, td, J=7.5, 1.1 Hz), 6.75 (2H, d, J=8.7 Hz), 4.57 (1H, t, J=7.8 Hz), 3.72 (2.7H, s, OC*H*$_3$), 3.71 (0.3H, s, OC*H*$_3$) 3.03 (1H, dd, J=15.2, 7.7 Hz), 2.93 (1H, dd, J=15.2, 8.1 Hz), 2.33 (3H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.53, 158.19, 144.03, 141.60, 140.29, 139.91, 136.01, 132.97, 130.22, 128.82, 128.71, 127.79, 127.58, 126.56, 124.56, 123.32, 122.88, 114.09, 55.29, 46.06, 44.38, 21.45; HRMS (ESI-TOF): m/z calcd for $C_{29}H_{27}KNO_3S^+$: 508.1343, found: 508.1370; FT-IR (cm^{-1}): 1694 (m, C=O), 1265 (s, C-O ether), 1022 (m, S=O); R_f (CyHex/EtOAc, 7/3): 0.42.

3-(4-chlorophenyl)-3-(3-methoxyphenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)propanamide III-2lC

Reaction was carried out using **III-1l** (84 mg) as substrate and 3-iodoanisole (50 µL, 2 equiv.) as coupling partner. Purification with CyHex/EtOAc (9:1) afforded the title compound (98 mg, 92%) as a yellow oil as a 85:15 mixture of diastereomers.

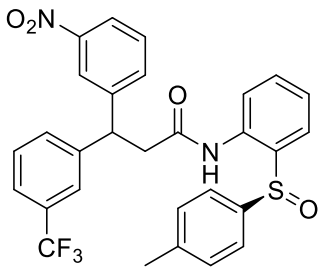


^{1}H NMR (400 MHz, $CDCl_3$): 10.45 (0.2H, br s, N*H*), 10.39 (0.8H, br s, N*H*), 8.24-8.35 (1H, m), 7.37-7.44 (2H, m), 7.28-7.34 (2H, m), 7.08-7.23 (8H, m), 8.75-6.81 (1H, m), 6.69-6.73 (2H, m), 4.52-4.61 (1H, m), 3.72-3.76 (3H, m, COCH3), 2.86-3.07 (2H, m), 2.37 (0.5H, s, PhC*H*$_3$), 2.34 (2.5H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.96, 159.76, 144.96, 144.74, 142.06 (0.2C), 141.75 (0.8C), 141.64 (0.2C), 141.55 (0.8C), 140.13, 139.71, 132.85, 132.33, 130.12 (0.2C), 130.10 (0.8C), 129.71 (0.2C), 129.66 (0.8C), 129.11, 128.73 (0.8C), 128.69 (0.2C), 127.50 (0.8C), 127.42 (0.2C), 124.43, 123.29 (0.8C), 123.25 (0.2C), 122.77, 119.82, 113.78, 111.83 (0.2C), 111.78 (0.8C), 55.16,

46.13 (0.8C), 45.93 (0.2C), 43.80 (0.2C), 43.75 (0.8C), 21.34; HRMS (ESI-TOF): m/z calcd for $C_{29}H_{27}ClNO_3S^+$: 504.1395, found: 504.1382; FT-IR (cm^{-1}): 1694 (m, C-O amide), 1585 (s, C-O ether), 1022 (s, S-O); R_f (CyHex/EtOAc, 7/3): 0.45.

3-(3-nitrophenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)-3-(3-(trifluoromethyl)phenyl)propanamide III-2ml

Reaction was carried out using **III-1m** (50 mg) as substrate and 1-iodo-3-nitrobenzene (60 mg, 2 equiv.) as coupling partner. Purification with CyHex/EtOAc (4:1) afforded the title compound (56 mg, 88%) as a thick clear oil as a 90:10 mixture of diastereomers.

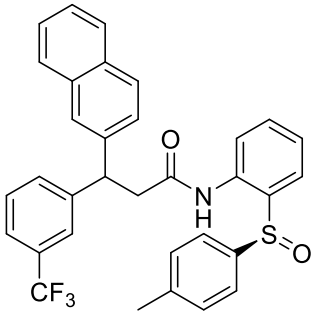


^{1}H NMR (400 MHz, $CDCl_3$): 10.45-10.56 (1H, m, N*H*), 8.25 (1H, d, *J*=8.4 Hz), 8.02-8.10 (2H, m), 7.35-7.53 (8H, m), 7.32 (2H, d, *J*=8.5 Hz), 7.20 (2H, d, *J*=8.4 Hz), 7.12 (1H, td, *J*=7.6, 1.1 Hz), 4.73-4.82 (1H, m), 3.06-3.14 (1H, m), 2.94-3.04 (1H, m), 2.35 (0.6H, s, PhC*H*$_3$), 2.34 (2.4H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 167.97, 148.49, 144.92 (0.8C), 144.65 (0.2C), 143.07 (0.8C), 142.56 (0.2C), 134.00 (0.8C), 133.92 (0.2C), 132.95 (0.8C), 132.73 (0.2C), 130.12, 124.48, 122.13 (0.2C), 121.99 (0.8C),[14] 46.17 (0.2C), 46.12 (0.8C), 43.14, 12.31 (0.2C), 21.26 (0.8C); ^{19}F NMR (377 MHz, $CDCl_3$): -62.54 (0.2F), -62.55 (0.8F); HRMS (ESI-TOF): m/z calcd for $C_{29}H_{24}F_3N_2O_4S^+$: 553.1403, found: 553.1386; FT-IR (cm^{-1}): 1697 (m, C-O), 1529 (s, N-O), 1328 (s, C-F), 1123 (s, C-F), 1022 (m, S-O); R_f (CyHex/EtOAc, 7/3): 0.29.

[14] Due to the complexity of the spectrum with the diastereomeric mixture and the presence of C-F couplings, some carbons were omitted between 122.00 and 144.93 ppm.

3-(naphthalen-2-yl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)-3-(3-(trifluoromethyl)phenyl)propanamide III-2mE

Reaction was carried out using **1n** (50 mg) as substrate and 2-iodonaphthalene (60 mg, 2 equiv.) as coupling partner. Purification with CyHex/EtOAc (95:5) afforded the title compound (46 mg, 72%) as a thick clear oil as a 90:10 mixture of diastereomers.



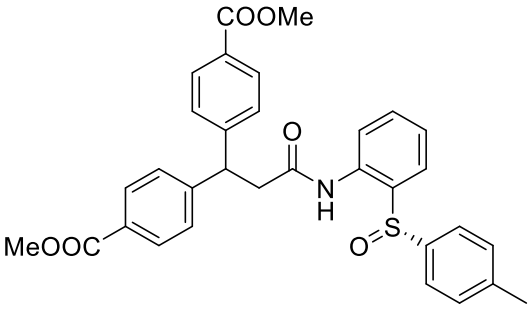
^{1}H NMR (400 MHz, $CDCl_3$): 10.52 (0.9H, br s, N*H*), 10.48 (0.1H, br s, N*H*), 8.28 (1H, d, J=8.3 Hz), 7.67-7.80 (4H, m), 7.35-7.55 (8H, m), 7.25-7.32 (3H, m), 7.09 (1H, td, *J*=7.5, 0.9 Hz), 6.99 (2H, d, *J*=8.2 Hz), 4.82-4.90 (1H, m), 2.99-3.25 (2H, m), 2.33 (0.3H, s, PhC*H*$_3$), 2.23 (2.7H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.76, 144.47, 141.56, 140.27, 140.11, 139.64, 133.49, 132.79, 132.39, 131.20, 130.88 (q, *J*=31.3 Hz), 130.02, 129.10, 128.59, 127.97, 127.62, 127.38, 126.28, 126.23, 126.08, 126.87, 124.73 (q, *J*=4.4 Hz), 124.44, 124.34, 124.12 (q, *J*=272 Hz), 123.56 (q, *J*=3.6 Hz), 123.34, 122.75, 46.57, 43.73, 21.22;[15] ^{19}F NMR (377 MHz, $CDCl_3$): -62.44 (0.1F), -62.47 (0.9F); HRMS (ESI-TOF): m/z calcd for $C_{33}H_{27}F_3NO_2S^+$: 558.1709, found: 558.1683; FT-IR (cm^{-1}): 1691 (m, C-O), 1328 (s, C-F), 1124 (s, C-F), 1021 (m, S-O); R_f (CyHex/EtOAc, 7/3): 0.55.

[15] For greater clarity, only the shifts corresponding to the major diastereomer are reported.

III.7.vi. One-pot double functionalization of aliphatic chains

dimethyl 4,4'-(3-oxo-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)amino)propane-1,1-diyl)-dibenzoate III-2oBB

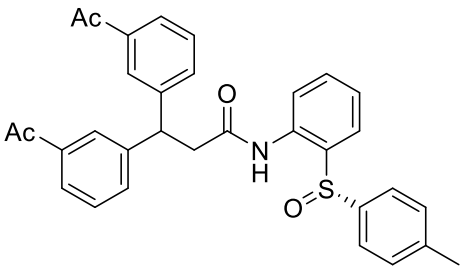
III-1o (35 mg, 0.12 mmol, 1 equiv.), methyl 4-iodobenzoate (80 mg, 0.30 mmol, 2.5 equiv.), silver acetate (85 mg, 0.51 mmol, 4 equiv.) and palladium(II) acetate (1.5 mg, 0.006 mmol, 5 mol%) were dissolved in 1 mL of a 4:1 mixture of toluene and 1,1,3,3-hexafluoroisopropanol. The resulting mixture was stirred 10 min at room temperature, then at 110 °C during 24h. After cooling to room temperature, the mixture was filtered through PTFE 45 µm filter with a syringe and evaporated under reduced pressure. The crude was purified by a short column chromatography on silica gel with CyHex/EtOAc (3:2) to afford the title compound (42 mg, 62%) as a yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.50 (1H, br s, N*H*), 8.26 (1H, d, J=8.4 Hz), 7.93 (2H, d, J=8.2 Hz), 7.88 (2H, d, J=8.3 Hz), 7.37-7.44 (2H, m), 7.31 (2H, d, J=8.2 Hz), 7.27 (2H, d, J=8.2 Hz), 7.17-7.23 (4H, m), 7.08-7.13 (1H, m), 4.74 (1H, t, J=7.6 Hz), 3.84-3.88 (6H, m, C(O)OC*H*$_3$), 3.08 (1H, dd, J=15.6, 7.3 Hz), 2.97 (1H, dd, J=15.4, 8.3 Hz), 2.36 (3H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.41, 166.78, 166.75, 148.04, 147.93, 141.67, 140.11, 139.70, 132.92, 130.15, 130.10, 130.07, 128.78, 128.64, 127.84, 127.78, 127.59, 127.16, 124.42, 123.35, 122.69, 52.08, 52.07, 46.48, 43.21, 43.21, 21.28; HRMS (ESI-TOF): m/z calcd for $C_{32}H_{29}NNaO_6S^+$: 578.1608, found: 578.1607; FT-IR (cm^{-1}) : 1721 (s, C=O), 1023 (m, S=O); $[\alpha]_D^{20}$= -11.40° (c=0.25, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.25.

(*S*)-3,3-*bis*(3-acetylphenyl)-*N*-(2-(*p*-tolylsulfinyl)phenyl)propenamide III-2oDD

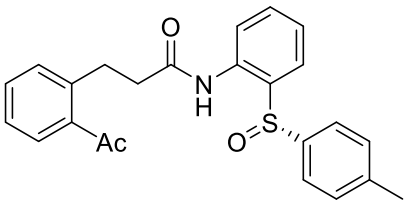
III-1o (20 mg, 0.07 mmol, 1 equiv.), 3'-iodoacetophenone (30 µL, 0.22 mmol, 3 equiv.), silver acetate (50 mg, 0.30 mmol, 4 equiv.) and palladium(II) acetate (0.6 mg, 0.003 mmol, 4 mol%) were dissolved in 600 µL of a 4:1 mixture of toluene and 1,1,3,3-hexafluoroisopropanol. The resulting mixture was stirred 10 min at room temperature, then at 110 °C during 24h. After cooling to room temperature, the mixture was filtered through PTFE 45 µm filter with a syringe and evaporated under reduced pressure. The crude was purified by a short column chromatography on silica gel with CyHex/EtOAc (3:2) to afford the title compound (32 mg, 88%) as a yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.38 (1H, br s, N*H*), 8.20 (1H, d, J=8.3 Hz), 7.78 (1H, s), 7.67-7.74 (2H, m), 7.29-7.40 (6H, m), 7.26 (2H, d, J=8.4 Hz), 7.13 (2H, d, J=8.2 Hz), 7.05 (1H, t, J=7.5 Hz), 4.69 (1H, t, J=7.7 Hz), 3.04 (1H, dd, J=15.1, 8.1 Hz), 2.94 (1H, dd, J=15.1, 7.3 Hz), 2.46-2.52 (6H, m), 2.29 (3H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 197.95, 197.91, 168.66, 143.79, 143.48, 140.00, 139.66, 137.56, 137.54, 132.84, 132.41, 132.30, 130.13, 130.05, 129.08, 129.01, 127.61, 127.58, 127.55, 127.49, 127.00, 126.88, 124.47, 123.45, 122.78, 46.56, 43.56, 26.72, 26.71, 21.33; HRMS (ESI-TOF): m/z calcd for $C_{32}H_{30}NO_4S^+$: 524.1890, found: 524.1879; FT-IR (cm-1): 1698 (s, C=O), 1022 (s, S=O); $[\alpha]_D^{20}$= -87.2° (c=0.20, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.22.

3-(2-acetylphenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)propenamide III-2oE

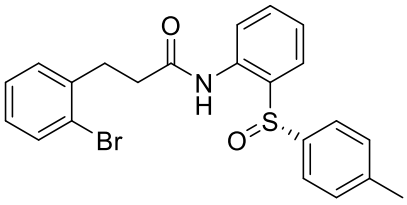
General arylation procedure was carried out using **III-1o** (70 mg) as substrate and 2'-iodoacetophenone (50 µL, 1.5 equiv.) as coupling partner. Purification with CyHex/EtOAc (7:3) afforded the title compound (89 mg, 90%) as an orange oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.10 (1H, br s, N*H*), 8.32 (1H, d, J=8.1 Hz), 7.71 (1H, dd, J=7.7, 1.5 Hz), 7.50 (1H, dd, J=7.8, 1.5 Hz), 7.40-7.45 (1H, m), 7.35-7.39 (3H, m), 7.25-7.30 (2H, m), 7.20 (2H, d, J=8.4 Hz), 7.12 (1H, td, J=7.6, 1.1 Hz), 3.09-3.22 (2H, m), 2.55-2.66 (5H, m), 2.33 (3H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 201.58, 170.95, 141.43, 141.19, 140.13, 139.74, 137.63, 132.98, 131.99, 131.71, 130.16, 129.87, 127.69, 126.57, 124.51, 123.40, 123.15, 119.95, 39.54, 30.06, 29.79, 21.49; HRMS (ESI-TOF): m/z calcd for $C_{24}H_{23}NNaO_3S^+$: 428.1291, found: 428.1291; FT-IR (cm^{-1}): 1683 (s, C=O), 1022 (m, S=O); $[\alpha]_D^{20}$= +34.9° (c=0.10, $CHCl_3$); R_f (CyHex/EtOAc, 7/3): 0.20.

3-(2-bromophenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)propionamide III-2oG

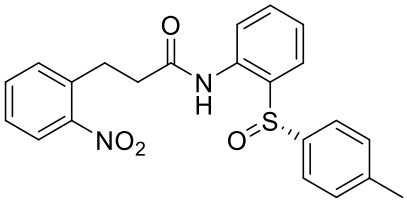
General arylation procedure was carried out using **III-1o** (70 mg) as substrate and 1-iodo-2-bromobenzene (50 µL, 1.5 equiv.) as coupling partner. Purification with CyHex/EtOAc (9:1) afforded the title compound (98 mg, 91%) as a yellow solid.



^{1}H NMR (400 MHz, $CDCl_3$): 10.19 (1H, br s, N*H*), 8.36 (1H, d, J=8.4 Hz), 7.49-7.55 (2H, m), 7.44-7.49 (1H, m), 7.35 (2H, d, J=8.4 Hz), 7.18-7.22 (4H, m), 7.12-7.17 (1H, m), 7.03-7.08 (1H, m), 3.03 (2H, t, J=7.8 Hz), 2.49-2.70 (2H, m), 2.33 (3H, s, PhC*H*$_3$) ; ^{13}C NMR (100 MHz, $CDCl_3$): 170.19, 141.34, 140.09, 139.84, 139.49, 133.00, 132.89, 130.55, 130.02, 128.07, 127.79, 127.65, 124.66, 124.36, 124.28, 123.26, 123.00, 37.47, 31.63, 21.32; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{20}BrNNaO_2S^+$: 464.0290, found: 464.0275; FT-IR (cm^{-1}): 1694 (s, C=O), 1034 (s, S=O); mp (°C): 157; $[\alpha]_D^{20}$= -57.0° (c=0.2, $CHCl_3$); R_f (CyHex/EtOAc, 8/2): 0.45.

3-(2-nitrophenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)propenamide III-2oP

General arylation procedure was carried out using **III-1o** (20 mg) as substrate and 2-iodonitrobenzene (25 mg, 1.5 equiv.) as coupling partner. Purification with CyHex/EtOAc (4:1) by preparative TLC afforded the title compound (25 mg, 89%) as an orange oil.

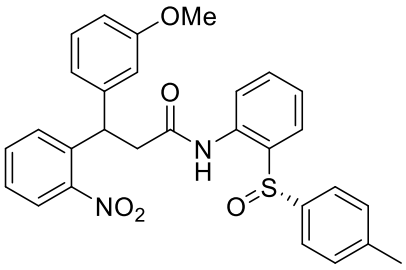


^{1}H NMR (400 MHz, $CDCl_3$): 10.20 (1H, br s, N*H*), 8.33 (1H, d, J=8.3 Hz), 7.93 (1H, d, J=8.0 Hz), 7.40-7.55 (3H, m), 7.28-7.39 (4H, m), 7.21 (2H, d, J=8.2 Hz), 7.14 (1H, t, J=7.7 Hz), 3.17 (2H, d, J=7.7 Hz), 2.58-2.76 (2H, m), 2.33 (3H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.93, 143.44, 141.55, 140.17, 139.64, 135.95, 133.39, 133.12, 132.43, 130.21, 128.35, 127.92, 127.70, 125.06, 124.40, 123.49, 123.10, 38.27, 28.61, 21.48; HRMS (ESI-TOF): m/z calcd for $C_{22}H_{20}KN_2O_4S^+$: 447.0775, found: 447.0772; FT-IR (cm^{-1}): 1698 (w, C=O), 1524 (s, N-O), 1022 (w, S=O); $[\alpha]_D^{20}$= +78.1° (c=0.15, $CHCl_3$); R_f (CyHex/EtOAc): 0.22.

3-(3-methoxyphenyl)-3-(2-nitrophenyl)-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)propenamide III-2oPC

III-1o (30 mg, 0.10 mmol, 1 equiv.), 2-nitroiodobenzene (26 mg, 0.10 mmol, 1 equiv.), silver acetate (40 mg, 0.23 mmol, 2.2 equiv.) and palladium(II) acetate (1 mg, 0.005 mmol, 5 mol%) were dissolved in 1 mL of a 4:1 mixture of toluene and 1,1,3,3-hexafluoroisopropanol. The resulting mixture was stirred 10 min at room temperature, then at 110 °C during 24h. The

mixture was cooled to room temperature and the conversion was checked by ^{1}H NMR. 3-iodoanisole (40 µL, 0.36 mmol, 3.5 equiv.) and more silver acetate (40 mg, 0.23 mmol, 2.2 equiv.) were added to the brown mixture, which was further stirred 24h at 130 °C. After cooling to room temperature, the mixture was filtered through PTFE 45 µm filter with a syringe and evaporated under reduced pressure. The crude was purified by a short column chromatography on silica gel with CyHex/EtOAc (5:2) to afford the title compound (42 mg, 78%) as an orange oil as a mixture of diastereomers. ^{1}H NMR of the crude showed a 7:3 diastereomeric ratio.

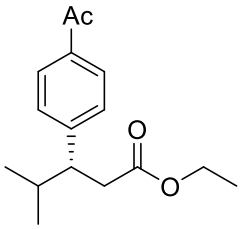


^{1}H NMR (400 MHz, $CDCl_3$): 10.37 (0.3H, br s, N*H*), 10.33 (0.7H, br s, N*H*), 8.23-8.28 (1H, m), 7.73-7.77 (1H, m), 7.26-7.53 (7H, m), 7.13-7.23 (3H, m), 7.10 (1H, t, J=7.5 Hz), 6.72-6.85 (3H, m), 5.28 (1H, t, J=7.7 Hz), 3.73 (3H, s, COC*H*$_3$), 3.03-3.13 (1H, m), 2.91-3.00 (1H, m), 2.36 (3H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 168.23 (0.7C), 168.19 (0.3C), 159.76, 149.89, 143.38 (0.7C), 143.11 (0.3C), 141.53 (0.7C), 141.49 (0.3C), 140.13 (0.3C), 140.11 (0.3C), 140.05 (0.7C), 139.77 (0.7C), 139.60, 137.74 (0.3C), 137.58 (0.7C), 132.92 (0.7C), 132.72 (0.3C), 132.51, 130.16 (0.7C), 130.12 (0.3C), 129.69 (0.3C), 129.61 (0.7C), 129.35, 127.49, 127.41 (0.7C), 127.27 (0.3C), 124.62, 124.49 (0.3C), 124.45 (0.7C), 124.39 (0.3C), 124.35 (0.7C), 123.26, 122.90, 120.09 (0.3C), 119.95 (0.7C), 114.10 (0.7C), 114.06 (0.3C), 112.20 (0.3C), 112.12 (0.7C), 55.18, 43.32 (0.7C), 43.18 (0.3C), 40.59 (0.3C), 40.49 (0.7C), 21.35; HRMS (ESI-TOF): m/z calcd for $C_{29}H_{27}N_2O_5S^+$: 515.1635, found: 515.1614; FT-IR (cm^{-1}): 1694 (m, C=O), 1525 (s, N-O), 1022 (m, S=O); R_f (CyHex/EtOAc, 7/3): 0.38.

III.7.vii. Deprotection experiments

ethyl (*R*)-3-(4-acetylphenyl)-4-methylpentanoate

To a stirred solution of **III-2nH** (50 mg, 0.12 mmol, 1 equiv.) in 0.5 mL of ethanol was added 1 mL 5M KOH solution in water. The resulting mixture was stirred at reflux during 18h. After cooling to room temperature, ethanol was evaporated under reduced pressure. Diethylether (20 mL) and more water (15 mL) were added. The aqueous layer was acidified with conc. HCl (few drops) to *ca*. pH 1. Diethylether (20 mL) was added and the organic layer was extracted, washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure. The crude was dissolved in 5 mL of ethanol and concentrated sulfuric acid (20 µL, 0.38 mmol, 2.5 equiv.) was added dropwise. The resulting mixture was stirred at reflux overnight. After cooling to room temperature, ethanol was evaporated under reduced pressure. Diethylether (20 mL) and water (10 mL) were added. The organic layer was extracted, washed with brine (20 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel with CyHex/EtOAc (95:5) to afford the title compound (24 mg, 82%) as a clear oil.



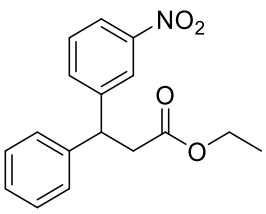
^{1}H NMR (400 MHz, $CDCl_3$): 7.86 (2H, d, J=8.2 Hz), 7.16-7.26 (2H, m), 3.85-3.99 (2H, m), 2.94 (1H, ddd, J=10.2, 7.7, 5.3 Hz), 2.78 (1H, dd, J=15.2, 5.3 Hz), 2.49-2.66 (4H, m), 1.75-1.93 (1H, m), 1.05 (3H, t, J=7.0 Hz), 0.94 (3H, d, J=6.8 Hz), 0.78 (3H, d, J=6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 197.89, 172.41, 148.88, 135.50, 128.49, 128.26, 60.31, 48.97, 38.24, 33.13, 26.57, 20.53, 20.38, 14.06 ; HRMS (ESI-TOF): m/z calcd for $C_{16}H_{23}O_3^+$: 263.1642, found: 263.1638; FT-IR (cm^{-1}): 1733 (C=O ester), 1683 (C=O ketone); $[\alpha]_D^{20}$= +6.75° (c=0.24, $CHCl_3$);[16] R_f (CyHex/EtOAc, 4/1): 0.5.

ethyl 3-(3-nitrophenyl)-3-phenylpropanoate

To a stirred solution of **III-2kI** (773 mg, 1.59 mmol, 1 equiv.) in 2 mL of ethanol was added 2 mL 5M KOH solution in water. The resulting mixture was stirred at reflux during 18h. After cooling to room temperature, ethanol was evaporated under reduced pressure. Diethylether (20 mL) and more water (15 mL) were added. The organic layer was extracted, washed with brine (20 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure to yield **APS** as a yellow oil (345 mg, 93%) with no loss of enantiomeric purity (checked by chiral HPLC). The aqueous layer was acidified with conc. HCl (few drops) to *ca*. pH 1. Diethylether (20 mL) was added and the

[16] The same procedure was applied for the minor diastereomer to yield the other enantiomer, which $[\alpha]_D^{20}$= -6.68° (c=0.25, $CHCl_3$). Assumed *ee*>95% with no loss of enantiomeric purity.

organic layer was extracted, washed with water (10 mL), brine (10 mL), dried (Na2SO4), filtered off and evaporated under reduced pressure. The crude was dissolved in 10 mL of ethanol and concentrated sulfuric acid (200 µL, 3.75 mmol, 2.5 equiv.) was added dropwise. The resulting mixture was stirred at reflux overnight. After cooling to room temperature, ethanol was evaporated under reduced pressure. Diethylether (20 mL) and water (10 mL) were added. The organic layer was extracted, washed with brine (20 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel with CyHex/EtOAc (9:1) to afford the title compound (457 mg, 96%) as a clear oil.[17]



^{1}H NMR (400 MHz, $CDCl_3$): 8.11 (1H, s), 8.05 (1H, ddd, J=8.2, 2.0, 0.8 Hz), 7.54-7.58 (2H, m), 7.43 (1H, t, J=7.9 Hz), 7.26-7.33 (2H, m), 7.18-7.24 (3H, m), 4.64 (1H, t, J=7.9 Hz), 4.03 (2H, q, J=7.2 Hz, C(O)OCH_2CH$_3$), 3.08 (2H, d, J=8.0 Hz), 1.11 (3H, t, J=7.1 Hz, C(O)OCH$_2$CH_3); ^{13}C NMR (100 MHz, CDCl3): 171.16, 145.67, 142.03, 134.15, 129.51, 128.94, 127.60, 127.19, 122.51, 121.78, 60.77, 46.71, 40.42, 14.08; HRMS (ESI-TOF): m/z calcd for $C_{17}H_{17}NNaO_4^+$: 322.1050, found: 322.1083; FT-IR (cm-1): 1733 (s, C=O ester), 1530 (s, N-O), 1348 (s, N-O); R_t (min, ODH, Hex/iPrOH, 80/20, 0.5 mL/min): 12.90 (75%), 15.31 (25%); R_f (CyHex/EtOAc, 8/2): 0.74.

(*R*)-2,3,5,6-tetrafluoro-4-methylbenzyl 4-methyl-3-phenylpentanoate III-3

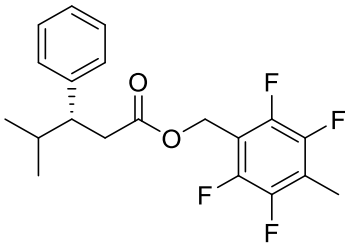
To a stirred solution of **III-2nK** (70 mg, 0.17 mmol, 1 equiv.) in 1.4 mL of ethanol was added a solution of KOH (70 mg, 1.25 mmol, 7.2 equiv.) in 0.6 mL of water. The resulting mixture was stirred at reflux during 18h. After cooling to room temperature, diethyl ether (10 mL) and more water (10 mL) were added. The organic layer was extracted, washed with water (3x 10 mL), brine (10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure to get back the chiral auxiliary **APS** (35 mg, 87%).

The combined aqueous layers were carefully acidified with conc. HCl (few drops) to reach *ca.* pH 1. Diethyl ether (10 mL) was added. The organic layer was washed with water (3x 10 mL) to reach *ca.* pH 7, brine (10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure to yield the crude acid as a yellow solid. To the crude was added 2,3,5,6-tetrafluoro-4-methylbenzyl alcohol (30 mg, 0.15 mmol, 1 equiv.) and 2 mL of acetonitrile. After complete

[17] When deprotection was performed in a solution of HCl in EtOH at 100°C, **APS** auxiliary could not be recovered, but decomposed to ethyl 4-methylbenzenesulfinate. HRMS (ESI-TOF): m/z calcd for $C_9H_{12}NaO_2S$: 207.0450, found: 207.0490.

dissolution of the solids, dicyclohexylcarbodiimide (40 mg, 0.19 mmol, 1.3 equiv.) and 4-(dimethylamino)-pyridine (2 mg, 0.016 mmol, 10 mol%) were added and the resulting mixture was stirred 10h at room temperature.

The precipitate of DCU was removed by filtration. Diethyl ether (10 mL) was added to the filtrate, which was washed with sat. $NaHCO_3$ sol. (2 x 10 mL), brine (3x 10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure. The crude was purified with CyHex/EtOAc (95:5) to afford the title compound (52mg, 91%) as a white solid.[18]



^{1}H NMR (400 MHz, $CDCl_3$): 7.16-7.22 (2H, m), 7.09-7.14 (1H, m), 7.04-7.08 (2H, m), 4.95-5.04 (2H, m), 2.74-2.88 (2H, m), 2.59 (1H, dd, J=14.4, 9.7 Hz), 2.25 (3H, t, J=2.2 Hz), 1.81 (1H, dq, J=13.7, 7.0 Hz), 0.91 (3H, d, J=6.8 Hz), 0.71 (3H, d, J=6.8 Hz); $[\alpha]_D^{25}$= -2.1° (c=1.05, CH_2Cl_2);[19] other data match the reported ones.

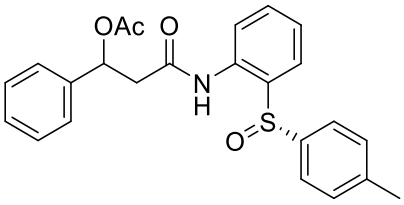
[18] Procedure adapted from *Bioorg. Med. Chem. Lett.*, **2014**, 24, pp. 2734-2736.

[19] In the litterature, $[\alpha]_D^{25}$ (*R*) = -2.3° (c=1, CH_2Cl_2) and $[\alpha]_D^{25}$ (*S*) = +1.9° (c=1, CH_2Cl_2).

III.7.viii. Acetoxylation

3-oxo-1-phenyl-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)amino)propyl acetate III-4

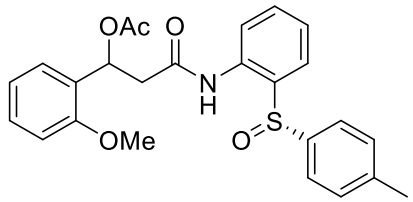
III-1k (70 mg, 0.19 mmol, 1 equiv.), (diacetoxyiodo)benzene (124 mg, 0.39 mmol, 2 equiv.) and palladium(II) acetate (2.8 mg, 0.01247 mmol, 5 mol%) were weighted in a pressure tube. Then, 1.5 mL of a 12:2:1 mixture of toluene, 1,1,3,3-hexafluoroisopropanol and acetic anhydride were added. The resulting mixture was stirred 10 min at room temperature, then 24h at 110 °C. After cooling to room temperature, the mixture was filtered through PTFE 45 µm filter with a syringe and evaporated under reduced pressure. The crude was purified by a short column chromatography on silica gel with CyHex/EtOAc (3:7) to afford the title compound (74 mg, 91%) as a yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): 10.19-10.32 (1H, br s, N*H*), 8.31 (0.7H, d, J=8.4 Hz), 8.24 (0.3H, d, J=8.4 Hz), 7.20-7.45 (10H, m), 7.05-7.14 (2H, m), 6.09-6.18 (1H, m, C*H*OC(O)CH_3), 2.76-2.91 (1H, m), 2.71 (0.3H, dd, J=15.0, 5.4 Hz), 2.56 (0.7H, dd, J=15.2, 4.4 Hz), 2.30 (1H, s, PhC*H*$_3$), 2.27 (2H, s, PhC*H*$_3$), 1.98 (2H, s, CHOC(O)C*H*$_3$), 1.91 (1H, s, CHC(O)C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.81 (0.7C), 169.68 (0.3C), 167.36 (0.7C), 167.19 (0.3C), 141.45 (0.7C), 141.43 (0.3C), 139.97 (0.3C), 139.71 (0.7C), 139.51 (0.7C), 139.34 (0.3C), 132.98 (0.7C), 132.95 (0.3C), 130.08 (0.3C), 130.04 (0.7C), 128.64, 128.33 (0.3C), 128.24 (0.7C), 127.90, 127.65 (0.3C), 127.63 (0.7C), 126.46 (0.3C), 126.42 (0.7C), 124.45 (0.3C), 124.26 (0.7C), 123.44, 122.99, 72.35 (0.7C), 72.21 (0.3C), 44.74 (0.7C), 44.52 (0.3C), 21.33 (0.3C), 21.30 (0.7C), 21.14 (0.7C), 21.08 (0.3C); HRMS (ESI-TOF): m/z calcd for $C_{24}H_{23}NNaO_4S^+$: 444.1240, found: 444.1223; FT-IR (cm^{-1}): 1743 (C=O ester), 1694 (C=O amide), 1022 (S=O); R_f (CyHex/EtOAc, 7/3): 0.21.

1-(2-methoxyphenyl)-3-oxo-3-((2-((*S*)-*p*-tolylsulfinyl)phenyl)amino)propyl acetate III-6

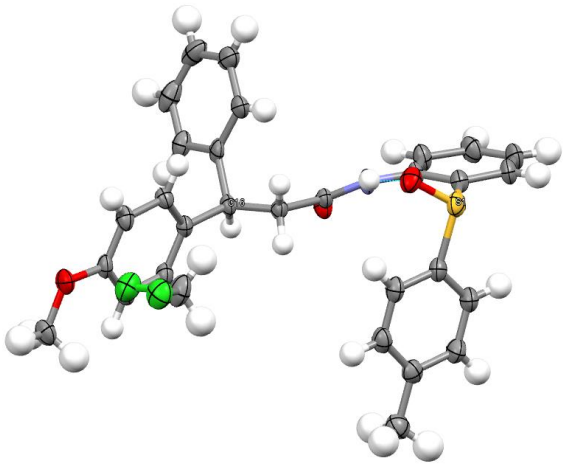
III-1o (100 mg, 0.35 mmol, 1 equiv.), 3-iodoanisole (45 µL, 0.35 mmol, 1 equiv.), silver acetate (120 mg, 0.75 mmol, 2.2 equiv.) and palladium(II) acetate (4 mg, 0.02 mmol, 5 mol%) were dissolved in 1 mL of a 4:1 mixture of toluene and 1,1,3,3-hexafluoroisopropanol. The resulting mixture was stirred 10 min at room temperature, then at 110 °C during 24 h. The mixture was cooled to room temperature and the conversion was checked by ^{1}H NMR. (Diacetoxyiodo)benzene (224 mg, 0.70 mmol, 2 equiv.) and more silver acetate (116 mg, 0.69 mmol, 2 equiv.) were added to the brown mixture, which was further stirred 24 h at 130 °C. After cooling to room temperature, the mixture was filtered through PTFE 45 µm filter with a syringe and evaporated under reduced pressure. The crude was purified by a short column chromatography on silica gel with CyHex/EtOAc (1:1) to afford the title compound (142 mg, 91%) as an orange oil as a mixture of diastereomers. ^{1}H NMR of the crude showed a 1.1:1 diastereomeric ratio.



^{1}H NMR (500 MHz, $CDCl_3$): 10.13-10.34 (1H, m, N*H*), 8.39 (0.5H, d, J=8.2 Hz), 8.30 (0.5H, d, J=8.3 Hz), 7.35-7.50 (3H, m), 7.22-7.32 (2H, m), 6.88 (1H, tdd, J=7.6, 2.6, 1.1 Hz), 6.82 (1H, dd, J=8.1, 4.3 Hz), 6.42-6.47 (1H, m), 3.77-3.83 (3H, m, COC*H*$_3$), 2.61-2.82 (2H, m), 2.24-2.31 (3H, m, PhC*H*$_3$), 2.02 (1.4H, s, C(O)OC*H*$_3$), 1.97 (1.6H, s, C(O)OC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): 168.70, 166.94, 154.95 (0.5C), 154.91 (0.5C), 140.39 (0.5C), 140.25 (0.5C), 139.07, 138.65 (0.5C), 138.52 (0.5C), 131.90, 129.12 (0.5C), 128.98 (0.5C), 128.02 (0.5C), 127.99 (0.5C), 127.16 (0.5C), 126.98 (0.5C), 126.83 (0.5C), 126.62 (0.5C), 126.51 (0.5C), 124.99 (0.5C), 124.94 (0.5C), 123.37 (0.5C), 123.31 (0.5C), 122.27, 122.05 (0.5C), 121.91 (0.5C), 109.66 (0.5C), 109.63 (0.5C), 66.89 (0.5C), 66.75 (0.5C), 54.46, 42.49 (0.5C), 42.24 (0.5C), 20.29, 20.11 (0.5C), 20.07 (0.5C); HRMS (ESI-TOF): m/z calcd for $C_{25}H_{25}NNaO_5S^+$: 474.1346, found: 474.1339; FT-IR (cm^{-1}) : 1737 (C-O ester), 1695 (C-O amide), 1037 (S-O); R_f (CyHex/EtOAc, 6/4): 0.25.

III.7.ix. X-Ray Data

3-(4-methoxyphenyl)-3-phenyl-*N*-(2-((*S*)-*p*-tolylsulfinyl)phenyl)propanamide



General data

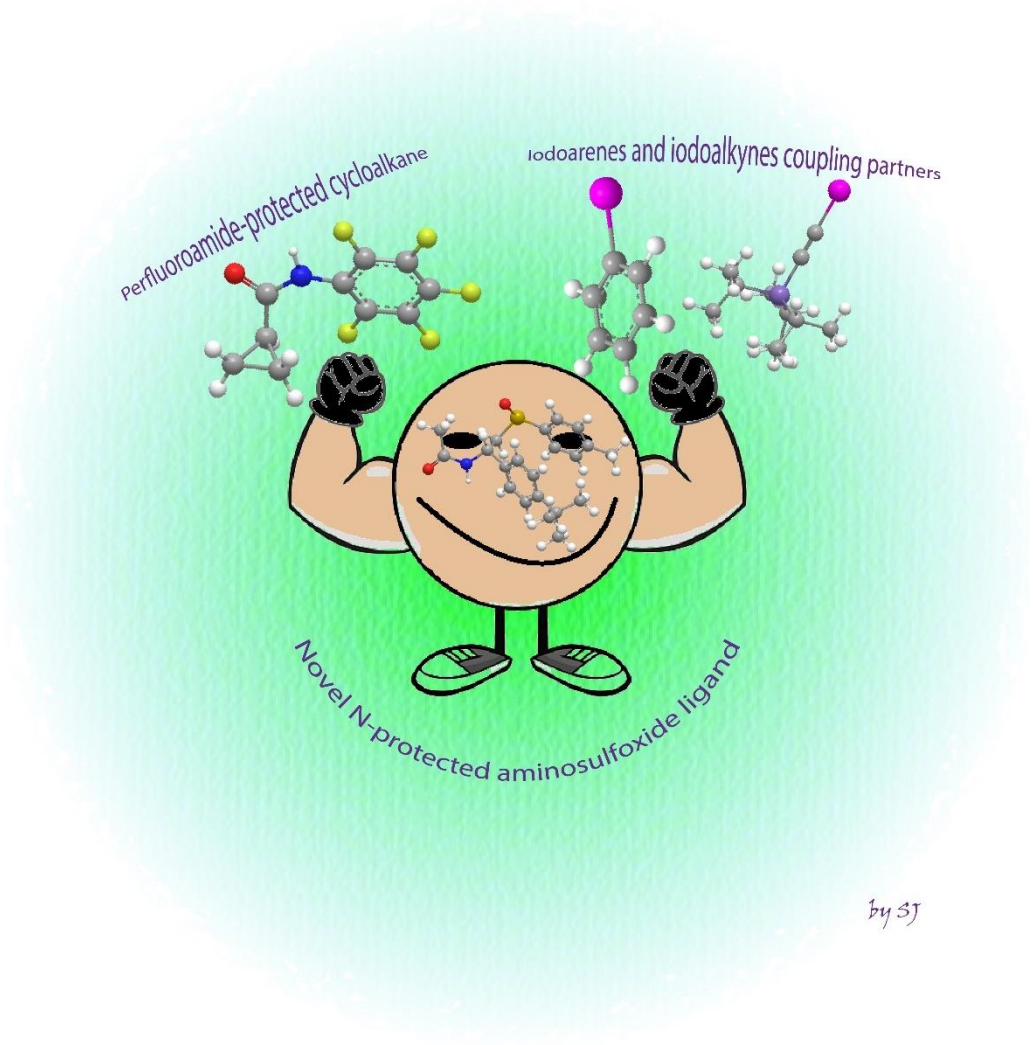
Compound	**III-2kO**
Structure identifier	**fcsj170511**
CCDC identifier	**1550280**
Formula	$C_{29}H_{27}NO_3S$, CH_2Cl_2
Space group	P $2_{1/C}$
Cell lengths	**a** 12.0253(3) **b** 8.4824(2) **c** 29.2991(7)
Cell angles	**α** 90 **β** 113.2630(10) **γ** 90
Cell volume	2745.64
Z, Z'	Z: 4 Z':0
Symmetry cell setting	Monoclinic
R_1	7.82%

III.8. Bibliographic references

[254] B. V. S. Reddy, L. R. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 3391–3394.
[255] Y. Feng, G. Chen, *Angew. Chem. Int. Ed.* **2010**, *49*, 958–961.
[256] W. R. Gutekunst, P. S. Baran, *J. Am. Chem. Soc.* **2011**, *133*, 19076–19079.
[257] K. Chen, Z.-W. Li, P.-X. Shen, H.-W. Zhao, Z.-J. Shi, *Chem. - Eur. J.* **2015**, *21*, 7389–7393.
[258] H. Keberle, J. W. Faigle, M. Wilhelm, *Gamma-Amino-Beta-(Para-Halophenyl)-Butyric Acids and Their Esters*, **1969**, US3471548A.
[259] D. R. Owen, D. M. Wood, J. R. H. Archer, P. I. Dargan, *Drug Alcohol Rev.* **2016**, *35*, 591–596.
[260] K. Mori, *Tetrahedron Asymmetry* **2005**, *16*, 685–692.
[261] S. Xu, H. Li, X. Wang, C. Chen, M. Cao, X. Cao, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2734–2736.
[262] J. Xiao, X.-W. Cong, G.-Z. Yang, Y.-W. Wang, Y. Peng, *Org. Lett.* **2018**, *20*, 1651–1654.

Chapter 4

New chiral aminosulfoxide ligands for the enantioselective C(sp^3)-H bond activation



Chapter 4 – Table of contents

IV.1. Introduction

IV.1.i. Summary of this work

In the continuity of our work on diastereoselective C(sp^3)-H bond functionalization using a chiral bidentate directing group, we subsequently explored enantioselective functionalization of aliphatic chain by means of a chiral ligand.

IV.1.ii. Background on enantioselective C-H bond functionalisation

The remarkable progresses in diastereoselective and achiral ligand-promoted C-H bond activation has led to the development of new classes of chiral ligands, used in catalytic amount, for enantioselective C(sp^3)-H bond functionalisation.

Asymmetric intramolecular C(sp^3)-H bond functionalisation has already been described previously (I.3) and will not be further detailed; consequently, we will focus this introduction on the intermolecular functionalisation, by means of desymmetrisation or selective functionalisation of a diastereotopic methylene unit (Figure 4.44).

