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A multicatalytic approach to enantio-, and diastereoselective arylation of alcohols

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List of abbreviations

APPI	Atmospheric pressure photoionization
d.r.	Diastereomeric ratio
dba	Dibenzylideneacetone
DCM	Dichloromethane
DG	Directing group
DIPEA	N,N-Diisopropylethylamine
DMF	Dimethylformamide
dppf	1,1′-Bis(diphenylphosphino)ferrocene
e.r.	Enantiomeric ratio
equiv	Equivalent
ESI	Electrospray ionisation
FID	Flame ionisation detector
GC	Gas chromatography
HAT	Hydrogen atom transfer
HRMS	High-resolution mass spectrometry
MS	Mas spectrometry
NMR	Nuclear magnetic resonance
SFC	Supercritical fluid chromatography
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCl	Trimethylsilyl chloride

Résumé

1. Introduction

Les alcools sont des groupes fonctionnels omniprésents dans les produits naturels, les composés bioactifs, les produits chimiques abondamment disponible et les produits chimiques fins. C'est pourquoi il est très souhaitable de développer des méthodes pour les diversifier. L'existence d'une pléthore de méthodologies de modification des alcools permet d'explorer de nouveaux espaces chimiques et de faciliter la synthèse de molécules bioactives.

Généralement, les alcools réagissent comme nucléophiles en position d'oxygène ou servent de source de protons.[1] Le groupe hydroxyle peut également servir de groupe directeur ou être converti en groupe partant. Cependant, pour fonctionnaliser les alcools à l'une des positions du carbone, cette réactivité inhérente doit être surmontée. Cela nécessite généralement des procédures lourdes en plusieurs étapes. L'objectif de cette thèse était de développer de nouvelles méthodologies pour modifier directement les alcools sur des sites intrinsèquement non réactifs, en éliminant le besoin d'étapes supplémentaires d'activation ou de protection.

En adaptant soigneusement les catalyseurs, il est possible d'exécuter des transformations qui modifient les molécules avec un contrôle élevé de la régio-, de la stéréo- et de l'énantio-sélectivité dans des conditions douces.[2] Cependant, ces réactions se produisent généralement sur des sites intrinsèquement réactifs et la fonctionnalisation de composés à des positions non biaisées reste un défi majeur en catalyse.[3]

En combinant plusieurs catalyseurs dans un seul récipient, il est possible de surmonter ce défi.[4,5] De cette manière, des positions de molécules classiquement non réactives peuvent être facilement modifiées. En outre, cette approche peut potentiellement rendre les transformations globales plus efficaces en termes de temps et de ressources et plus faciles à exécuter pour un expérimentateur. Dans l'ensemble, la multicatalyse peut être un outil clé pour développer des réactions nouvelles et efficaces, qui permettent la fonctionnalisation de molécules sur des sites intrinsèquement non réactifs.

La thèse est divisée en 4 chapitres, qui sont brièvement résumés ici. Dans le premier chapitre, les développements récents de la multicatalyse en tant qu'outil de diversification structurelle ont été résumés, tout en se concentrant sur les méthodes qui permettent la fonctionnalisation des alcools.[6] Dans le deuxième chapitre, une nouvelle méthode pour la β-arylation énantiosélective des alcools primaires, qui a été développée dans notre groupe, est divulguée. Basée sur les principes de l'emprunt d'hydrogène, la méthode combine un catalyseur d'arylation à base de Pd avec un catalyseur de transfert d'hydrogène chiral pour faciliter la transformation globale. Le troisième chapitre est consacré à un relais multicatalytique qui permet la synthèse d'alcools benzyliques secondaires énantioenrichis à partir d'alcools (homo)allyliques.[7] En incorporant des catalyseurs multiples, l'utilité de la méthode pourrait être encore étendue pour commencer à partir d'alcènes, au lieu d'alcools allyliques. Le dernier chapitre est consacré à une méthode d'α-arylation énantiosélective d'alcools primaires.[8] En combinant un catalyseur de transfert d'hydrogène et un catalyseur d'hydroarylation, on obtient des alcools benzyliques secondaires énantioenrichis en partant directement d'alcools primaires.

2. Résultats et discussions

2.1 Diversification des structures variables par la multicatalyse : le cas des alcools (chapitre 1)

Étant donné que les groupements alcooliques sont présents dans une grande diversité de produits chimiques fins précieux issus de la nature et de la synthèse, les méthodes permettant de diversifier leur structure sont très recherchées. La catalyse s'est avérée permettre le développement de nouvelles transformations qui vont au-delà de la réactivité inhérente des alcools. Cependant, la modification de la structure des alcools à certaines positions non biaisées reste un défi majeur ou nécessite des procédures fastidieuses en plusieurs étapes. Récemment, une attention accrue a été accordée à la mutlicatalyse, qui combine plusieurs réactions et catalyseurs au sein d'un même système, ce qui permet de découvrir des réactivités précédemment inaccessibles ou d'augmenter l'efficacité globale des transformations en plusieurs étapes. Ce chapitre se concentre sur la démonstration de divers aspects de la conception de tels systèmes multicatalytiques qui modifient la structure des composés contenant un groupement alcool. Une attention particulière est accordée à la mise en évidence des défis et des avantages de la multicatalyse et, dans un contexte plus large, à la discussion sur la manière dont le domaine de la catalyse peut progresser vers des systèmes plus complexes.[6]

2.2 β-Arylation énantiosélective d'alcools primaires via un relais multicalatytique (chapitre 2)

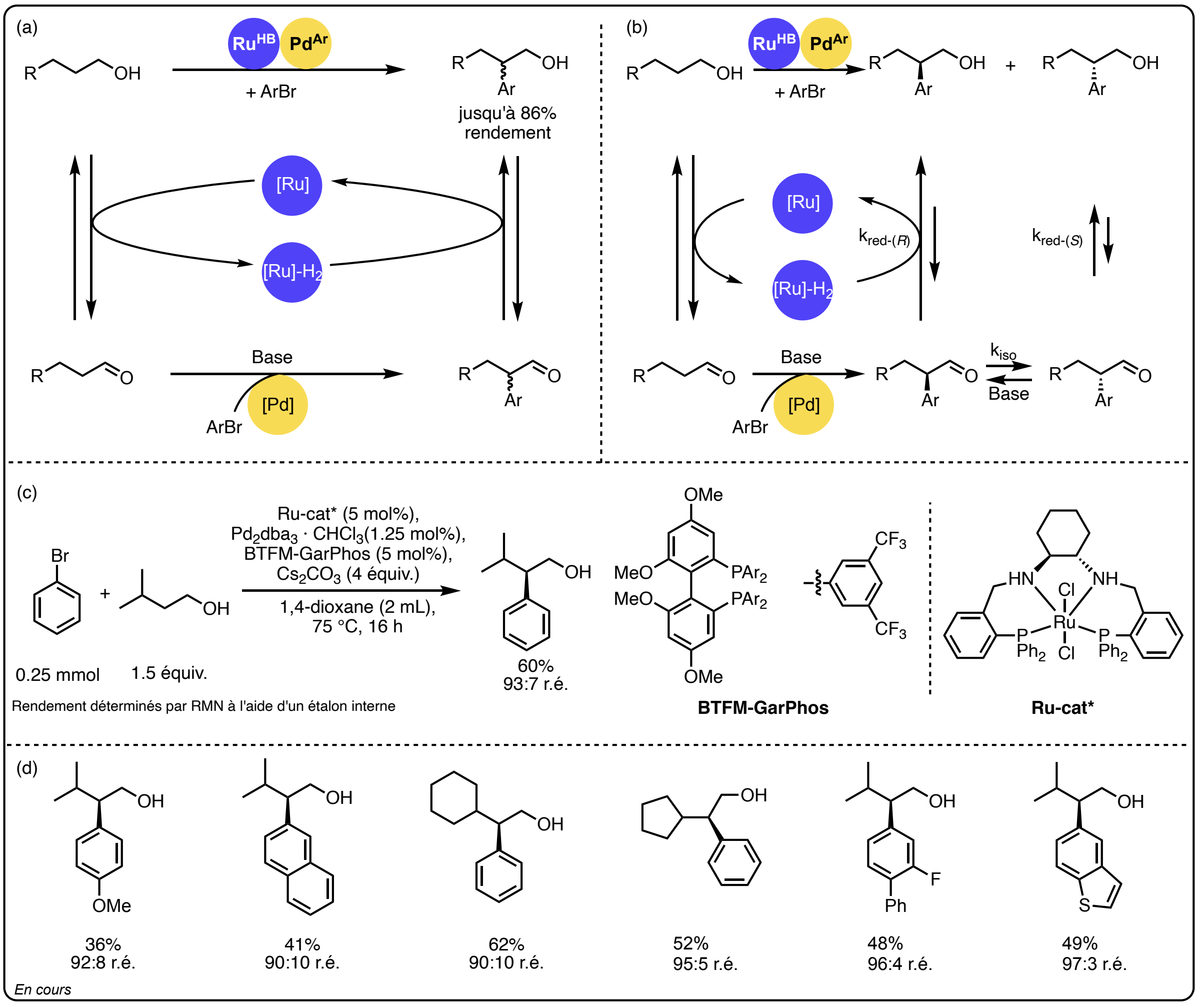
Un exemple de transformation ciblant une position intrinsèquement non réactive des alcools est la β-arylation des alcools primaires (**schéma 1a**).[9]