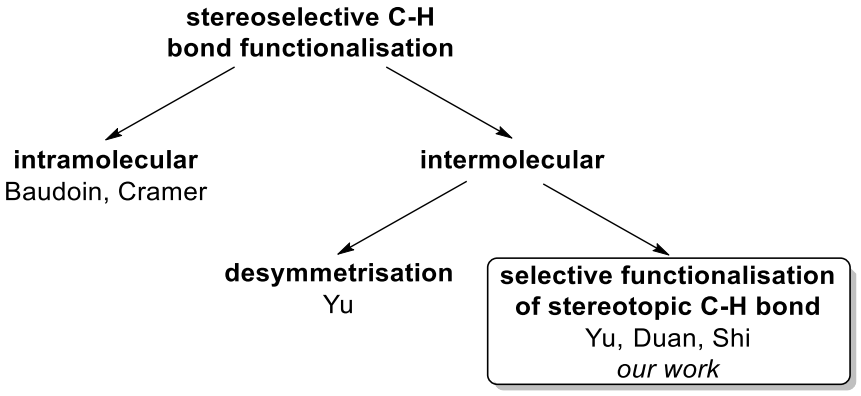
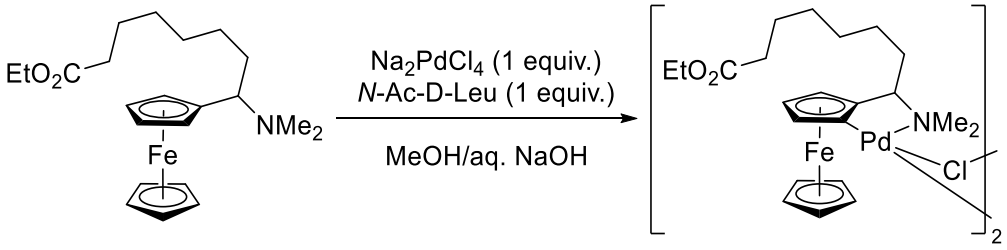


Figure 4.44 Subdivision of stereoselective functionalisations

IV.1.iii. Metal-catalysed desymmetrisation of C-H bonds

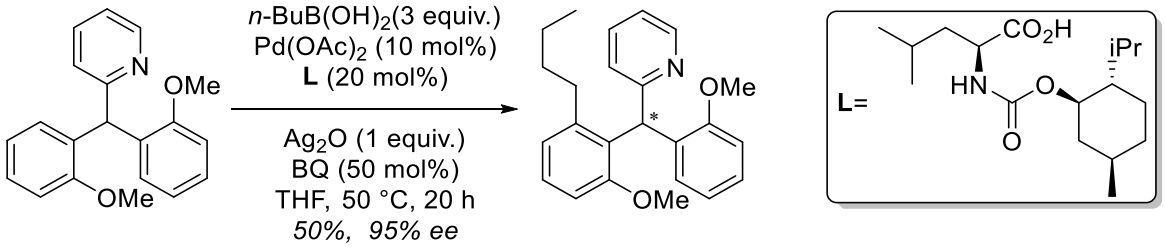
IV.1.iii.1. In prochiral substrates

Back in 1983, Sokolov and co-workers synthesized a chiral ferrocene complex by reaction of palladium salt and a protected amino acid with a ferrocene derivative. Interestingly, while the authors assumed that the dimethylamino group directs the cyclopalladation, we can hypothesize the major role of the chiral N-protected amino acid to orient and favour the C-H bond activation (Scheme 4.112).[263]



Scheme 4.112 Sokolov's synthesis of chiral ferrocenes

Yu and co-workers continued this work by screening amino acid derivatives for the enantioselective coupling of prochiral 2-benzhydrylpyridine with boronic acids.[264] Good to excellent enantiomeric excesses were obtained (Scheme 4.113), however when using 2-isopropylpyridine as prochiral substrate, C(sp^3)-H bond functionalisation with *n*-butylboronic acid gave only 38 % yield and 37 % enantiomeric excess.



Scheme 4.113 Yu's desymmetrisation of 2-benzhydrylpyridine

They proposed a stereochemical model in which the isobutyl side chain of the ligand pushes backwards the large menthyl carbamate group. In consequence, steric repulsion between the carbamate and the *ortho*-anisole disfavours one enantiomer from the other.

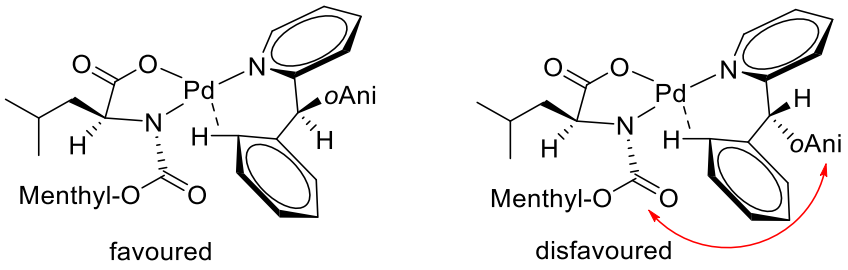
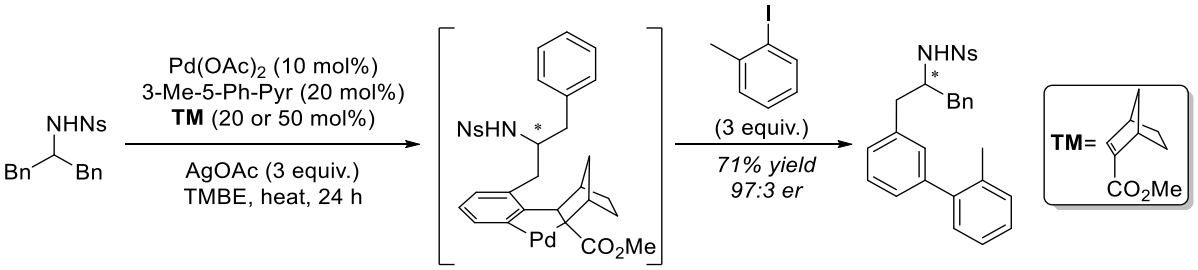


Figure 4.45 Proposed model for the desymmetrisation of 2-benzhydrylpyridines

Following this pioneering work, many catalytic systems have been designed to allow enantioselective desymmetrisation, allowing synthesis of a variety of C-stereogenic molecules such as in Scheme 4.114, reporting an elegant methodology for the *meta*-functionalisation of phenyl rings using a chiral transient mediator.[265]



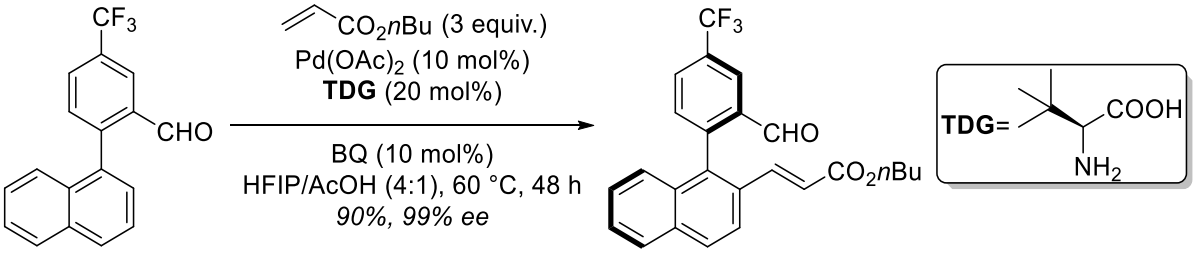
Scheme 4.114 Yu's desymmetrisation of homobenzylamines

IV.1.iii.2. By kinetic resolution of racemic substrates

Various strong diastereoselective methodologies implying DKR were developed in our group the past few years (I.5.iv.4). Since then, You and co-workers designed a C_2-symmetric chiral Cp ligand for the enantioselective rhodium(III)-catalysed olefination by dynamic resolution and further improved the stereocontrol by the design of a novel chiral spiro Cp ligand (Chart 4.20).[266,267]

Chart 4.20 You's rhodium complexes for biaryl DKR

This seminal work was recently followed by the development of a new methodology based on the formation of a transient imine for the DKR of biaryl moieties by Shi and co-workers.[268] DKR allowed highly enantioselective olefination of racemic substrates (Scheme 4.115).

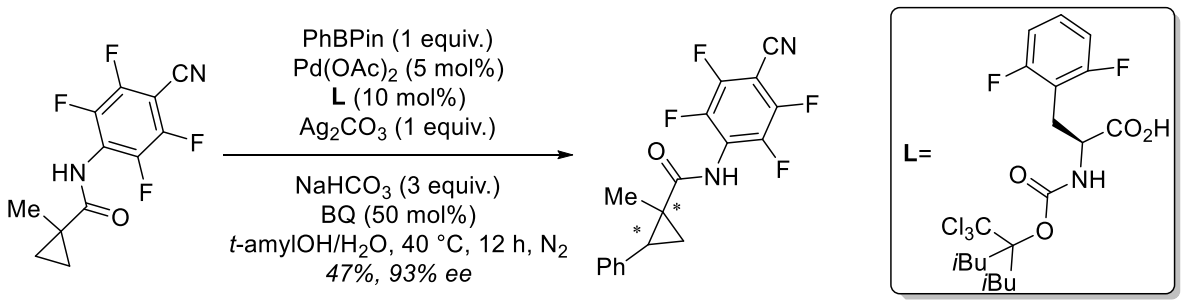


Scheme 4.115 You's desymmetrisation of biaryl using a transient directing group

IV.1.iv. Enantioselective C-C bond formation in methylene units

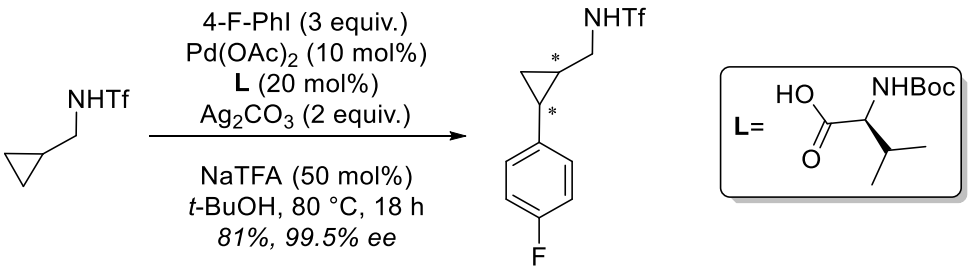
IV.1.iv.1. In cycloalkane rings

Encouraged by the precedents in using amino acids as chiral inductors, Yu and co-workers developed a new methodology for the asymmetric β-C(sp^3)-H activation of *N*-perfluoroaryl cyclopropanecarboxamide. Amino acid derivatives proved once more to be excellent chiral inductors and arylation of the cyclopropane ring could be performed with 80 % yield and 93 % enantiomeric excess. Nevertheless, no example with α-hydrogen bearing substrate was described (Scheme 4.116).[23]



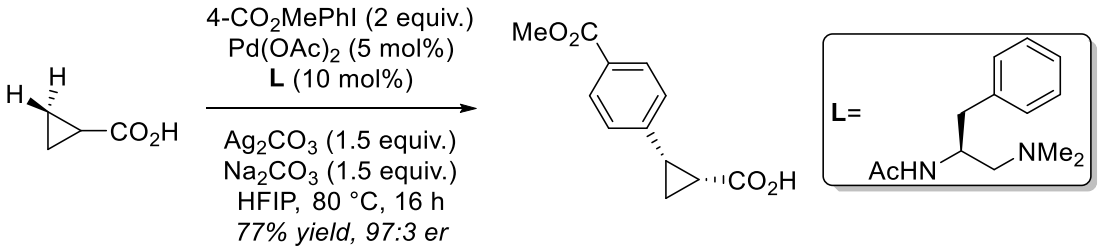
Scheme 4.116 Yu's arylation of α-substituted cyclopropanes

In 2015, after showing that mono protected amino acids (MPAA) ligands enabled the γ-C(sp^3)-H bond functionalisation of triflate-protected amines, Yu and co-workers reported a highly enantioselective method for the arylation of triflyl-protected cyclopropylamines.[22,269] Boc-protected-L-Valine was used as ligand and the reaction was compatible with various aryl iodides, including sterically hindered *ortho*-substituted coupling partners (Scheme 4.117).



Scheme 4.117 Yu's enantioselective arylation of cyclopropylamines

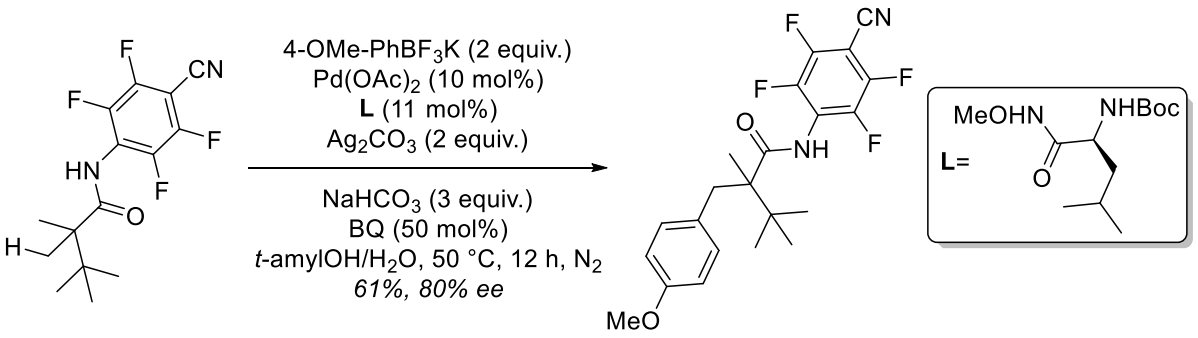
In the middle of 2018, Yu and co-workers overrode the necessity of using a perfluoroamide protecting group for the enantioselective β-C(sp^3)-H functionalisation of cyclic acids. It was commonly recognised that β-C(sp^3)-H bond activation of free acids suffers from low reactivity due to the weak directing ability of the carboxyl groups but also the conformation of the acid is more flexible than the amide, making enantiocontrol more difficult. This great challenge was overcome by designing a new chiral diamine ligand, obtained in four steps from natural *L*-phenylalanine, they were able to perform the β-arylation of various cyclopropane carboxylic acids with excellent enantiomeric excesses and overall good yields (Scheme 4.118). Nevertheless, the arylation of acyclic compounds gave lower enantiomeric excesses.[270]



Scheme 4.118 Yu's arylation of free carboxylic acids

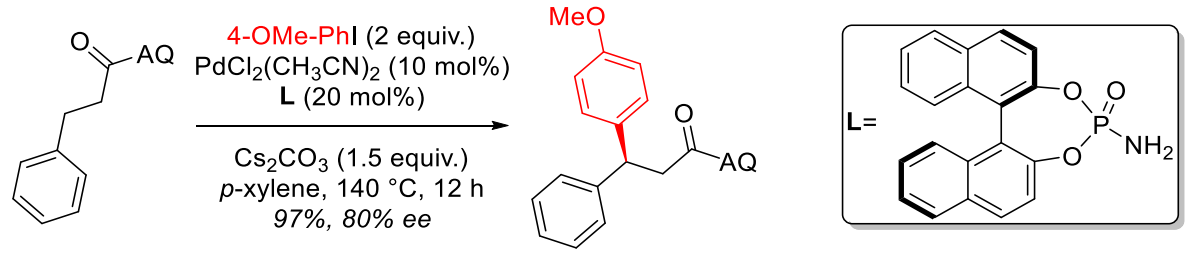
IV.1.iv.2. In aliphatic chains

After optimization of both protecting group for the carboxylic acid and nitrogen of the chiral mono-*N*-protected amino acid ligand (MPAA), Yu and co-workers reported an elegant method for the enantioselective synthesis of cyclobutane rings using *N*-protected *α*-amino-*O*-methylhydroxamic acid (PAHA). They also conducted a preliminary study on acyclic C(sp^3)-H activation on geminal dimethyl substrates to get moderate to good desymmetrisation (Scheme 4.119). In both examples, the weakly coordinating perfluorinated *N*-arylamide auxiliary was crucial to perform the C(sp^3)-H bond activation.[271]



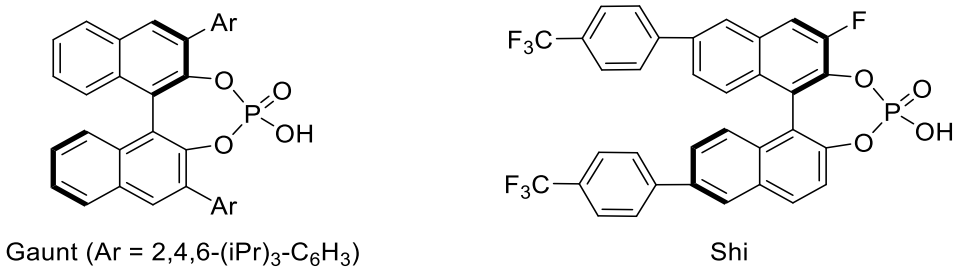
Scheme 4.119 Yu's arylation of geminal dimethyl substrates

In 2015, Duan and co-workers used a chiral phosphoramide ligand to introduce enantioselectively aryl moieties in the benzylic β-position of aminoquinoline-protected carboxylic acids, with good enantiomeric excesses and lower stereoinduction for aliphatic chains (Scheme 4.120).[272]



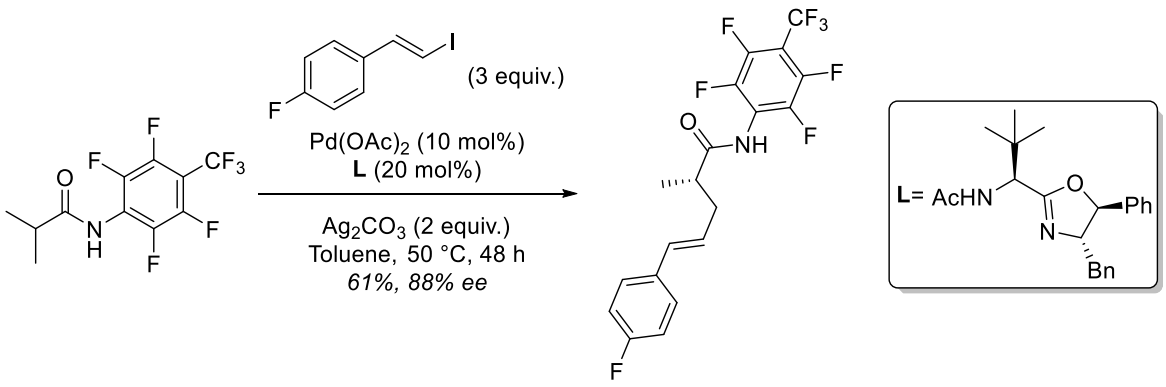
Scheme 4.120 Duan's enantioselective arylation of hydrocinnamic acid derivatives

This seminal report was followed in 2017 by the development by Gaunt and co-workers of chiral phosphoric acids for the enantioselective activation of aliphatic amines to form fused aziridines with high enantiomeric excess.[273] In 2018, Shi and co-workers disclosed a new ligand for arylation of aliphatic chains. Interestingly, this methodology uses cheaper aryl bromide as coupling partners and moderate to very good enantiomeric induction was observed (Scheme 4.121).[274]



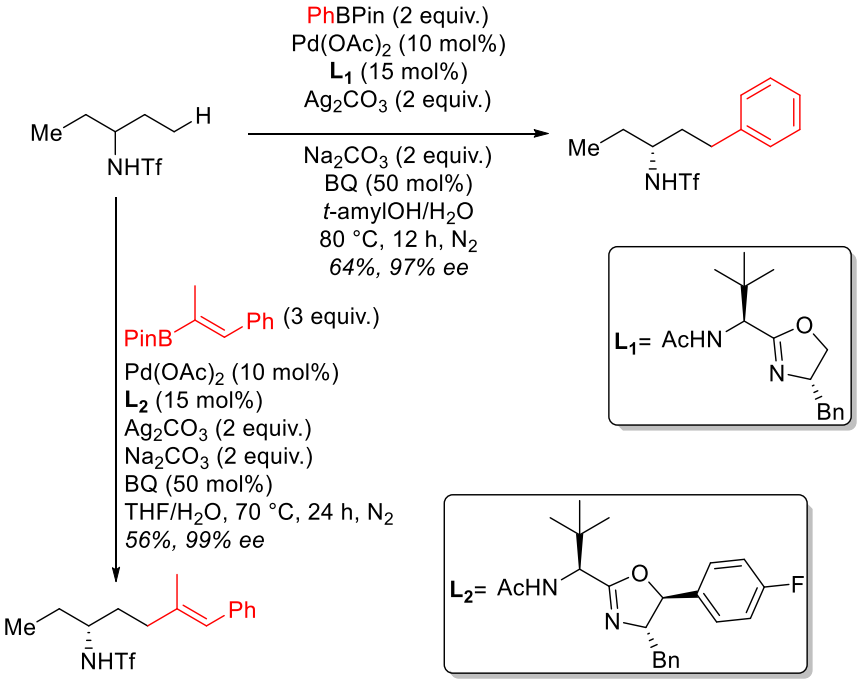
Scheme 4.121 Phosphoric acid ligands for C(sp^3)-H arylation

All the previous methodologies reported ligand-promoted arylation, and there are only few reported examples of other challenging asymmetric intermolecular C-C bond diversification of aliphatic chains. In early 2017, Yu and co-workers reported arylation, alkenylation and alkynylation of protected isobutyric acid using a chiral modified amino acid (APAO) ligand (Scheme 4.122).[275]



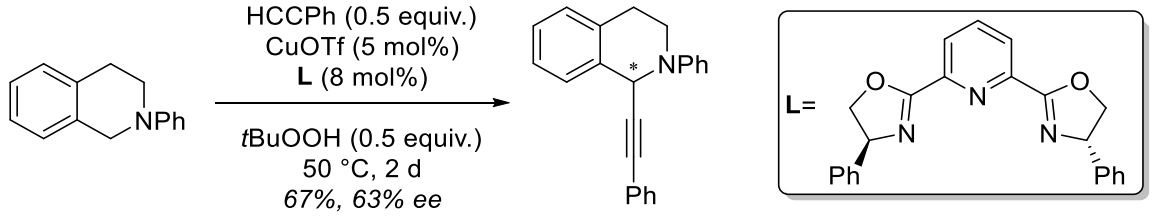
Scheme 4.122 Yu's desymmetrisation of isobutyric acid derivatives

Beside β-functionalisation of carboxylic acid derivatives, Yu and co-workers, following their work on Ir(I)-catalysed alkylation of azacycles (I.4.i), disclosed a few reports dealing with enantioselective γ-desymmetrisation of protected-amines.[276,277] Sulfonamides were found to be the best protecting groups and alkylation, vinylation and arylation were permitted by acetyl-protected amino oxazoline (APAO) ligands (Scheme 4.123).



Scheme 4.123 Yu's enantioselective γ-functionalisation of amines

Nowadays, other methodologies have been developed, for example an enantioselective copper-catalysed alkynylation of prochiral C(sp^3)-H bonds adjacent to the nitrogen in tetrahydroisoquinoline ring as disclosed by Li and co-workers. Nevertheless, only moderate chiral induction was observed (Scheme 4.124).[278] This work follows the respective arylation which gave similar enantioselectivity using the same PhPyBox chiral ligand.[279]

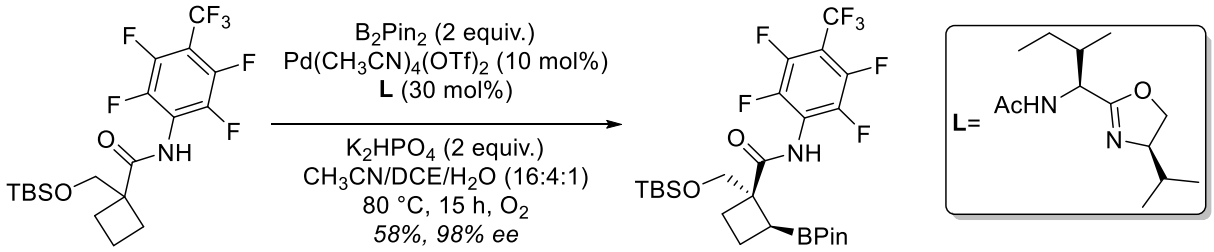


Scheme 4.124 Enantioselective α-alkynylation to amines

IV.1.v. Ligand-enabled enantioselective C-heteroatom bond formation

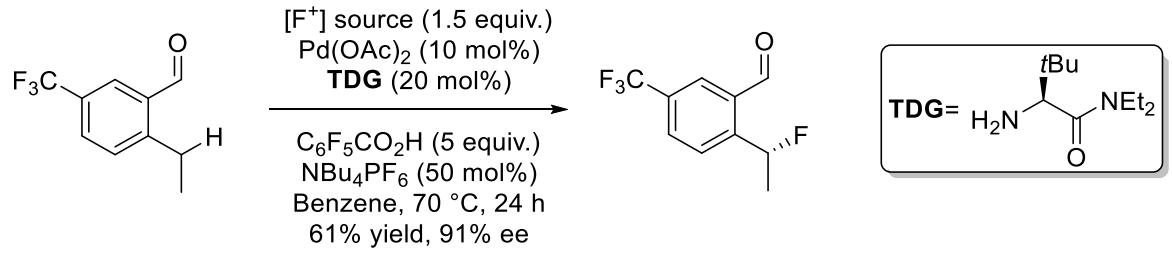
Due to the modification of the reaction mechanism when comparing direct C-C and C-X bond formation, and related to a more difficult reductive elimination, C-heteroatom bond formating reactions are clearly less explored.

For example, the enantioselective borylation on cyclobutane ring was first performed by Yu and co-workers in 2017 using APAO ligand. Excellent enantiomeric ratios were obtained (usually > 98:2 *er*) and the methodology could even be extended to other moieties such as cyclopropane (95% *ee*) or isopropyl (66% *ee*) with slight decrease in stereoinduction (Scheme 4.125).[280]



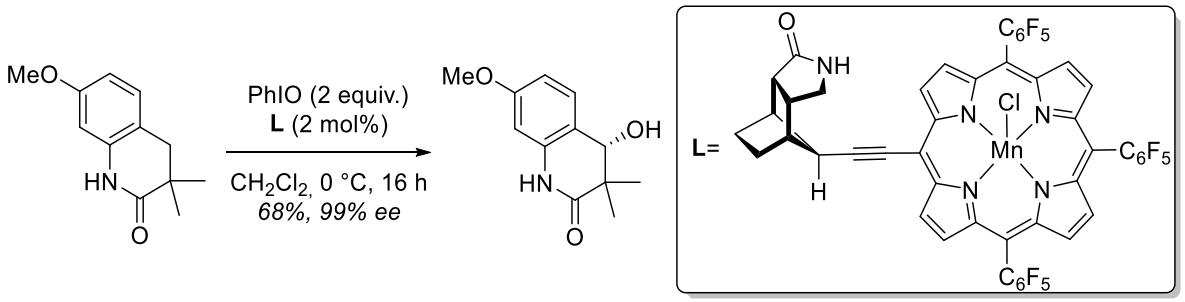
Scheme 4.125 Yu's enantioselective borylation using APAO ligand

Another important example is the enantioselective fluorination and acetoxylation occuring at benzylic position of *ortho*-alkyl substituted benzaldehydes. Interestingy, in this case a transient DG is generated *in situ* via imine formation between the aldehyde and the aminoacid-derived ligand (Scheme 4.126).[281]



Scheme 4.126 Yu's asymmetric fluorination of benzylic positions

A recent example by Bach and co-workers disclosed the site and enantio-selective oxygenation of 3,4-dihydroquinolinones using a chiral manganese catalyst and iodosobenzene as oxidant (Scheme 4.127).[282] They proposed a stereochemical model with hydrogen bonds between the two lactames of the substrate and the catalyst which would eventually direct the oxygenation in one side of the quinolinone and result in high enantiomeric excesses.



Scheme 4.127 Bach's enantioselective oxidation of dihydroquinolinones

IV.1.vi. Towards a new methodology for unactivated C-H bond functionalisation

Although these extraordinary advances achieved, the field of enantioselective C(sp^3)-H bond activation is still rather limited, and the development of new methodologies is highly appealing. For this purpose, we endeavoured on designing enantioselective protocols for the direct functionalisation of cyclopropane in presence of sulfoxide as source of chirality. Two approaches have been envisioned:

- Enantioselective C-H activation directed by transient imine formation;
- Enantioselective C-H activation promoted by an external ligand.

IV.2. Enantioselective transformations promoted by *in situ* sulfinylimine formation

As previously mentioned (I.4.i), imines early showed the ability to coordinate palladium species and to promote the C-H bond cleavage.[46] By using a chiral auxiliary, the induction of chirality should occur in a diastereoselective manner, however leading to an enantioenriched product after *in situ* hydrolysis. The key difficulty in such a transformation consists in developing reaction conditions allowing 1) imine formation between a carbonyl substrate and an imine auxiliary, 2) stereoselective C-H functionalisation and 3) *in situ* hydrolysis of the imine TDG to liberate and recycle the auxiliary (Figure 4.46).

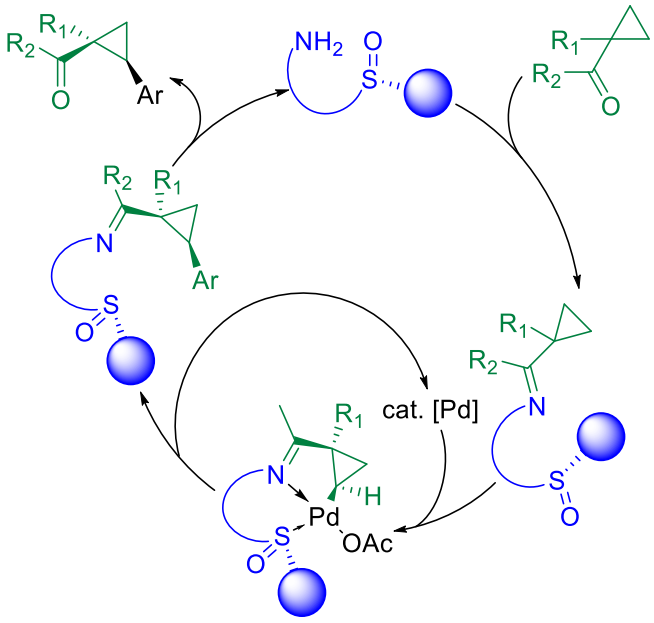
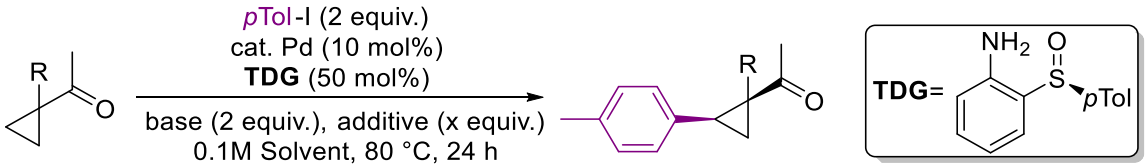


Figure 4.46 General catalytic cycle for imine-promoted C-H bond activation

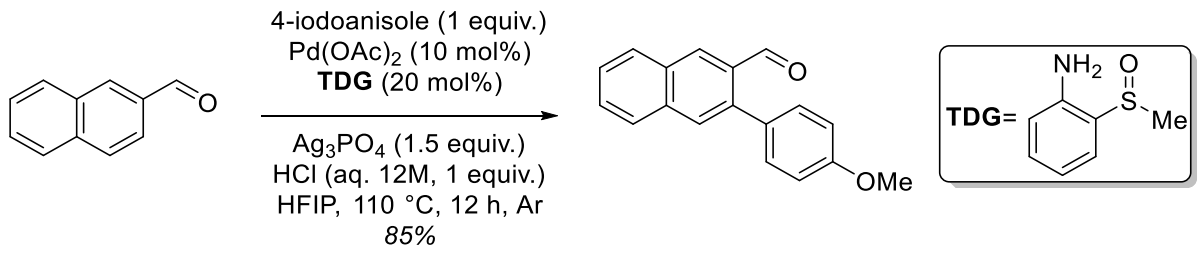
Before any optimisation of the structure of the transient directing group, we wanted to check wheter our sulfinylaniline APS auxiliary would be able to form an imine with ketylcyclopropanes (Table 4.18). 1-cyclopropylethan-1-one was used as substrate, and replaced by 1-(1-methylcyclopropyl)ethan-1-one to favour Thorpe-Ingold effect on the system (Entries 2, and 5 to 11). Screening of various sources of palladium and base showed that only trifluoroacetate sources were effective, however with low conversion. Acetic acid was suspected to promote the turnover of the imine formation (Entries 7 to 9). Deceivingly, we were not able to improve the conversion of the cyclopropane ring into the corresponding functionalised product.

Table 4.18 Preliminary tests on sulfinylimine-promoted C-H activation



Entry	R	cat. Pd	base	additive (x)	Solvent	Conversion
1	H	$Pd(OAc)_2$	Ag_2CO_3	NaTFA (2)	Toluene	0
2	Me	$Pd(OAc)_2$	Ag_2CO_3	NaTFA (2)	Toluene	0
3	H	$Pd(OAc)_2$	AgOAc	NaTFA (2)	Toluene	0
4	H	$Pd(OAc)_2$	Ag_2CO_3	NaTFA (2)	HFIP:AcOH (2:1)	0
5	Me	$Pd(OAc)_2$	Ag_2CO_3	NaTFA (2)	HFIP	0
6	Me	$Pd(OAc)_2$	Ag_2CO_3	NaTFA (2)	HFIP:AcOH (4:1)	0
7	Me	$Pd(TFA)_2$	AgTFA	-	Toluene:HFIP (4:1)	<5
8	Me	$Pd(TFA)_2$	AgTFA	-	HFIP:AcOH (4:1)	<5
9	Me	$Pd(TFA)_2$	AgTFA	NaTFA (0.5)	HFIP:AcOH (4:1)	<5
10	Me	$Pd(TFA)_2$	AgTFA	NaTFA (0.5)	HFIP:AcOH (2:1)	0
11	Me	$Pd(TFA)_2$	AgTFA	-	Toluene	0

As our first tests were not conclusive and as at the same moment we had a promising result in the ligand-promoted C-H activation, this project was discontinued. However, Chen and co-workers disclosed in 2018 that *ortho*-arylation of benzaldehydes was possible using 2-methylsulfinylaniline with good yields (Scheme 4.128). It was hypothesized that the acid helped hydrolysing the imine. Moreover, the silver salt type was crucial for the reactivity as almost no conversion was observed using other silver sources.[283] With these reaction conditions in hand, we could hereafter explore the use of the chiral transient DG APS on aldehydes to promote C(sp^3)-H bond activation.



Scheme 4.128 Chen's sulfinylaniline promoted arylation of benzaldehyde derivatives

IV.3. Development of a new class of ligands for enantioselective transformations

IV.3.i. Towards new ligands for the asymmetric C(sp^3)-H bond functionalisation

As described previously, ligand-enabled C-H bond functionalization is highly appealing compared to the diastereoselective way, as it obviates the need of a stoichiometric amount of a chiral auxiliary. From the bibliographic analysis (IV.1.ii), it undoubtedly appears that very few families of chiral ligands have been used for intermolecular C(sp^3)-H bond functionalisation. The clear majority of examples implies the use of monoprotected amino acids and more recently chiral phosphoramides have shown up as appealing alternatives. However, the limited number of efficient catalytic systems for the palladium-catalysed C(sp^3)-H bond activation is very surprising. Accordingly, in order to expand this underdeveloped field, we have endeavoured on designing new ligands with original and unexplored N,S architecture for a direct metal-catalysed functionalisation of aliphatic prochiral substrates. (Figure 4.47). Notably, this coordinating moiety offers a unique possibility to install a chiral element near the metal catalyst. In addition, the inherent structure of the sulfoxide with the presence of two distinct chelating atoms, ie. oxygen and sulphur, gives a unique opportunity to adjust its coordination mode to the electronic and steric requirements of a metal during the overall catalytic process.

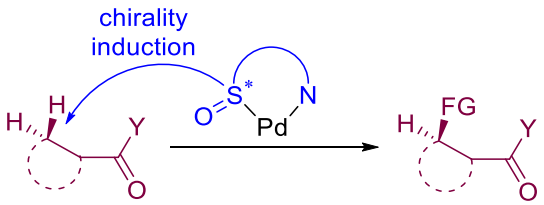


Figure 4.47 Aminosulfoxide ligand for enantioselective C(sp^3)-H functionalisation

The design of a new family of ligands presents two mains challenges, firstly to be able to find a suitable ligand, secondly a compatible DG on the substrate must be determined:

- They both need to be poorly to moderately coordinating to avoid the formation of unreactive species such as dimers but coordinating enough to bind both to the metal centre. From our previous experience with sulfinylaniline directing groups for the diastereoselective functionalisation of aliphatic chains and drawing inspiration from the work of Yu and co-workers, it seems that bicoordinating N,S ligand could be an interesting choice to chelate the palladium centre (Figure 4.48);

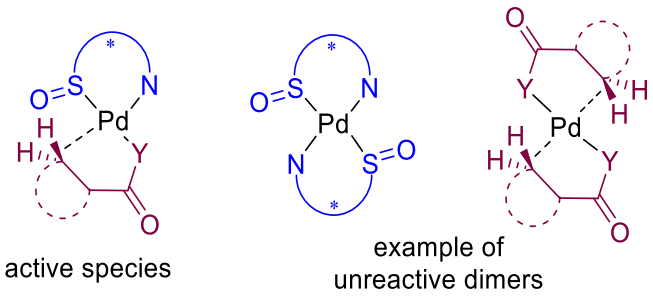


Figure 4.48 Palladium, ligand and substrate species

- When the active species is formed, as the metal centre has no vacant orbitals for an external base, the CMD must occur in an intramolecular way (IV.6). Using a ligand bearing a coordinating nitrogen moiety, installation of a carbonyl group through an amide or carbamate seems attractive to promote electrophilic assistance for the C-H bond cleavage (Figure 4.49);

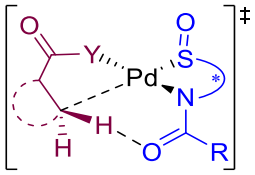


Figure 4.49 Ligand-promoted C-H activation via CMD mechanism

- Chirality must be transferred from the ligand to the newly formed stereogenic carbon. Consequently, in order to facilitate the chirality induction, stereocentre(s) must be in spatial proximity to the metal with configurations such as both bulky substituents are on the same side of the metallacycle. For example, for an aminosulfoxide ligand bearing the two bulky substituents below, we could expect repulsive interactions with the side chain R_1 of the substrate which will disfavour one isomer compared to the other (Figure 4.50).

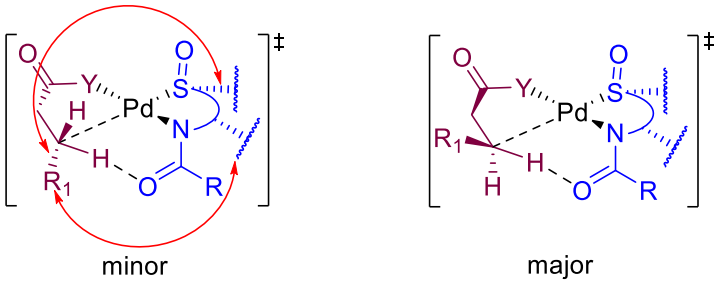


Figure 4.50 Expected transition-states and repulsive interactions

IV.3.ii. Preliminary investigations

IV.3.ii.1. Test of different families of ligands

Aminosulfoxides seem to be highly appealing to promote enantioselective C-H bond activation. Therefore, a large panel of families were tested in order to select the best class for a simple transformation, the β-arylation of cyclopropane carboxylic acid derivatives. Yu-Wasa auxiliary, *ie.* 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline, was initially chosen as protecting group for the acid for the first tests. The ligand **L1** corresponding to the *N*-acetyl **APS** deceivingly exhibited no activity. Besides ligands **L5** and **L6** bearing both sulfinyl group and chiral oxazoline displayed also no reactivity at all; notably, ligand **L5** was used by White and co-workers for oxidative allylation.[13] **L8**, a sulfinyl quinolone as well as **L9** with a triaryl backbone bearing two axial chirality axes developed in our group in 2018,[11] gave likewise no result. Regarding the studies of Yu and co-workers and in particular the flexibility of two different ligands giving either five or six membered chelates,[284] we investigated more flexible chains such as **L2** which rewardingly displayed 15% conversion. Restriction of the degrees of freedom in **L3** was beneficial for both stereoinduction and reactivity. Interestingly, **L4** with both carbon and sulphur stereogenic centers showed excellent 90 % conversion to the expected mono-arylated product and a promising enantiomeric ratio of 85:15 (Figure 4.51). No diarylation product was detected suggesting that the steric hindrance of the ligands is high enough to prevent another C-H functionalisation.

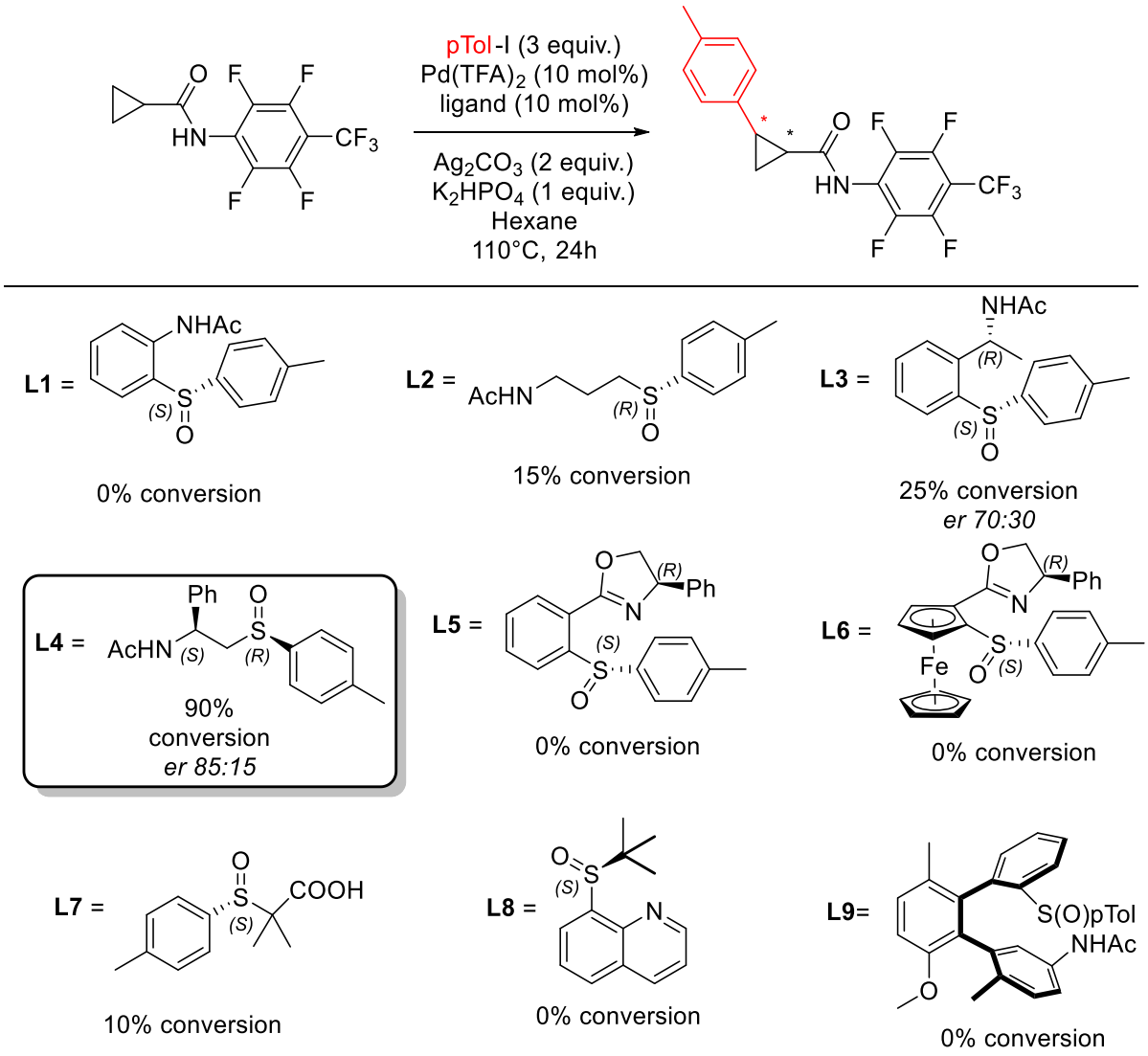


Figure 4.51 Screening of different families for enantioselective functionalisation of cyclopropanes

IV.3.ii.2. Test of different substrate protecting groups

Once the promising ligand architecture determined, the directing group installed on the substrate was optimised to substitute the expensive 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline. Remarkably, use of a simple phenylamide instead of electron-deficient amide drastically changed the outcome of the reaction as the desired product was generated only in trace amount. Consequently, as described by Yu in 2012, the use of electron-deficient amide, *ie.* weakly coordinating substrates, proved to be the best option to get both stereoinduction and high yield.[285] Thus, conserving good yield and enantiomeric induction, our choice went to the cheapest 2,3,4,5,6-pentafluorophenylamide (noted Ar^F in the rest of the chapter) protecting group (Figure 4.52).

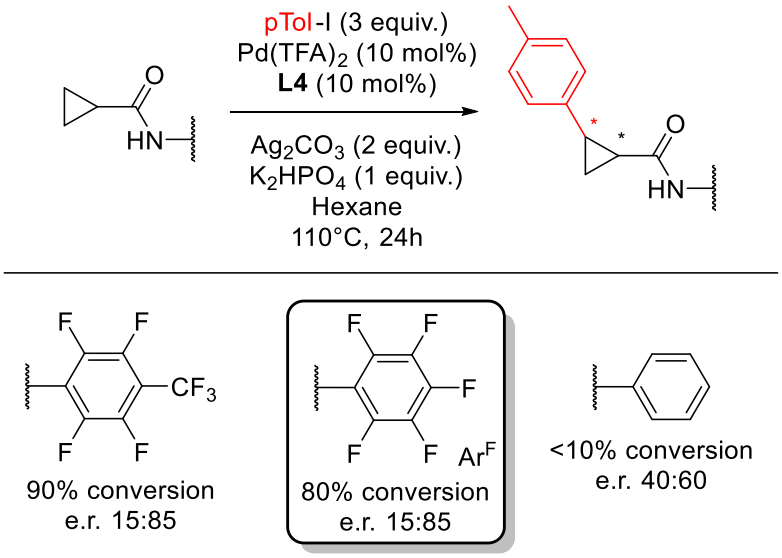


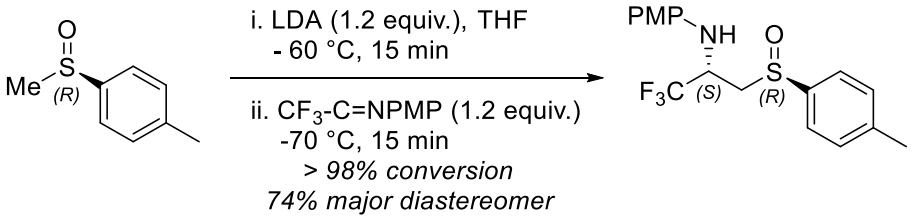
Figure 4.52 Screening of the carboxylic acid protecting group

IV.3.iii. Synthesis of various 2-sulfinylethanamine moieties

IV.3.iii.1. Obtention of the two diastereomers of **L4**

The promising arylation test carried out with **L4** conducted us to finely tune the architecture of this family of 2-sulfinylethanamine moieties in order to increase the enantioselectivity.