Ici, l'alcool est activé de manière réversible par un catalyseur de transfert d'hydrogène à base de Ru, qui oxyde l'alcool et "stocke" l'hydrogène dans le système. L'aldéhyde peut ensuite réagir avec un bromure d'aryle électrophile en présence d'un catalyseur de métal de transition approprié pour donner un aldéhyde arylé, qui est finalement réduit avec l'hydrogène "stocké" dans le système pour donner le produit.

Pour accroître encore l'utilité du relais de β-arylation, nous avons tenté de rendre la transformation énantiosélective (**schéma 1b**). L'obtention de l'énantiosélectivité par l'incorporation d'une arylation énantiosélective catalysée par le Pd n'était pas viable dans le système initial, car l'aldéhyde arylé formé subit une racémisation dans les conditions de réaction. Cependant, nous avons cherché à tirer parti de cette situation en incluant un catalyseur de transfert d'hydrogène chiral pour effectuer ce que l'on appelle une résolution cinétique dynamique (RCD).[10,11] Pour que la RCD réussisse, les conditions suivantes devaient être remplies. Premièrement, la réduction de l'un des énantiomères devait être plus rapide que celle de l'autre (kred-(R) > kred-(S)). Deuxièmement, l'isomérisation de l'aldéhyde arylé devait être plus rapide que les taux de réduction de l'aldéhyde (kiso >> kred).

Lors de la conception de ce relais orthogonal, de multiples aspects ont dû être pris en compte. Tout d'abord, le catalyseur d'hydrogénation devait fournir le produit avec une énantiosélectivité élevée. Cela peut s'avérer difficile à des températures élevées, requises pour l'arylation. En outre, une attention particulière doit être accordée aux réactions secondaires potentielles des alcools et des aldéhydes en présence du catalyseur à base de Pd. Ceci est d'autant plus crucial qu'un excès d'alcool sera présent dans le système, et que le catalyseur doit donc être hautement sélectif pour la réaction d'arylation souhaitée de l'aldéhyde transitoire.

Schéma 1. a) β-Arylation directe d'alcools primaires. b) Conception du système pour la β-arylation énantiosélective d'alcools primaires. c) Conditions de réaction pour la β-arylation énantiosélective d'alcools primaires. d) Exemples de champ d'application sélectionnés.



Rendement déterminés par RMN à l'aide d'un étalon interne

La combinaison d'un catalyseur d'emprunt d'hydrogène chiral à base de Ru et d'un catalyseur à base de Pd utilisant le BTFM-GarPhos racémique comme ligand a permis d'obtenir le produit souhaité avec un rendement de 60 % et un rapport énantiomérique de 93:7 (**schéma 1c**). Il est intéressant de noter que ce rendement correspond à la transformation complète après trois processus catalytiques distincts et orthogonaux. La tolérance des groupes fonctionnels de la réaction est actuellement étudiée (**schéma 1d**).

Par conséquent, cette étude démontre la grande utilité de l'incorporation d'une résolution cinétique dynamique dans un relais orthogonal. La présence d'un catalyseur chiral dans ce système dynamique peut permettre d'obtenir un produit enrichi en énantioenrichi, même lorsque la réaction conduisant à la formation du stéréocentre n'est pas sélective isolément.

2.3 Approche multicatalytique de la synthèse stéréosélective en un point des alcools benzyliques secondaires (chapitre 3)

Les alcools benzyliques secondaires enrichis en antigène sont un motif important, courant dans les molécules bioactives.[12] Il est donc essentiel d'y accéder directement à partir des matières premières disponibles. Classiquement, ils peuvent être obtenus par hydrogénation catalytique asymétrique des cétones.[12] Cependant, cela nécessite que le squelette de carbone soit assemblé au préalable. En revanche, lorsque des aldéhydes sont disponibles, une addition-1,2 énantiosélective d'un nucléophile permet d'obtenir le produit désiré.[13]

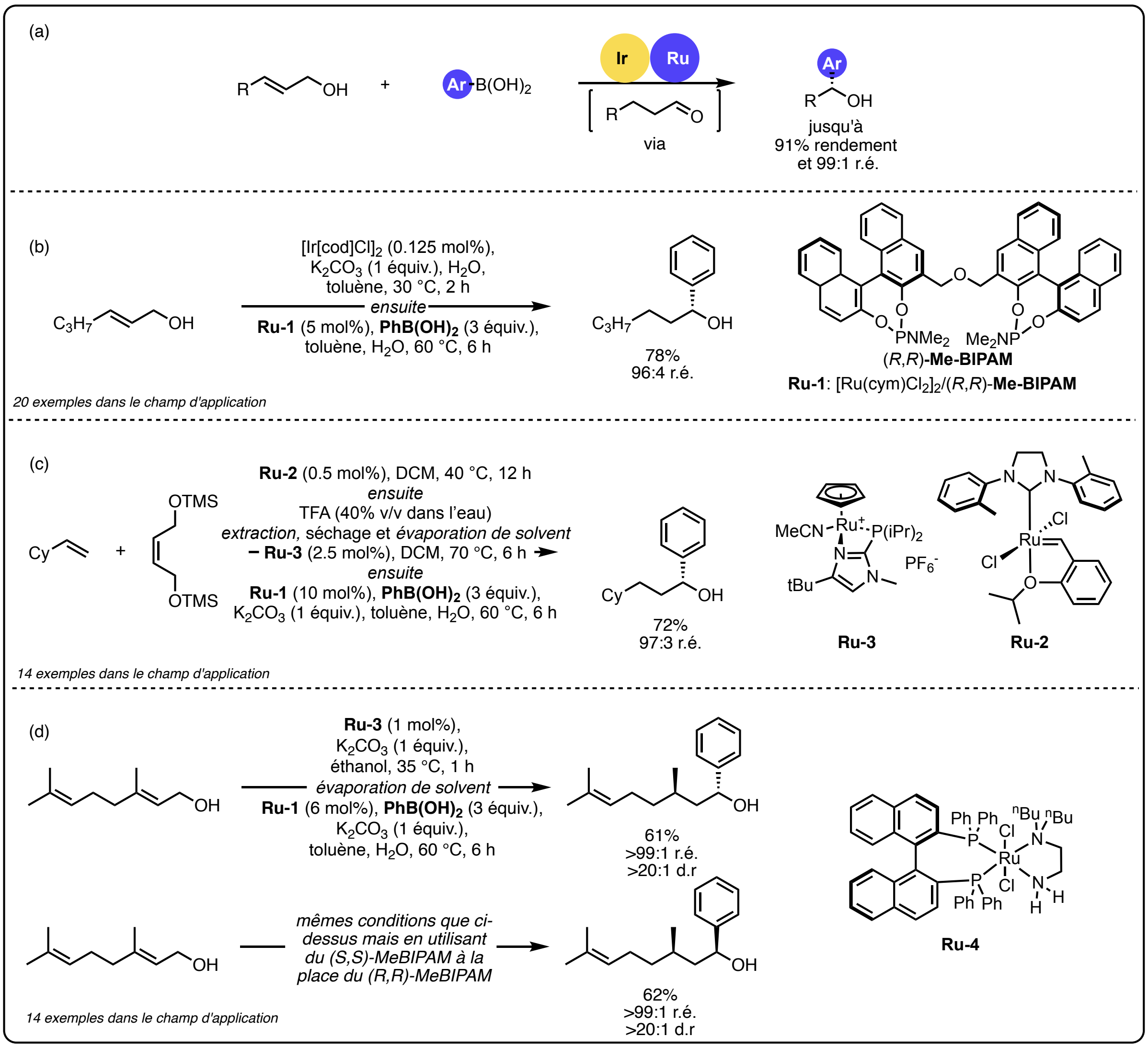
En tirant parti des possibilités offertes par la multicatalyse, nous avons proposé une séquence d'isomérisation-addition énantiosélective pour les alcools aliphatiques comportant une liaison insaturée, conduisant à des alcools benzyliques secondaires énantioenrichis (**schéma 2a**).[7] Nous avons imaginé que l'isomérisation de la double liaison pourrait fournir un intermédiaire aldéhyde, qui réagirait ensuite avec un nucléophile. Cette stratégie s'est avérée fructueuse lorsque l'on combine un catalyseur d'isomérisation à base d'Ir avec un catalyseur d'hydroarylation à base de Ru. Dans un relais séquentiel, les produits souhaités ont été obtenus à partir d'une large gamme d'alcools allyliques et d'acides boroniques avec des rendements et des énantiosélectivités élevés (**schéma 2b**). Il est intéressant de noter que les alcools contenant des doubles liaisons éloignées ont également donné les produits souhaités.