Enantioenriched 2-sulfinylethanamine moieties were firstly described in 1997 by Bravo and co-workers by addition of *p*-tolylsulfinylmethyllithium on α-(fluoroalkyl)aldimines.[286,287] Induction of chirality on the diastereotopic C=N double bond was possible thanks to the stereogenic character of the sulfoxide and good diastereomeric excesses were obtained (Scheme 4.129).



Scheme 4.129 Bravo's synthesis of fluoroaminosulfoxides

Regarding the imine protecting group, multiple transition states were described, explaining the diastereoselectivity of the reaction.[24,26] More precisely, using *p*-methoxyphenyl-protected imines, the six-membered transition state, with a possible steric clash between the aryl moiety and the oxygen of the sulfoxide, may explain the predominance of the expected (*S*, R_S) diastereomer (Figure 4.53).

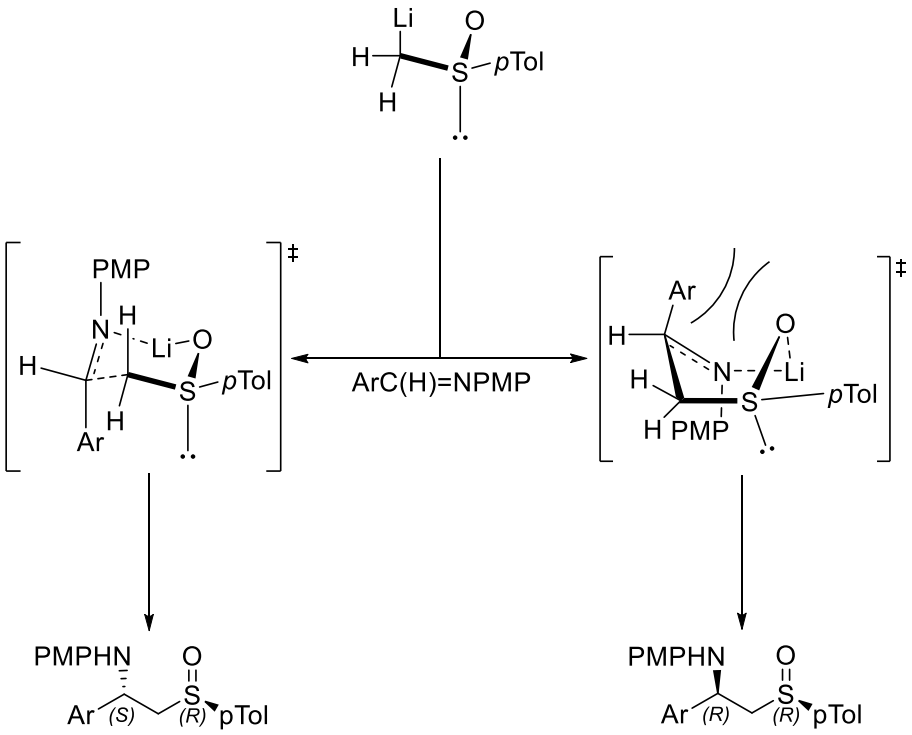
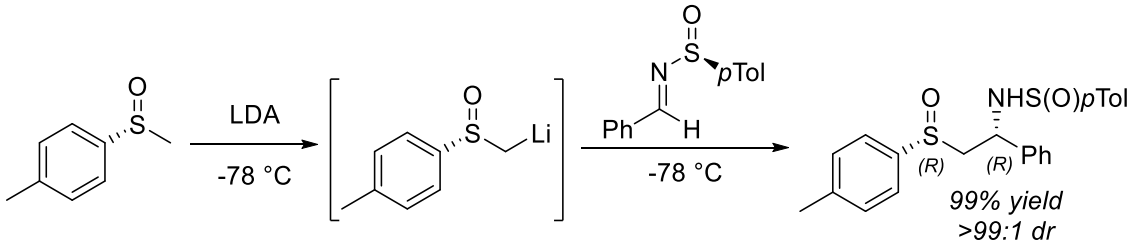


Figure 4.53 Origin of the diastereoselectivity in the reaction with PMP-imines

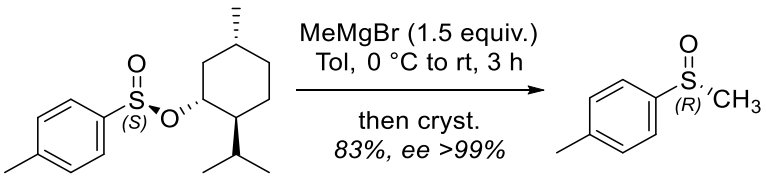
In contrast with the use of PMP-protecting group which afforded in majority (*S*, R_S) or (*R*, S_S) compounds, García Ruano and co-workers used sulfinylimines originally developed by Ellman to obtain (*S*, S_S) or (*R*, R_S) with good to excellent diastereomeric excess (Scheme 4.130).[24,288] In this case, the observed diasteroselectivity is mainly due to the chiral auxiliary on the imine group.



Scheme 4.130 García Ruano's synthesis of chiral 2-sulfinylethanamines

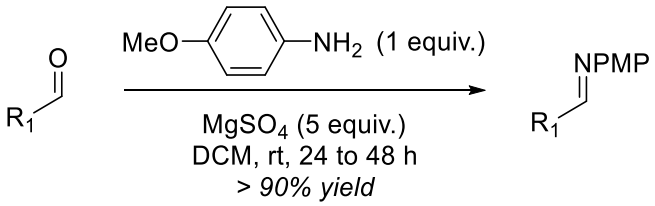
IV.3.iii.2. Novel access to (S, R_S)-aminosulfoxides ligands

The enantiopure methyl (*R*)-*p*-tolylsulfoxide was obtained by addition of methylmagnesium bromide on (1*R*,2*S*,5*R*)-menthyl (*S*)-*p*-toluenesulfinate. The reaction proceeded with full conversion at room temperature and the product crystallized in petroleum ether at – 18 °C (Scheme 4.131). The optical purity of the compound was determined by chiral HPLC.



Scheme 4.131 Synthesis of enantiopure methyl (*R*)-*p*-tolylsulfoxide

Concerning the other part of the ligand skeleton, we decided to synthesize the PMP-imines as they would lead to the desired (*S*, R_S) diastereomer. Starting from benzaldehyde derivatives, reaction with *p*-anisidine in presence of an excess magnesium sulphate drove the reaction to completion and the desired products were obtained with excellent yield (Scheme 4.132). Notably, no purification was needed. Obtention of α-hydrogen bearing aldimines was tedious and often resulted in an imine/enamine mixture. Concerning ketimines, they could not be obtained due to the poor reactivity of both aniline and ketone derivatives.



Scheme 4.132 Synthesis of PMP-imines

After accessing enantiopure methyl *p*-tolylsulfoxide and various PMP-imines, we embarked first to the Bravo's condensation of the lithiated anion of methyl *p*-tolylsulfoxide to the 4-*tert*-butylphenyl-PMP-imine and we noticed that the isolation of the major diastereomer could be performed by column chromatography on silica gel but, more interestingly, it precipitates in ethyl acetate/cyclohexane mixture, affording the pure ligand **PMP-L12** with good yield and excellent diastereomeric ratio. Rewardingly, the absolute configuration of this major diastereomer was confirmed by X-Ray diffraction analysis after obtention of single crystals by slow evaporation of hexane and chloroform (Figure 4.54).[24] This structure shows clearly the pincer ability of this type of ligand and the steric hindrance provided by both the *p*-tolyl and the 4-*tert*-butyl phenyl moieties on one side of a plane bearing both sulphur and nitrogen atoms.

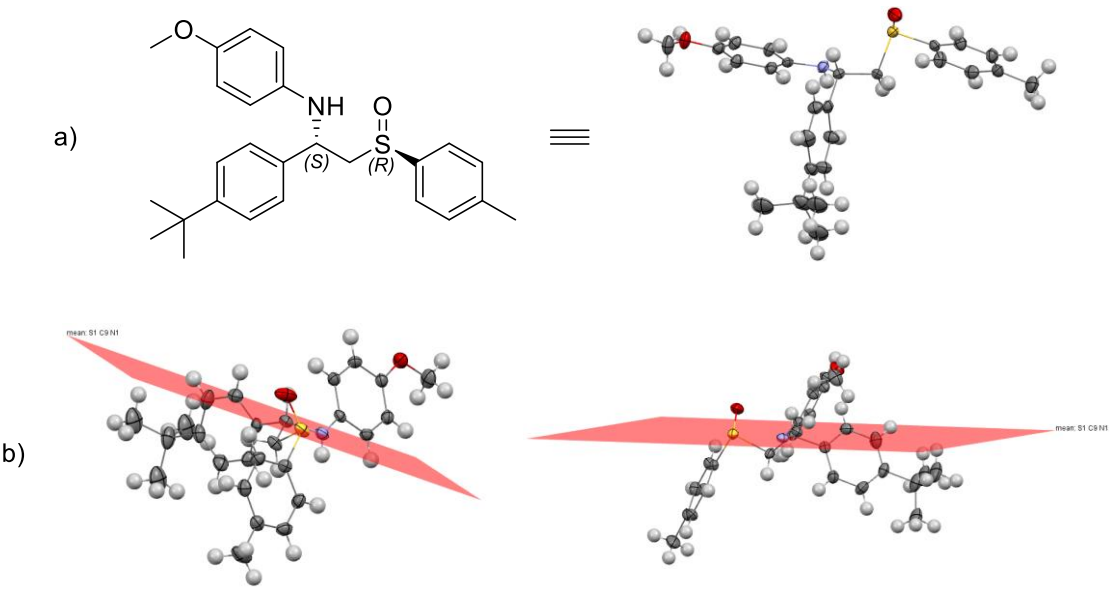
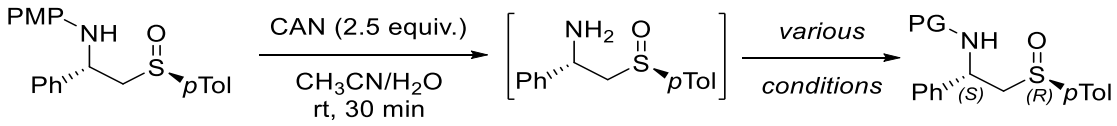


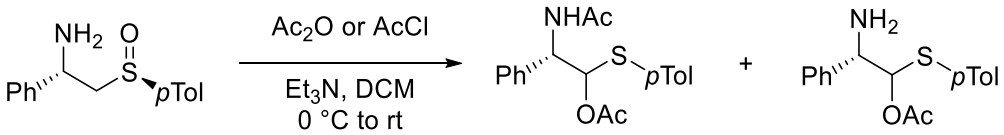
Figure 4.54 ORTEP views of one addition product, key intermediate for PMP-L12

Then, deprotection of the PMP using cerium ammonium nitrate (CAN) afforded the free amine. Two equivalents of CAN are required for each equivalent of PMP. The amine and *p*-methoxybenzaldehyde are released. Even if oxidative-deprotection resulted in a difficult extraction of the product due to the cerium salts, other pathways were either not efficient or caused degradation of the product: especially, racemisation of the sulphur atom was observed under strongly acidic conditions. Then, amidation of the nitrogen atom using T3P-mediated coupling afforded *N*-protected aminosulfoxides in good to excellent yields (Scheme 4.133). Other protection such in carbamate for example were performed by standard procedures (IV.8.ii).



Scheme 4.133 Synthesis of the ligands from the PMP-protected amines

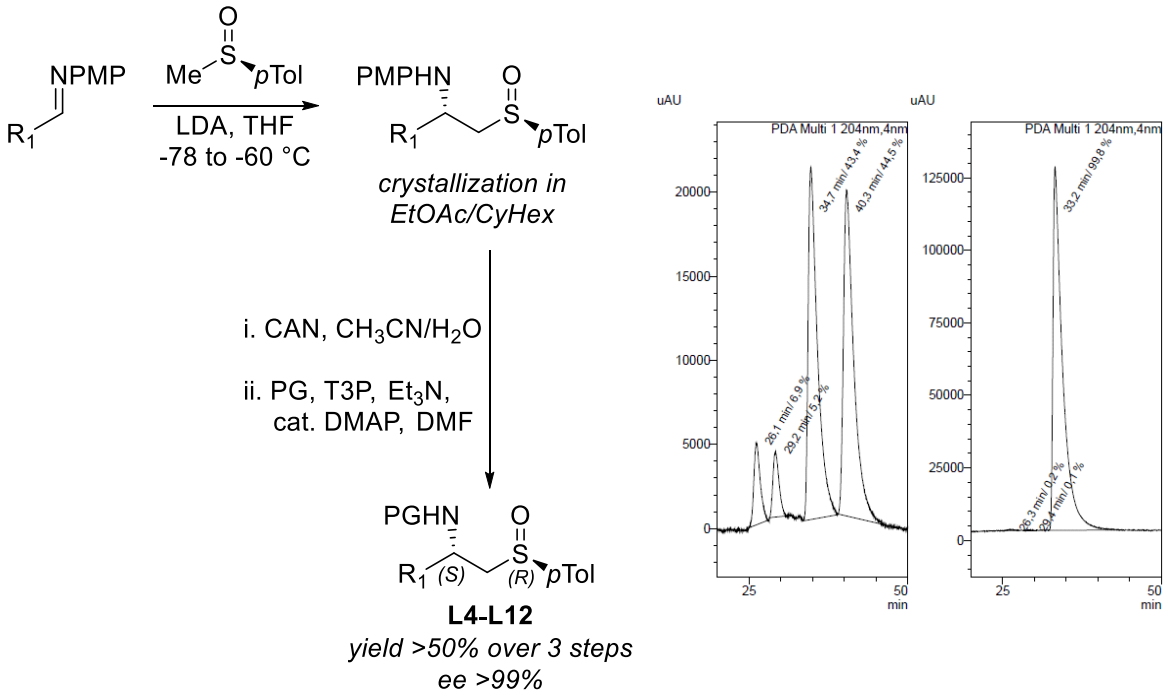
Notably, the nitrogen protection with acyl chlorides or anhydrides and triethylamine often resulted in undesired Pummerer rearrangement (Scheme 4.134).[151–153]



Scheme 4.134 Pummerer rearrangement of a free aminosulfoxide

Other imine protecting groups were tested, such as chiral sulfinamides, and the addition of the lithiated anion of the (*R*)-methyl *p*-tolylsulfoxide gave almost exclusively access to the (*R*,*R*$_S$) diastereomer.

Finally, the synthetic sequence involving consecutive addition of methyl *p*-tolylsulfinyllithium on PMP-imines followed by crystallisation, deprotection and protection of the nitrogen was used successfully to prepare numerous ligands derived from **L4** and offers high modularity on the aryl moiety R_1 as well as the protecting group of the amide or the substituent on the sulfoxide. The sequence was also generally high yielding (71% yield from the starting benzaldehyde for **L12**) and enantiopure products were isolated with only one column chromatography after final nitrogen protection (Scheme 4.135).

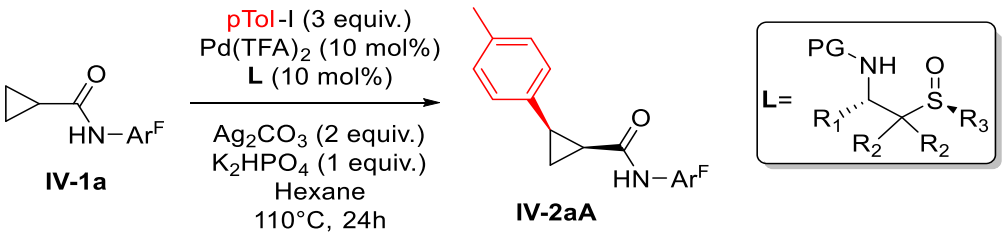


Scheme 4.135 (*S*, *R*$_S$)-aminosulfoxide ligand synthesis from PMP-imines and chiral HPLC chart of L12

IV.3.iv. Ligand optimization

With the encouraging results obtained using **L4** in the enantioselective C-H bond functionalization of unsubstituted cyclopropane, we focused our studies on the fine tuning of each part of the ligand, ie the protecting group PG on the nitrogen, the substituent of the carbon stereocentre R_1, on the methylene R_2 and the substituent on the sulfoxide R_3. Obviously, *N*-acetyl protected ligands were crucial to get both good stereoinduction and yield while flexibility between the two coordinating sites was also important for the reactivity of the whole system (Entries 1, 2 and 6, Table 4.19). The role of the acetamide is indeed decisive for the CMD and further insights will be detailed in the mechanistic studies (IV.6). Besides increasing the hindrance of the substituent on the sulphur atom did not allow any improvement.

Table 4.19 Screening of the different parts of the ligand



Entry	PG	R1	R2	R3	Conversion (%)	*er*
1	Ac	Ph	H	*p*Tol	80	15:85
2	Ac	Ph	H	*t*Bu	15	*nd*
3	Boc	Ph	H	*p*Tol	25	40:60
4	$CH_3CH_2CO_2$	Ph	H	*p*Tol	10	*nd*
5	TFA	Ph	H	*p*Tol	60	15:85
6	Ac	Ph	CH_3	*p*Tol	25	30:70
7	Ts	Ph	H	*p*Tol	10	*nd*
8	PMP	Ph	H	*p*Tol	10	*nd*

Then, we studied the importance of the presence of two chiral centres on our ligand as well as the relative configuration (Chart 4.21). Benzylic amide was crucial to achieve good conversion; this could be explained by the lower pk_A of the nitrogen in **L4** compared to **prim-L4**, which facilitates the deprotonation and thus the formation of the chelate with palladium. Surprisingly, when we reduced the sulfoxide into a *p*-tolyl thioether **thio-L4**, we noticed a similar conversion and a slight decrease of the enantiomeric ratio suggesting that the enantioselectivity is mainly controlled by the stereogenic carbon centre. Indeed, **dia-L4** with inversion of the chirality of the stereogenic carbon atom gave lower conversion and expected inversion of the enantiomeric ratio.

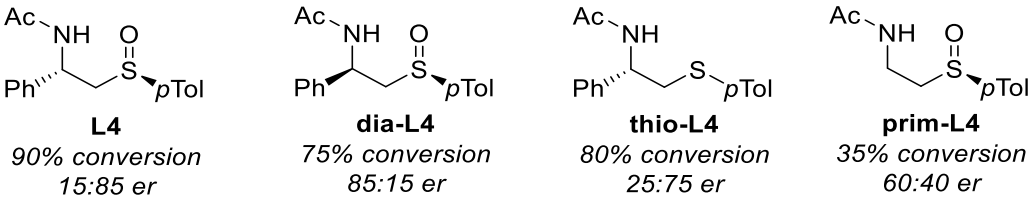


Chart 4.21 Screening of the different parts of the ligand

With the variation of all distinct parts of **L4**, we came up with an optimised ligand structure as drawn in Chart 4.22.

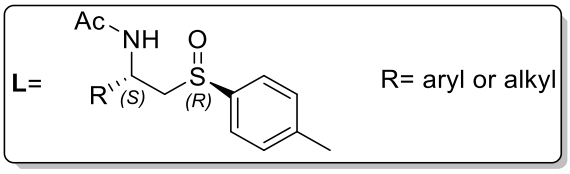


Chart 4.22 Optimal ligand structure for enantioselective functionalisation of cyclopropanes

Thanks to the large variety of aldehyde available, we had access to a vast number of ligands bearing different R substituents. However, when trying the addition of the *p*-tolylsulfinyl methyllithium on alkylimines, such as *tert*-butyl or isopropyl derivatives, no addition occurred, restricting the R group to aryl moieties. Moreover, *ortho* substituents on the aromatic ring were not tolerated, forcing us to focus our study on *meta* and *para* substituents on the aryl moieties (Chart 4.23). Synthesis of various ligands occurred smoothly and efficiently, as in each case the major diastereomer precipitated after addition of the methyl *p*-tolylsulfoxide. Only one column chromatography was performed after acetamide protection to yield pure compounds which were tested for the arylation of cyclopropane.

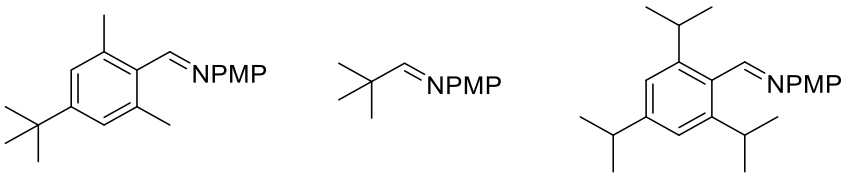
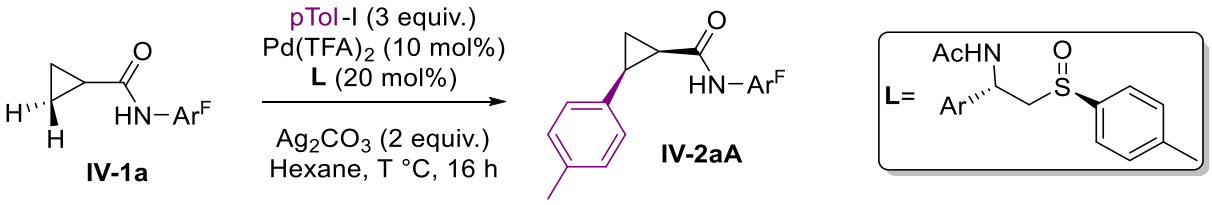


Chart 4.23 Unreactive imines

Interestingly, enhancement of the steric hindrance in *meta* or *para* position such as in Entry 2 or 3 resulted in a better enantiomeric ratio, further improved by the decrease of the reaction mixture temperature to 80 °C (Table 4.20, Entry 4). A sterically hindered substituent such as *t*-butyl in *para* position (Ligand **L12**, Entry 5) allowed a slight increase of the stereoselectivity up to 88% *ee*. Besides a *para* methoxy group caused a large decrease in yield (Entry 6) while a *para*-methyl or *para*-trifluoromethyl gave the coupling product in similar conversion and 80% *ee* suggesting no influence of the electronic richness of the ring (Entries 7 and 8). **L16** with two *tert*-butyl in *meta* position, could not be obtained, maybe because of high steric hindrance which did not allow attack of the *p*-tolylsulfinyl methyllithium on the corresponding imine.

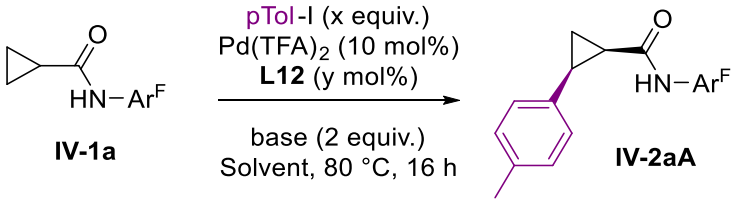
Table 4.20 Screening of the different parts of the ligand



Entry	L	Ar	T (°C)	Conversion (%)	*er*
1	**L4**	phenyl	110	90	15:85
2	**L10**	3,5-dimethylphenyl	110	30	13:87
3	**L11**	2-naphthyl	110	85	12:88
4	**L11**	2-naphthyl	80	80	10:90
5	**L12**	4-*tert*-butylphenyl	80	75	6:94
6	**L13**	4-methoxyphenyl	110	15	*nd*
7	**L14**	4-methylphenyl	110	70	10:90
8	**L15**	4-trifluoromethylphenyl	110	60	10:90
9	**L16**	3,5-di-*tert*-butylphenyl	*nd*	*nd*	*nd*

Using **L12**, we started the optimisation of the reaction conditions by lowering the amount of ligand from 20 to 15 mol%, which did not impact the enantiomeric ratio of the reaction, even if the overall conversion had sensitively dropped. But a decrease up to 10 mol% lowered the enantiomeric ratio to 14:86. Remarkably, as our previous studies suggested the importance of the solvent for this type of transformation, we noticed that a 2:1 mixture of hexane and chloroform was optimal for both reactivity and enantioselectivity as shown in Entry 5. The modification of the base from silver carbonate to other sources of silver (Ag_2CO_3 in Entry 8, AgTFA in Entry 9) or other sources of carbonate (K_2CO_3 in Entry 10) was detrimental to reactivity. As in few cases double arylation was observed, the excess of iodoarene coupling partner was lowered from 3 to 2, affording the expected product with 60% yield, comparable enantiomeric excess and no observed di-arylation (Table 4.21).

Table 4.21 Optimisation of the arylation of cycloalkanes I

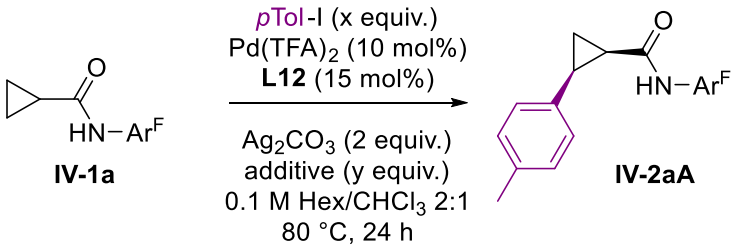


Entry	x	y	base	solvent (M)	Conversion (%)	*er*
1	3	20	Ag_2CO_3	Hex (0.2)	75	6:94
2	3	15	Ag_2CO_3	Hex (0.1)	45	6:94
3	3	10	Ag_2CO_3	Hex (0.1)	45	14:86
4	3	15	Ag_2CO_3	Hex/$CHCl_3$ (3:1) (0.1)	60	5:95
5	3	15	Ag_2CO_3	Hex/$CHCl_3$ (2:1) (0.1)	70	4:96
6	3	15	Ag_2CO_3	Hex/$CHCl_3$ (1:2) (0.1)	70	11:89
7	3	15	Ag_2CO_3	$CHCl_3$ (0.1)	50	13:87
8	3	15	AgTFA	Hex/$CHCl_3$ (2:1) (0.1)	<5	*nd*
9	3	15	AgOAc	Hex/$CHCl_3$ (2:1) (0.1)	20	20:80
10	3	15	K_2CO_3	Hex/$CHCl_3$ (2:1) (0.1)	*<10*	*nd*
11[20]	2	15	Ag_2CO_3	Hex/$CHCl_3$ (2:1) (0.1)	50	5:95

[20] The reaction mixture was stirred 24 h at 80 °C.

Finally, we considered the possible influence of additives on our reaction (Table 4.22). Interestingly, besides improving the global conversion in general, sodium trifluoroacetate helped avoiding homocoupling of the iodoarene, thus allowing to decrease the amount of coupling partner to 2 equivalents as shown in Entry 7. This study shows the crucial role of trifluoroacetate anions in the reaction mixture (Entries 2, 5, 6 and 7). One possible role of this additive, beside balancing the overall pH of the reaction mixture, would be promoting the formation of the bidentate chelate.

Table 4.22 Optimisation of the arylation of cycloalkanes II



Entry	x	Additive (y equiv.)	Conversion (%)	*er*
1	3	-	70	4:96
2	3	NaTFA (1)	75	4:96
3	3	Cs_2CO_3 (1)	<10	*nd*
4	3	Na_2CO_3 (1)	<20	*nd*
5	3	NaTFA (0.5)	80	4:96
6	3	NaTFA (0.2)	70	4:96
7	2	NaTFA (0.5)	80	4:96

Encouraged by these results, we investigated two last ligands derived from **L12**, **L17** and **L18**. For these molecules, both key intermediates, respectively 4-(adamantan-1-yl)-benzaldehyde and (-)-menthyl (*S*)-(4-(*tert*-butyl-phenyl))sulfinate were synthesized according to reported procedures. Unfortunately, the PMP-amine derivative of **L17** did not crystallized selectively and column chromatography afforded an unseparable mixture of diastereomer while, for **L18**, addition of methyl *p*-*tert*-butylphenylsulfinyl lithium on the imine did not proceed. Other structures such as **L19** or **L20** can be imagined but have not been tested yet (Chart 4.24). Benzylamides could indeed promote one precise geometry by π-stacking with the *tert*-butylphenyl moiety; moreover, ortho-protection of the benzylamide is required to avoid any intramolecular β- or γ-C-H bond activation.

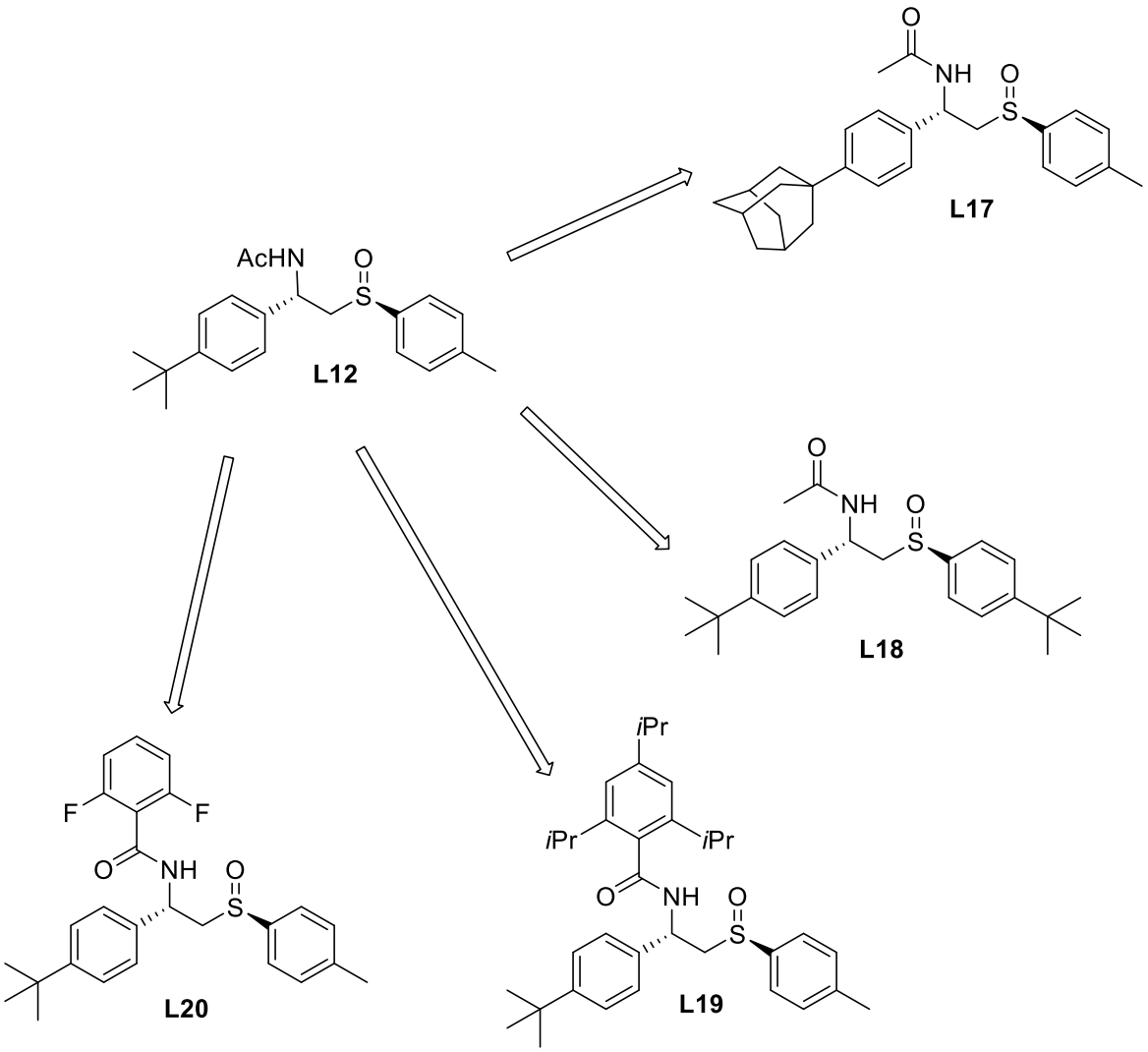


Chart 4.24 Possible amelioration of L12

IV.4. Application to the C(sp^3)-H bond functionalization of cycloalkanes

IV.4.i. Enantioselective arylation

Our detailed optimization allowed us to select **L12** as the optimal accelerator and chiral inductor, and we showed that good to excellent enantiomeric induction was possible using a large variety of iodoarene coupling partners.

Electron-rich iodoarenes such as anisoles gave excellent excesses, such as in **IV-2Ac** and electron-poor ones also gave excellent results, such as in the sterically hindered **IV-2aG**, isolated with 87% yield and 94:6 enantiomeric ratio. Sensitive aldehyde was even tolerated, affording the coupling product **IV-2aM** in 88% yield and 93:7 enantiomeric ratio. *Meta*-substituted iodoarenes also performed remarkably well, as compound **IV-2aD** was isolated in 58% yield and 90% enantiomeric excess. Biologically relevant fluorinated motifs such as CF_3 and OCF_3 were also well tolerated. The lowest enantiomeric excesses (60%) were mainly observed with poorly reactive 2-iodoanisole and 2,4-difluoroiodobenzene (Figure 4.55).

Compatibility with heterocycles is rather moderate, as thiophene or indole were not well tolerated and gave either low conversion or total absence of reactivity.

Notably, our methodology even worked on gram scale using 3-iodoanisole as coupling partner and 70 % conversion to the desired mono-arylated compound was observed with 97:3 enantiomeric ratio on the crude mixture.

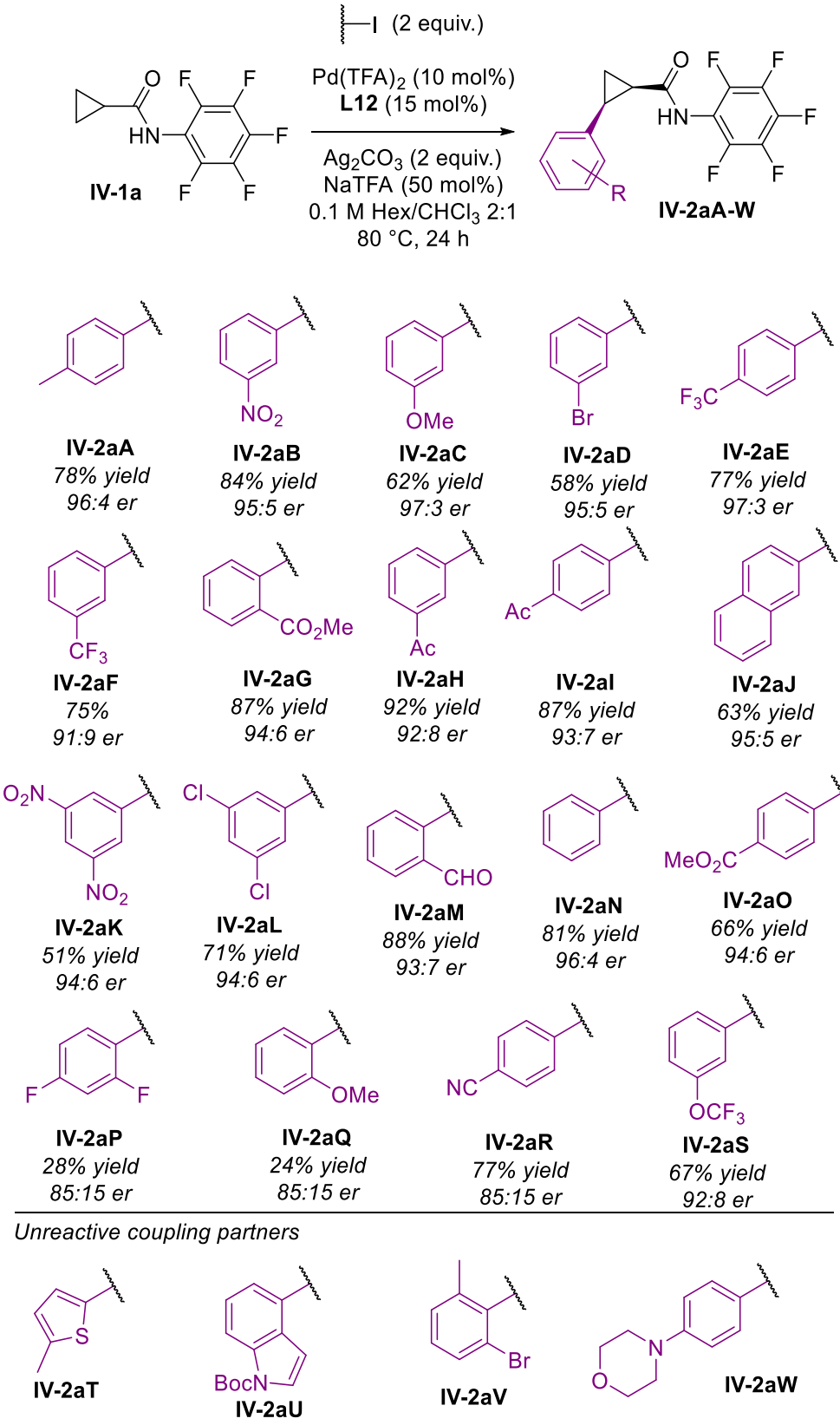


Figure 4.55 Scope of enantioselective arylation on cyclopropane

The absolute configuration of the compounds was attributed by analogy with **IV-2aR**, which afforded single crystals suitable for X-Ray diffraction analysis by slow evaporation of hexane and chloroform (Figure 4.56). Preliminary DFT studies stand in agreement with the absolute configuration observed (IV.6).

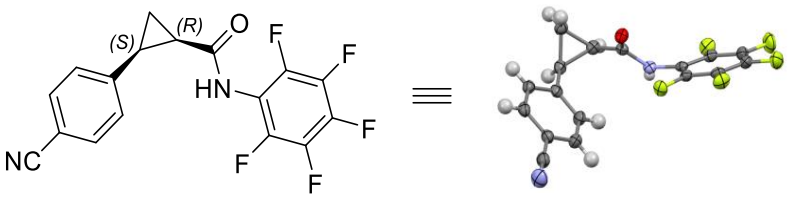


Figure 4.56 ORTEP view of IV-2aR

Arylation was extended to larger cycles such as cyclobutane. Deceivingly, the enantiomeric excess was lower (around 60 %) and no additional tests were performed on this substrate (Figure 4.57). This transformation clearly shows the potential of *N*-protected aminosulfoxide ligands for asymmetric induction, although further optimisation of the ligand is needed to higher the stereoinduction on larger cycloalkanes.

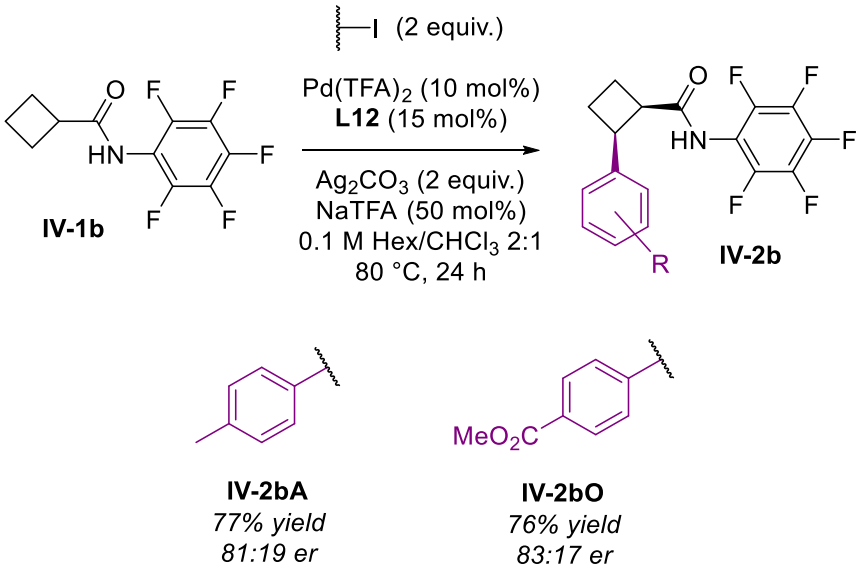


Figure 4.57 Scope of enantioselective arylation on cyclobutane

Perfluorophenylamide is a suitable auxiliary for the C-H functionalisation of aliphatic chains and can be removed under mild conditions: either Yu's conditions mediated by glycidyl methyl ether in presence of potassium acetate in ethanol (Figure 4.58.a), or our conditions developed for the mild deprotection of arylamide (Figure 4.58.b and c) proved to be efficient. Recrystallization of **IV-4** afforded mono-crystals suitable for X-Ray diffraction analysis, showing the conservation of the two stereocentres and no epimerisation; noteworthy this purification technique allowed further enrichment of the compound, which was finally obtained with excellent 82% yield and almost perfect enantiomeric excess. Finally, deprotection of the compound **IV-2aN** without subsequent esterification afforded the know compound **IV-5**. The absolute configuration was unambiguously assigned for all our C-H functionalised cyclopropanes according to the X-Ray structure of **IV-4** and the optical rotation of **IV-5**.

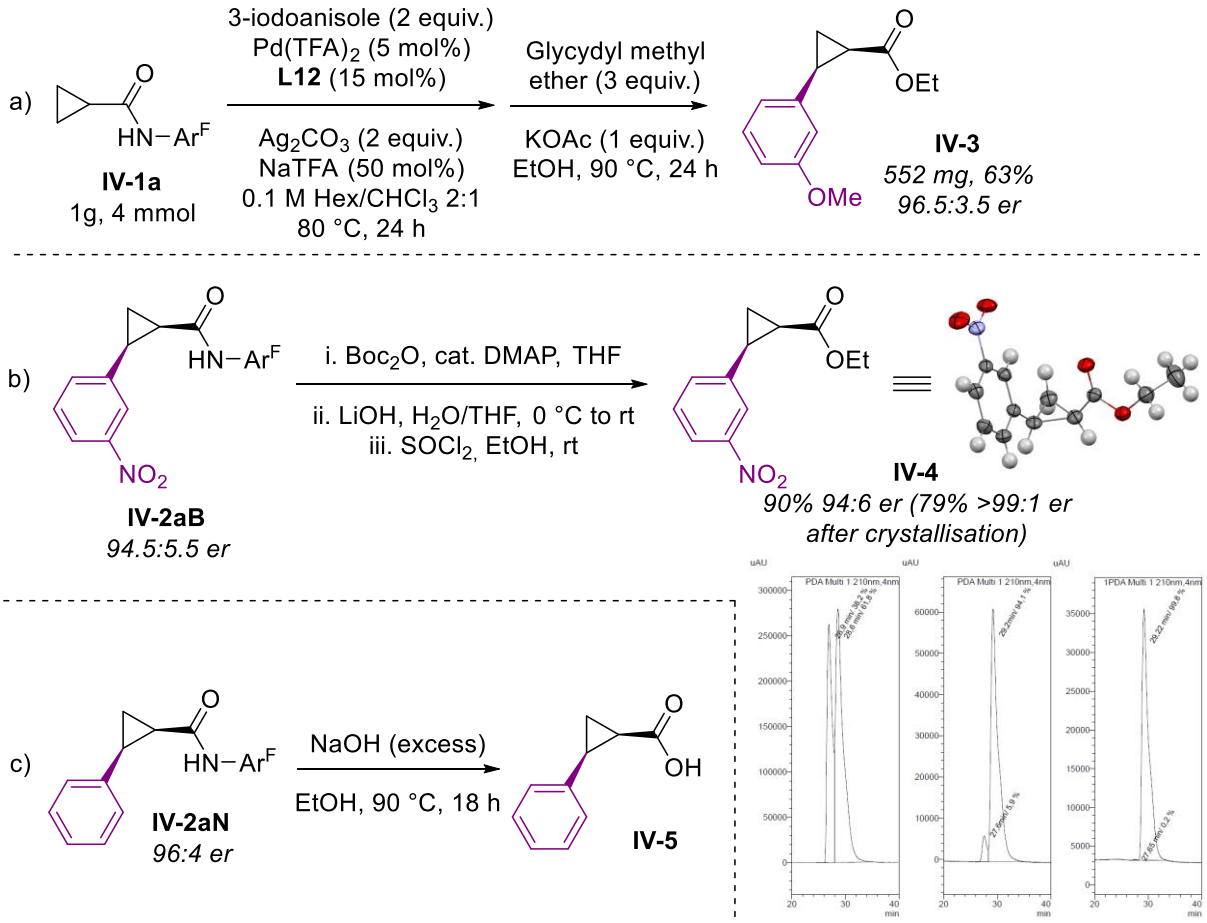
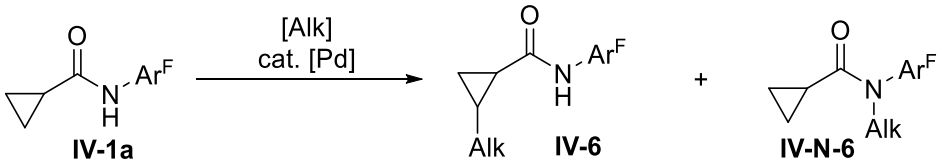


Figure 4.58 Deprotection of the perfluoroamide moeity and chiral HPLC chart for IV-4

IV.4.ii. Enantioselective alkylation

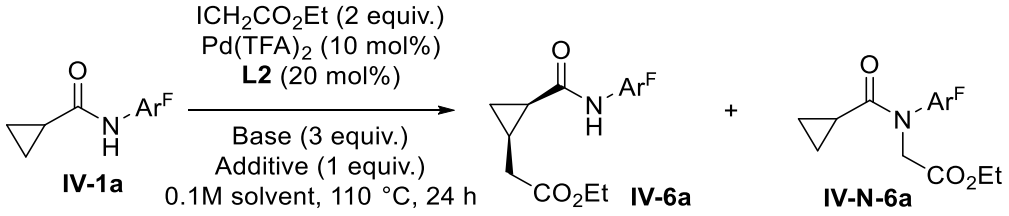
Ligand-promoted alkylation remains a significant challenge. The major issue is the high probability of *N*-alkylation over actual C-H bond functionalisation, therefore poisoning the catalytic by avoiding coordination with the palladium (Scheme 4.136). Moreover, the similar polarity of **IV-1a**, **IV-6** and **IV-N-6** results in a tedious separation of the crude material.



Scheme 4.136 Regioselectivity of Pd-catalysed C(sp^3)-H alkylation

Preliminary tests were carried out with the ligand **L2** and showed a crucial role of additive on the obtention of **IV-6** or **IV-N-6**, obviously helping the deprotonation of the amide moiety and resulting in higher *N*-alkylated product (Entries 1 and 3). In contrast, removing the additive resulted in a lower conversion in all tested solvents (Table 4.23). Further tests, especially done with the optimized ligand **L12** and other coupling partners such as iodomethane or isopropyl iodide, were not conclusive, hence the asymmetric enantioselective alkylation was not explored in more details.

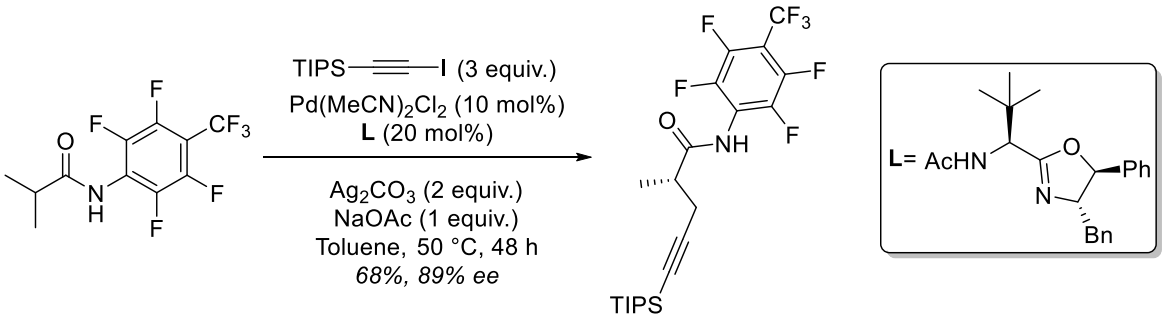
Table 4.23 Optimisation of the alkylation of cycloalkanes



Entry	Base	Additive	Solvent	Conversion	Ratio IV-6a/IV-N-6a
1	Ag_2CO_3	-	Hexane	50	30/70
2	Ag_2CO_3	-	*t*-amylOH	30	10/90
3	Ag_2CO_3	Cs_2CO_3	Hexane	100	>5/95
4	Ag_2CO_3	-	DCE	<10	*nd*
5	AgOAc	Cs_2CO_3	Hexane	100	>5/95
6	Ag_2CO_3	NaOAc	Hexane	95	10/90
7	Ag_2CO_3	CsF	Hexane	40	>5/95
8	AgOPiv	-	Hexane	95	>5/95
9	AgOPiv	NaOPiv	Hexane	50	>5/95

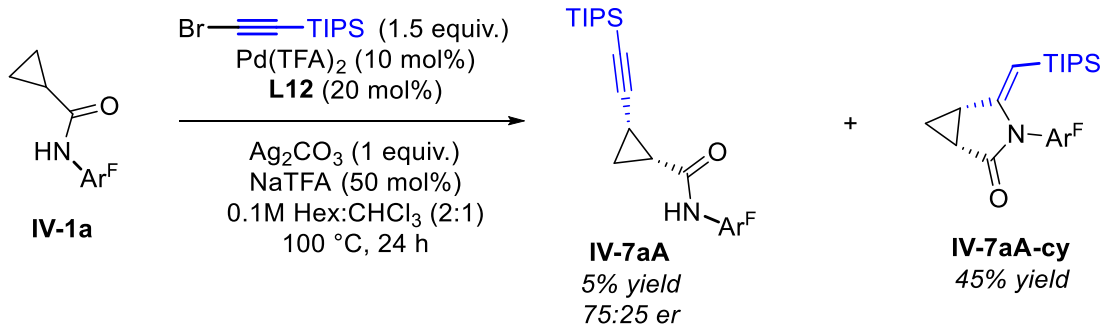
IV.4.iii. Enantioselective alkynylation

To this day, there is only one reported example of enantioselective alkynylation on C(sp^3)-H bonds reported by Yu and co-workers in 2017 (Scheme 4.137).[275]



Scheme 4.137 Yu's enantioselective alkynylation of isobutyric acid derivative

Thus, we investigated this challenging transformation using 1-halo-2-triisopropylsilyl acetylene as coupling partner. On the preliminary tests, in our previously optimised reaction conditions, using the bromo-derivative as coupling partner, encouraging 50% conversion and 75:25 enantiomeric ratio have been observed. However, the main isolated product **IV-7aA-cy** resulted from intramolecular cyclization through addition of the nitrogen on the triple bond (Scheme 4.138).



Scheme 4.138 Preliminary alkynylation test on IV-1a

We hypothesized that the mechanism involves carbopalladation followed by an *in situ* promoted cyclisation to get **IV-7aA-cy**. This mechanistic pathway was supported by the stereochemistry of the resulting double bond. In contrast, if iodo derivative is used, the oxidative addition should be facilitated, thus allowing a switch of mechanism and resulting in the exclusive formation of **IV-7aA** (Figure 4.59).

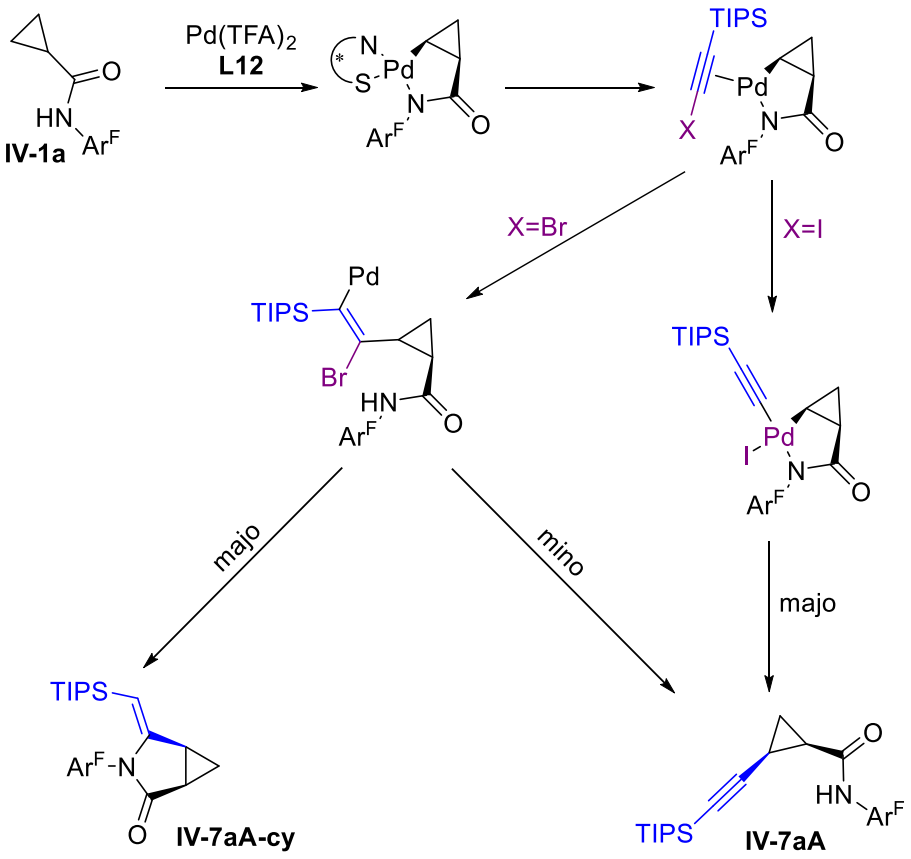
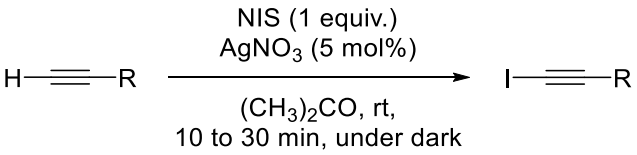


Figure 4.59 Different alkynylation pathways with respect to the haloalkyne

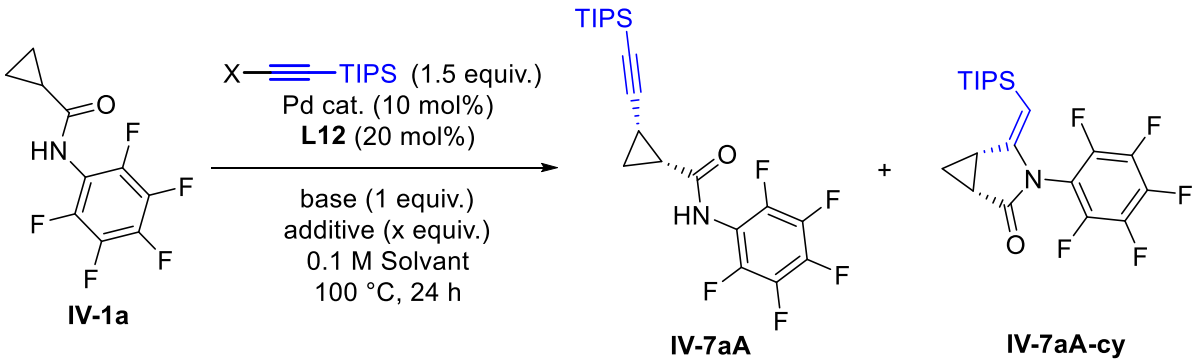
Iodoalkynes were synthesized using *N*-iodosuccinimide as electrophile in presence of silver nitrate in acetone and under dark. Full conversion of the starting material was usually observed after 10 to 30 min and simple filtration over silica using pentane as eluent afforded the desired compounds in high yields (Scheme 4.139).[289]



Scheme 4.139 Synthesis of iodoalkyne derivatives

Indeed, switching the bromo-alkyne by iodo-alkyne improved both conversion and selectivity between opened and cyclized products (Entry 2) while enantiomeric ratio remained similar. Interestingly, silver and palladium acetates revealed to be the best oxidant and catalyst for this type of transformation, allowing the high conversion of **IV-7Aa** with 85:15 enantiomeric ratio (Entry 3). Further optimization of the additive lead to almost full conversion to the desired opened product and good enantiomeric excess of 84% (Entry 5). The chloroalkyne derivative was ineffective coupling partner, as well as the free alkyne, and other aromatic solvents drastically lowered the conversion (Table 4.24).

Table 4.24 Optimisation of the alkynylation of cycloalkanes



Entry	X	base	Additive (equiv.)	catalyst	Solvent	Conv. (%)	Ratio opened-cyclized	*er*
1	Br	Ag_2CO_3	NaTFA (0.5)	$Pd(TFA)_2$	Hex:$CHCl_3$ (2:1)	50	1:8	75:25
2	I	Ag_2CO_3	NaTFA (0.5)	$Pd(TFA)_2$	Hex:$CHCl_3$ (2:1)	80	>10:1	80:20
3	I	AgOAc	NaTFA (0.5)	$Pd(OAc)_2$	Hex:$CHCl_3$ (2:1)	90	>10:1	85:15
4	I	AgOAc	none	$Pd(OAc)_2$	Toluene	50	>10:1	90:10
5	I	AgOAc	$KHCO_3$ (1)	$Pd(OAc)_2$	Toluene	95	>10:1	92:8
6	I	AgOAc	$KHCO_3$ (5)	$Pd(OAc)_2$	Toluene	95	>10:1	92:8
7	Cl	AgOAc	$KHCO_3$ (1)	$Pd(OAc)_2$	Toluene	0	*nd*	*nd*
8	H	AgOAc	$KHCO_3$ (1)	$Pd(OAc)_2$	Toluene	0	*nd*	*nd*
9	I	AgOAc	$KHCO_3$ (1)	$Pd(OAc)_2$	$PhCF_3$	40	1:1	*nd*
10	I	AgOAc	$KHCO_3$ (1)	$Pd(OAc)_2$	PhCl	<10	*nd*	*nd*

With our optimised conditions in hand, we performed the alkynylation on the cyclopropane substrate with various silyl-protected iodoalkynes, giving the desired product with good yield and unchanged enantiomeric ratio of 92:8. Alkynylation of cyclobutane **IV-1b** was less selective as we observed for the arylation. Finally, mono-alkynylation of racemic substrate **IV-1c** gave the desired non-cyclized product in good 71% yield and moderate enantiomeric excess, with partial resolution of the remaining starting material (measured 60:40 enantiomeric ratio). Disappointingly, alkynylation with iodo-ethynyl arene or *t*-butyl-iodoacetylene gave in both cases low conversion.

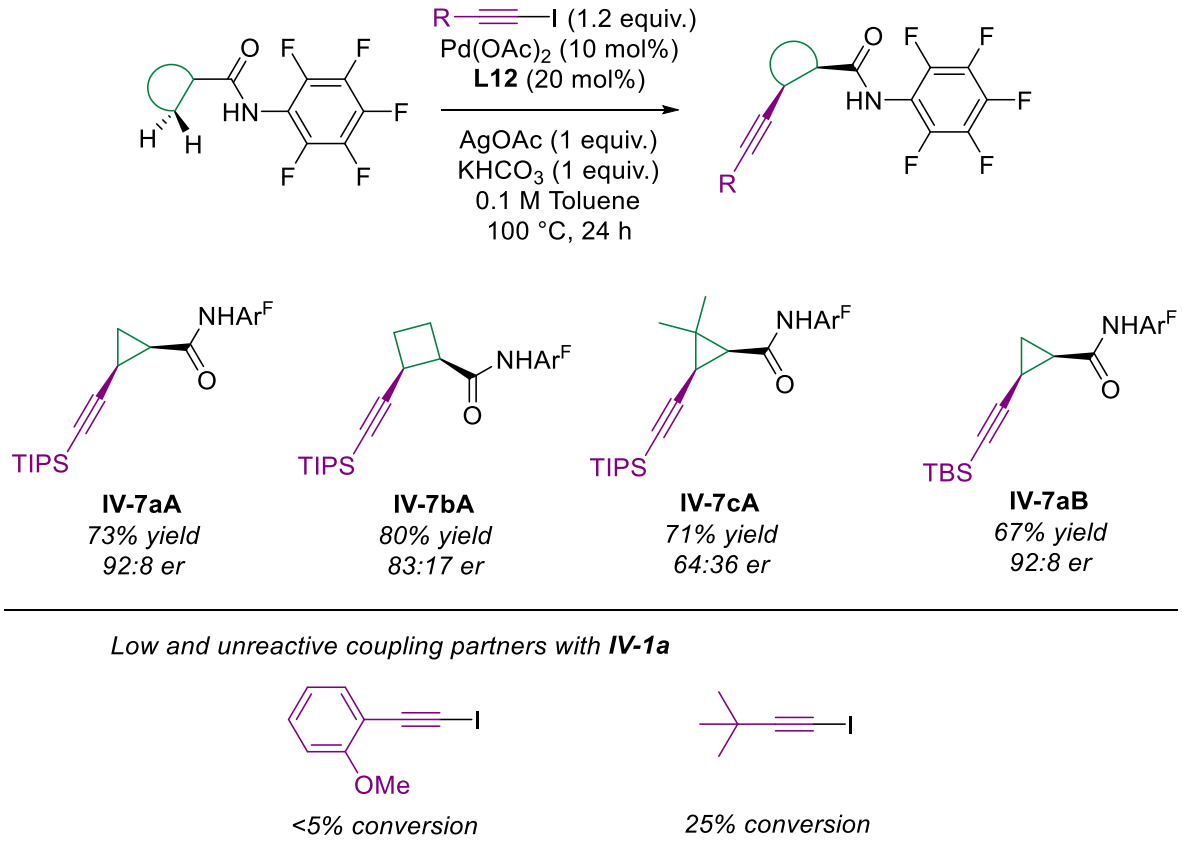
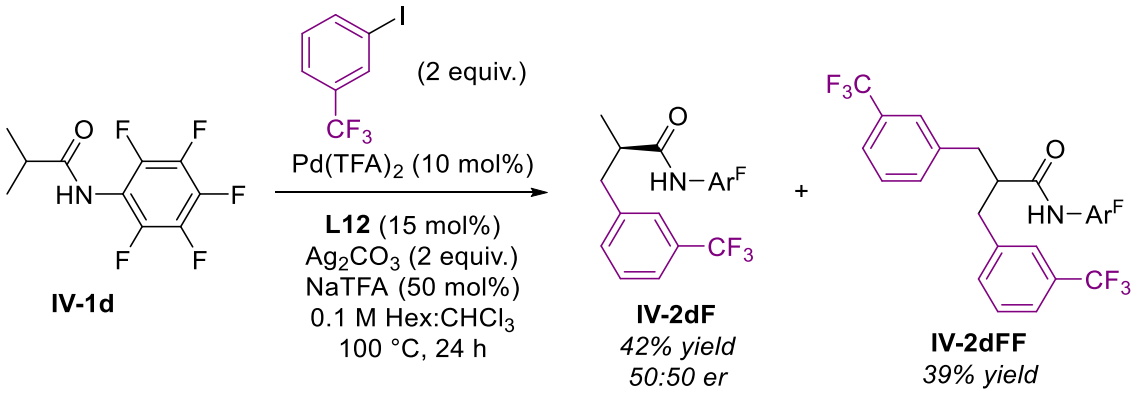


Figure 4.60 Scope of enantioselective alkynylation on cycloalkanes

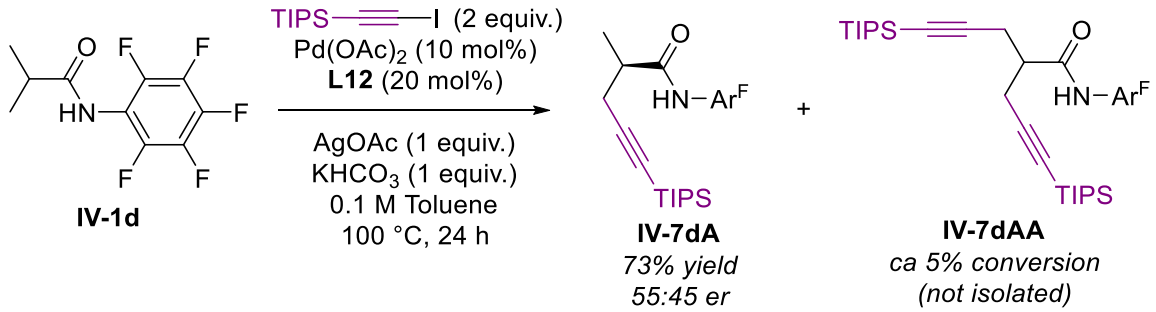
IV.5. Extension to linear chains

Regarding the high activity of our ligand **L12**, as both excellent promotor and stereoinductor, we envisaged to use it for the functionalisation of linear aliphatic substrates, and in particular for the desymmetrisation of isobutyric acid derivate, as described by Yu and co-workers in 2017.[275] Deceivingly, arylation of **IV-1d** gave no enantiomeric induction and both mono- and di-arylated products were isolated in good 81% total yield (Scheme 4.140).



Scheme 4.140 Enantioselective arylation of isobutyric acid derivative

Concerning the enantioselective alkynylation of **IV-1d**, the mono-alkynylated product **IV-7dA** was isolated with excellent 73% yield, but again low enantiomeric induction (Scheme 4.141).



Scheme 4.141 Enantioselective alkynylation of isobutyric acid derivative

These two examples highlight the potential of our ligand system, as both reactions are ineffective in absence of an external auxiliary. However, the low enantiomeric induction suggests that further improvement of **L12** is needed to efficiently transfer the chiral information in case of acyclic substrates.

IV.6. Mechanistic insights

Considering the unprecedented architecture of the ligand, we undertook mechanistic studies to elucidate the mechanism of this coupling considering the system consisting of **IV-1a**, **L12** and $Pd(TFA)_2$ and assuming that the key step in enantioselectivity is the formation of the heteroleptic bischelated palladacyclic intermediates by C(sp^3)-H bond activation at the cyclopropyl residue.

As good to excellent enantiomeric excesses were observed, we suspected the formation of an active catalyst from palladium(II) trifluoroacetate and **L12**. The resulting chelate synthesis has been endeavoured. Mixing the palladium source and the ligand resulted in the partial formation of a suspected protonated chelate and addition of one equivalent of silver carbonate to the reaction mixture afforded quantitatively **Pd-L12** (Figure 4.61). Besides strong shifts in both ^{1}H and ^{13}C NMRs, infrared spectra of the chelate showed clearly the involvement of the amide (IR stretch of the C-O bond displaced from 1656 to 1716 cm^{-1}) and of the sulfoxide (IR stretch of the S-O bond displaced from 1037 to 1076 cm^{-1}) into the palladium coordination sphere.

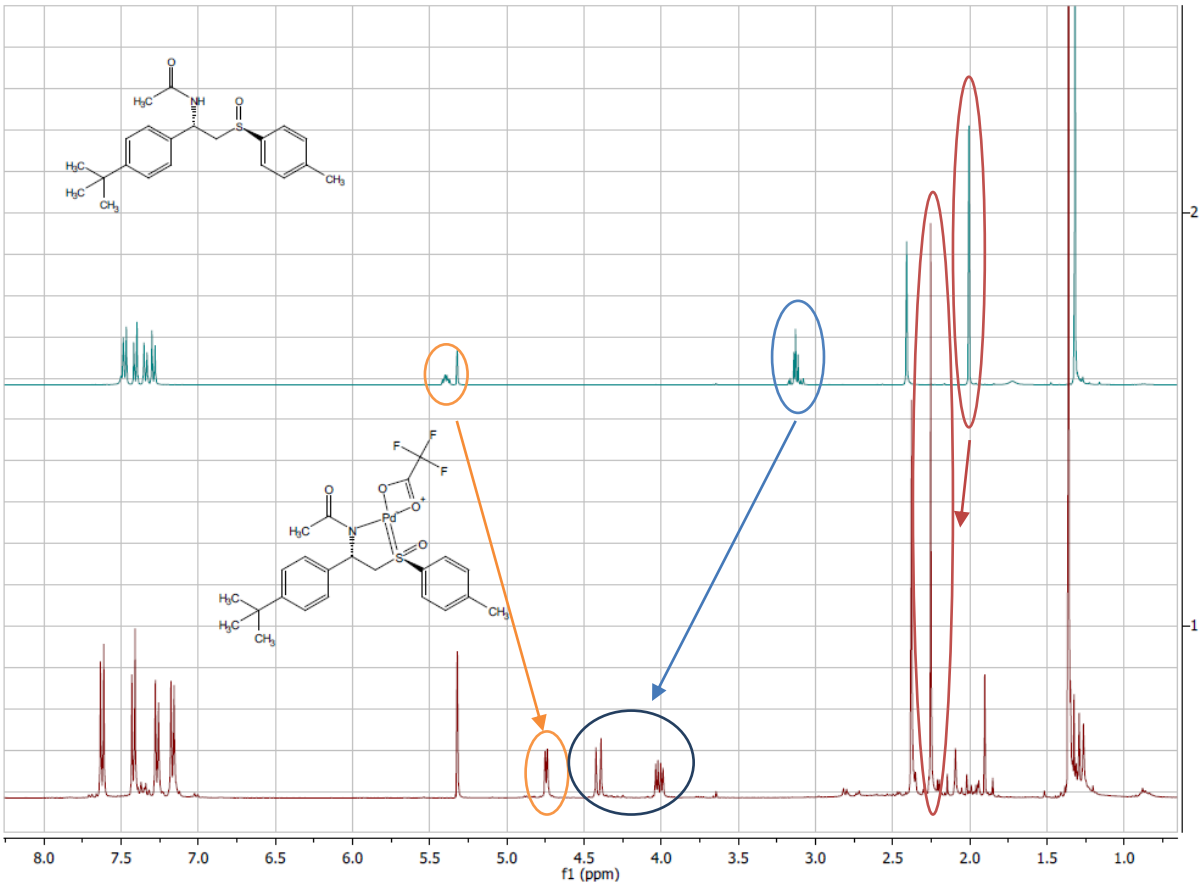


Figure 4.61 Formation of Pd-L12 chelate

Many attempts to crystallize **IV-Pd-L12** have been undertaken but decomposition was mainly observed. By slow evaporation of dichloromethane, the compound started decomposing but the resulting complex furnished mono-crystals suitable for X-Ray diffraction analysis (Figure 4.62.a). This complex clearly shows coordination of both sulphur and nitrogen to the palladium centre (Figure 4.62.b). It is important to notice that this resulting solid coordination polymer may not represent the reality observed in solution during the catalysis.

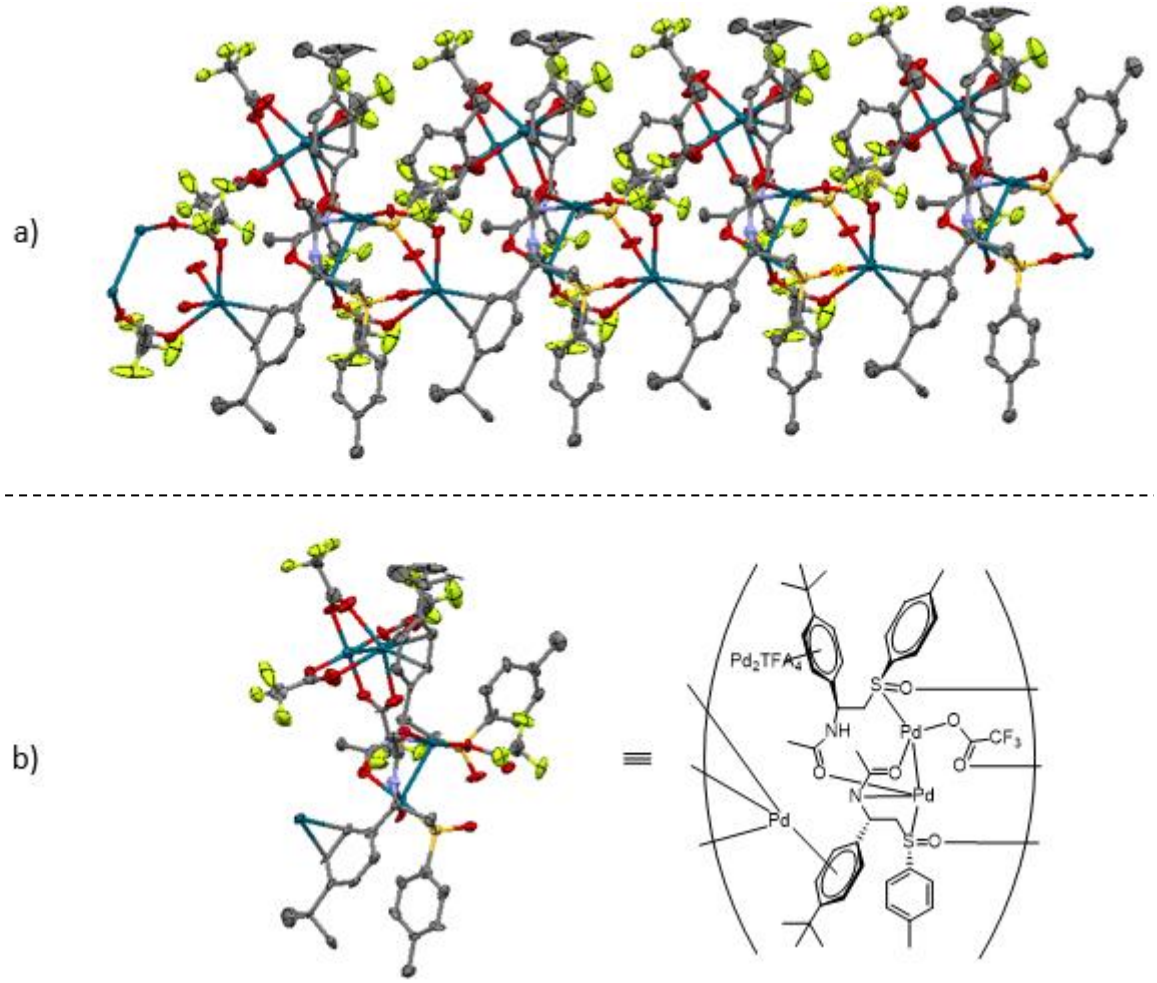


Figure 4.62 ORTEP-views of the a) IV-Pd-L12 chelate polymer and b) monomer

Formation of the **IV-Pd-L12** complex is certainly followed by chelation of the substrate **IV-1a**. DFT calculations demonstrated that the formation of **IV-pre-dia1** and **IV-pre-dia2** is favourable with an overall Gibbs enthalpy around – 100 kcal/mol (Figure 4.63).

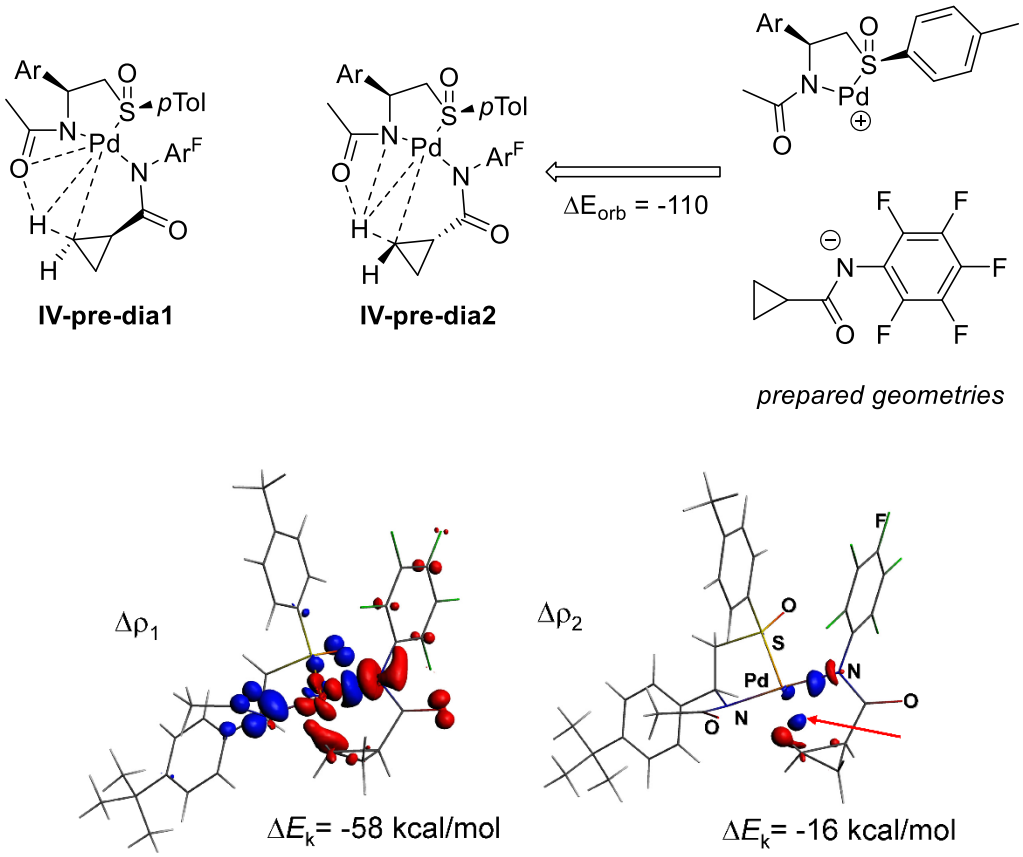


Figure 4.63 ETS-NOCV analysis of the bischelate formation

The exergonic conversion of **IV-pre-dia1** and **IV-pre-dia2** into **IV-Pd-dia1** and **IV-Pd-dia2** respectively involves transition states **IV-TS-dia1** (ν_{TS}= 403 *i*cm^{-1}) and **IV-TS-dia2** (ν_{TS}= 415 *i*cm^{-1}), but in a formal barrier-less fashion for **IV-pre-dia2** and with a low Gibbs activation energy around 1 kcal/mol for **IV-pre-dia1**. Noncovalent interactions (NCI) analysis coupled to extended transition state-natural orbital for chemical valence decomposition suggest that in **IV-pre-dia2** the more extended contribution of attractive noncovalent interactions is responsible for the easiest C-H bond activation. Note that in all models optimal π–π stacking of the C_6F_5 and *p*-tolyl group contributes in stabilizing the *trans* N-Pd-N stereochemistry. In **IV-pre-dia2**, NCI support the weakly covalent "agostic" Pd-to-H_{cy}-C_{cy} interaction (Pd-H_{cy}= 2.038 Å, Pd-C_{cy}= 2.394 Å, H_{cy}-O= 1.926 Å), embodied by the "covalent hole" within the NCI attractive isosurface, in two ways: by spreading out attractive Pd-to-H_{cy}-C_{cy} NCI and by H_{cy}-O NCI (Figure 1b) that are absent in **IV-pre-dia1**. Interestingly, the H_{cy}-C_{cy} bond in **IV-pre-dia2** is slightly more elongated (1.133 Å) than that

in **IV-pre-dia1** (1.119 Å). In stark contrast with the accepted base-assisted Pd(II) C-H bond activation mechanism but in rather good accord with the mechanism proposed by Yu and co-workers for a different Pd(II) initiated alkyl C-H bond activation displaying a higher activation barrier of *ca*. 10 kcal/mol,[284] the hydrogen atom of the cyclopropyl migrates to the vicinal acetamide oxygen atom with the assistance of an attractive noncovalent H_{Cy}-Pd interaction in both **IV-TS-dia1** and **IV-TS-dia2** according to NCI isosurface plots. In view of these results and due to the thin difference in energies in the reaction energy profile that warrants caution, it can only be speculated that the preference given to **IV-Pd-dia2** in the catalysis results from its higher kinetic reactivity in the subsequent arylation step entailing the iodoarene oxidative addition to the Pd(II) centre. **IV-Pd-dia1** and **IV-Pd-dia2** display indeed different topologies, with a marked helical distortion of the latter that tilts the 4-*tert*-butylphenyl group about 40-45° out of the mean coordination plane of the Pd centre, whereas in **IV-Pd-dia1**, the same aryl group remains roughly in the mean coordination plane. It is speculated that this marked distortion of the amidosulfoxide ligand might be detrimental to the subsequent oxidative-addition of halogeno-arenes due to enhanced steric strains, thus creating a sufficient discrimination between these two palladacycles to induce enantio-differenciation (Figure 4.64).

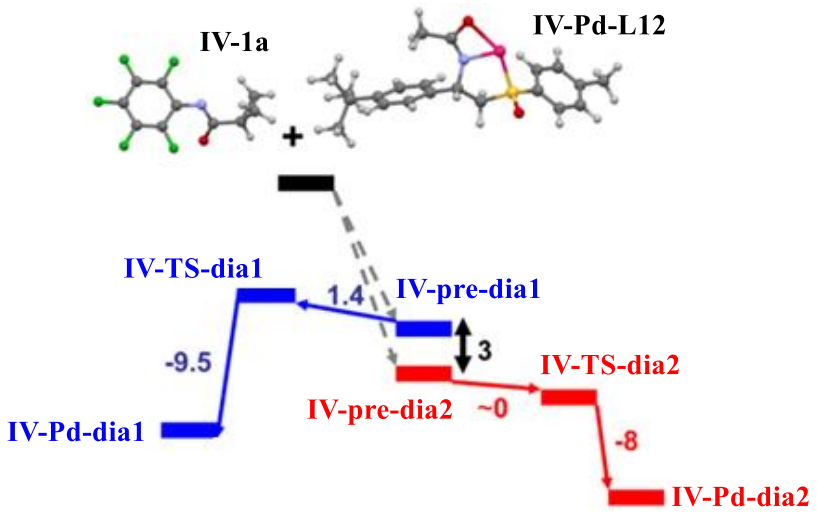


Figure 4.64 Gibbs-energy profile (in kcal/mol) of the formation of the two palladacycles IV-Pd-dia1 and IV-Pd-dia2

The role of the C_6F_5 moiety in **IV-1b** was investigated by replacing all fluorine atoms by H in **IV-pre-dia1** and **IV-pre-dia2**. According to energy decomposition analysis (EDA) the resulting **IV-pre-dia1$_H$** displays a coordinative cohesion stronger by ca. 10 kcal/mol compensated by a less tight phenyl-tolyl π–π stacking, the C_{ipso}-C_{ipso} interannular distance amounting ca 3.9 Å in **IV-pre-**

dia1$_H$ vs. 3.7 Å in **IV-pre-dia1**. Moreover, the activation energy for the **IV-pre-dia2$_H$** to **IV-TS-dia2$_H$** transit is about twice that of **IV-pre-dia2** to **IV-TS-dia2** (Figure 4.65).

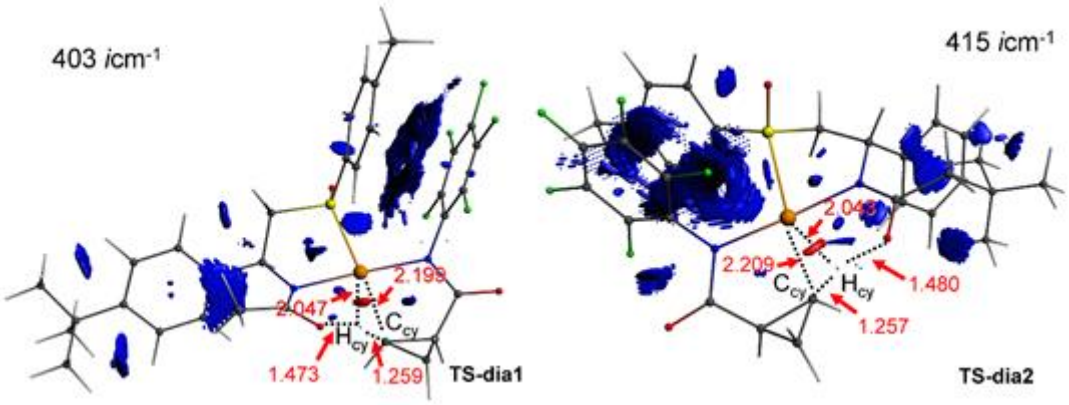


Figure 4.65 NCI isosurfaces for IV-TS-dia1 and IV-TS-dia2

These preliminary mechanistic studies cannot settle about one pathway or the other, because of the similar energies of **IV-Pd-dia1** and **IV-Pd-dia2** (about 3 kcal/mol difference). However, the observed significant impact of both chiral centres on the enantioselectivity (IV.3.iv) could be explained by the potential repulsive interactions in **IV-Pd-dia1** as shown in Figure 4.66.

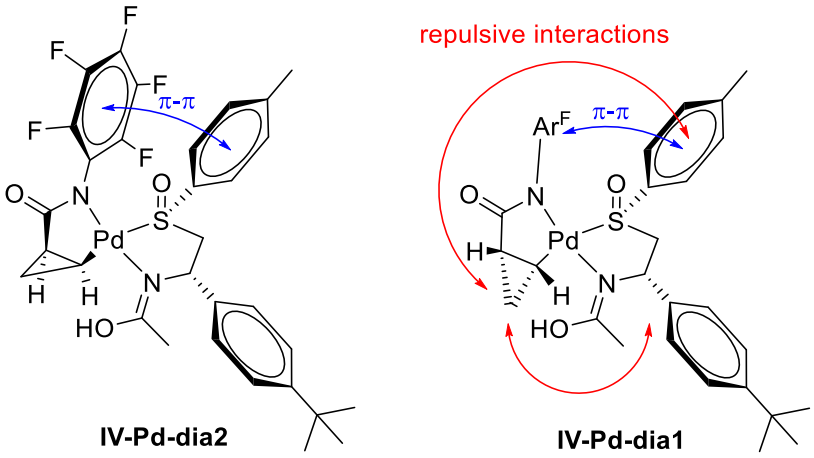


Figure 4.66 Proposed asymmetric induction model in enantioselective C(sp^3)-H activation of cyclopropanes

According to the studies conducted by Yu and co-workers for ligand-enabled C-H activation and to our preliminary DFT calculations, we can propose a first catalytic cycle. Palladium(II) trifluoroacetate will undergo ligand exchange with **L12** to obtain in situ the active catalyst **IV-Pd-L12**. Coordination of the substrate and further C-H bond activation would lead to the two diastereomers **IV-Pd-dia1** and **IV-Pd-dia2**. Then, oxidative addition with the iodoarene coupling partner would lead to the Pd(IV) species **IV-Pd-ar**. Reductive elimination followed by ligand exchange would regenerate the active palladium species **IV-Pd-L12** (Figure 4.67).

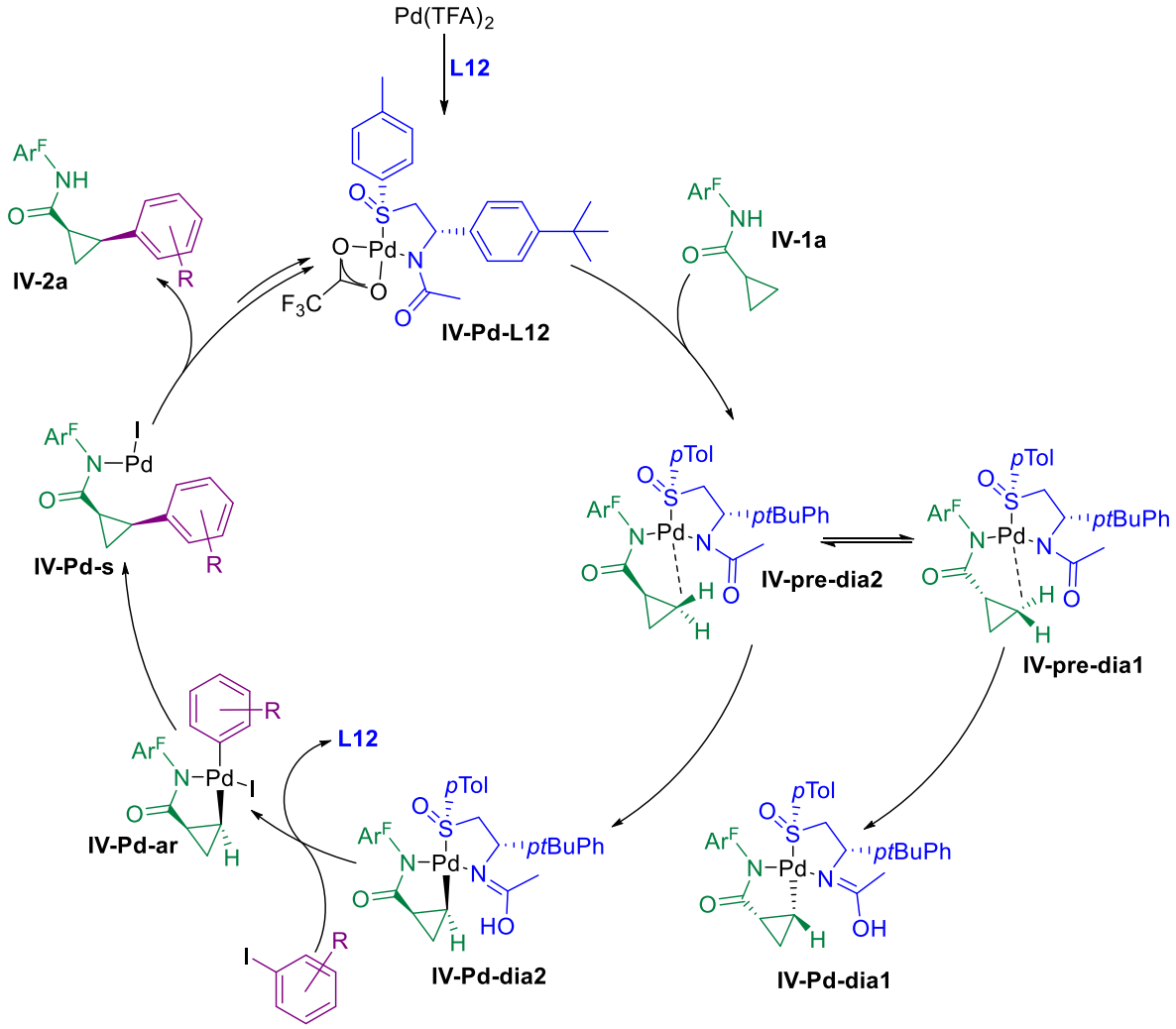


Figure 4.67 Preliminary catalytic cycle for the enantioselective arylation of cycloalkanes using L12

IV.7. Conclusion

With this last challenging project, we conducted enantioselective arylation and alkynylation of cycloalkanes with our optimized ligand **L12**, an *N*-protected aminosulfoxide. High yields and enantiomeric excesses were obtained. All these encouraging preliminary results were submitted for publication in a scientific journal in 2018.

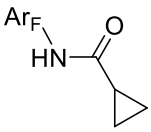
The main challenge remains to improve the structure of **L12** to facilitate highly asymmetric transformations on various types of C(sp^3)-H bonds, and many perspectives, such as enantiodifferenciation of phosphinamides, could be imagined.

IV.8. Experimental section

IV.8.i. Substrate synthesis

_N_-(2,3,4,5,6-pentafluorophenyl)-cyclopropanecarboxamide IV-1a

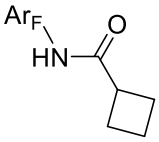
To a stirred solution of 2,3,4,5,6-pentafluoroaniline (1.6 g, 8.8 mmol, 1 equiv.) in 20 mL of anhydrous toluene was added dropwise an acyl chloride (800 µL, 8.8 mmol, 1 equiv.) under vigorous stirring. The resulting mixture was stirred 24 h at reflux. Upon cooling, the mixture was evaporated under reduced pressure. Crystallization with EtOAc/CyHex afforded the title compound.



^{1}H NMR (400 MHz, $CDCl_3$): 6.98 (1H, br s, N*H*), 1.57-1.68 (1H, m), 1.09-1.17 (2H, m), 0.95 (2H, dt, *J*=8.0, 3.5 Hz); other data match the reported ones.

_N_-(2,3,4,5,6-pentafluorophenyl)-cyclobutanecarboxamide IV-1b

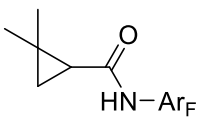
The general procedure was performed using 800 µL of cyclopropanecarbonyl chloride. Crystallization afforded the title compound (1.87 g, 87 %) as white needles.



^{1}H NMR (400 MHz, $CDCl_3$): 6.78 (1H, br s, N*H*), 3.17-3.35 (1H, m), 2.33-2.46 (2H, m), 2.17-2.33 (2H, m), 1.88-2.14 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 39.7, 25.5, 18.3; ^{19}F NMR (376 MHz, $CDCl_3$): -145.15, -156.79, -162.52; FT-IR (cm^{-1}): 3256 (m, *N-H*), 1683 (s, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{11}H_9F_5NO^+$ $[M+H]^+$: 266.0599, found: 266.0605.

2,2-dimethyl-_N_-(2,3,4,5,6-pentafluorophenyl)-cyclopropanecarboxamide IV-1c

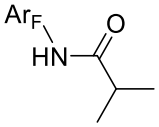
The general procedure was performed using 1 mL of 2,2-dimethylcyclopropane-1-carbonyl chloride. Crystallization afforded the title compound (1.32 g, 49 %) as an off-white solid.



^{1}H NMR (400 MHz, $CDCl_3$): 6.87 (1H, br s, N*H*), 1.44-1.55 (1H, m), 1.15-1.34 (7H, m), 0.92 (1H, dd, *J*=7.9, 4.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 27.1, 23.9, 21.7, 18.6; ^{19}F NMR (377 MHz, $CDCl_3$): -145.01, -157.14, -162.60; FT-IR (cm^{-1}): 3244 (w, *N-H*), 1671 (m, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{12}H_{11}F_5NO^+$ $[M+H]^+$: 280.0755, found: 280.0769; Rt (min, CHIRALPAK ® ADH, Hex/iPrOH 99/1, 0.5 mL/min): 50.11 (50 %), 55.43 (50 %).

***N*-(2,3,4,5,6-pentafluorophenyl)-isobutyramide IV-1d**

The general procedure was performed using 0.9 mL of isobutyryl chloride. Crystallization afforded the title compound (2.1 g, 97 %) an off-white solid.

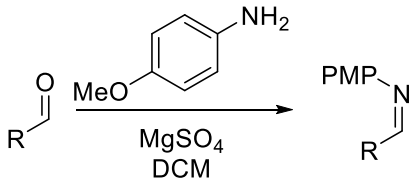


^{1}H NMR (400 MHz, $CDCl_3$): 6.98 (1H, br, N*H*), 2.64 (1H, hept, *J*=6.8 Hz), 1.27 (6H, d, *J*=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 175.8, 35.7, 19.6; ^{19}F NMR (376 MHz, $CDCl_3$): -145.24, -156.69, -162.58; FT-IR (cm^{-1}): 3251 (m, *N-H*), 1681 (s, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{10}H_9F_5NO^+$ $[M+H]^+$: 254.0599, found: 254.0612.

IV.8.ii. Ligand synthesis

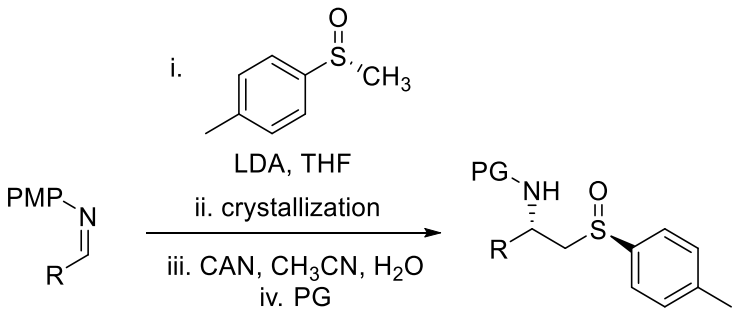
IV.8.ii.1. Synthesis of (*S*, R_S)-aminosulfoxide type ligands

General procedure for the synthesis of PMP-imines



Aldehyde (1 equiv.) and *p*-anisidine (1 equiv.) were dissolved in 50 mL of dichloromethane, followed by addition of $MgSO_4$ (5 equiv.). The resulting mixture was stirred 24 to 48 h at room temperature. Then, it was filtered and evaporated under reduced pressure to yield pure PMP-imines as solids.

General procedure for the asymmetric addition of (R_S)-methyl *p*-tolylsulfinyllithium on PMP-imines

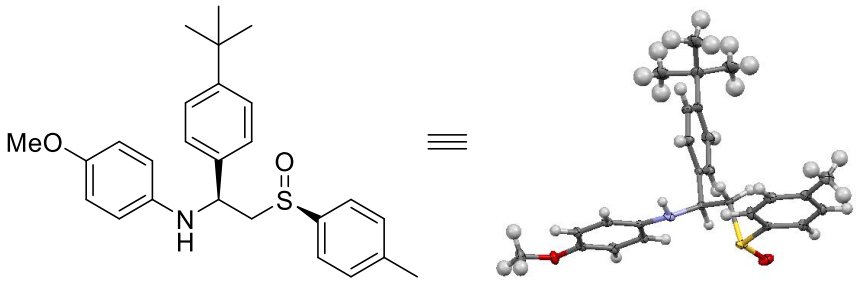


To a stirred solution of (R_S)-methyl *p*-tolylsulfoxide (200 mg, 1.3 mmol, 1.3 equiv.) in anhydrous THF was added dropwise and at – 78 °C LDA (560 µL, 2 M in THF/heptane/ethylbenzene, 1.13 mmol, 1.1 equiv.). The resulting yellowish mixture was stirred 30 min at – 78 °C before slow

addition of a solution of PMP-imine (1.2 equiv.) in anhydrous THF. After 2 h at – 78 to – 60 °C, the solution was quenched with MeOH (few drops). Solvent were evaporated under reduced pressure. The major diastereomer was directly precipitated from the crude mixture with addition of CyHex/EtOAc and the absolute stereochemistry was proven by X-Ray diffraction analysis of ***N*-((*S*)-1-(4-(*tert*-butyl)phenyl)-2-((*R*$_S$)-*p*-tolylsulfinyl)ethyl)-4-methoxyaniline**.[26] The (*S*, *R*$_S$) diastereomer was dissolved in acetonitrile and added slowly to a solution of CAN (2.5 equiv.) in water at 0 °C. The resulting brownish mixture was stirred 1 h at room temperature before addition of 1 M HCl sol. and diethyl ether. The aqueous layer was extracted and the organic layer back-extracted with 1 M HCl sol. (3x). The combined aqueous layers were carefully basified with solid Na_2CO_3 until pH ca 10. CH_2Cl_2 was added. The organic layer was extracted, washed with brine, dried (Na_2SO_4), filtered off and evaporated under reduced pressure to yield almost pure aminosulfoxide. The crude was taken up in DMF before addition of acetic acid (1 equiv.), triethylamine (3.5 equiv.) and propylphosphonic anhydride (1.2 equiv.). The resulting mixture was stirred 3 h at room temperature. Brine and ethyl acetate were added. The organic layer was washed with brine, sat. $NaHCO_3$ sol. and brine, dried (Na_2SO_4), filtered off and evaporated under reduced pressure. The crude was purified by column chromatography on silica gel with cyclohexane/ethyl acetate (typically 2:3 or 1:4) to afford the pure ligand.

N-((*S*)-1-(4-(*tert*-butyl)phenyl)-2-((*R*$_S$)-*p*-tolylsulfinyl)ethyl)-4-methoxyaniline PMP-L12

The title compound was obtained as a white solid. Slow evaporation in Hex/$CHCl_3$ at room temperature afforded mono crystals suitable for X-Ray diffraction analysis which were analysed on the Nonius Kappa-CCD diffractometer. The methyls of the *tert*-butyl group are disordered over two positions with an occupancy ratio of 0.55/0.45.

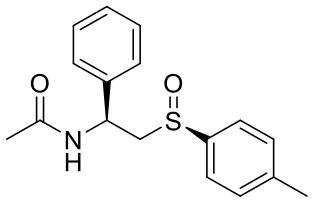


^{1}H NMR (400 MHz, $CDCl_3$): 7.50 (2H, d, *J*=8.2 Hz), 7.21-7.35 (6H, m), 6.69 (2H, d, *J*=9.0 Hz), 6.53 (2H, d, *J*=8.9 Hz), 4.81 (1H, br s, N*H*), 4.77 (1H, dd, *J*=8.6, 4.3 Hz), 3.70 (3H, s, PhOC*H*$_3$); 3.00-3.17 (2H, m), 2.40 (3H, s, PhC*H*$_3$), 1.28 (9H, s, PhC(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 152.5, 150.7, 141.7, 141.0, 140.3, 138.5, 130.2, 126.1, 126.0, 124.2, 115.5, 114.8, 64.6, 55.8, 54.9, 34.6, 31.5, 21.5; FT-IR (cm^{-1}): 3322 (m, *N-H*), 2831 (w,

C-O ether), 1012 (s, *S-O*); HRMS (ESI-TOF): m/z calcd for $C_{26}H_{32}NO_2S^+$ $[M+H]^+$: 422.2148, found: 422.2146.

_N_-((_S_)-1-phenyl-2-((_R_$_S$)-_p_-tolylsulfinyl)ethyl)acetamide L4

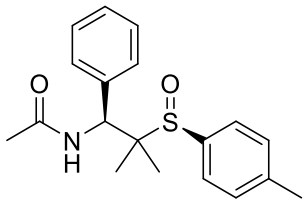
The title compound was obtained as a white solid. The absolute stereochemistry was assigned according to **PMP-L12**.



^{1}H NMR (400 MHz, $CDCl_3$): 7.66 (1H, br d, *J*=7.5 Hz, NH), 7.47 (2H, d, *J*=8.2 Hz), 4.40 (4H, app d, *J*=4.4 Hz), 7.29-7.35 (3H, m), 5.50 1(H, ddd, *J*=7.5, 6.4, 3.7 Hz), 3.21 (1H, dd, *J*=13.5, 3.6 Hz), 3.12 (1H, dd, *J*=13.5, 6.3 Hz), 2.41 (3H, s, PhC*H*$_3$), 2.07 (3H, s, C(O)C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.7, 142.3, 139.9, 139.6, 130.3, 129.1, 128.1, 126.6, 124.1, 62.3, 51.6, 23.6, 21.6; FT-IR (cm^{-1}): 3271 (w, *N-H*), 1652 (s, *C-O*), 1026 (m, *S-O*); HRMS (ESI-TOF): m/z calcd for $C_{17}H_{20}NO_2S^+$ $[M+H]^+$: 302.1209, found: 302.1198.

_N_-((_S_)-2-methyl-1-phenyl-2-((_S_$_S$)-_p_-tolylsulfinyl)propyl)acetamide Me-L4

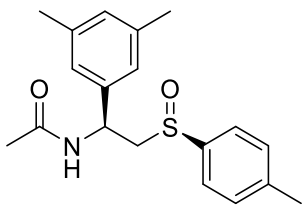
The title compound was obtained as a brownish solid. The absolute stereochemistry was assigned according to **PMP-L12**.



^{1}H NMR (400 MHz, $CDCl_3$): 8.20 (1H, d, *J*=8.7 Hz, N*H*), 7.52 (2H, d, *J*=7.1 Hz), 7.20-7.44 (7H, m), 5.17 (1H, d, *J*=8.8 Hz), 2.39 (3H, s, PhC*H*$_3$), 2.03 (3H, s, C(O)C*H*$_3$), 1.17 (3H, s), 0.96 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): 169.4, 142.4, 137.8, 134.8, 129.5, 129.0, 128.3, 128.1, 126.7, 62.9, 59.5, 23.6, 21.4, 17.6; FT-IR (cm^{-1}): 3270 (w, *N-H*), 1662 (s, *C-O*), 1035 (m, *S-O*); HRMS (ESI-TOF): m/z calcd for $C_{19}H_{23}NNaO_2S^+$ $[M+Na]^+$: 352.1342, found: 352.1348.

_N_-((_S_)-1-(3,5-dimethylphenyl)-2-((_R_$_S$)-_p_-tolylsulfinyl)ethyl)acetamide L10

The title compound was obtained as a white solid. The absolute stereochemistry was assigned according to **PMP-L12**.

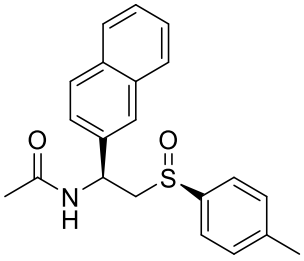


^{1}H NMR (400 MHz, $CDCl_3$): 7.61 (1H, d, *J*=7.5 Hz, N*H*), 7.47 (2H, d, *J*=8.2 Hz), 7.32 (2H, d, *J*=8.0 Hz), 6.98 (2H, s), 6.93 (1H, s), 5.41 (1H, td, *J*=6.8., 3.8 Hz), 3.18 (1H, dd, *J*=13.5, 3.8 Hz), 3.09 (1H, dd, *J*=13.4, 6.3 Hz), 2.41 (3H, s, S(O)PhC*H*$_3$), 2.32 (6H, s, Ph(C*H*$_3$)$_2$), 2.06 (3H, s, C(O)C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.6, 142.1, 140.0, 139.5, 138.6, 130.3, 129.8, 124.3,

124.1, 62.4, 51.5, 23.6, 21.6; FT-IR (cm^{-1}): 3269 (w, *N-H*), 1654 (s, *C-O*), 1027 (m, *S-O*); HRMS (ESI-TOF): m/z calcd for $C_{19}H_{23}NNaO_2S^+$ $[M+Na]^+$: 352.1342, found: 352.1363.

***N*-((*S*)-1-(naphthalen-2-yl)-2-((*R*$_S$)-*p*-tolylsulfinyl)ethyl)acetamide L11**

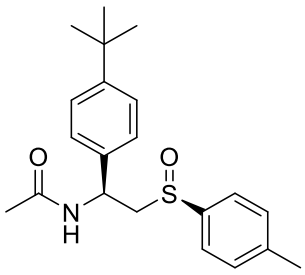
The title compound was obtained as a white solid. The absolute stereochemistry was assigned according to **PMP-L12**.



^{1}H NMR (400 MHz, $CDCl_3$): 7.77-7.90 (5H, m), 7.42-7.53 (5H, m), 7.31 (2H, d, *J*=8.2 Hz), 5.67 (1H, ddd, *J*=8.1, 6.6, 3.7 Hz), 3.28 (1H, dd, *J*=13.5, 3.7 Hz), 3.20 (1H, dd, *J*=13.5, 6.1 Hz), 2.41 (3H, s), 2.11 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): 169.7, 142.3, 139.9, 137.0, 133.5, 133.1, 130.3, 129.0, 128.2, 127.8, 126.6, 126.3, 125.4, 124.5, 124.1, 62.2, 51.8, 23.7, 21.6; FT-IR (cm^{-1}): 3262 (m, *N-H*), 1663 (s, *C-O*), 1045 (s, *S-O*); HRMS (ESI-TOF): m/z calcd for $C_{21}H_{21}NNaO_2S^+$ $[M+Na]^+$: 374.1185, found: 374.1204.

***N*-((*S*)-1-(4-(*tert*-butyl)phenyl)-2-((*R*$_S$)-*p*-tolylsulfinyl)ethyl)acetamide L12**

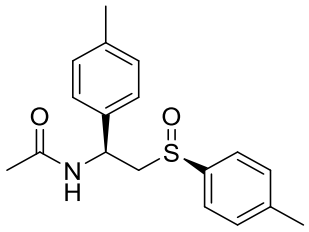
The title compound was obtained as an orange solid. The absolute stereochemistry was assigned according to **PMP-L15**.



^{1}H NMR (400 MHz, $CDCl_3$): 7.62 (1H, d, *J*=7.6 Hz, N*H*), 7.47 (2H, d, *J*=8.2 Hz), 7.38 (2H, d, *J*=8.5 Hz), 7.27-7.35 (4H, m), 5.37-5.53 (1H, m), 3.09-3.30 (2H, m), 2.40 (3H, s, PhC*H$_3$*), 2.04 (3H, s, C(O)C*H$_3$*), 1.30 (9H, s, PhC(C*H$_3$*)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.6, 150.9, 142.1, 140.1, 136.5, 130.2, 126.2, 125.9, 124.1, 62.4, 51.0, 34.6, 31.4, 23.6, 21.5; FT-IR (cm^{-1}): 3274 (m, *N-H*), 1656 (s, *C-O*), 1037 (s, *S-O*); HRMS (ESI-TOF): m/z calcd for $C_{21}H_{27}NNaO_2S^+$ $[M+Na]^+$: 380.1655, found: 380.1674; R_t (min, CHIRALPAK ® IA, Hex/*i*PrOH 90/10, 0.5 mL/min): 33.23 (> 99.5 %).

***N*-((*S*)-1-(*p*-tolyl)-2-((*R*$_S$)-*p*-tolylsulfinyl)ethyl)acetamide L14**

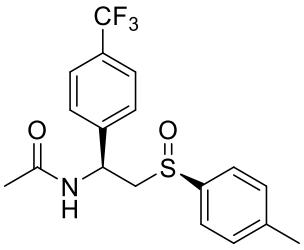
The title compound was obtained as a brownish solid. The absolute stereochemistry was assigned according to **PMP-L12**.



^{1}H NMR (400 MHz, $CDCl_3$): 7.65 (1H, d, *J*=7.6 Hz, N*H*), 7.46 (2H, d, J=8.2 Hz), 7.24-7.35 (4H, m), 7.18 (2H, d, *J*=7.9 Hz), 5.44 (1H, td, *J*=6.9, 3.9 Hz), 3.18 (1H, dd, *J*=13.4, 3.8 Hz), 3.11 (1H, dd, *J*=13.4, 6.4 Hz), 2.40 (3H, s), 2.34 (3H, s), 2.04 (3H, s, C(O)C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.6, 142.1, 140.0, 137.8, 136.6, 130.3, 129.7, 126.4, 124.1, 62.5, 51.2, 23.6, 21.5, 21.2; FT-IR (cm^{-1}): 3304 (w, *N-H*), 1658 (s, *C-O*), 1032 (s, *S-O*); HRMS (ESI-TOF): m/z calcd for $C_{18}H_{21}NNaO_2S^+$ $[M+Na]^+$: 338.1185, found: 338.1186.

_N_-((_S_)-1-(4-(trifluoromethyl)phenyl)-2-((_R_$_S$_)-_p_-tolylsulfinyl)ethyl)acetamide L15

The title compound was obtained as a white solid. The absolute stereochemistry was assigned according to **PMP-L12**.

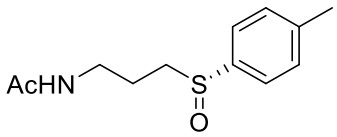


^{1}H NMR (400 MHz, $CDCl_3$): 7.89 (1H, d, *J*=7.2 Hz, N*H*), 7.62 (2H, d, *J*=8.2 Hz), 7.50 (2H, d, *J*=8.4 Hz), 7.46 (2H, d, *J*=8.2 Hz), 7.32 (2H, d, *J*=7.9 Hz), 5.50 (1H, td, *J*=6.7, 3.9 Hz), 3.18 (1H, dd, *J*=13.6, 3.8 Hz), 3.13 (1H, dd, *J*=13.6, 6.4 Hz), 2.41 (3H, s, PhC*H*$_3$), 2.07 (3H, s, C(O)C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.9, 143.8, 142.5, 141.8, 139.4, 130.4, 127.0, 126.0 (q, *J*=4 Hz), 125.9 (q, *J*=272 Hz), 124.0, 61.5, 51.4, 23.5, 21.6; ^{19}F NMR (377 MHz, $CDCl_3$): -62.56; FT-IR (cm^{-1}): 3271 (w, *N-H*), 1681 (s, *C-O*), 1014 (s, *S-O*); HRMS (ESI-TOF): m/z calcd for $C_{18}H_{19}F_3NO_2S^+$ $[M+H]^+$: 370.1083, found: 370.1104.

IV.8.ii.2. Other new ligands

(_R_$_S$_)-_N_-(3-(_p_-tolylsulfinyl)propyl)acetamide L2

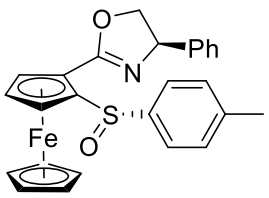
The title compound was obtained as a yellow solid.



^{1}H NMR (400 MHz, $CDCl_3$): 7.46 (2H, d, *J*=8.2 Hz); 7.31 (2H, d, *J*=7.9 Hz), 6.56 (1H, br s, N*H*), 3.32 (2H, q, *J*=6.4 Hz), 2.82-2.93 (1H, m), 2.73-2.81 (1H, m), 2.39 (3H, s, PhC*H*$_3$), 1.87-2.02 (4H, m), 1.75-1.86 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 170.6, 141.8, 139.9, 130.1, 124.1, 54.7, 38.3, 23.3, 22.8, 21.5; FT-IR (cm^{-1}): 3286 (br m, *N-H*), 1651 (s, *C-O*), 1027 (s, *S-O*); HRMS (ESI-TOF): m/z calcd for $C_{12}H_{18}NO_2S^+$ $[M+H]^+$: 240.1053, found: 240.1063.

(*R*)-4-phenyl-2-(2-((*S*$_S$)-*p*-tolylsulfinyl)ferrocenyl)-4,5-dihydrooxazole L6

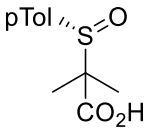
The title compound was obtained as a greenish solid.



^{1}H NMR (400 MHz, $CDCl_3$): 7.68 (1H, d, *J*=8.2 Hz), 7.27-7.41 (5H, m), 7.17 (2H, d, *J*=8.0 Hz), 5.30 (1H, dd, *J*=9.9, 7.4 Hz), 5.05 (1H, dd, *J*=2.6, 1.6 Hz), 4.88 (1H, dd, *J*=2.5, 1.6 Hz), 4.72 (1H, dd, *J*=9.9, 8.2 Hz), 4.53 (1H, t, *J*=2.6 Hz), 4.47 (4H, s), 4.14-4.21 (1H, m), 2.33 (3H, s, PhC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 165.5, 156.4, 144.8, 129.6, 128.9, 127.7, 126.5, 125.2, 74.9, 72.2, 71.9, 70.6, 69.9, 66.8, 21.5; FT-IR (cm^{-1}): 1648 (s, *C-O*), 1042 (s, *S-O*); HRMS (ESI-TOF): m/z calcd for $C_{26}H_{24}FeNO_2S^+$ $[M+H]^+$: 470.0872, found: 470.0875.

(*S*)-2-methyl-2-(*p*-tolylsulfinyl)propanoic acid L7

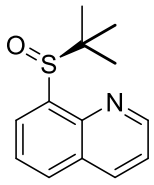
The title compound was obtained as a white solid.



^{1}H NMR (400 MHz, DMSO-*d*$_6$): 13.13 (1H, s, COO*H*), 7.41-7.48 (2H, m), 7.38 (2H, d, *J*=8.0 Hz), 2.38 (3H, s, PhC*H*$_3$), 1.38 (3H, s), 1.08 (3H, s); ^{13}C NMR (100 MHz, DMSO-*d*$_6$): 177.3, 146.9, 142.1, 134.5, 130.8, 70.7, 26.2, 24.6, 21.1; FT-IR (cm^{-1}): 3250 (m, *C-O*), 1054 (s, *S-O*).

(*S*$_S$)-8-(*tert*-butylsulfinyl)quinoline L8

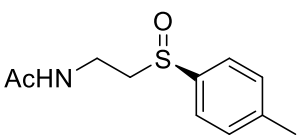
The title compound was obtained as a clear oil.



^{1}H NMR (400 MHz, $CDCl_3$): 8.94 (1H, dd, *J*=4.2, 1.8 Hz), 8.28 (1H, dd, *J*=7.3, 1.4 Hz), 8.22 (1H, dd, *J*=8.4, 1.8 Hz), 7.95 (1H, dd, *J*=8.1, 1.4 Hz), 7.75 (1H, dd, *J*=8.0, 7.4 Hz), 7.47 (1H, dd, *J*=8.3, 4.2 Hz), 1.24 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): 150.4, 146.1, 140.0, 136.4, 130.8, 129.0, 128.2, 126.4, 121.9, 58.7, 23.7; FT-IR (cm^{-1}): 1045 (s, *S-O*); HRMS (ESI-TOF): m/z calcd for $C_{13}H_{16}NOS^+$ $[M+H]^+$: 234.0953, found: 234.0967.

(*R*$_S$)-*N*-(2-(*p*-tolylsulfinyl)ethyl)acetamide prim-L4

The title compound was obtained as a white solid.

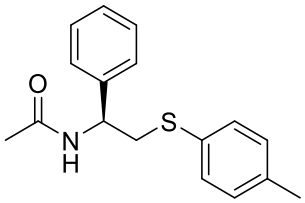


^{1}H NMR (400 MHz, $CDCl_3$): 7.48 (2H, d, *J*=8.2 Hz), 7.32 (2H, d, *J*=7.9 Hz), 6.84 (1H, br s, N*H*), 3.75 (1H, dtd, *J*=14.6, 6.2, 4.4 Hz), 3.55 (1H, dddd, *J*=14.4, 9.3, 5.4, 4.0 Hz), 3.14 (1H, ddd, *J*=13.0, 8.5, 4.4 Hz), 2.81 (1H, ddd, *J*=13.6, 6.4, 4.0 Hz), 2.40 (3H, s, PhC*H*$_3$), 1.93 (3H, s, C(O)C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 170.7, 141.9, 139.6, 130.3, 124.0, 55.5, 34.2, 23.2, 21.5; FT-IR (cm^{-1}): 3280 (br w, *N-H*),

1652 (s, *C-O*), 1038 (s, *S-O*); HRMS (ESI-TOF) : m/z calcd for $C_{11}H_{15}NNaO_2S^+$ $[M+Na]^+$: 248.0716, found: 248.0705.

(*S*)-*N*-(1-phenyl-2-(*p*-tolylthio)ethyl)acetamide thio-L4

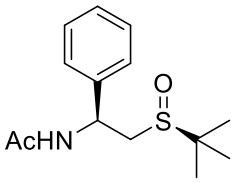
The title compound was obtained as a clear oil.



^{1}H NMR (400 MHz, $CDCl_3$): 7.23-7.36 (7H, m), 7.10 (2H, d, *J*=7.9 Hz), 6.01 (1H, d, *J*=7.0 Hz, N*H*), 5.15 (1H, app q, *J*=7.0 Hz), 3.33 (1H, dd, *J*=13.6, 7.1 Hz), 3.27 (1H, dd, *J*=13.6, 6.2 Hz), 2.32 (3H, s, PhC*H*$_3$), 1.95 (3H, s, C(O)C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 169.6, 140.6, 137.0, 131.8, 130.8, 130.0, 128.9, 127.9, 126.7, 53.0, 40.7, 23.4, 21.2; FT-IR (cm^{-1}): 3250 (br m, *N-H*), 1647 (s, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{17}H_{20}NOS^+$ $[M+H]^+$: 286.1311, found: 286.1321.

***N*-((*S*)-2-((*R*$_S$)-*tert*-butylsulfinyl)-1-phenylethyl)acetamide *t*Bu-L4**

The title compound was obtained as a white solid.



^{1}H NMR (400 MHz, $CDCl_3$): 7.28-7.41 (5H, m), 6.97 (1H, br s, N*H*), 5.39 (1H, br s), 3.02 (1H, br s), 2.76 (1H, br s), 2.03 (3H, s, C(O)C*H*$_3$), 1.27 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 170.3, 141.4, 129.1, 128.1, 126.4, 52.3, 29.8, 23.6, 22.9, 14.3; FT-IR (cm^{-1}): 3230 (br w, *N-H*), 1654 (s, *C-O*), 1012 (s, *S-O*).

IV.8.iii. Enantioselective arylation of cycloalkanes

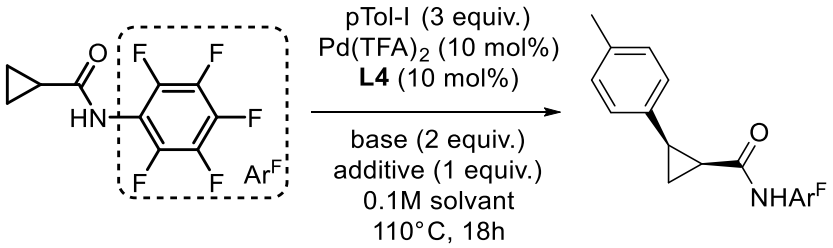
IV.8.iii.1. Optimization of the reaction conditions

Screening of different families of ligands and carboxylic acid protecting group

This section is already described in the manuscript.

Screening of base, additive and solvent using L4

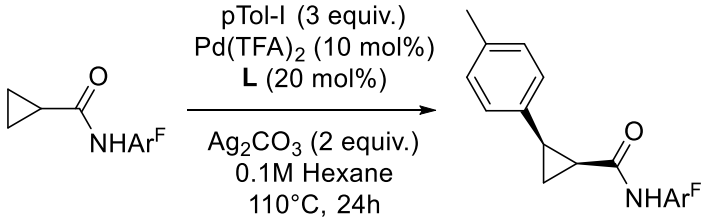
N-(2,3,4,5,6-pentafluorophenyl)-cyclopropanecarboxamide **IV-1a** (18 mg, 0.06 mmol, 1 equiv.), 4-iodotoluene (40 mg, 0.18 mmol, 3 equiv.), appropriate base (2 equiv.), appropriate additive (1 equiv.), palladium(II) trifluoroacetate (2 mg, 0.006 mmol, 10 mol%) and **L4** (4 mg, 0.012 mmol, 20 mol%) were weighted in a pressure tube. Solvent (600 µL) was added and the reaction mixture was stirred 30 min at room temperature, followed by heating at 110 °C during 18 h. After cooling to room temperature, the mixture was filtered with 0.2 µm PTFE membrane, washed with chloroform and evaporated under reduced pressure. The crude was analysed by ^{1}H NMR and chiral HPLC using CHIRALPAK ® ADH column.

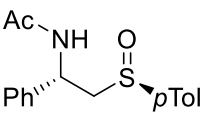


Entry	Base	additive	Solvent	Conversion (%)	*er*
1	Ag_2CO_3	K_2HPO_4	Hexane	80	85:15
2	Ag_2CO_3	-	Hexane	85	85:15
3	Ag_2CO_3	-	Heptane	60	85:15
4	Ag_2CO_3	Li_2CO_3	Hexane	<10	*nd*
5	Ag_2CO_3	Cs_2CO_3	Hexane	40	*nd*
6	AgTFA	K_2HPO_4	HFIP	0	*nd*
7	AgOAc	K_2HPO_4	Hexane	<20	*nd*

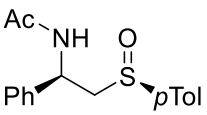
Screening of ligands derived from L4

N-(2,3,4,5,6-pentafluorophenyl)-cyclopropanecarboxamide (18 mg, 0.06 mmol, 1 equiv.), 4-iodotoluene (40 mg, 0.18 mmol, 3 equiv.), silver carbonate (42 mg, 0.15 mmol, 2.5 equiv.), potassium phosphate dibasic (10 mg, 0.06 mmol, 1 equiv.), palladium(II) trifluoroacetate (2.1 mg, 0.006 mmol, 10 mol%) and appropriate ligand (20 mol%) were weighted in a pressure tube. Hexane (600 µL) was added and the reaction mixture was stirred 30 min at room temperature, followed by heating at 110 °C during 18 h. After cooling to room temperature, the mixture was filtered with 0.2 µm PTFE membrane, washed with chloroform and evaporated under reduced pressure. The crude was analyzed by ^{1}H NMR and chiral HPLC using CHIRALPAK ® ADH column.

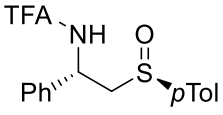




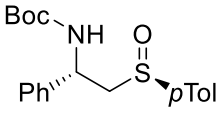
L7
90% conversion
15:85 er



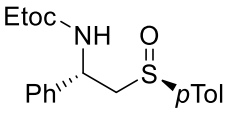
dia-L7
75% conversion
85:15 er



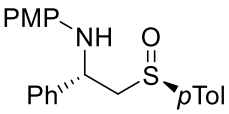
TFA-L7
60% conversion
15:85 er



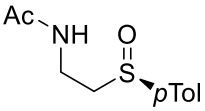
Boc-L7
25% conversion
40:60 er



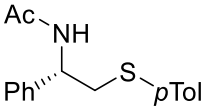
Etoc-L7
10% conversion
er nd



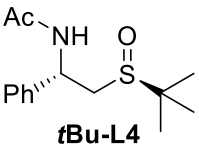
PMP-L7
10% conversion
er nd



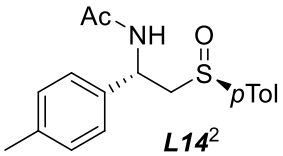
prim-L4
35% conversion
60:40 er



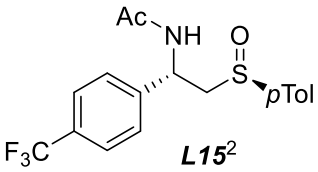
thio-l4
80% conversion
25:75 er



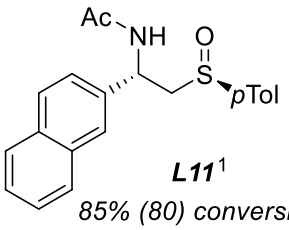
***t*Bu-L4**
15% conversion
er nd



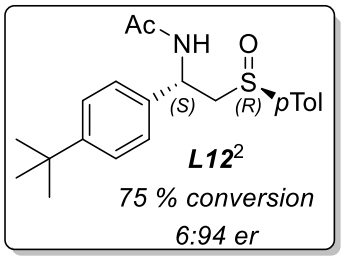
***L14*[2]**
70% conversion
10:90 er



***L15*[2]**
60% conversion
10:90 er



***L11*[1]**
85% (80) conversion
12:88 (10:90) er

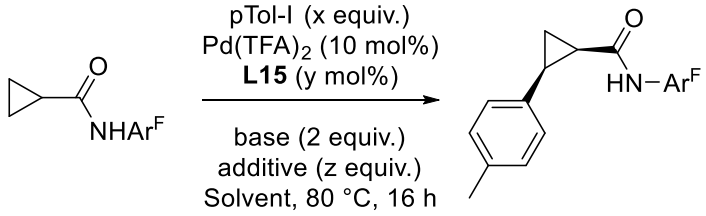


***L12*[2]**
75 % conversion
6:94 er

[21] Between brackets, conversion and er when running the reaction at 80 °C
[22] Reaction was carried out at 80 °C

Final optimization of the reaction conditions using L12

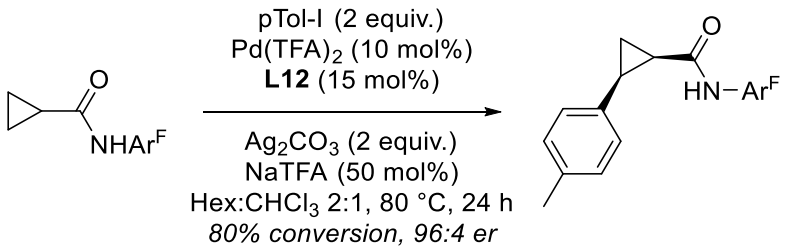
N-(2,3,4,5,6-pentafluorophenyl)-cyclopropanecarboxamide **IV-1a** (1 equiv.), 4-iodotoluene, appropriate base, appropriate additive, appropriate catalyst and **L12** were weighted in a pressure tube. Solvent were added, and the reaction mixture was stirred 30 min at room temperature, followed by heating at 80 °C during 18 h. After cooling to room temperature, the mixture was filtered with 0.2 µm PTFE membrane, washed with chloroform and evaporated under reduced pressure. The crude was analyzed by ^{1}H NMR and chiral HPLC using CHIRALPAK ® ADH column.



Entry	x	y	base	Additive (z)	solvent (M)	Conversion (%)	*er*
1	3	20	Ag_2CO_3	None	Hex (0.2)	75	94:6
2	3	15	Ag_2CO_3	None	Hex (0.1)	45	94:6
3	3	15	Ag_2CO_3	None	Hex/$CHCl_3$ (3:1) (0.1)	60	95:5
4	3	15	Ag_2CO_3	None	Hex/$CHCl_3$ (2:1) (0.1)	70	96:4
5	3	15	Ag_2CO_3	None	Hex/$CHCl_3$ (1:2) (0.1)	70	89:11
6	3	15	Ag_2CO_3	None	$CHCl_3$ (0.1)	50	87:13
7	3	15	AgTFA	None	Hex/$CHCl_3$ (2:1) (0.1)	<5	*nd*
8	3	15	AgOAc	None	Hex/$CHCl_3$ (2:1) (0.1)	20	80:20
9	3	15	K_2CO_3	None	Hex/$CHCl_3$ (2:1) (0.1)	*<10*	*nd*
10[23]	2	15	Ag_2CO_3	none	Hex/$CHCl_3$ (2:1) (0.1)	70	95:5
11[3]	3	15	Ag_2CO_3	NaTFA (1)	Hex/$CHCl_3$ (2:1) (0.1)	75	96:4
12[3]	3	15	Ag_2CO_3	Cs_2CO_3 (1)	Hex/$CHCl_3$ (2:1) (0.1)	<10	*nd*
13[3]	3	15	Ag_2CO_3	Na_2CO_3 (1)	Hex/$CHCl_3$ (2:1) (0.1)	<20	*nd*
14[3]	3	15	Ag_2CO_3	NaTFA (0.5)	Hex/$CHCl_3$ (2:1) (0.1)	80	96:4
15[3]	3	15	Ag_2CO_3	NaTFA (0.2)	Hex/$CHCl_3$ (2:1) (0.1)	70	96:4
16[3]	2	15	Ag_2CO_3	NaTFA (0.5)	Hex/$CHCl_3$ (2:1) (0.1)	80	96:4

[23] The reaction mixture was stirred 24 h at 80 °C.

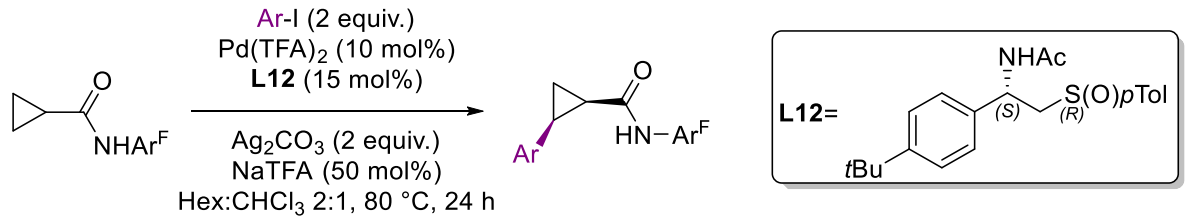
Variations from standard conditions



No $Pd(TFA)_2$	0% conversion
No ligand	*ca* 5% conversion
No Ag_2CO_3	0% conversion
No NaTFA	70% conversion

IV.8.iii.2. Scope of the reaction

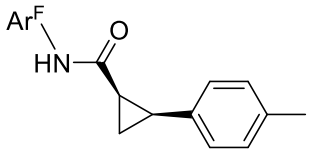
General procedure for the enantioselective mono-arylation of cycloalkanes



N-(2,3,4,5,6-pentafluorophenyl)-cycloalkanecarboxamide **IV-1a** (50 mg, 0.2 mmol, 1 equiv.), iodoarene (2 equiv.), silver carbonate (110 mg, 0.40 mmol, 2 equiv.), sodium trifluoroacetate (14 mg, 0.10 mmol, 50 mol%), palladium(II) trifluoroacetate (7 mg, 0.02 mmol, 10 mol%) and **L12** (11 mg, 0.03 mmol, 15 mol%) were weighted in a pressure tube. Hexane (1.3 mL) and chloroform (0.7 mL) were added and the reaction mixture was stirred 30 min at room temperature, followed by heating at 80 °C during 24 h. After cooling to room temperature, the mixture was filtered with 0.2 µm PTFE membrane, washed with chloroform and evaporated under reduced pressure. The crude was purified by column chromatography or preparative thin layer chromatography, typically with pentane/ethyl acetate or toluene/ethyl acetate eluent, to afford the title compound.

(1*R*,2*S*)-*N*-(pentafluorophenyl)-2-(*p*-tolyl)cyclopropane-1-carboxamide IV-2aA

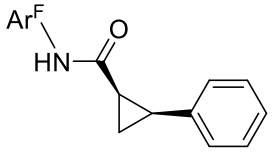
The general procedure was performed using 4-iodotoluene (90 mg) as coupling partner. Preparative thin layer chromatography using toluene/ethyl acetate (95:5) as eluent afforded the title compound (53 mg, 78 %, 92 % *ee*) as a white solid. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (400 MHz, $CDCl_3$): 7.17 (2H, d, *J*=8.0 Hz), 7.08 (2H, d, *J*=7.9 Hz), 6.66 (1H, br s, N*H*), 2.64 (1H, app q, *J*=8.5 Hz), 2.29 (3H, s, PhC*H*$_3$), 2.05-2.20 (1H, m), 1.67-1.87 (1H, m), 1.39-1.46 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 168.5, 136.8, 132.6, 129.1, 129.0, 25.9, 23.4, 21.2, 11.5, carbons corresponding to the pentafluoroamide moiety are not reported; ^{19}F NMR (376 MHz, $CDCl_3$): -144.95, -157.39, -162.72; FT-IR (cm^{-1}): 3270 (m, *N-H*), 1678 (s, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{17}H_{13}F_5NO^+$ $[M+H]^+$: 342.0912, found: 342.0934; R_t (min, CHIRALPAK® ADH, Hex/*i*PrOH 95/5, 0.5 mL/min): 18.84 (4 %), 33.98 (96 %).

(1*R*,2*S*)-2-phenyl-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide IV-2aN

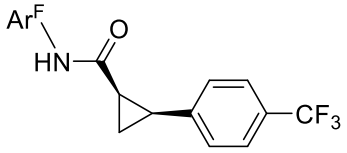
The general procedure was performed using iodobenzene (50 µL) as coupling partner. Preparative thin layer chromatography using toluene/ethyl acetate (95:5) as eluent afforded the title compound (53 mg, 81 %, 92 % *ee*) as a yellow solid. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (400 MHz, $CDCl_3$): 7.28 (4H, d, *J*=4.4 Hz), 7.21 (1H, dq, *J*=8.7, 4.1 Hz), 6.71 (1H, br s, N*H*), 2.67 (1H, app q, *J*=8.7 Hz), 2.15 (1H, app q, *J*=8.3 Hz), 1.78-1.95 (1H, m), 1.40-1.53 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 168.2, 135.7, 129.1, 128.4, 127.2, 26.2, 23.6, 11.3, carbons corresponding to the pentafluoroamide moiety are not reported; ^{19}F NMR (376 MHz, $CDCl_3$): -144.92, -157.27, -162.69; FT-IR (cm^{-1}): 3250 (br w, *N-H*), 1678 (m, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{16}H_{10}F_5NNaO^+$ $[M+Na]^+$: 350.0575, found: 350.0562; R_t (min, CHIRALPAK ® ADH, Hex/*i*PrOH 95/5, 0.5 mL/min): 21.06 (4 %), 29.32 (96 %).

(1*R*,2*S*)-2-(4-(trifluoromethyl)phenyl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide IV-2aE

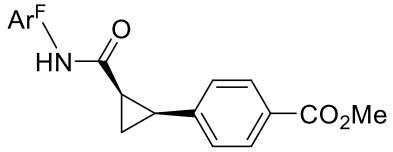
The general procedure was performed using 4-iodobenzotrifluoride (60 µL) as coupling partner. Column chromatography on silica gel using pentane/ethyl acetate (4:1) as eluent afforded the title compound (74 mg, 94 %, 95 % *ee*) as an orange oil. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (400 MHz, $CDCl_3$): 7.52 (2H, d, *J*=8.1 Hz), 7.38 (2H, d, *J*=8.1 Hz), 6.82 (1H, br s, N*H*), 2.68 (1H, app q, *J*=8.4 Hz), 2.20 (1H, app q, *J*=8.0 Hz), 1.86-1.95 (1H, m), 1.46-1.56 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 167.6, 140.0, 129.5, 129.1, 125.7 (q, *J*=271 Hz), 125.2 (q, *J*=4 Hz), 26.0, 23.7, 11.6, carbons corresponding to the pentafluoroamide moiety are not reported; ^{19}F NMR (376 MHz, $CDCl_3$): -62.49, -145.07, -156.62, -162.32; FT-IR (cm^{-1}): 1677 (m, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{17}H_{10}F_8NO^+$ $[M+H]^+$: 396.0629, found: 396.0630; R_t (min, CHIRALPAK ® ADH, Hex/*i*PrOH 95/5, 0.5 mL/min): 18.86 (2.5 %), 36.08 (97.5 %).

methyl (1*R*,2*S*)-4-(2-((pentafluorophenyl)carbamoyl)cyclopropyl)benzoate IV-2aO

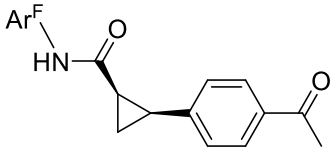
The general procedure was performed using methyl 4-iodobenzoate (105 mg) as coupling partner. Column chromatography on silica gel using pentane/ethyl acetate (7:3) as eluent afforded the title compound (51 mg, 66 %, 89 % *ee*) as a yellow solid. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (400 MHz, $CDCl_3$): 7.93 (2H, d, *J*=8.3 Hz), 7.33 (2H, d, *J*=8.2 Hz), 6.96 (1H, br s, N*H*), 3.88 (3H, s, CO_2CH_3), 2.67 (1H, app q, *J*=8.4 Hz), 2.20 (1H, app q, *J*=7.5 Hz), 1.86-1.96 (1H, m), 1.45-1.55 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 167.8, 167.2, 141.4, 129.6, 129.2, 128.9, 52.2, 26.2, 23.8, 11.6, carbons corresponding to the pentafluoroamide moiety are not reported; ^{19}F NMR (376 MHz, $CDCl_3$): -144.93, -156.83, -162.43; FT-IR (cm^{-1}): 3263 (br w, *N-H*), 1722 (m, *C-O ester*), 1679 (m, *C-O amide*); HRMS (ESI-TOF): m/z calcd for $C_{18}H_{12}F_5NNaO_3^+$ $[M+Na]^+$: 408.0630, found: 408.0622; R_t (min, CHIRALPAK ® ADH, Hex/iPrOH 90/10, 0.5 mL/min): 16.48 (5.5 %), 28.65 (94.5 %).

(1*R*,2*S*)-2-(4-acetylphenyl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide IV-2aI

The general procedure was performed using 4'-iodoacetophenone (100 mg) as coupling partner. Column chromatography on silica gel using pentane/ethyl acetate (7:3) as eluent afforded the title compound (64 mg, 87 %, 86 % *ee*) as a clear oil. The absolute stereochemistry was assigned according to **IV-2aR**.

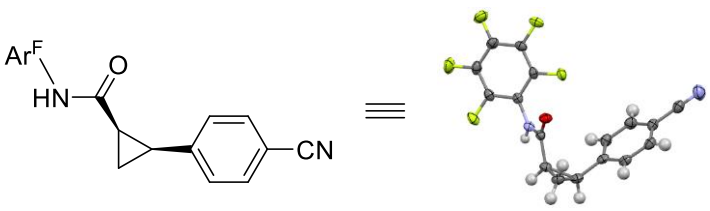


^{1}H NMR (400 MHz, $CDCl_3$): 7.86 (2H, d, *J*=8.4 Hz), 7.36 (2H, d, *J*=8.1 Hz), 7.10 (1H, br s, N*H*), 2.68 (1H, app q, *J*=8.5 Hz), 2.56 (3H, s, PhC(O)C*H*$_3$), 2.17-2.28 (1H, m), 1.86-1.95 (1H, m), 1.45-1.55 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 198.1, 163.6, 141.7, 135.9, 129.4, 128.3, 26.7, 26.1, 11.6, carbons corresponding to the pentafluoroamide moiety are not reported; ^{19}F NMR (376 MHz, $CDCl_3$): -144.95, -156.77, -162.43; FT-IR (cm^{-1}): 3261 (w, *N-H*), 1678 (s, *C-O ester*), 1607 (s, *C-O ketone*); HRMS (ESI-TOF): m/z calcd for $C_{18}H_{12}F_5NNaO_2^+$ $[M+Na]^+$: 392.0680, found: 392.0696; R_t (min, CHIRALPAK® ADH, Hex/*i*PrOH 90/10, 0.5 mL/min): 18.78 (7 %), 50.26 (93 %).

(1*R*,2*S*)-2-(4-cyanophenyl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide IV-2aR

The general procedure was performed using 4-iodobenzonitrile (100 mg) as coupling partner. Column chromatography on silica gel using pentane/ethyl acetate (7:3) as eluent afforded the

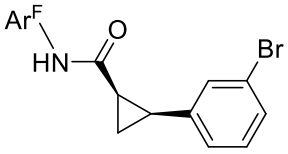
title compound (41 mg, 58 %, 70 % *ee*) as a clear oil. Slow evaporation in Hex/CH_2Cl_2 at 3 – 5 °C afforded mono crystals suitable for X-Ray diffraction analysis which were analysed on the Bruker APEX II DUO Kappa-CCD diffractometer.



^{1}H NMR (400 MHz, $CDCl_3$): 7.56 (2H, d, *J*=8.4 Hz), 7.38 (2H, d, *J*=8.1 Hz), 6.91 (1H, br s, N*H*), 2.68 (1H, app q, *J*=8.5 Hz), 2.23 (1H, app q, *J*=7.9 Hz), 1.91 (1H, ddd, *J*=9.1, 7.6, 5.5 Hz), 1.53 (1H, ddd, *J*=11.3, 8.1, 5.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 141.6, 132.0, 130.0, 119.0, 110.8, 26.2, 24.0, 11.7, carbons corresponding to the pentafluoroamide moiety are not reported and the carbon of the amide was nearly invisible; ^{19}F NMR (376 MHz, $CDCl_3$): -145.04, -156.28, -162.13; FT-IR (cm^{-1}): 3266 (w, *N-H*), 2229 (m, *C-N nitrile*), 1679 (m, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{17}H_{10}F_5N_2O^+$ $[M+H]^+$: 353.0708, found: 353.0704; R_t (min, CHIRALPAK® ADH, Hex/*i*PrOH 90/10, 0.5 mL/min): 17.68 (15 %), 46.65 (85 %).

(1*R*,2*S*)-2-(3-bromophenyl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide IV-2aD

The general procedure was performed using 3-iodobromobenzene (50 µL) as coupling partner. Preparative thin layer chromatography using toluene/ethyl acetate (95:5) as eluent afforded the title compound (47 mg, 58 %, 90 % *ee*) as a clear oil. The absolute stereochemistry was assigned according to **IV-2aR**.

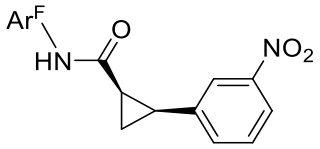


^{1}H NMR (400 MHz, $CDCl_3$): 7.44 (1H, s), 7.33 (1H, dt, *J*=7.7, 1.4 Hz), 7.11-7.22 (2H, m), 6.80 (1H, br s, N*H*), 2.62 (1H, app q, *J*=8.6 Hz), 2.15 (1H, app q, *J*=8.2 Hz), 1.80-1.86 (1H, m), 1.41-1.49 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 138.3, 132.5, 130.3, 129.8, 127.7, 122.3, 25.7, 23.5, 11.4, carbons corresponding to the pentafluoroamide moiety are not reported and the carbon of the amide was nearly invisible; ^{19}F NMR (376 MHz, $CDCl_3$): -144.87, -156.79, -162.42; FT-IR (cm^{-1}): 3249 (br w, *N-H*), 1677 (m, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{16}H_9BrF_5NNaO^+$ $[M+Na]^+$: 427.9680, found: 427.9659; R_t (min, CHIRALPAK® ADH, Hex/*i*PrOH 95/5, 0.5 mL/min): 22.02 (5 %), 32.74 (95%).

(1*R*,2*S*)-2-(3-nitrophenyl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide IV-2aB

The general procedure was performed using 3-iodonitrobenzene (100 mg) as coupling partner. Column chromatography on silica gel using pentane/ethyl acetate (6:4) as eluent afforded the

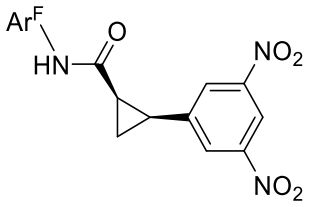
title compound (62 mg, 84 %, 89 % *ee*) as a clear oil. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (400 MHz, $CDCl_3$): 8.17 (1H, s), 8.02-8.12 (1H, m), 7.60 (1H, d, *J*=7.7 Hz), 7.44 (1H, t, *J*=7.9 Hz), 7.11 (1H, br s, N*H*), 2.73 (1H, app q, *J*=8.4 Hz), 2.24 (1H, app q, *J*=7.7 Hz), 1.93 (1H, ddd, *J*=8.9, 7.3, 5.4 Hz), 1.55 (1H, ddd, *J*=11.1, 8.2, 5.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 148.1, 138.2, 135.4, 129.1, 124.5, 122.2, 25.7, 23.5, 11.6, carbons corresponding to the pentafluoroamide moiety are not reported and the carbon of the amide was nearly invisible; ^{19}F NMR (376 MHz, $CDCl_3$): -145.07, -156.35, -162.25; FT-IR (cm^{-1}): 3255 (w, *N-H*), 1678 (m, *C-O*), 1522 (s, *N-O*), 1350 (s, *N-O*); HRMS (ESI-TOF): m/z calcd for $C_{16}H_9F_5N_2NaO_3^+$ $[M+Na]^+$: 395.0426, found: 395.0448; R_t (min, CHIRALPAK® ADH, Hex/*i*PrOH 90/10, 0.5 mL/min): 15.32 (5.5 %), 22.75 (94.5 %).

(1*R*,2*S*)-2-(3,5-dinitrophenyl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide IV-2aK

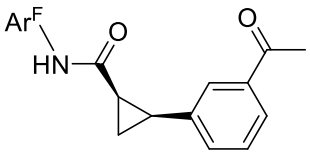
The general procedure was performed using 3,5-dinitroiodobenzene (120 mg) as coupling partner. Column chromatography on silica gel using pentane/ethyl acetate (4:1) as eluent afforded the title compound (42 mg, 51 %, 87 % *ee*) as a yellow solid. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (400 MHz, $CDCl_3$): 8.90 (1H, t, *J*=2.0 Hz), 8.49 (1H, dd, *J*=2.2, 0.8 Hz), 7.08 (1H, br s, N*H*), 2.83 (1H, app q, *J*=8.4 Hz), 2.34 (1H, app q, *J*=8.3 Hz), 2.00-2.13 (1H, m), 1.66-1.77 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 167.3, 148.3, 140.9, 12s9.8, 117.6, 25.5, 12.4, 9.0, carbons corresponding to the pentafluoroamide moiety are not reported; ^{19}F NMR (376 MHz, $CDCl_3$): -144.94, -157.27, -162.69; FT-IR (cm^{-1}): 1679 (m, *C-O*), 1542 (s, *N-O*), 1346 (s, *N-O*); HRMS (ESI-TOF): m/z calcd for $C_{16}H_9F_5N_3O_5^+$ $[M+H]^+$: 418.0457, found: 418.0467; R_t (min, CHIRALPAK ® ADH, Hex/*i*PrOH 90/10, 0.5 mL/min): 21.39 (6.5 %), 29.49 (93.5 %).

(1*R*,2*S*)-2-(3-acetylphenyl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide IV-2aH

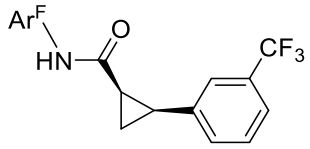
The general procedure was performed using methyl 3'-iodoacetophenone (100 mg) as coupling partner. Column chromatography on silica gel using pentane/ethyl acetate (3:2) as eluent afforded the title compound (68 mg, 92 %, 84 % *ee*) as an orange oil. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (400 MHz, $CDCl_3$): 7.90 (1H, s), 7.79 (1H, d, *J*=7.7 Hz), 7.47 (1H, d, *J*=7.6 Hz), 7.37 (1H, t, *J*=7.7 Hz), 7.23 (1H, br s, N*H*), 2.69 (1H, app q, *J*=10.8 Hz), 2.58 (3H, s, PhC(O)C*H*$_3$), 2.11-2.26 (1H, m), 1.90 (1H, app q, *J*=5.4 Hz), 1.48 (1H, app q, *J*=8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 198.6, 168.0, 137.0, 136.7, 133.8, 129.2, 128.5, 127.3, 26.8, 26.0, 23.4, 11.4, carbons corresponding to the pentafluoroamide moiety are not reported; ^{19}F NMR (376 MHz, $CDCl_3$): -145.00, -156.94, -162.57; FT-IR (cm^{-1}): 3261 (br w, *N-H*), 1683 (s, *C-O amide* and *ketone*); HRMS (ESI-TOF): m/z calcd for $C_{18}H_{12}F_5NNaO_2^+$ $[M+Na]^+$: 392.0680, found: 392.0671; R_t (min, CHIRALPAK ® ADH, Hex/*i*PrOH 95/5, 0.5 mL/min): 31.30 (8 %), 48.50 (92 %).

(1*R*,2*S*)-2-(3-trifluoromethylphenyl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide IV-2aF

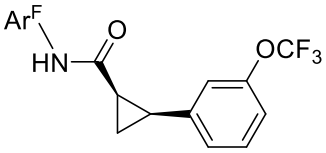
The general procedure was performed using 3-iodobenzotrifluoride (60 µL) as coupling partner. Column chromatography on silica gel using pentane/ethyl acetate (85:15) as eluent afforded the title compound (59 mg, 75 %, 82 % *ee*) as a yellow solid. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (500 MHz, Acetone-d_6): 9.34 (1H, br s, N*H*), 7.62 (1H, s), 7.57 (1H, d, *J*=7.5 Hz), 7.42-7.54 (2H, m), 2.77 (1H, app q, *J*=8.5 Hz), 2.51 (1H, app q, *J*=8.1 Hz), 1.80 (1H, ddd, *J*=7.4, 5.5, 5.0 Hz), 1.47 (1H, ddd, *J*=8.5, 7.8, 4.8 Hz); ^{13}C NMR (120 MHz, Acetone-d_6): 168.6, 139.4, 134.0, 130.5 (q, *J*=32 Hz), 129.5, 126.9 (q, *J*=4 Hz), 125.5 (q, *J*=272 Hz), 124.0 (q, *J*=4 Hz), 25.9, 23.9, 11.1, carbons corresponding to the pentafluoroamide moiety are not reported; ^{19}F NMR (470 MHz, Acetone-d_6): -63.09, -146.84, -160.67, -166.00; FT-IR (cm^{-1}): 1677 (s, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{17}H_{10}F_8NO^+$ $[M+H]^+$: 396.0629, found: 396.0610; R_t (min, CHIRALPAK ® ADH, Hex/*i*PrOH 95/5, 0.5 mL/min): 15.67 (9 %), 22.34 (91 %).

(1*R*,2*S*)-2-(3-(trifluoromethoxy)phenyl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide IV-2aS

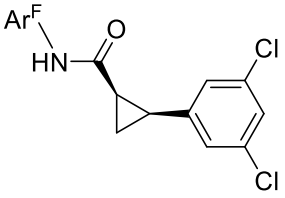
The general procedure was performed using 3-(trifluoromethoxy)iodobenzene (115 mg) as coupling partner. Column chromatography on silica gel using pentane/ethyl acetate (9:1) as eluent afforded the title compound (55 mg, 67 %, 84 % *ee*) as a brown oil. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (400 MHz, Acetone-d_6): 9.31 (1H, br s, N*H*), 7.28-7.40 (2H, m), 7.22 (1H, s), 7.12 (1H, dd, *J*=8.4, 1.7 Hz), 2.72 (1H, app q, *J*=8.6 Hz), 2.44-2.54 (1H, m), 1.76 (1H, ddd, *J*=7.4, 5.6, 4.9 Hz), 1.44 (1H, ddd, *J*=8.6, 7.8, 4.8 Hz); ^{13}C NMR (100 MHz, Acetone-d_6): 168.4, 149.6 (q, *J*=3 Hz), 140.8, 130.2, 129.1, 122.6, 121.9 (q, *J*=254 Hz), 119.7, 25.8, 24.1, 11.2, carbons corresponding to the pentafluoroamide moiety are not reported; ^{19}F NMR (377 MHz, Acetone-d_6): -58.44, -146.76, -160.76, -166.04; FT-IR (cm^{-1}): 3254 (br m, *N-H*), 1678 (m, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{17}H_9F_8NNaO_2^+$ $[M+Na]^+$: 434.0398, found: 434.0420; R_t (min, CHIRALPAK ® ADH, Hex/iPrOH 98/2, 0.5 mL/min): 39.64 (8 %), 56.98 (92 %).

(1*R*,2*S*)-2-(3,5-dichlorophenyl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide IV-2aL

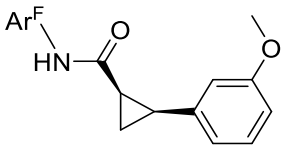
The general procedure was performed using 3,5-dichloroiodobenzene (110 mg) as coupling partner. Preparative thin layer chromatography using toluene/ethyl acetate (95:5) as eluent afforded the title compound (56 mg, 71 %, 84 % *ee*) as a yellow solid. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (400 MHz, $CDCl_3$): 7.20 (1H, t, *J*=1.8 Hz), 7.14-7.16 (2H, m), 6.94 (1H, br s, N*H*), 2.58 (1H, app q, *J*=8.5 Hz), 2.15 (1H, app q, *J*=8.2 Hz), 1.67-1.89 (1H, m), 1.41-1.52 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 167.6, 139.5, 134.7, 127.9, 127.4, 25.4, 23.3, 11.5, carbons corresponding to the pentafluoroamide moiety are not reported; ^{19}F NMR (376 MHz, $CDCl_3$): -144.95, -156.40, -162.24; FT-IR (cm^{-1}): 1677 (m, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{16}H_9Cl_2F_5NO^+$ $[M+H]^+$: 395.9976, found: 395.9973; R_t (min, CHIRALPAK ® ADH, Hex/iPrOH 95/5, 0.5 mL/min): 19.82 (8 %), 23.95 (92 %).

(1*R*,2*S*)-2-(3-methoxyphenyl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide IV-2aC

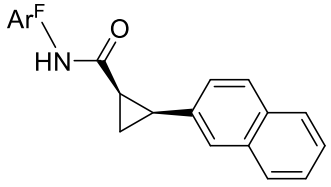
The general procedure was performed using 3-iodoanisole (50 µL) as coupling partner. Column chromatography on silica gel using pentane/ethyl acetate (9:1) as eluent afforded the title compound (44 mg, 62 %, 93 % *ee*) as a yellow oil. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (400 MHz, $CDCl_3$): 7.19 (1H, t, *J*=7.9 Hz), 6.87 (1H, d, *J*=8.3 Hz), 6.81-6.85 (1H, m), 6.71-6.80 (2H, m), 3.77 (3H, s, PhOC*H*$_3$), 2.64 (1H, app q, *J*=8.6 Hz), 2.09-2.20 (1H, m), 1.81 (1H, ddd, *J*=8.5, 7.5, 5.4 Hz), 1.44 (1H, ddd, *J*=11.0, 8.1, 5.3 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$): 159.6, 137.5, 129.4, 121.4, 114.9, 112.7, 55.3, 26.1, 26.1, 11.5, carbons corresponding to the pentafluoroamide moiety are not reported; ^{19}F NMR (376 MHz, $CDCl_3$): -144.96, -157.30, -162.70; FT-IR (cm^{-1}): 3250 (m, *N-H*), 1678 (m, *C-O* amide), 1005 (s, *C-O ether*); HRMS (ESI-TOF): m/z calcd for $C_{17}H_{13}F_5NO_2^+$ $[M+H]^+$: 358.0861, found: 358.1777; R_t (min, CHIRALPAK® ADH, Hex/iPrOH 95/5, 0.5 mL/min): 26.91 (3.5 %), 36.28 (96.5 %).

(1*R*,2*S*)-2-(naphthalen-2-yl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide IV-2aJ

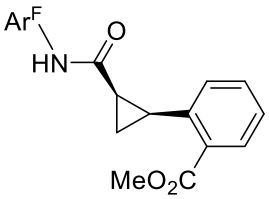
The general procedure was performed using 2-iodonaphthalene (110 mg) as coupling partner. Preparative thin layer chromatography using toluene/ethyl acetate (97:3) as eluent afforded the title compound (47 mg, 63 %, 91 % *ee*) as a clear oil. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (400 MHz, Acetone-*d6*): 9.33 (1H, br s, N*H*), 7.72-7.86 (4H, m), 7.34-7.52 (3H, m), 2.75-2.84 (1H, m), 2.42-2.61 (1H, m), 1.82-1.93 (1H, m), 1.47 (1H, ddd, *J*=8.2, 5.4, 4.6 Hz); ^{13}C NMR (100 MHz, Acetone-*d6*): 168.7, 135.5, 134.2, 133.4, 128.7, 128.6, 128.4, 128.3, 128.0, 126.6, 126.2, 26.5, 23.8, 11.2, carbons corresponding to the pentafluoroamide moiety are not reported; ^{19}F NMR (376 MHz, Acetone-*d6*): -146.65, -160.97, -166.02; FT-IR (cm^{-1}): 3250 (br w, *N-H*), 1680 (m, *C-O* amide); HRMS (ESI-TOF): m/z calcd for $C_{20}H_{13}F_5NO^+$ $[M+H]^+$: 378.0912, found: 378.0910; R_t (min, CHIRALPAK® ADH, Hex/*i*PrOH 95/5, 0.5 mL/min): 26.39 (4.5 %), 40.02 (95.5 %).

methyl (1*R*,2*S*)-2-(2-((pentafluorophenyl)carbamoyl)cyclopropyl)benzoate IV-2aG

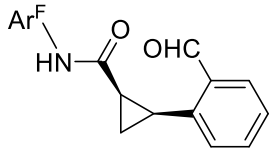
The general procedure was performed using methyl 2-iodobenzoate (60 µL) as coupling partner. Column chromatography on silica gel using pentane/ethyl acetate (3:2) as eluent afforded the title compound (67 mg, 87 %, 87 % *ee*) as an orange oil. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (500 MHz, $CDCl_3$): 7.92 (1H, dd, *J*=7.8, 1.3 Hz), 7.62 (1H, br s, N*H*), 7.41-7.47 (1H, m), 7.32 (1H, d, *J*=7.7 Hz), 7.29 (1H, d, *J*=7.6 Hz), 3.93 (3H, s, CO_2CH_3), 2.86 (1H, app q, *J*=8.2 Hz), 2.37-2.52 (1H, m), 1.93-2.02 (1H, m), 1.39-1.48 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 168.9, 138.1, 132.9, 131.1, 130.5, 130.4, 127.5, 52.5, 25.8, 25.6, 10.7, carbons corresponding to the pentafluoroamide moiety are not reported and the carbon of the amide was nearly invisible; ^{19}F NMR (470 MHz, $CDCl_3$): -145.8, -158.4, -163.1; FT-IR (cm^{-1}): 1722 (s, *C-O ester*), 1679 (m, *C-O amide*); HRMS (ESI-TOF): m/z calcd for $C_{18}H_{12}F_5NNaO_3^+$ $[M+Na]^+$: 408.0630, found: 408.0624; R_t (min, CHIRALPAK ® ADH, Hex/*i*PrOH 95/5, 0.5 mL/min): 13.42 (6.5 %), 19.34 (93.5 %).

(1*R*,2*S*)-2-(2-formylphenyl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide IV-2aM

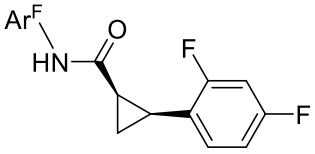
The general procedure was performed using 2-iodobenzaldehyde (95 mg) as coupling partner. Column chromatography on silica gel using pentane/ethyl acetate (4:1) as eluent afforded the title compound (62 mg, 88 %, 86 % *ee*) as a yellow solid. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (400 MHz, $CDCl_3$): 10.21 (1H, s, C*H*O), 7.77 (1H, dd, *J*=7.3, 1.8 Hz), 7.54 (1H, td, *J*=7.6, 1.4 Hz), 7.40-7.49 (2H, m), 7.21 (1H, s, N*H*), 3.02 (1H, app q, *J*=8.4 Hz), 2.41-2.50 (1H, m), 1.95-2.02 (1H, m), 1.51 (1H, ddd, *J*=8.0, 7.7, 5.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 194.4, 168.4, 137.9, 135.2, 135.1, 134.1, 130.9, 127.8, 25.3, 24.3, 11.3, carbons corresponding to the pentafluoroamide moiety are not reported; ^{19}F NMR (377 MHz, $CDCl_3$): -145.29, -157.41, -162.78; FT-IR (cm^{-1}): 1691 (s, *C-O aldehyde*), 1653 (m, *C-O amide*); HRMS (ESI-TOF): m/z calcd for $C_{17}H_{11}F_5NO_2^+$ $[M+H]^+$: 356.0704, found: 356.0701; R_t (min, CHIRALPAK ® ADH, Hex/iPrOH 90/10, 0.5 mL/min): 10.82 (7 %), 18.46 (93 %).

(1*R*,2*S*)-2-(2,4-difluorophenyl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide IV-2aP

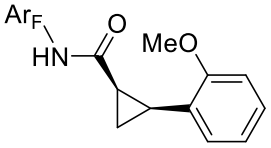
The general procedure was performed using 2,4-difluoroiodobenzene (50 µL) as coupling partner. Preparative thin layer chromatography using toluene/ethyl acetate (95:5) as eluent afforded the title compound (20 mg, 28 %, 72 % *ee*) as a yellow solid. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (400 MHz, $CDCl_3$): 7.20 (1H, td, *J*=8.6, 6.7 Hz), 6.91 (1H, br s, N*H*), 6.70-6.85 (2H, m), 2.57 (1H, app q, *J*=8.2 Hz), 2.15-2.27 (1H, m), 1.77-1.86 (1H, m), 1.41-1.52 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 168.0, 163.6 (dd, *J*=30, 12 Hz), 161.0 (d, *J*=30 Hz), 131.6 (dd, *J*=10, 5 Hz), 119.2 (dd, *J*=15, 4 Hz), 111.0 (dd, *J*=21, 4 Hz), 103.5 (t, *J*=26 Hz), 22.5, 19.9, 10.5, carbons corresponding to the pentafluoroamide moiety are not reported; ^{19}F NMR (376 MHz, $CDCl_3$): -111.54, -113.15, -145.21, -156.94, -162.51; FT-IR (cm^{-1}): 3254 (br w, *N-H*), 1676 (m, *C-O*), 1139 (s, *C-F*); HRMS (ESI-TOF): m/z calcd for $C_{16}H_9F_7NO^+$ $[M+H]^+$: 364.0567, found: 364.0553; R_t (min, CHIRALPAK ® ADH, Hex/iPrOH 95/5, 0.5 mL/min): 17.47 (14 %), 38.48 (86 %).

(1*R*,2*S*)-2-(2-methoxyphenyl)-*N*-(perfluorophenyl)cyclopropane-1-carboxamide IV-2aQ

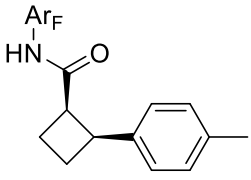
The general procedure was performed using 2-iodoanisole (55 µL) as coupling partner. Preparative thin layer chromatography using toluene/ethyl acetate (9:1) as eluent afforded the title compound (17 mg, 24 %, 74 % *ee*) as a yellow solid. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (500 MHz, $CDCl_3$): 7.15-7.22 (2H, m), 6.89 (1H, td, *J*=7.5, 0.9 Hz), 6.84 (1H, d, *J*=8.2 Hz), 6.81 (1H, br s, N*H*), 2.58 (1H, app q, J=8.4 Hz), 2.22 (1H, ddd, *J*= 8.4, 6.7, 5.5 Hz), 1.71-1.94 (1H, m), 1.36-1.46 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$): 168.7, 158.8, 130.0, 128.6, 124.3, 120.5, 109.9, 55.4, 22.9, 21.8, 10.4; ^{19}F NMR (470 MHz, $CDCl_3$): -145.64, -158.11, -162.92; FT-IR (cm^{-1}): 3251 (br w, *N-H*), 1679 (m, *C-O amide*), 1251 (s, *C-O ether*), 1005 (m, *C-O ether*); HRMS (ESI-TOF): m/z calcd for $C_{17}H_{12}F_5NNaO_2^+$ $[M+Na]^+$: 380.0680, found: 380.0668; R_t (min, CHIRALPAK ® ADH, Hex/iPrOH 95/5, 0.5 mL/min): 17.69 (13 %), 23.92 (87 %).

(1*R*,2*S*)-2-(4-methylphenyl)-*N*-(perfluorophenyl)cyclobutane-1-carboxamide IV-2bA

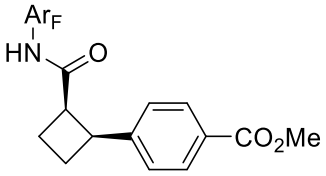
The general procedure was performed using 4-iodotoluene (55 µL) as coupling partner. Preparative thin layer chromatography using toluene/ethyl acetate (95:5) as eluent afforded the title compound (57 mg, 77 %, 62 % *ee*) as a white solid. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (400 MHz, $CDCl_3$): 7.14 (4H, app q, *J*=8.1 Hz), 6.19 (1H, br s, N*H*), 4.00 (1H, app q, *J*=8.7 Hz), 3.53-3.67 (1H, m), 2.54-2.67 (1H, m), 2.45-2.54 (1H, m), 2.22-2.40 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 171.2, 137.1, 136.9, 129.5, 127.3, 46.4, 42.9, 25.4, 21.2, 20.9; ^{19}F NMR (376 MHz, $CDCl_3$): -144.53, -157.68, -162.95; FT-IR (cm^{-1}): 3252 (br w, *N-H*), 1674 (m, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{18}H_{15}F_5NO^+$ $[M+H]^+$: 356.1068, found: 356.1096; R_t (min, CHIRALPAK ® ADH, Hex/iPrOH 98/2, 0.5 mL/min): 34.74 (19 %), 49.95 (81 %).

methyl (1*R*,2*S*)-4-(2-((perfluorophenyl)carbamoyl)cyclobutyl)benzoate IV-2bO

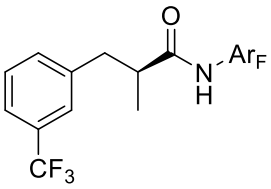
The general procedure was performed using methyl 4-iodobenzoate (100 mg) as coupling partner. Column chromatography on silica gel using pentane/ethyl acetate (4:1) as eluent afforded the title compound (57 mg, 76 %, 66 % *ee*) as a clear oil. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (400 MHz, $CDCl_3$): 7.96 (2H, d, *J*=8.3 Hz), 7.32 (2H, d, *J*=8.2 Hz), 6.46 (1H, br s, N*H*), 4.08 (1H, app q, *J*=8.6 Hz), 3.90 (3H, s, CO_2CH_3), 3.59-3.72 (1H, m), 2.60-2.76 (1H, m), 2.45-2.58 (1H, m), 2.25-2.42 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 170.8, 167.2, 145.6, 130.0, 128.9, 127.4, 52.2, 46.3, 43.0, 25.1, 21.0; ^{19}F NMR (376 MHz, $CDCl_3$): -144.51, -157.00, -162.51; FT-IR (cm^{-1}): 3272 (br w, *N-H*), 1723 (s, *C-O ester*), 1683 (m, *C-O amide*), 1281 (s, *C-O ester*); HRMS (ESI-TOF): m/z calcd for $C_{19}H_{14}F_5NNaO_3^+$ $[M+Na]^+$: 422.0786, found: 422.0817; R_t (min, CHIRALPAK ® ADH, Hex/iPrOH 90/10, 0.5 mL/min): 14.19 (17 %), 24.56 (83 %).

(*S*)-*N*-pentafluorophenyl-2-methyl-3-(3-(trifluoromethyl)phenyl)propanamide IV-2dF

The general procedure was performed using methyl 3-(trifluoromethyl)iodobenzene (100 mg) as coupling partner. Column chromatography on silica gel using pentane/ethyl acetate (6:1) as eluent afforded the title compound (49 mg, 42 %, <5 % *ee*) as a clear oil. The absolute stereochemistry was assigned according to **IV-2aR**.

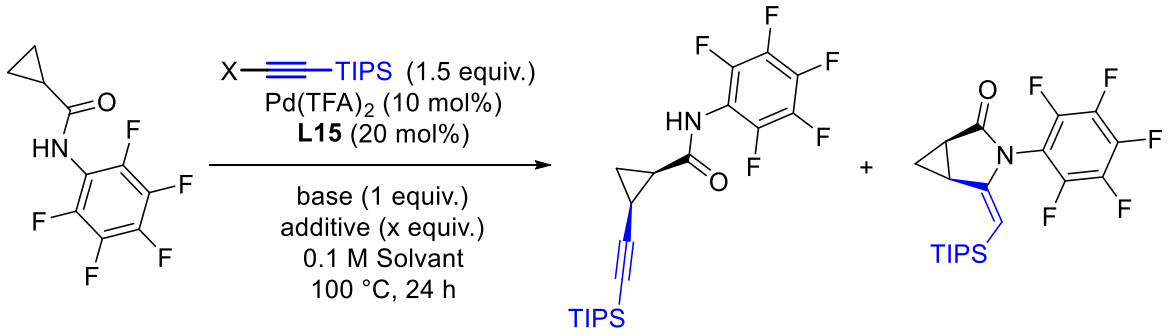


^{1}H NMR (400 MHz, $CDCl_3$): 7.35-7.56 (4H, m), 6.62 (1H, br s, N*H*), 3.13 (1H, dd, *J*=13.5, 8.7 Hz), 2.82-2.89 (1H, m), 2.69-2.80 (1H, m), 1.34 (3H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 173.7, 139.9, 132.5, 131.0 (q, *J*=32 Hz), 129.1, 125.5 (q, *J*=4 Hz), 124.1 (q, *J*=272 Hz), 123.6 (q, *J*=4 Hz), 43.7, 39.9, 18.0; ^{19}F NMR (376 MHz, $CDCl_3$): -62.69, -144.85, -156.18, -162.30; FT-IR (cm^{-1}): 3299 (br w, *N-H*), 1677 (s, *C-O amide*); HRMS (ESI-TOF): m/z calcd for $C_{17}H_{12}F_8NO^+$ $[M+H]^+$: 398.0786, found: 398.0776; R_t (min, CHIRALPAK ® ODH, Hex/iPrOH 98/2, 0.5 mL/min): 42.52 (50 %), 49.66 (50 %).

IV.8.iv. Enantioselective alkynylation of cycloalkanes

IV.8.iv.1. Optimization of the reaction conditions

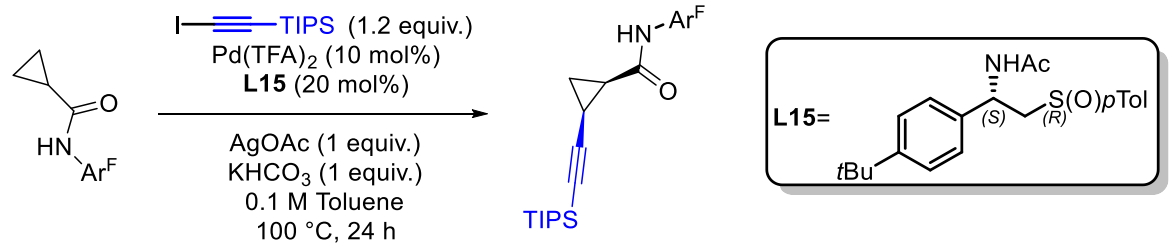
N-(2,3,4,5,6-pentafluorophenyl)-cyclopropanecarboxamide (15 mg, 0.06 mmol, 1 equiv.), (halogenoethynyl)triisopropylsilane (1.5 equiv.), base (1 equiv.), additive, catalyst (10 mol%) and **L12** (20 mol%) were weighted in a pressure tube. Solvent was added, and the reaction mixture was stirred 30 min at room temperature, followed by heating at 100 °C during 24 h. After cooling to room temperature, the mixture was filtered with 0.2 µm PTFE membrane, washed with dichloromethane and evaporated under reduced pressure. The crude was analyzed by ^{1}H NMR and chiral HPLC using CHIRALPAK ® ODH column.



Entry	X	base	Additive (equiv.)	catalyst	Solvent	Conversion	Ratio	er
1	Br	Ag_2CO_3	NaTFA (0.5)	$Pd(TFA)_2$	Hex:$CHCl_3$ (2:1)	50	1:8	75:25
2	I	Ag_2CO_3	NaTFA (0.5)	$Pd(TFA)_2$	Hex:$CHCl_3$ (2:1)	80	>10:1	80:20
3	I	AgOAc	none	$Pd(OAc)_2$	Toluene	50	>10:1	90:10
4	I	AgOAc	$KHCO_3$ (1)	$Pd(OAc)_2$	Toluene	95	>10:1	92:8
5	I	AgOAc	$KHCO_3$ (5)	$Pd(OAc)_2$	Toluene	95	>10:1	92:8
6	Cl	AgOAc	$KHCO_3$ (1)	$Pd(OAc)_2$	Toluene	0	*nd*	*nd*
7	H	AgOAc	$KHCO_3$ (1)	$Pd(OAc)_2$	Toluene	0	*nd*	*nd*
8	I	AgOAc	$KHCO_3$ (1)	$Pd(OAc)_2$	$PhCF_3$	40	1:1	*nd*
9	I	AgOAc	$KHCO_3$ (1)	$Pd(OAc)_2$	PhCl	<10	*nd*	*nd*

IV.8.iv.2. Scope of the reaction

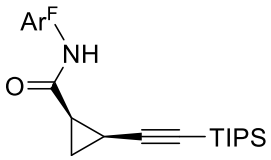
General procedure for the enantioselective mono-alkynylation of cycloalkanes



N-(2,3,4,5,6-pentafluorophenyl)-cycloalcanecarboxamide **1b** (0.18 mmol, 1 equiv.), 1-iodo-2-triisopropylsilyl acetylene (70 mg, 0.23 mmol, 1.2 equiv.), silver acetate (31 mg, 0.18 mmol, 1 equiv.), potassium bicarbonate (19 mg, 0.18 mmol, 1 equiv.), palladium(II) acetate (4.3 mg, 0.018 mmol, 10 mol%) and **L15** (13.5 mg, 0.038 mmol, 20 mol%) were weighted in a pressure tube. 2 mL of toluene were added, and the reaction mixture was stirred 30 min at room temperature, followed by heating at 100 °C during 24 h. After cooling to room temperature, the mixture was filtered with 0.2 µm PTFE membrane, washed with dichloromethane and evaporated under reduced pressure. The crude was purified by preparative thin layer chromatography with toluene/ethyl acetate to afford the title compound.

(1*R*,2*S*)-*N*-(pentafluorophenyl)-2-((triisopropylsilyl)ethynyl)cyclopropane-1-carboxamide IV-7aA

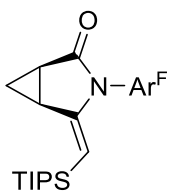
The title compound (57 mg, 74 %, 85 % *ee*) was obtained as a white solid. The absolute stereochemistry was assigned according to **8**.



^{1}H NMR (500 MHz, $CDCl_3$): 7.37 (1H, br s, N*H*), 1.96-2.04 (2H, m), 1.46-1.50 (1H, m), 1.40-1.45 (1H, m), 0.87-1.09 (21H, m, [(C*H*$_3$)$_2$C*H*]$_3$Si); ^{13}C NMR (125 MHz, $CDCl_3$): 168.1, 104.8, 83.2, 23.4, 18.6, 15.6, 11.3, 10.2, carbons corresponding to the pentafluoroamide moiety are not reported; ^{19}F NMR (470 MHz, $CDCl_3$): -144.34, -156.58, -162.57; FT-IR (cm^{-1}): 3244 (m, *N-H*), 2163 (w, *C-C alkyne*), 1676 (m, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{21}H_{27}F_5NOSi^+$ $[M+H]^+$: 432.1777, found: 432.1762; R_t (min, CHIRALPAK ® ADH, Hex/*i*PrOH 99.5/0.5, 0.5 mL/min): 60.48 (92.5 %), 88.70 (7.5 %).

(1*R*,5*S*,*E*)-3-(pentafluorophenyl)-4-((triisopropylsilyl)methylene)-3-azabicyclo[*3.1.0*]hexan-2-one IV-7aA-cy

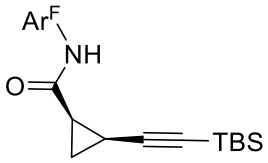
The title compound (6 mg, 5 %) was obtained as a yellow solid. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (500 MHz, $CDCl_3$): 4.08 (1H, s), 2.68 (1H, dd, *J*=11.7, 6.4 Hz), 2.33-2.45 (1H, m), 1.43-1.50 (1H, m), 1.13-1.22 (4H, m), 1.02-1.09 (18H, m, [(C*H*$_3$)$_2$CH]$_3$Si); ^{13}C NMR (125 MHz, $CDCl_3$): 173.1, 150.0, 93.2, 21.3, 20.2, 18.8, 17.5, 12.1, carbons corresponding to the pentafluoroamide moiety are not reported; ^{19}F NMR (377 MHz, $CDCl_3$): -142.91, -144.93, -152.02, -160.81, -161.22; FT-IR (cm^{-1}): 1745 (s, *C-O*), 1634 (s, *C-C alkene*); HRMS (ESI-TOF): m/z calcd for $C_{21}H_{27}F_5NOSi^+$ $[M+H]^+$: 432.1777, found: 432.1774.

(1*R*,2*S*)-2-((*tert*-butyldimethylsilyl)ethynyl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide IV-7aB

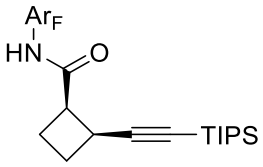
The title compound (67 mg, 86 %, 84 % *ee*) was obtained as a brownish solid. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (400 MHz, $CDCl_3$): 7.41 (1H, br s, N*H*), 2.00-2.09 (1H, m), 1.91-2.00 (1H, m), 1.44-1.50 (1H, m), 1.37-1.44 (1H, m), 0.87 (9H, s, [(C*H*$_3$)$_3$Si(CH$_3$)$_2$]), 0.05 (6H, d, *J*=2.0 Hz, [(CH$_3$)$_3$Si(C*H*$_3$)$_2$]); ^{13}C NMR (100 MHz, $CDCl_3$): 168.1, 103.8, 85.4, 26.0, 23.5, 16.5, 15.4, 10.0, -4.6, carbons corresponding to the pentafluoroamide moiety are not reported; ^{19}F NMR (377 MHz, $CDCl_3$): -144.37, -156.70, -162.53; FT-IR (cm^{-1}): 3249 (m, *N-H*), 2169 (m, *C-C alkyne*), 1682 (s, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{18}H_{21}F_5NOSi^+$ $[M+H]^+$: 390.1307, found: 390.1285; Rt (min, CHIRALPAK ® ODH, Hex/*i*PrOH 99/1, 0.5 mL/min): 78.05 (8 %), 86.72 (92 %).

(1*R*,2*S*)-*N*-(perfluorophenyl)-2-((triisopropylsilyl)ethynyl)cyclobutane-1-carboxamide IV-7bA

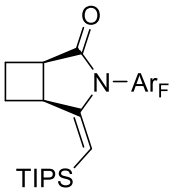
The title compound (67 mg, 80 %, 66 % *ee*) was obtained as an off-white solid. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (500 MHz, $CDCl_3$): 7.68 (1H, br s, N*H*), 3.53 (1H, app q, *J*=7.8 Hz), 3.41 (1H, app q, *J*=8.3 Hz), 2.50-2.65 (1H, m), 2.36-2.46 (1H, m), 2.25-2.35 (1H, m), 2.13-2.23 (1H, m), 1.00 (21H, s, [(C*H*$_3$)$_2$C*H*]$_3$Si); ^{13}C NMR (125 MHz, $CDCl_3$): 170.5, 108.0, 87.1, 43.5, 29.3, 27.9, 23.8, 18.6, 11.2; ^{19}F NMR (470 MHz, $CDCl_3$): -143.69, -156.84, -162.64; FT-IR (cm^{-1}): 3248 (m, *N-H*), 2161 (w, *C-C alkyne*), 1678 (s, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{22}H_{29}F_5NOSi^+$ $[M+H]^+$: 446.1933, found: 446.1914; R_t (min, CHIRALPAK ® ODH, Hex/iPrOH 99/1, 0.5 mL/min): 28.01 (17 %), 32.09 (83 %).

(1*R*,2*S*,*E*)-3-(perfluorophenyl)-4-((triisopropylsilyl)methylene)-3-azabicyclo[*3.2.0*]heptan-2-one IV-7bA-cy

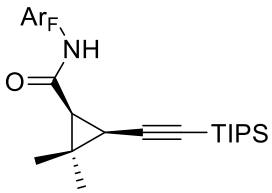
The title compound (3 mg, 4 %) was obtained as a yellow oil. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (500 MHz, $CDCl_3$): 4.02 (1H, s), 3.67 (1H, app q, *J*=7.6 Hz), 3.32 (1H, app q, *J*=7.0 Hz), 2.55-2.67 (2H, m), 2.29-2.39 (1H, m), 2.19-2.29 (1H, m), 0.94-1.13 (21H, m, [(C*H*$_3$)$_2$C*H*]$_3$Si); ^{13}C NMR (125 MHz, $CDCl_3$): 177.4, 154.6, 91.9, 40.3, 37.9, 28.7, 23.5, 18.8, 12.0; ^{19}F NMR (470 MHz, $CDCl_3$): -143.16, -144.07, -152.09, -160.78, -161.13; FT-IR (cm^{-1}): 1751 (s, *C-O*), 1632 (s, *C-C alkene*); HRMS (ESI-TOF): m/z calcd $C_{22}H_{29}F_5NOSi^+$ $[M+H]^+$: 446.1933, found: 446.1947.

(1*S*,3*R*)-2,2-dimethyl-*N*-perfluorophenyl-3-((triisopropylsilyl)ethynyl)cyclopropane-1-carboxamide IV-7cA

The title compound (58 mg, 70 %, 20 % *ee*) was obtained as a pale yellow solid. The absolute stereochemistry was assigned according to **IV-2aR**.

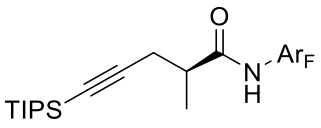


^{1}H NMR (500 MHz, $CDCl_3$): 8.19 (1H, br s, N*H*), 1.81-1.89 (2H, m), 1.37 (3H, s, C*H*$_3$), 1.31 (3H, s, C*H*$_3$), 1.01 (21H, s, [(C*H*$_3$)$_2$C*H*]$_3$Si); ^{13}C NMR (125 MHz, $CDCl_3$): 168.1, 104.7, 87.6, 34.6, 27.5, 26.3, 20.9, 18.6, 16.8, 11.3; ^{19}F NMR (470 MHz, $CDCl_3$): -143.96, -155.98, -162.44; FT-IR (cm^{-1}): 3294

(m, *N-H*), 2159 (m, *C-C alkyne*), 1684 (m, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{23}H_{31}F_5NOSi^+$ $[M+H]^+$: 460.2090, found: 460.2072; R_t (min, CHIRALPAK ® ADH, Hex/iPrOH 99/1, 0.5 mL/min): 10.69 (40 %), 15.72 (60 %).

(*S*)-2-methyl-*N*-(perfluorophenyl)-5-(triisopropylsilyl)pent-4-ynamide IV-7dA

The title compound (62 mg, 72 %, 12 % *ee*) was obtained as a white solid. The absolute stereochemistry was assigned according to **IV-2aR**.



^{1}H NMR (400 MHz, $CDCl_3$): 7.32 (1H, br s, N*H*), 2.71-2.81 (1H, m, C*H*CH_3), 2.54-2.69 (2H, m), 1.39 (3H, d, *J*=6.9 Hz, CHC*H*$_3$), 1.04 (21H, s, [(C*H*$_3$)$_2$C*H*]$_3$Si); ^{13}C NMR (100 MHz, $CDCl_3$): 173.4, 105.5, 84.2, 40.7, 24.4, 18.7, 17.2, 11.3; ^{19}F NMR (377 MHz, $CDCl_3$): -144.67, -156.37, -162.40; FT-IR (cm^{-1}): 3255 (m, *N-H*), 2177 (m, *C-C alkyne*), 1680 (s, *C-O*); HRMS (ESI-TOF): m/z calcd for $C_{21}H_{29}F_5NOSi^+$ $[M+H]^+$: 431.1933, found: 431.1924; Rt (min, CHIRALPAK ® ODH, Hex/iPrOH 98/2, 0.5 mL/min): 18.02 (56 %), 20.90 (44 %).

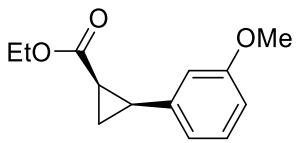
IV.8.v. Large scale and deprotection experiments

Large scale synthesis of (1*R*,2*S*)-2-(3-methoxyphenyl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide

N-(2,3,4,5,6-pentafluorophenyl)-cyclopropanecarboxamide **IV-1a** (1 g, 4 mmol, 1 equiv.), 3-iodoanisole (1 mL, 8.3 mmol, 2.1 equiv.), silver carbonate (2.1 g, 8 mmol, 2 equiv.), sodium trifluoroacetate (280 mg, 2 mmol, 50 mol%), palladium(II) trifluoroacetate (70 mg, 0.2 mmol, 5 mol%) and **L12** (213 mg, 0.6 mmol, 15 mol%) were weighted in a pressure tube. Hexane (8 mL) and chloroform (4 mL) were added and the reaction mixture was stirred 30 min at room temperature, followed by heating at 80 °C during 24 h. After cooling to room temperature, the mixture was filtered through celite, washed with chloroform and evaporated under reduced pressure. ^{1}H NMR showed around 70% conversion and chiral HPLC 94% *ee*. The crude was directly used for the deprotection step without further purification.

ethyl (1*R*,2*S*)-2-(3-methoxyphenyl)cyclopropane-1-carboxylate IV-3

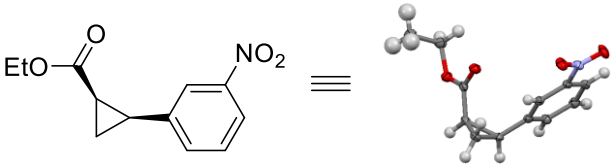
To a stirred solution of the crude (1*R*,2*S*)-2-(3-methoxyphenyl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide obtained in the previous step (assumed 1 – 1.2 g) in ethanol were added potassium acetate (290 mg, 2.95 mmol, 1 equiv.) and glycidyl methyl ether (800 µL, 82 mmol, 3 equiv.). After inertion (vacuum/argon), the mixture was heated at 90 °C and stirred 24 h. After cooling to room temperature, solvents were evaporated under reduced pressure, and the crude was directly purified by column chromatography on silica gel using pentane/ethyl acetate (95:5) to afford the title compound (552 mg, 57 % over 2 steps, 93 % *ee*) as a clear oil and pentane/ethyl acetate (1:7) to recover the ligand (203 mg, 95 %, >99% *ee*) as an off-orange solid.[290] The absolute configuration of the title compound was assigned according to **IV-5**.



^{1}H NMR (500 MHz, $CDCl_3$): 7.17 (1H, t, *J*=7.9 Hz), 6.86 (1H, dd, *J*=8.0, 1.1 Hz), 6.82 (1H, t, *J*=1.9 Hz), 6.74 (1H, dd, *J*=8.2, 5.5 Hz), 3.90 (2H, q, J=7.1 Hz, CH_2CH_3), 3.78 (3H, s, $COCH_3$), 2.55 (1H, app q, *J*=8.7 Hz), 2.07 (1H, ddd, *J*=9.3, 7.8, 5.6 Hz), 1.69-1.73 (1H, m), 1.31 (1H, ddd, *J*=8.6, 7.9, 5.1 Hz), 1.00 (3H, t, *J*=7.1 Hz, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 171.1, 159.4, 138.4, 129.0, 121.9, 115.1, 112.4, 60.4, 55.3, 25.6, 21.9, 14.2, 11.4; FT-IR (cm^{-1}): 1726 (s, *C-O ester*), 1047 (m, *C-O ether*); HRMS (ESI-TOF): m/z calcd for $C_{13}H_{16}NaO_3^+$ $[M+Na]^+$: 243.0992, found: 243.0974; R_t (min, CHIRALPAK ® ODH, Hex/*i*PrOH 99/1, 0.5 mL/min): 19.64 (96.5 %), 24.82 (3.5 %).

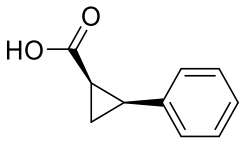
ethyl (1*R*,2*S*)-2-(3-nitrophenyl)cyclopropane-1-carboxylate IV-4

To a stirred solution of (1*R*,2*S*)-2-(3-nitrophenyl)-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide **IV-2aB** (44 mg, 0.12 mmol, 1 equiv.) in 2 mL of anhydrous THF was added di-*tert*-butyl-dicarbonate (26 mg, 0.12 mmol, 1 equiv.) and one crystal of 4-(dimethylamino)-pyridine. After 1 h, a solution of lithium hydroxide (8.5 mg, 0.35 mmol, 3 equiv.) in water was added to the mixture, which was further stirred 2 h at room temperature. The mixture was diluted with diethyl ether and basified using 1M NaOH sol. (10 mL). The aqueous layer was extracted, carefully acidified with 2M HCl and diluted with diethyl ether. The organic layer was extracted, washed with brine and evaporated under reduced pressure. The crude was directly dissolved in absolute ethanol before dropwise addition of thionyl chloride (10 µL, 0.15 mmol, 1.3 equiv.). After stirring for 18 h, the mixture was evaporated under reduced pressure and the crude was directly purified by column chromatography on silica gel using pentane/ethyl acetate (9:1) to afford the title compound (25 mg, 90 %, 88 % *ee*) as a white solid. Diffusion with Et_2O/Hexane at 3 – 5 °C afforded mono crystals (22 mg, 79 %, >99% *ee*) suitable for X-Ray diffraction analysis which were analysed on the Bruker APEX II DUO Kappa-CCD diffractometer.



^{1}H NMR (500 MHz, $CDCl_3$): 8.14 (1H, t, *J*=1.8 Hz), 8.07 (1H, dd, *J*=8.4, 2.0 Hz), 7.57-7.63 (1H, m), 7.44 (1H, t, *J*=7.9 Hz), 3.91 (2H, q, *J*=7.1 Hz, CH_2CH_3), 2.63 (1H, app q, *J*=8.6 Hz), 2.17 (1H, ddd, *J*=9.2, 8.0, 5.7 Hz), 1.68-1.81 (1H, m), 1.45 (1H, ddd, J=8.7, 8.0, 5.3 Hz), 1.03 (3H, t, *J*=7.1 Hz, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 170.7, 148.1, 139.0, 135.7, 128.9, 124.6, 121.9, 60.7, 25.0, 22.1, 14.2, 11.8; FT-IR (cm^{-1}): 1725 (s, *C-O*), 1528 (s, *N-O*), 1349 (s, *N-O*), 1186 (s, *C-O*); mp (°C): 94; HRMS (ESI-TOF): m/z calcd for $C_{12}H_{14}NO_4^+$ $[M+H]^+$: 236.0917, found: 236.0934; R_t (min, CHIRALPAK ® ODH, Hex/*i*PrOH 99.8/0.2, 1 mL/min): 27.57 (6 %), 29.23 (94 %) and after crystallization 27.65 (0.2 %), 29.22 (99.8 %).

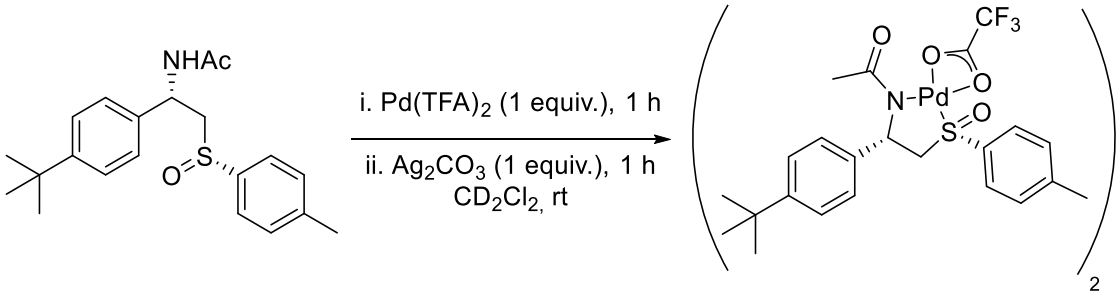
(1*R*,2*S*)-2-phenylcyclopropane-1-carboxylic acid IV-5



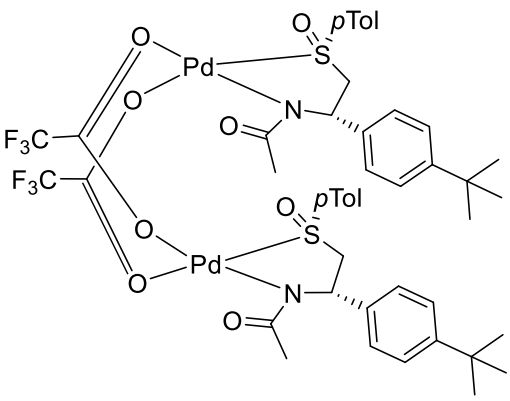
To a stirred solution of (1*R*,2*S*)-2-phenyl-*N*-(pentafluorophenyl)cyclopropane-1-carboxamide **IV-2aN** (30 mg, 0.09 mmol, 1 equiv.) in 5 mL of ethanol was added sodium hydroxide (18 mg, 0.45 mmol, 5 equiv.). The resulting mixture was stirred at reflux during 18 h. Ethanol was removed under reduced pressure and diethyl ether (20 mL) and water (10 mL) were added. The aqueous layer was extracted and subsequently carefully acidified with 1M HCl sol. Dichloromethane (20 mL) was added. The organic layer was extracted, washed with brine (10 mL), dried (Na_2SO_4), filtered off and evaporated under reduced pressure to yield the title compound (14 mg, 94 %) as a yellow oil. The absolute configuration of this carboxylic acid was determined to be (1*R*, 2*S*) by optical rotation: $[\alpha]_D^{20} = -24°$ (c=1.1, $CHCl_3$), lit. $[\alpha]_D^{20} = -28°$ (c = 1.02, $CHCl_3$). Other data match the reported ones.[291]

IV.8.vi. Mechanistic studies

IV.8.vi.1. Synthesis of the bis(TFA-Pd(II)-**L12**) chelate



To a solution of *N*-((*S*)-1-(4-(*tert*-butyl)phenyl)-2-((*R*)-*p*-tolylsulfinyl)ethyl)acetamide **L15** (10.8 mg, 0.03 mmol, 1 equiv.) in CD_2Cl_2 was added palladium(II) trifluoroacetate (10.1 mg, 0.03 mmol, 1 equiv.). After 1 h, NMR showed half conversion to the pre-chelate. Silver carbonate (8.5 mg, 0.03 mmol, 1 equiv.) was added, and the resulting mixture was stirred 1 h at room temperature. The mixture was filtered, and NMR showed full conversion to the desired chelate.



^{1}H NMR (500 MHz, CD_2Cl_2): 7.62 (2H, d, *J*=8.5 Hz), 7.42 (2H, d, *J*=8.5 Hz), 7.27 (2H, d, *J*=8.2 Hz), 7.17 (2H, d, *J*=8.3 Hz), 4.75 (1H, d, *J*=5.8 Hz), 4.41 (1H, d, *J*=13.1 Hz), 4.01 (1H, dd, *J*=13.2, 6.0 Hz), 2.38 (3H, s, PhC*H*$_3$), 2.25 (3H, s, C(O)C*H*$_3$), 1.36 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (125 MHz, CD_2Cl_2): 183.4, 165.6 (q, *J*=42 Hz), 153.3, 147.3, 136.5, 132.6, 131.0, 127.1, 126.5, 126.0, 115.2 (q, *J*=283 Hz), 72.7, 64.0, 35.2, 31.6, 22.7, 22.0; ^{19}F NMR (470 MHz, CD_2Cl_2): -74.20; FT-IR (cm^{-1}): 1715 (s, *C-O amide*), 1666 (s, *C-O trifluoroacetamide*), 1076 (m, *S-O*); HRMS (ESI-TOF): m/z calcd for $C_{46}H_{52}F_6N_2NaO_8Pd_2S_2^+$ $[M+Na]^+$: 1175.1052, found: 1175.1066.

IV.8.vi.2. Preliminary DFT studies

ETS-NOCV analysis of IV-pre-dia1

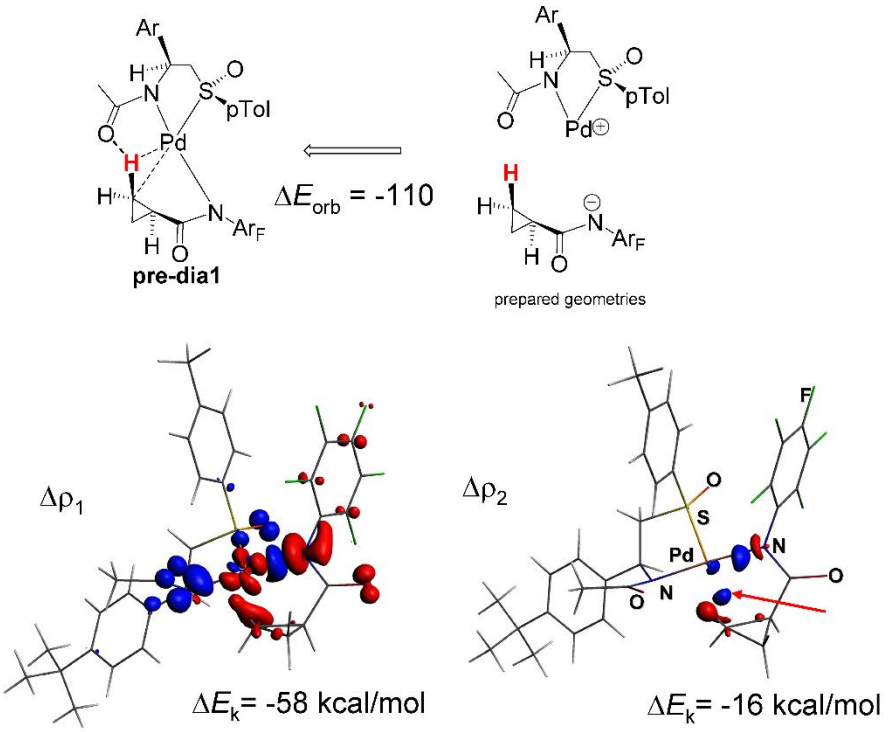


Figure 1. Plots of density deformation isosurfaces (0.005 e/bohr3) arising from the ETS-NOCV analysis of the interaction of the an-1b anion with the cat-Pd-L15 cation in their « prepared » geometries giving pre-dia1. Deformation density $\Delta\rho_2$ materialises, apart from the coordinative N-Pd interaction, the weak donor-acceptor « agostic » interaction between the vicinal C_{cy}-H_{cy} bond and the Pd(II) centre. $\Delta\rho_2$ contributes to about 14 % of the total interfragment orbital interaction energy. Blue and red isosurfaces are associated with density accepting and donating orbital contributors. The occurrence of a blue isosurface in an interatomic space is associated with the formation of a covalent bond. Red isosurfaces explicit the origin of the electron density contributing to the formation of this bond or to the population of the blue-colored orbital components.

ETS-NOCV analysis of IV-pre-dia2

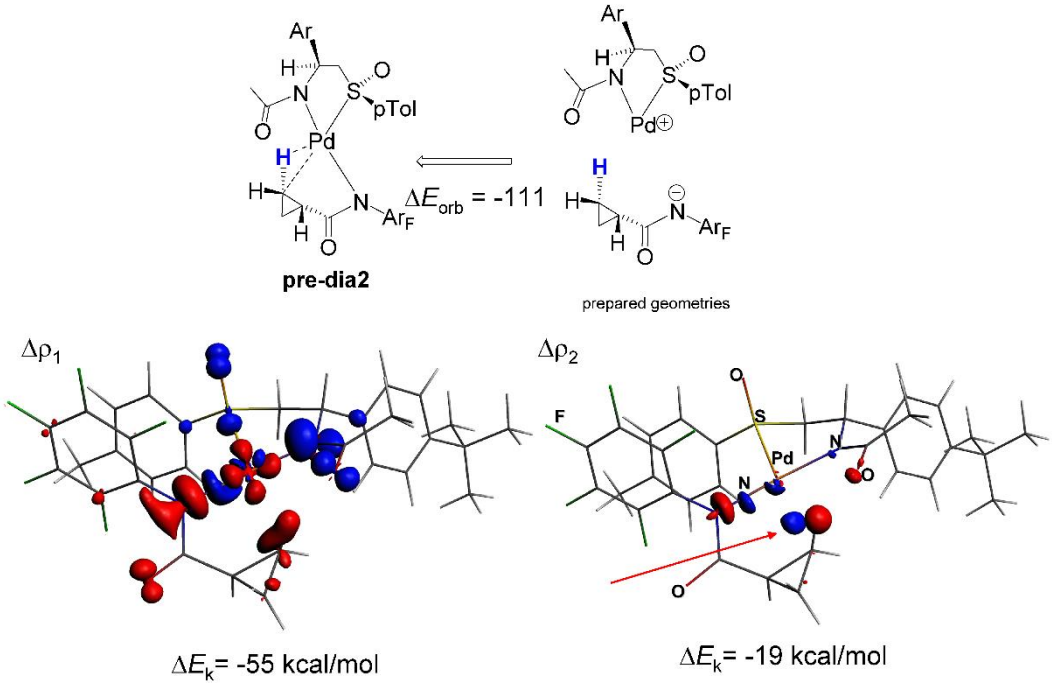


Figure 2. Plots of density deformation isosurfaces (0.005 e/bohr3) arising from the ETS-NOCV analysis of the interaction of the an-1b anion with the cat-Pd-L15 cation in their « prepared » geometries giving pre-dia2. Deformation density $\Delta\rho_2$ materialises, apart from the coordinative N-Pd interaction, the weak donor-acceptor « agostic » interaction (red arrow) between the vicinal C_{cy}-H_{cy} bond and the Pd(II) centre. $\Delta\rho_2$ contributes to about 17 % of the total interfragment orbital interaction energy. Blue and red isosurfaces are associated with density accepting and donating orbital contributors. The occurrence of a blue isosurface in an interatomic space is associated with the formation of a covalent bond. Red isosurfaces explicit the origin of the electron density contributing to the formation of this bond or to the population of the blue-colored orbital components.

NCI plot of IV-pre-dia1

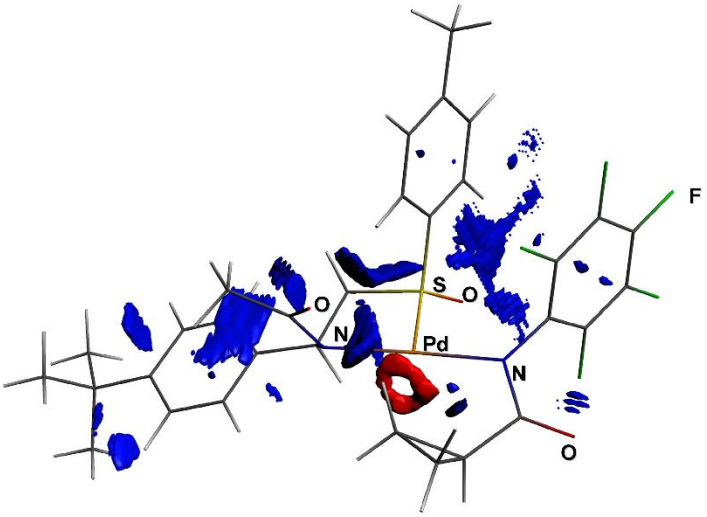


Figure 3. NCI isosurface plot of intermediate pre-dia1 showing significant attractive non-covalent support (note the « covalent hole » in the isosurface) to the weakly covalent component (see ETS-NOCV analysis) of the « agostic » C_{cy}-H_{cy}-Pd interaction in pre-dia1. NCI plot of attractive (red colored) and repulsive or non bonded (blue colored isosurfaces) noncovalent interactions are materialized by reduced density gradient isosurfaces (cut-off value s= 0.02 a.u., ρ= 0.05 a.u.) colored according to the sign of the signed density $\lambda_2\rho$.

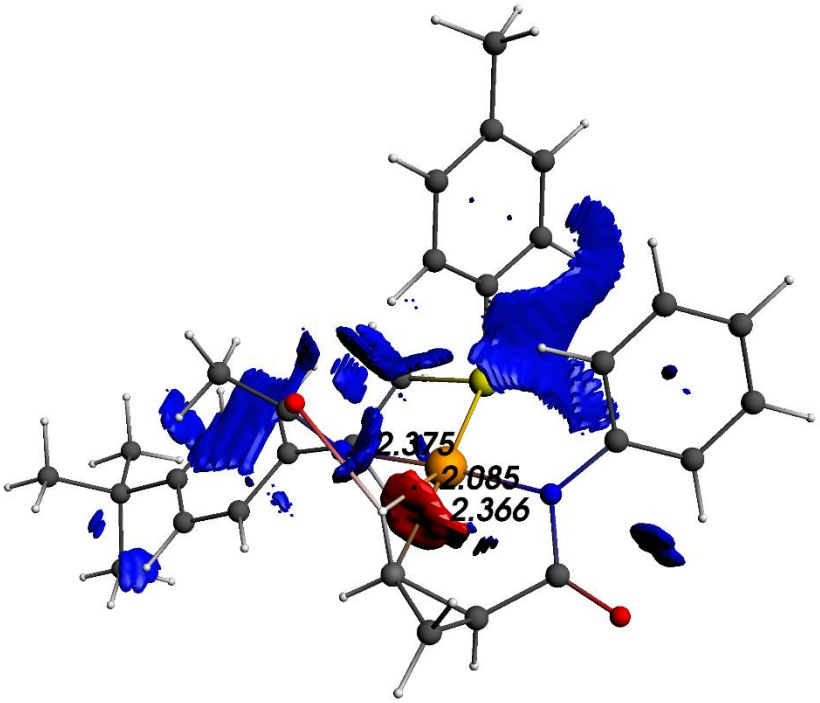


Figure 4. NCI isosurface plot of the intermediate pre-dia1 showing significant attractive non-covalent support to the « agostic » C_{cy}-H_{cy}-Pd interaction in pre-dia1$_H$. NCI plot of attractive (red colored) and repulsive or non bonded (blue colored isosurfaces) noncovalent interactions are materialized by reduced density gradient isosurfaces (cut-off value s= 0.02 a.u., ρ= 0.05 a.u.) colored according to the sign of the signed density $\lambda_2\rho$.

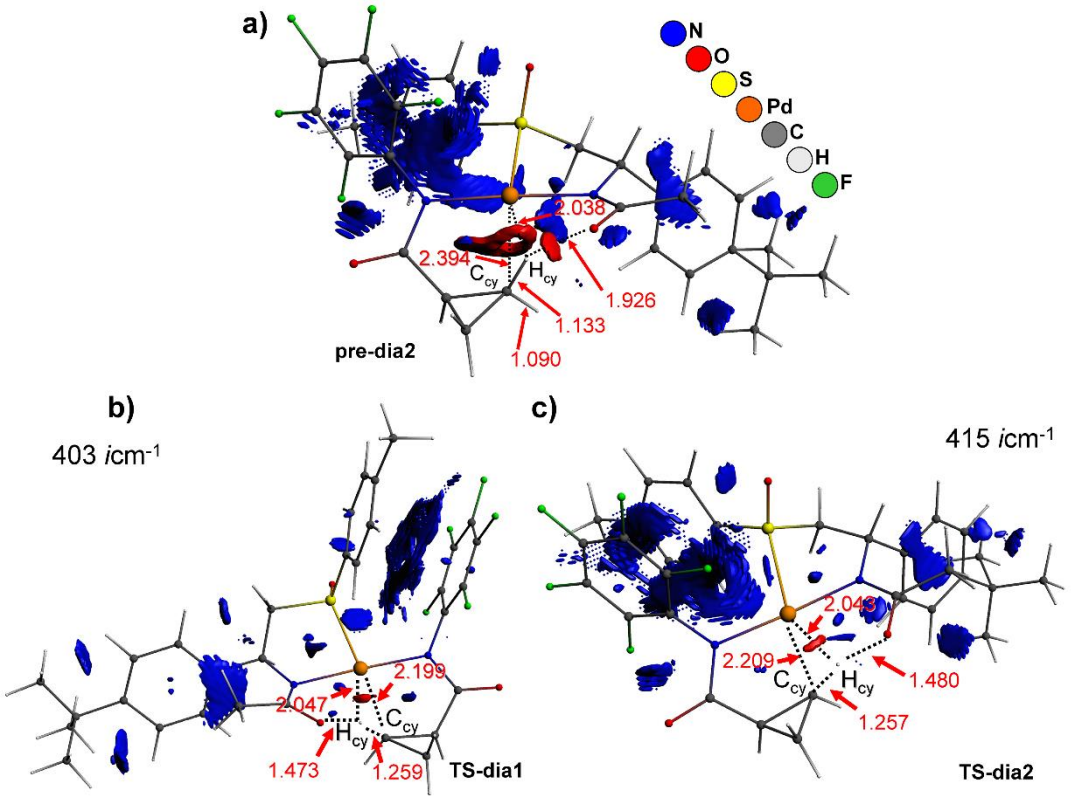


Figure 5. DFT calculations were carried out with singlet gas phase geometries optimized at the ZORA-PBE-D3(BJ)/all electron TZP level (see SI for details): a) NCI plot of attractive (red colored) and repulsive or non bonded (blue colored isosurfaces) noncovalent interactions materialized by reduced density gradient isosurfaces (cut-off value *s*= 0.02 a.u., *r*= 0.05 a.u.) colored according to the sign of the signed density l_2r for pre-dia2 with significant interatomic distances (red colored fonts, in Å); b) and c) NCI isosurfaces in TS-dia1 and TS-dia2 with significant interatomic distances and the imaginary frequency associated to the C_{cy}-H_{cy}activation assisted by the vicinal Pd and O centres.[292,293]

Note that in all models optimal *pi-pi* stacking of the C_6F_5 and *p*-tolyl group contributes in stabilizing the *trans* N-Pd-N stereochemistry. In **pre-dia2** NCI support the weakly covalent "agostic" Pd-to-H_{cy}-C_{cy} interaction (Pd-H_{cy}= 2.038 Å, Pd-C_{cy}= 2.394 Å, H_{cy}-O= 1.926 Å), embodied by the "covalent hole" within the NCI attractive isosurface, in two ways: by spread out attractive Pd-to-H_{cy}-C_{cy} NCI and by H_{cy}-O NCI (Figure SX) that are absent in **pre-dia1**. Interestingly, the H_{cy}-C_{cy} bond in **pre-dia2** is slightly more elongated (1.133 Å) than that in **pre-dia1** (1.119 Å).

Energies (please see separate SI document in the xyz format for cartesian coordinates)

IV-cat-Pd-L12

	hartree	eV	kcal/mol	kJ/mol
Pauli Repulsion				
Kinetic (Delta T^0):	116.528722568589288	3170.9079	73122.89	305946.12
Delta V^Pauli Coulomb:	-57.232195629763758	-1557.3673	-35913.75	-150263.11
Delta V^Pauli LDA-XC:	-15.252637425222694	-415.0454	-9571.18	-40045.79
Delta V^Pauli GGA-Exchange:	0.744881476714600	20.2693	467.42	1955.69
Delta V^Pauli GGA-Correlation:	-0.163630997867099	-4.4526	-102.68	-429.61
Total Pauli Repulsion: (Total Pauli Repulsion = Delta E^Pauli in BB paper)	44.625139992450336	1214.3118	28002.70	117163.29
Steric Interaction				
Pauli Repulsion (Delta E^Pauli):	44.625139992450336	1214.3118	28002.70	117163.29
Electrostatic Interaction: (Electrostatic Interaction = Delta V_elstat in the BB paper)	-9.200410371868596	-250.3559	-5773.35	-24155.67
Total Steric Interaction: (Total Steric Interaction = Delta E^0 in the BB paper)	35.424729620581743	963.9559	22229.36	93007.61
Orbital Interactions				
A:	-46.594581570183891	-1267.9031	-29238.54	-122334.06
Total Orbital Interactions:	-46.608755966837016	-1268.2888	-29247.44	-122371.27
Alternative Decomposition Orb.Int.				
Kinetic:	-106.102263164410715	-2887.1895	-66580.18	-278571.45
Coulomb:	54.926971118806797	1494.6389	34467.20	144210.74
XC:	4.566536078766899	124.2618	2865.54	11989.44
Total Orbital Interactions:	-46.608755966837016	-1268.2888	-29247.44	-122371.27
Residu (E=Steric+OrbInt+Res):	0.000021628538019	0.0006	0.01	0.06
Dispersion Energy:	-0.075244331952986	-2.0475	-47.22	-197.55
Total Bonding Energy:	-11.259249049670240	-306.3798	-7065.29	-29561.15

IV-an-1b

	hartree	eV	kcal/mol	kJ/mol
Pauli Repulsion				
Kinetic (Delta T^0):	64.144229362057047	1745.4533	40251.12	168410.65
Delta V^Pauli Coulomb:	-33.792074948519243	-919.5291	-21204.85	-88721.08
Delta V^Pauli LDA-XC:	-8.008413412526675	-217.9200	-5025.36	-21026.09
Delta V^Pauli GGA-Exchange:	0.371651536232235	10.1132	233.21	975.77
Delta V^Pauli GGA-Correlation:	-0.075260745555775	-2.0479	-47.23	-197.60
Total Pauli Repulsion: (Total Pauli Repulsion = Delta E^Pauli in BB paper)	22.640131791687590	616.0693	14206.90	59441.66
Steric Interaction				
Pauli Repulsion (Delta E^Pauli):	22.640131791687590	616.0693	14206.90	59441.66
Electrostatic Interaction: (Electrostatic Interaction = Delta V_elstat in the BB paper)	-4.886686177920446	-132.9735	-3066.44	-12829.99
Total Steric Interaction: (Total Steric Interaction = Delta E^0 in the BB paper)	17.753445613767145	483.0958	11140.46	46611.66
Orbital Interactions				
A:	-22.971271557009306	-625.0801	-14414.69	-60311.06
Total Orbital Interactions:	-22.978988573931396	-625.2901	-14419.53	-60331.33
Alternative Decomposition Orb.Int.				
Kinetic:	-59.580202523278970	-1621.2598	-37387.15	-156427.80
Coulomb:	34.062042984611054	926.8753	21374.26	89429.88
XC:	2.539170964736515	69.0944	1593.35	6666.59
Total Orbital Interactions:	-22.978988573931399	-625.2901	-14419.53	-60331.33
Residu (E=Steric+OrbInt+Res):	0.000026877289204	0.0007	0.02	0.07
Dispersion Energy:	-0.024454105305534	-0.6654	-15.35	-64.20
Total Bonding Energy:	-5.249970188180581	-142.8590	-3294.41	-13783.79

IV-pre-dia1

	hartree	eV	kcal/mol	kJ/mol
Pauli Repulsion				
Kinetic (Delta T^0):	183.898098826870751	5004.1219	115397.81	482824.39
Delta V^Pauli Coulomb:	-93.413911761735221	-2541.9219	-58618.12	-245258.19
Delta V^Pauli LDA-XC:	-23.699159553781623	-644.8869	-14871.45	-62222.13
Delta V^Pauli GGA-Exchange:	1.163476427574039	31.6598	730.09	3054.71
Delta V^Pauli GGA-Correlation:	-0.258151216988630	-7.0247	-161.99	-677.78
Total Pauli Repulsion: (Total Pauli Repulsion = Delta E^Pauli in BB paper)	67.690352721939320	1841.9482	42476.34	177721.00
Steric Interaction				
Pauli Repulsion (Delta E^Pauli):	67.690352721939320	1841.9482	42476.34	177721.00
Electrostatic Interaction: (Electrostatic Interaction = Delta V_elstat in the BB paper)	-14.262137000142767	-388.0925	-8949.63	-37445.24
Total Steric Interaction: (Total Steric Interaction = Delta E^0 in the BB paper)	53.428215721796555	1453.8557	33526.72	140275.76
Orbital Interactions				
A:	-69.984978396964223	-1904.3882	-43916.24	-183745.53
Total Orbital Interactions:	-70.009903613327396	-1905.0664	-43931.88	-183810.98
Alternative Decomposition Orb.Int.				
Kinetic:	-168.755464957400562	-4592.0698	-105895.66	-443067.41
Coulomb:	91.276411431725776	2483.7575	57276.82	239646.18
XC:	7.469149912347384	203.2459	4686.96	19610.25
Total Orbital Interactions:	-70.009903613327396	-1905.0664	-43931.88	-183810.98
Residu (E=Steric+OrbInt+Res):	-0.000020390795223	-0.0006	-0.01	-0.05
Dispersion Energy:	-0.119505361873726	-3.2519	-74.99	-313.76
Total Bonding Energy:	-16.701213644199790	-454.4631	-10480.17	-43849.03

IV-TS-dia1

	hartree	eV	kcal/mol	kJ/mol
Pauli Repulsion				
Kinetic (Delta T^0):	185.024827617711566	5034.7817	116104.84	485782.62
Delta V^Pauli Coulomb:	-94.084853224015006	-2560.1791	-59039.14	-247019.75
Delta V^Pauli LDA-XC:	-23.850266689881760	-648.9988	-14966.27	-62618.87
Delta V^Pauli GGA-Exchange:	1.174239553836827	31.9527	736.85	3082.97
Delta V^Pauli GGA-Correlation:	-0.260342258012473	-7.0843	-163.37	-683.53
Total Pauli Repulsion: (Total Pauli Repulsion = Delta E^Pauli in BB paper)	68.003604999639151	1850.4722	42672.91	178543.44
Steric Interaction				
Pauli Repulsion (Delta E^Pauli):	68.003604999639151	1850.4722	42672.91	178543.44
Electrostatic Interaction: (Electrostatic Interaction = Delta V_elstat in the BB paper)	-14.370831862552707	-391.0502	-9017.83	-37730.61
Total Steric Interaction: (Total Steric Interaction = Delta E^0 in the BB paper)	53.632773137086446	1459.4220	33655.08	140812.83
Orbital Interactions				
A:	-70.207569972059588	-1910.4452	-44055.92	-184329.95
Total Orbital Interactions:	-70.207569972059588	-1910.4452	-44055.92	-184329.95
Alternative Decomposition Orb.Int.				
Kinetic:	-169.617189081791992	-4615.5186	-106436.40	-445329.87
Coulomb:	91.846568029890108	2499.2723	57634.60	241143.13
XC:	7.563051079842242	205.8011	4745.89	19856.79
Total Orbital Interactions:	-70.207569972059645	-1910.4452	-44055.92	-184329.95
Residu (E=Steric+OrbInt+Res):	0.000002930821021	0.0001	0.00	0.01
Dispersion Energy:	-0.121951418095485	-3.3185	-76.53	-320.18
Total Bonding Energy:	-16.696745322247605	-454.3416	-10477.37	-43837.30

IV-Pd-dia1

	hartree	eV	kcal/mol	kJ/mol
Pauli Repulsion				
Kinetic (Delta T^0):	184.627203558914260	5023.9618	115855.33	484738.65
Delta V^Pauli Coulomb:	-93.919861731392686	-2555.6895	-58935.61	-246586.56
Delta V^Pauli LDA-XC:	-23.807293682113791	-647.8294	-14939.30	-62506.04
Delta V^Pauli GGA-Exchange:	1.173537527769312	31.9336	736.41	3081.12
Delta V^Pauli GGA-Correlation:	-0.261329831381756	-7.1111	-163.99	-686.12
Total Pauli Repulsion: (Total Pauli Repulsion = Delta E^Pauli in BB paper)	67.812255841795334	1845.2654	42552.84	178041.05
Steric Interaction				
Pauli Repulsion (Delta E^Pauli):	67.812255841795334	1845.2654	42552.84	178041.05
Electrostatic Interaction: (Electrostatic Interaction = Delta V_elstat in the BB paper)	-14.304144308310562	-389.2356	-8975.99	-37555.53
Total Steric Interaction: (Total Steric Interaction = Delta E^0 in the BB paper)	53.508111533484772	1456.0298	33576.85	140485.53
Orbital Interactions				
A:	-70.101716997158718	-1907.5648	-43989.50	-184052.03
Total Orbital Interactions:	-70.101716997158732	-1907.5648	-43989.50	-184052.03
Alternative Decomposition Orb.Int.				
Kinetic:	-169.416630216673667	-4610.0611	-106310.55	-444803.30
Coulomb:	91.752420150343539	2496.7104	57575.52	240895.95
XC:	7.562493069171386	205.7859	4745.54	19855.32
Total Orbital Interactions:	-70.101716997158746	-1907.5648	-43989.50	-184052.03
Residu (E=Steric+OrbInt+Res):	-0.000026828070429	-0.0007	-0.02	-0.07
Dispersion Energy:	-0.121777683455515	-3.3137	-76.42	-319.73
Total Bonding Energy:	-16.715409975199904	-454.8494	-10489.08	-43886.30

IV-pre-dia2

	hartree	eV	kcal/mol	kJ/mol
Pauli Repulsion				
Kinetic (Delta T^0):	184.118776637857366	5010.1268	115536.29	483403.78
Delta V^Pauli Coulomb:	-93.518695799252271	-2544.7732	-58683.87	-245533.30
Delta V^Pauli LDA-XC:	-23.741089379181112	-646.0279	-14897.76	-62332.22
Delta V^Pauli GGA-Exchange:	1.167783143496074	31.7770	732.80	3066.01
Delta V^Pauli GGA-Correlation:	-0.259453120194953	-7.0601	-162.81	-681.19
Total Pauli Repulsion: (Total Pauli Repulsion = Delta E^Pauli in BB paper)	67.767321482725094	1844.0426	42524.64	177923.08
Steric Interaction				
Pauli Repulsion (Delta E^Pauli):	67.767321482725094	1844.0426	42524.64	177923.08
Electrostatic Interaction: (Electrostatic Interaction = Delta V_elstat in the BB paper)	-14.291243521508585	-388.8845	-8967.89	-37521.65
Total Steric Interaction: (Total Steric Interaction = Delta E^0 in the BB paper)	53.476077961216511	1455.1581	33556.75	140401.42
Orbital Interactions				
A:	-70.036728208713328	-1905.7963	-43948.72	-183881.40
Total Orbital Interactions:	-70.062523108895462	-1906.4983	-43964.90	-183949.13
Alternative Decomposition Orb.Int.				
Kinetic:	-168.985450784654688	-4598.3281	-106039.98	-443671.24
Coulomb:	91.421206870250899	2487.6976	57367.68	240026.34
XC:	7.501720805508277	204.1322	4707.40	19695.77
Total Orbital Interactions:	-70.062523108895519	-1906.4983	-43964.90	-183949.13
Residu (E=Steric+OrbInt+Res):	-0.000004826837290	-0.0001	0.00	-0.01
Dispersion Energy:	-0.121218995415677	-3.2985	-76.07	-318.26
Total Bonding Energy:	-16.707668969931920	-454.6388	-10484.22	-43865.98

IV-TS-dia2

	hartree	eV	kcal/mol	kJ/mol
Pauli Repulsion				
Kinetic (Delta T^0):	185.210458524910138	5039.8330	116221.33	486269.99
Delta V^Pauli Coulomb:	-94.199635765293337	-2563.3025	-59111.17	-247321.11
Delta V^Pauli LDA-XC:	-23.872832382016419	-649.6128	-14980.43	-62678.11
Delta V^Pauli GGA-Exchange:	1.176001391012875	32.0006	737.95	3087.59
Delta V^Pauli GGA-Correlation:	-0.261143723668217	-7.1061	-163.87	-685.63
Total Pauli Repulsion: (Total Pauli Repulsion = Delta E^Pauli in BB paper)	68.052848044945037	1851.8122	42703.81	178672.73
Steric Interaction				
Pauli Repulsion (Delta E^Pauli):	68.052848044945037	1851.8122	42703.81	178672.73
Electrostatic Interaction: (Electrostatic Interaction = Delta V_elstat in the BB paper)	-14.386843746878053	-391.4859	-9027.88	-37772.65
Total Steric Interaction: (Total Steric Interaction = Delta E^0 in the BB paper)	53.666004298066980	1460.3263	33675.93	140900.07
Orbital Interactions				
A:	-70.249854841093281	-1911.5958	-44082.45	-184440.97
Total Orbital Interactions:	-70.249854841093281	-1911.5958	-44082.45	-184440.97
Alternative Decomposition Orb.Int.				
Kinetic:	-169.800866126748446	-4620.5167	-106551.66	-445812.11
Coulomb:	91.973434546954252	2502.7245	57714.21	241476.22
XC:	7.577576738700848	206.1964	4755.00	19894.92
Total Orbital Interactions:	-70.249854841093352	-1911.5958	-44082.45	-184440.97
Residu (E=Steric+OrbInt+Res):	0.000002366821108	0.0001	0.00	0.01
Dispersion Energy:	-0.121999695376577	-3.3198	-76.56	-320.31
Total Bonding Energy:	-16.705847871581771	-454.5893	-10483.08	-43861.20

IV-Pd-dia2

	hartree	eV	kcal/mol	kJ/mol
Pauli Repulsion				
Kinetic (Delta T^0):	184.717635809454094	5026.4226	115912.08	484976.08
Delta V^Pauli Coulomb:	-93.985500942038399	-2557.4756	-58976.80	-246758.90
Delta V^Pauli LDA-XC:	-23.818109070279093	-648.1237	-14946.09	-62534.44
Delta V^Pauli GGA-Exchange:	1.174428484154348	31.9578	736.97	3083.46
Delta V^Pauli GGA-Correlation:	-0.261670555402469	-7.1204	-164.20	-687.02
Total Pauli Repulsion: (Total Pauli Repulsion = Delta E^Pauli in BB paper)	67.826783725888475	1845.6607	42561.95	178079.20
Steric Interaction				
Pauli Repulsion (Delta E^Pauli):	67.826783725888475	1845.6607	42561.95	178079.20
Electrostatic Interaction: (Electrostatic Interaction = Delta V_elstat in the BB paper)	-14.315274111694475	-389.5384	-8982.97	-37584.75
Total Steric Interaction: (Total Steric Interaction = Delta E^0 in the BB paper)	53.511509614193997	1456.1223	33578.98	140494.45
Orbital Interactions				
A:	-70.114085399716245	-1907.9013	-43997.26	-184084.51
Total Orbital Interactions:	-70.114085399716259	-1907.9013	-43997.26	-184084.51
Alternative Decomposition Orb.Int.				
Kinetic:	-169.481664097504961	-4611.8307	-106351.36	-444974.05
Coulomb:	91.801470349908527	2498.0451	57606.30	241024.73
XC:	7.566108347880169	205.8843	4747.81	19864.81
Total Orbital Interactions:	-70.114085399716259	-1907.9013	-43997.26	-184084.51
Residu (E=Steric+OrbInt+Res):	0.000007873386808	0.0002	0.00	0.02
Dispersion Energy:	-0.121521838230908	-3.3068	-76.26	-319.06
Total Bonding Energy:	-16.724089750366364	-455.0856	-10494.53	-43909.09

IV-pre-dia1$_H$

	hartree	eV	kcal/mol	kJ/mol
Pauli Repulsion				
Kinetic (Delta T^0):	171.655057753852560	4670.9718	107715.19	450680.29
Delta V^Pauli Coulomb:	-84.381011793199519	-2296.1242	-52949.89	-221542.32
Delta V^Pauli LDA-XC:	-22.406935616855204	-609.7237	-14060.57	-58829.40
Delta V^Pauli GGA-Exchange:	1.083590473487849	29.4860	679.96	2844.97
Delta V^Pauli GGA-Correlation:	-0.234513483665914	-6.3814	-147.16	-615.72
Total Pauli Repulsion: (Total Pauli Repulsion = Delta E^Pauli in BB paper)	65.716187333619771	1788.2284	41237.53	172537.83
Steric Interaction				
Pauli Repulsion (Delta E^Pauli):	65.716187333619771	1788.2284	41237.53	172537.83
Electrostatic Interaction: (Electrostatic Interaction = Delta V_elstat in the BB paper)	-13.489420311594126	-367.0658	-8464.74	-35416.47
Total Steric Interaction: (Total Steric Interaction = Delta E^0 in the BB paper)	52.226767022025648	1421.1626	32772.79	137121.36
Orbital Interactions				
A:	-68.778536466105393	-1871.5592	-43159.19	-180578.02
Total Orbital Interactions:	-68.798605432838897	-1872.1053	-43171.78	-180630.71
Alternative Decomposition Orb.Int.				
Kinetic:	-156.258508704749914	-4252.0104	-98053.70	-410256.66
Coulomb:	81.026669027421548	2204.8478	50845.01	212735.49
XC:	6.433234244489471	175.0572	4036.92	16890.45
Total Orbital Interactions:	-68.798605432838897	-1872.1053	-43171.78	-180630.71
Residu (E=Steric+OrbInt+Res):	0.000024918081608	0.0007	0.02	0.07
Dispersion Energy:	-0.118093235530774	-3.2135	-74.10	-310.05
Total Bonding Energy:	-16.689906728262418	-454.1555	-10473.08	-43819.34

IV-pre-dia2$_H$

	hartree	eV	kcal/mol	kJ/mol
Pauli Repulsion				
Kinetic (Delta T^0):	172.191992466556513	4685.5825	108052.12	452090.01
Delta V^Pauli Coulomb:	-84.706311628276097	-2304.9760	-53154.02	-222396.39
Delta V^Pauli LDA-XC:	-22.477788705781233	-611.6518	-14105.03	-59015.43
Delta V^Pauli GGA-Exchange:	1.089262914607577	29.6404	683.52	2859.86
Delta V^Pauli GGA-Correlation:	-0.236879504161481	-6.4458	-148.64	-621.93
Total Pauli Repulsion: (Total Pauli Repulsion = Delta E^Pauli in BB paper)	65.860275542945274	1792.1493	41327.95	172916.13
Steric Interaction				
Pauli Repulsion (Delta E^Pauli):	65.860275542945274	1792.1493	41327.95	172916.13
Electrostatic Interaction: (Electrostatic Interaction = Delta V_elstat in the BB paper)	-13.536707320146304	-368.3525	-8494.41	-35540.62
Total Steric Interaction: (Total Steric Interaction = Delta E^0 in the BB paper)	52.323568222798968	1423.7967	32833.54	137375.51
Orbital Interactions				
A:	-68.883567273742713	-1874.4172	-43225.10	-180853.78
Total Orbital Interactions:	-68.904190502329442	-1874.9784	-43238.04	-180907.93
Alternative Decomposition Orb.Int.				
Kinetic:	-156.771478884861409	-4265.9690	-98375.60	-411603.46
Coulomb:	81.380317782105180	2214.4711	51066.93	213663.99
XC:	6.486970600426828	176.5195	4070.64	17031.54

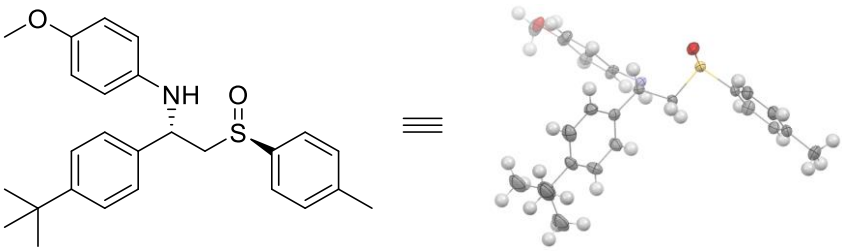
Total Orbital Interactions:	-68.904190502329399	-1874.9784	-43238.04	-180907.93
Residu (E=Steric+OrbInt+Res):	-0.000001335921227	0.0000	0.00	0.00
Dispersion Energy:	-0.120957190522050	-3.2914	-75.90	-317.57
Total Bonding Energy:	-16.701580805973748	-454.4731	-10480.40	-43849.99

IV-TS-dia2$_H$

	hartree	eV	kcal/mol	kJ/mol
Pauli Repulsion				
Kinetic (Delta T^0):	172.781326936069377	4701.6191	108421.93	453637.31
Delta V^Pauli Coulomb:	-85.159481167622289	-2317.3074	-53438.39	-223586.19
Delta V^Pauli LDA-XC:	-22.556075310884946	-613.7820	-14154.15	-59220.97
Delta V^Pauli GGA-Exchange:	1.094008015263668	29.7695	686.50	2872.32
Delta V^Pauli GGA-Correlation:	-0.237783254510834	-6.4704	-149.21	-624.30
Total Pauli Repulsion:	65.921995218314976	1793.8288	41366.68	173078.17
(Total Pauli Repulsion = Delta E^Pauli in BB paper)				
Steric Interaction				
Pauli Repulsion (Delta E^Pauli):	65.921995218314976	1793.8288	41366.68	173078.17
Electrostatic Interaction:	-13.588451656356135	-369.7606	-8526.88	-35676.47
(Electrostatic Interaction = Delta V_elstat in the BB paper)				
Total Steric Interaction:	52.333543561958841	1424.0682	32839.80	137401.70
(Total Steric Interaction = Delta E^0 in the BB paper)				
Orbital Interactions				
A:	-68.909995898131058	-1875.1364	-43241.68	-180923.17
Total Orbital Interactions:	-68.909995898131058	-1875.1364	-43241.68	-180923.17
Alternative Decomposition Orb.Int.				
Kinetic:	-157.295290854168144	-4280.2226	-98704.30	-412978.73
Coulomb:	81.829989215585329	2226.7073	51349.10	214844.61
XC:	6.555305740451751	178.3789	4113.52	17210.95
Total Orbital Interactions:	-68.909995898131058	-1875.1364	-43241.68	-180923.17
Residu (E=Steric+OrbInt+Res):	0.000007137853071	0.0002	0.00	0.02
Dispersion Energy:	-0.119540745159353	-3.2529	-75.01	-313.85
Total Bonding Energy:	-16.695985943478497	-454.3209	-10476.89	-43835.30

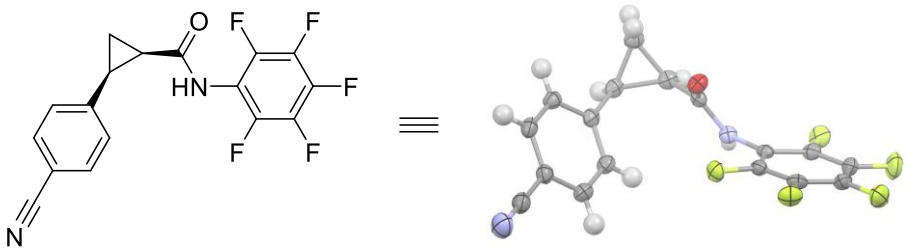
IV.8.vii. X-Ray data

IV.8.vii.1. Compound **PMP-L12**



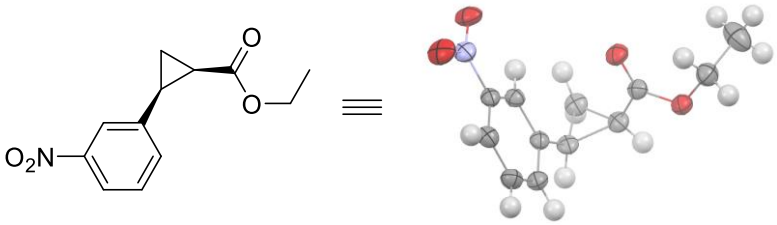
CCDC Identifier	XXX
Structure Identifier	fcsj180529
Formula	$2(C_{26}H_{31}NO_2S),CHCl_3$
Space Group	C2
Cell lengths	**a** 23.8039(6) **b** 5.82060(10) **c** 18.7532(5)
Cell angles	**α** 90 **β** 101.3900(10) **γ** 90
Cell volume	2547.14
Z, Z'	**Z**: 2 **Z'**: 0
R-Factor (%)	7.89
Flack parameter	0.09(6)
Recrystallisation Solvent	Hexane/Dichloromethane/Chloroform

IV.8.vii.2. Compound **IV-2aR**



CCDC Identifier	1859147
Structure Identifier	fcsj180612
Formula	$C_{17}H_9F_5N_2O$
Space Group	P 2_1
Cell lengths	**a** 4.83520(10) **b** 9.9490(2) **c** 15.4991(3)
Cell angles	**α** 90 **β** 92.1150(10) **γ** 90
Cell volume	745.083
Z, Z'	**Z**: 2 **Z'**: 0
R-Factor (%)	2.75
Flack parameter	0.03(3)
Recrystallisation Solvent	Hexane/Dichloromethane

IV.8.vii.3. Compound **IV-4**



CCDC Identifier	XXX
Structure Identifier	fcsj180724
Formula	$C_{12}H_{13}NO_4$
Space Group	P 2_1
Cell lengths	**a** 6.13820(10) **b** 5.7205(2) **c** 16.5239(4)
Cell angles	**α** 90 **β** 96.248(2) **γ** 90
Cell volume	576.767
Z, Z'	**Z**: 2 **Z'**: 0
R-Factor (%)	3.83
Flack parameter	0.13(15)
Recrystallisation Solvent	Dichloromethane/Diethyl ether

IV.9. Bibliographic references

[263] V. I. Sokolov, L. L. Troitskaya, N. S. Khrushchova, *J. Organomet. Chem.* **1983**, *250*, 439–446.
[264] B.-F. Shi, N. Maugel, Y.-H. Zhang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2008**, *47*, 4882–4886.
[265] H. Shi, A. N. Herron, Y. Shao, Q. Shao, J.-Q. Yu, *Nature* **2018**, *558*, 581–585.
[266] J. Zheng, S.-L. You, *Angew. Chem. Int. Ed.* **2014**, *53*, 13244–13247.
[267] J. Zheng, W.-J. Cui, C. Zheng, S.-L. You, *J. Am. Chem. Soc.* **2016**, *138*, 5242–5245.
[268] Q.-J. Yao, S. Zhang, B.-B. Zhan, B.-F. Shi, *Angew. Chem. Int. Ed.* **2017**, *56*, 6617–6621.
[269] K. S. L. Chan, M. Wasa, L. Chu, B. N. Laforteza, M. Miura, J.-Q. Yu, *Nat. Chem.* **2014**, *6*, 146–150.
[270] P.-X. Shen, L. Hu, Q. Shao, K. Hong, J.-Q. Yu, *J. Am. Chem. Soc.* **2018**, *140*, 6545–6549.
[271] Y. Wei, H. Tang, X. Cong, B. Rao, C. Wu, X. Zeng, *Org. Lett.* **2014**, *16*, 2248–2251.
[272] S.-B. Yan, S. Zhang, W.-L. Duan, *Org. Lett.* **2015**, *17*, 2458–2461.
[273] A. P. Smalley, J. D. Cuthbertson, M. J. Gaunt, *J. Am. Chem. Soc.* **2017**, *139*, 1412–1415.
[274] S.-Y. Yan, Y.-Q. Han, Q.-J. Yao, X.-L. Nie, L. Liu, B.-F. Shi, *Angew. Chem. Int. Ed.* **2018**, *57*, 9093–9097.
[275] Q.-F. Wu, P.-X. Shen, J. He, X.-B. Wang, F. Zhang, Q. Shao, R.-Y. Zhu, C. Mapelli, J. X. Qiao, M. A. Poss, et al., *Science* **2017**, *355*, 499–503.
[276] Q. Shao, J. He, Q.-F. Wu, J.-Q. Yu, *ACS Catal.* **2017**, *7*, 7777–7782.
[277] Q. Shao, Q.-F. Wu, J. He, J.-Q. Yu, *J. Am. Chem. Soc.* **2018**, *140*, 5322–5325.
[278] Z. Li, C.-J. Li, *Org. Lett.* **2004**, *6*, 4997–4999.
[279] O. Baslé, C.-J. Li, *Org. Lett.* **2008**, *10*, 3661–3663.
[280] J. He, Q. Shao, Q. Wu, J.-Q. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 3344–3347.
[281] H. Park, P. Verma, K. Hong, J.-Q. Yu, *Nat. Chem.* **2018**, *10*, 755–762.
[282] F. Burg, M. Gicquel, S. Breitenlechner, A. Pöthig, T. Bach, *Angew. Chem. Int. Ed.* **2018**, *57*, 2953–2957.
[283] D. Mu, G. He, G. Chen, *Chem. - Asian J.* **2018**, DOI 10.1002/asia.201800581.
[284] Y.-F. Yang, G. Chen, X. Hong, J.-Q. Yu, K. N. Houk, *J. Am. Chem. Soc.* **2017**, *139*, 8514–8521.
[285] K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788–802.
[286] P. Bravo, A. Farina, V. P. Kukhar, A. L. Markovsky, S. V. Meille, V. A. Soloshonok, A. E. Sorochinsky, F. Viani, M. Zanda, C. Zappalà, *J. Org. Chem.* **1997**, *62*, 3424–3425.
[287] P. Bravo, M. Guidetti, F. Viani, M. Zanda, A. L. Markovsky, A. E. Sorochinsky, I. V. Soloshonok, V. A. Soloshonok, *Tetrahedron* **1998**, *54*, 12789–12806.
[288] G. Liu, D. A. Cogan, J. A. Ellman, *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914.
[289] K. C. Nicolaou, G. Bellavance, M. Buchman, K. K. Pulukuri, *J. Am. Chem. Soc.* **2017**, *139*, 15636–15639.
[290] Q.-L. Pei, G.-D. Che, R.-Y. Zhu, J. He, J.-Q. Yu, *Org. Lett.* **2017**, *19*, 5860–5863.
[291] K. Yamaguchi, Y. Kazuta, H. Abe, A. Matsuda, S. Shuto, *J. Org. Chem.* **2003**, *68*, 9255–9262.
[292] J. Contreras-García, E. R. Johnson, S. Keinan, R. Chaudret, J.-P. Piquemal, D. N. Beratan, W. Yang, *J. Chem. Theory Comput.* **2011**, *7*, 625–632.
[293] E. R. Johnson, S. Keinan, P. Mori-Sánchez, J. Contreras-García, A. J. Cohen, W. Yang, *J. Am. Chem. Soc.* **2010**, *132*, 6498–6506.

Chapter 5
Conclusion and outlook

V.1. Conclusion

The main question addressed in this manuscript was: can the sulfoxide moiety be used to induce a chiral information during a C(sp^3)-H activation?

When the project *Sulf-As-CH* started, many examples of regioselective C(sp^3)-H bond activation, using bidentate directing groups, have already been disclosed. However, the diastereoselective functionalisation of aliphatic chains was scarce and only two reports were recently published (Chart 5.25).

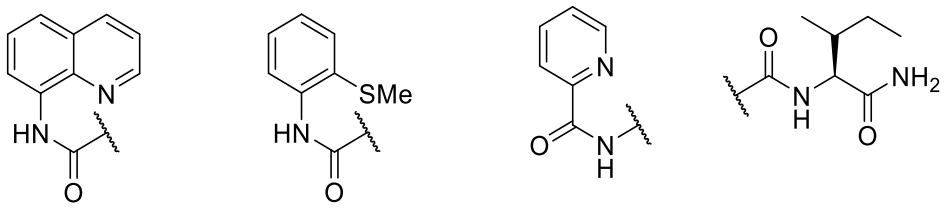
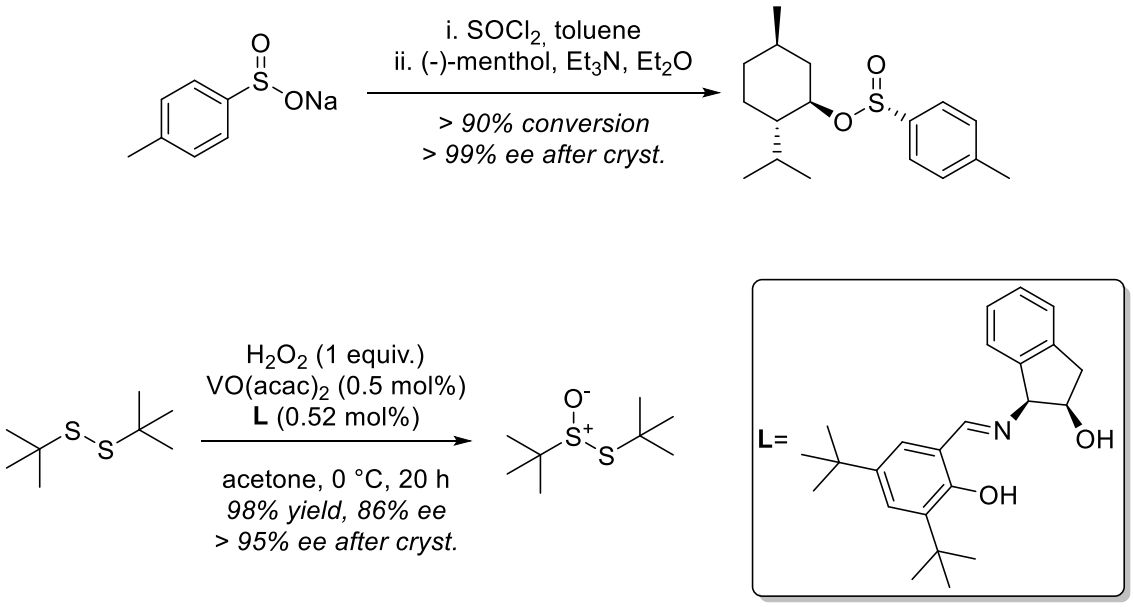


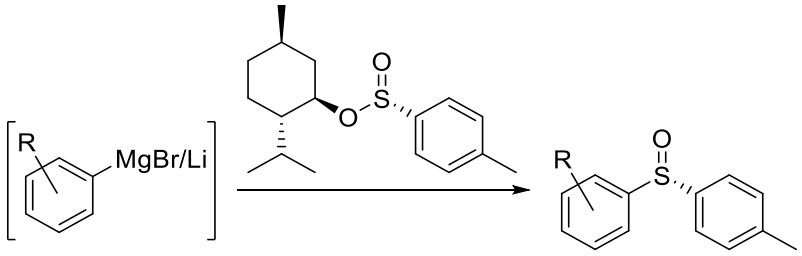
Chart 5.25 Representative bidentate directing groups for the C(sp^3)-H bond functionalisation

In the meantime, sulfoxides proved to be highly efficient directing groups for asymmetric reactions, especially in metal-catalysed transformations and total synthesis of natural products. Their simple access through the diastereoselective synthesis of sulfinates (e.g. Andersen methodology) or enantioselective oxidation of sulphides (e.g. Ellmann methodology) brought them to light (Scheme 5.142).



Scheme 5.142 Representative synthesis of enantiopure sulfoxides

Within our research group, *p*-tolylsulfinyl moiety showed excellent chiral induction ability. This group is generally obtained by attack of a nucleophile reagent on the enantiopure Andersen's reagent, (-)-menthyl (*S*)-*p*-tolylsulfinate (Scheme 5.143). Its use has been recognized, for example in the atroposelective synthesis of multiarene scaffolds and total synthesis of natural compounds. Post-functionalisation of the sulfinyl moiety by means of the sulfoxide-lithium exchange resulted in its replacement by an array of functional groups allowing the obtention of ligands which demonstrated excellent enantiomeric induction ability for various reactions.



Scheme 5.143 Synthesis of biarylsulfoxides

In this context, we took inspiration from Daugulis' and Babu's bidentate auxiliary, ie. 2-(methylthio)aniline, to design a new chiral directing group in order to apply it for challenging stereoselective transformations (Figure 5.68).

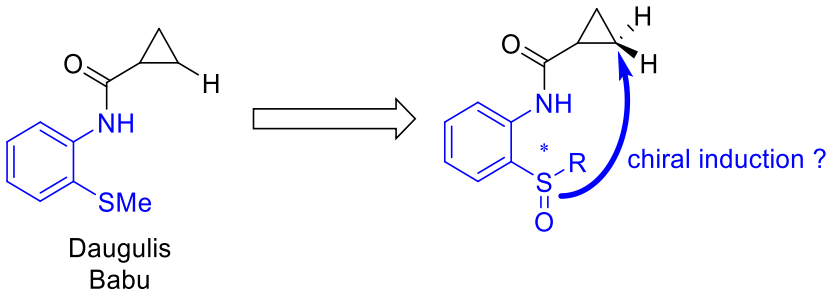
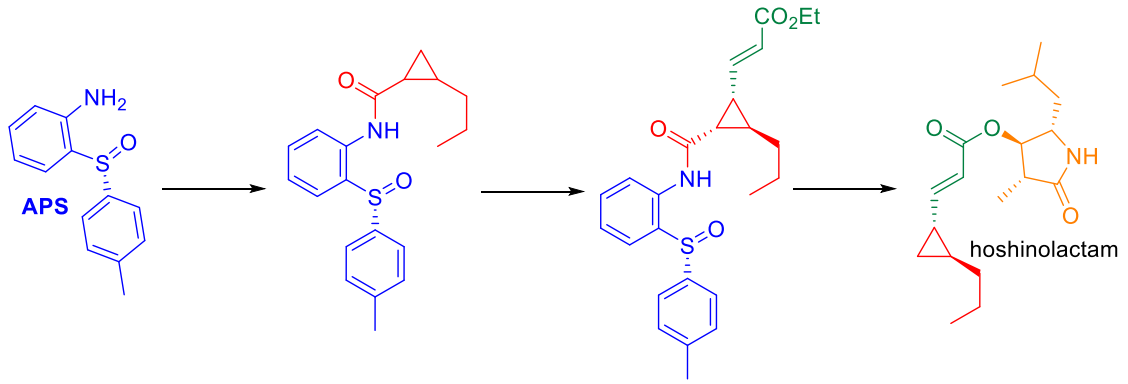


Figure 5.68 Design of a new auxiliary bearing a chiral sulfoxide

Thus, we designed (*S*)-2-(*p*-tolylsulfinyl)aniline (APS) and used this chiral auxiliary for the asymmetric arylation, olefination and alkylation of cycloalkanes. Although new and interesting, our methodology suffered from 1) no reactivity with linear aliphatic chains, 2) a lack of reactivity with electron-rich coupling partners and 3) a poor diastereoselectivity which were the main limitations of this catalytic system. However, the straightforward separation of the two diastereomers by simple column chromatography allowed the obtention of complex enantiopure compounds. The APS chiral auxiliary was also easily deprotected under basic conditions and recovered without loss of optical purity, making it a fully recyclable DG. With this new catalytic system, we developed an expedient synthesis of cyclopropane-based natural

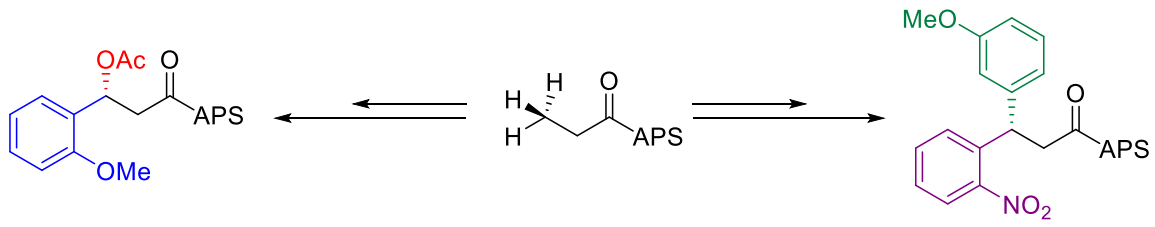
products, such as hoshinolactam obtained in five steps and 30% total yield from APS (Scheme 5.144). Our methodology is based on the interplay of peptidic couplings, challenging C-H bond activation and deprotection of the chiral auxiliary. Interestingly, alkylation and olefination could be performed and the diastereomers separated by column chromatography. Deprotection of the chiral auxiliary yielded a traceless carboxylic acid, removed in the Barton-Motherwell conditions to get an enantiopure *trans*-disubstituted cyclopropane intermediate.



Scheme 5.144 APS-based total synthesis of hoshinolactam

Considering the novelty of this chiral auxiliary, preliminary DFT studies have been conducted in collaboration with Jean-Pierre Djukic.

This work on the C-H bond functionalisation of cycloalkanes was followed by the extension of the methodology to acyclic compounds. Mainly, the modification of the reaction medium from an HFIP/water solvent system to toluene/HFIP allowed high conversion to the desired β-functionalised product. Consequently, we performed diastereoselective arylation and acetoxylation on aliphatic and benzylic substrates, with moderate to good diastereomeric excesses. From the ubiquitous propionic acid, protected with APS, we also achieved one-pot di-functionalisation reactions, affording complex scaffolds (Scheme 5.145). Diastereopure compounds were obtained with 3:2 to 9:1 crude diastereomeric ratio and yields up to 91%.



Scheme 5.145 One-pot two sequential C-H bond functionalisation

With our expertise in diastereoselective C(sp^3)-H bond functionalisation using the APS as chiral directing group, we endeavoured enantioselective transformations, using an aminosulfoxide chiral ligand. Following this goal, we designed a new ligand for the enantioselective functionalisation of cyclopropane (Figure 5.69.a). *N*-((*S*)-1-(4-(*tert*-butyl)phenyl)-2-((*R*)-*p*-tolylsulfinyl)ethyl)acetamide (NBSA) allowed us to reach 92% enantiomeric excess and 78% yield for the arylation of cyclopropane using 4-iodotoluene as coupling partner (Figure 5.69.b).

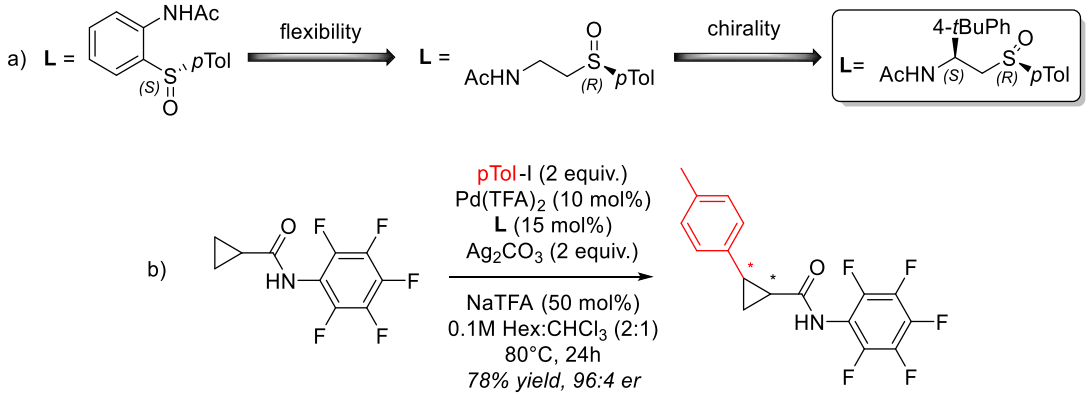


Figure 5.69 Design of new aminosulfoxide ligand from APS

Following the optimisation of the ligand, we applied it for the arylation and the challenging undescribed alkynylation of cycloalkanes. Good to excellent yields and enantiomeric excesses were obtained, showcasing the potential of this class of ligands (Chart 5.26).

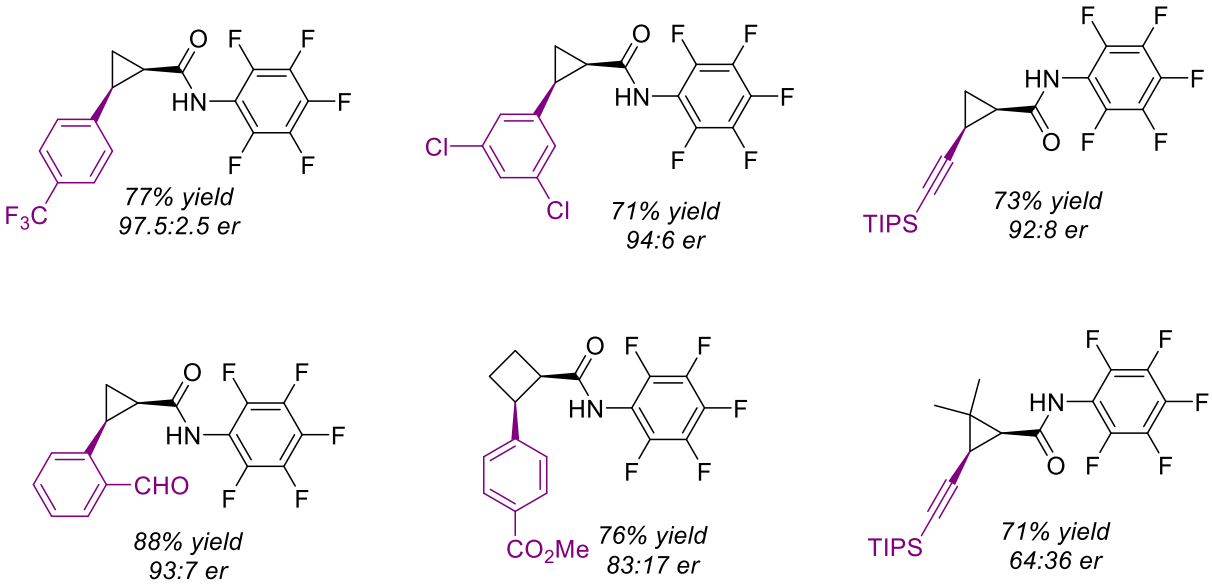


Chart 5.26 Representative products using NBSA ligand

Our NBSA ligand was also effective to enable the C-H bond cleavage in isobutyric acid derivatives, although with relatively poor chiral induction (Chart 5.27).

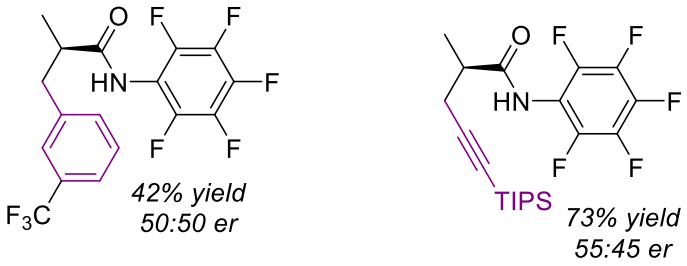


Chart 5.27 Functionalisation of isobutyramides using NBSA ligand

Considering the unprecedented architecture of this ligand, preliminary mechanistic studies have been undertaken to elucidate this catalytic system, in collaboration with Jean-Pierre Djukic. This interesting study revealed a unique mode of action of the NBSA ligand and the importance of the perfluoroamide moiety to stabilize the heteroleptic bischelated complex by π – π stacking interactions. We also proposed a model for the asymmetric induction observed in the functionalisation of cyclopropanes (Figure 5.70).

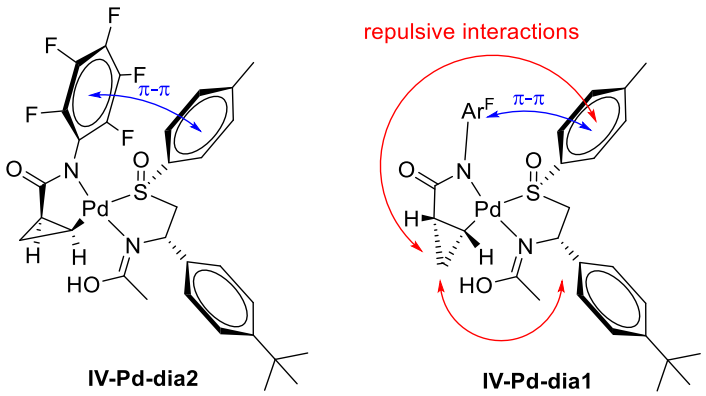


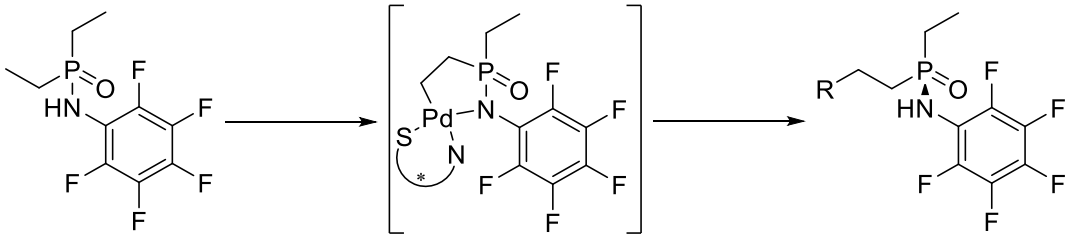
Figure 5.70 Proposed asymmetric induction model in the enantioselective C(sp^3)-H activation of cyclopropanes

V.2. Outlook

The first chiral N,S auxiliary developed in our group, APS, showcased a good ability to coordinate palladium and thus directing the C(sp^3)-H bond activation to allow various transformations such as arylation or olefination.

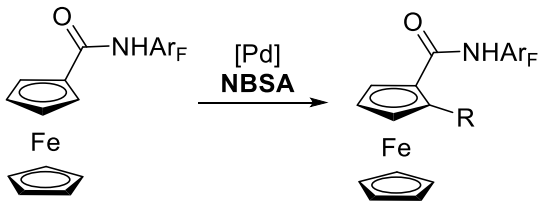
Considering the development of the NBSA ligand, the high enantiomeric induction and yields observed using it in combination with substrates bearing a pentafluoroamide moiety opens new perspectives for the asymmetric C-H bond activation. There are undeniably many challenges to respond in the field of asymmetric C-H bond functionalisation. However, taking into account the importance of the newly accessed products, we are interested in desymmetrisation of some important scaffolds.

For example the desymmetrisation of phosphinic acids remains underdeveloped and only C(sp^2)-H functionalisation has been reported.[294,295] Chiral phosphorus compounds are prevalent in a broad range of areas such as pharmacology and biochemistry; using dialkyl phosphinamides and NBSA ligand, the design of transformations allowing the C(sp^3)-H bond activation followed by subsequent enantioselective functionalisation appears as a highly challenging project (Scheme 5.146).



Scheme 5.146 Enantioselective functionalisation of phosphinamides

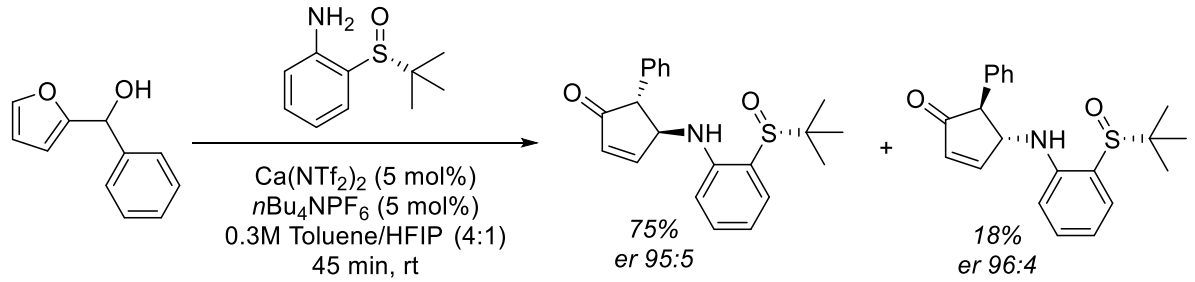
NBSA ligand could also be used for the desymmetrisation of ferrocene carboxylic acid derivatives (Scheme 5.147). As chiral ferrocenes such as JOSIPHOS analogues can be used as ligands for asymmetric transformations,[296] efficient access to this type of structures seems highly appealing.



Scheme 5.147 Enantioselective desymmetrisation of ferrocenes

Considering the sulfinylaniline chiral auxiliary acting as directing group in C(sp^3)-H bond activation, our results inspired another research group to use the inherent chirality of the sulfoxide to perform challenging stereoselective organic transformations giving access to complex structures.

Indeed Leboeuf and Gandon endeavoured the diastereoselective aza-Piancatelli rearrangement involving a 4π conrotatory cyclisation,[297,298] using (*S*)-2-(*tert*-butylsulfinyl)aniline (ATS) as chiral directing group (Scheme 5.148). The resulting 4-aminocyclopentenones are potential intermediates to aminocyclopentitol scaffolds, present in various drugs and natural products such as peramivir[299] or trehazolin.[300] The main outlook on this project is to find a suitable pathway to remove traceless the chiral auxiliary.



Scheme 5.148 Diastereoselective aza-Piancatelli using ATS

V.3. Scientific contributions

Oral communications:

- "*C(sp^3)-H functionalization of cycloalkane derivatives using a bidentate directing group bearing a chiral sulfoxide*" at the Journées de la Chimie Organique (Palaiseau, France, September 2016);
- "*(S)-2-(p-tolylsulfinyl)aniline: a versatile chiral tool for the stereoselective C(sp^3)-H bond functionalization of carboxamides*" at the Chirality Day (Strasbourg, France, October 2017);
- "*Sulfoxides: novel strategies for the asymmetric C(sp^3)-H bond functionalization*" at the Journées Scientifiques de l'Institut de Chimie (Strasbourg, France, December 2017);
- "*Sulfoxide: novel strategy for the asymmetric C(sp^3)-H bond activation*" at Janssen Pharmaceutica (Beerse, Belgium, February 2018);
- "A Sulfinyl Aniline as a Versatile Chiral Tool for Stereoselective C(sp^3)-H Bond Functionalisation" at ChemCYS 2018 (Blankenberge, Belgium, February 2018, 2nd award of the best oral presentation in Organic and Organometallic chemistry).

Poster sessions:

- "*Novel aminosulfoxide ligands: Towards the enantioselective C(sp^3)-H bond arylation and alkynylation of carboxamides*" at the Regio Symposium 38 (Fribourg, Germany, September 2018).

Scientific publications:

- "*Enantiopure sulfinyl aniline as removable and recyclable chiral auxiliary for asymmetric C(sp^3)-H bond activation*" Jerhaoui, S., Chahdoura F., Rose, C., Djukic, J.-P., Wencel-Delord, J., Colobert, F. *Chem. Eur. J.*, **2016**, 22, 17397;
- "*Stereoselective Sulfinyl Aniline Promoted Pd-catalyzed C-H Arylation and Acetoxylation Of Carboxamides*" Jerhaoui, S., Djukic, J.-P., Wencel-Delord, J., Colobert, F. *Chem. Eur. J.*, **2017**, 23, 15594;
- "*Stereospecific C-H activation as a key step for asymmetric synthesis of various biologically active cyclopropanes*" Jerhaoui, S., Poutrel, P., Djukic, J.-P., Wencel-Delord, J., Colobert, F. *Org. Chem. Front.*, **2018**, 5, 409;

- "*Synthesis of axially chiral C-N scaffolds via asymmetric coupling with enantiopure sulfinyl iodanes*" Rae, J., Frey, J., Jerhaoui, S., Choppin, S., Wencel-Delord, J., Colobert, F. *ACS Catal.*, **2018**, 8, 2805;
- "*N*-protected a*minosulfoxides as a new family of chiral ligands for asymmetric C-H activation*" Jerhaoui, S., Djukic, J.-P., Wencel-Delord, J., Colobert, F., *Manuscript in preparation*, **2018**.

Other contributions:

- Project ScienceLab in Chemistry with the Jardin des Sciences (2015 – 2016);
- Practical classes in organic chemistry (2016 – 2018);
- Participation at "*Ma thèse en 180 secondes*" in 2018.

V.4. Bibliographic references

[294] Y.-H. Chen, X.-L. Qin, J. Guan, Z.-J. Du, F.-S. Han, *Tetrahedron Asymmetry* **2017**, *28*, 522–531.
[295] Y. Sun, N. Cramer, *Angew. Chem. Int. Ed.* **2017**, *56*, 364–367.
[296] E. A. Bercot, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 10248–10249.
[297] D. Lebœuf, E. Schulz, V. Gandon, *Org. Lett.* **2014**, *16*, 6464–6467.
[298] D. Lebœuf, L. Marin, B. Michelet, A. Perez-Luna, R. Guillot, E. Schulz, V. Gandon, *Chem. - Eur. J.* **2016**, *22*, 16165–16171.
[299] F. Jia, J. Hong, P.-H. Sun, J.-X. Chen, W.-M. Chen, *Synth. Commun.* **2013**, *43*, 2641–2647.
[300] A. Boiron, P. Zillig, D. Faber, B. Giese, *J. Org. Chem.* **1998**, *63*, 5877–5882.

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Soufyan JERHAOUI

Sulfoxydes : nouvelle stratégie pour l'activation C(sp^3)-H asymétrique

Résumé

Pendant de nombreuses années, les liaisons C-H aliphatiques ont été considérées comme dormantes, difficilement exploitables dans le contexte de la chimie organique. Le défi le plus important est de sélectionner une liaison C-H parmi toutes celles que contient une molécule. L'approche la plus utilisée à ce jour est l'utilisation d'un groupement directeur qui permet, en se liant à un métal, de diriger l'activation d'une liaison C-H en particulier. Suite au développement des groupements bicoordinants, nous avons développé notre propre groupement bicoordinant chiral. Cet auxiliaire nous a permis de réaliser de nombreuses transformations diastéréosélectives sur des carbones aliphatiques telles que l'arylation et l'oléfination. Nous l'avons également utilisé pour développer une méthodologie innovante pour la synthèse de produits naturels. Suite à ces travaux, nous avons développé un nouveau ligand chiral qui a été utilisé dans l'arylation et l'alkynylation énantiosélectives de cycloalcanes.

Mots clés : Activation C-H, sulfoxyde, catalyse homogène, synthèse totale, chiralité, palladium, ligands, hoshinolactame

Abstract

Over the decades, non-activated C-H bonds have been considered as dormant functionalities, hardly exploitable in the context of multistep synthesis of complex scaffolds. The main challenge is to select one C-H bond among all contained in one molecule. To answer to this problem bicoordinating directing groups allowing directed C(sp^3)-H activation have been developed. Following the work of Daugulis and Babu, we developed our own chiral bicoordinating directing group, (*S*)-2-(*p*-tolylsulfinyl)aniline. This chiral auxiliary allowed us to realise various diastereoselective transformations on aliphatic chains such as arylation, olefination or acetoxylation. We also used it to develop a brand-new methodology for the total synthesis of cyclopropane-bearing natural products. Moreover we developed a new chiral sulfinyl ligand, N-((*S*)-1-(4-(*tert*-butyl)phenyl)-2-((*R*)-*p*-tolylsulfinyl)ethyl)acetamide, that has been used for the enantioselective arylation and alkynylation of cycloalkanes.

Keywords: C-H activation, sulfoxide, homogenous catalysis, total synthesis, chirality, palladium, ligands, hoshinolactam