Pour élargir encore l'utilité, d'autres catalyseurs pourraient être incorporés dans le relais pour permettre l'accès aux produits à partir d'alcènes (**schéma 2c**). En ajoutant un catalyseur de métathèse à la séquence, les alcènes pourraient être transformés en alcools allyliques. Ceux-ci pourraient alors subir une séquence similaire à celle décrite ci-dessus pour donner l'alcool benzylique secondaire enrichi en énantioenrichi.

Lors de l'utilisation d'alcools allyliques contenant une double liaison pro-chirale dans la séquence relais, les produits formés contiennent deux stéréocentres. En adaptant le catalyseur d'isomérisation, il a été possible de contrôler la chiralité du stéréocentre formé lors de la première étape, tout en conservant un contrôle élevé de l'énantiocontrôle lors de l'étape d'addition 1,2 (**schéma 2d**). Globalement, la transformation a pu être réalisée pour produire tous les stéréoisomères possibles avec d'excellentes diastéréo- et énantiosélectivités, étant donné que la formation de chaque stéréocentre est déterminée uniquement par le catalyseur impliqué dans la transformation.

Dans l'ensemble, cette étude démontre que la combinaison de plusieurs catalyseurs dans des relais séquentiels permet d'accroître rapidement la complexité des molécules, avec une préparation nulle ou minimale entre les deux, à partir de matériaux de départ simples et abondants.

Schéma 2. a) Conception du système pour la transformation d'alcools allyliques en alcools benzyliques secondaires énantioenrichis b) Conditions de réaction pour la transformation à partir d'alcools allyliques c) Conditions de réaction pour la transformation à partir d'alcènes d) Conditions de réaction pour la transformation d'alcools allyliques portant une double liaison pro-chirale

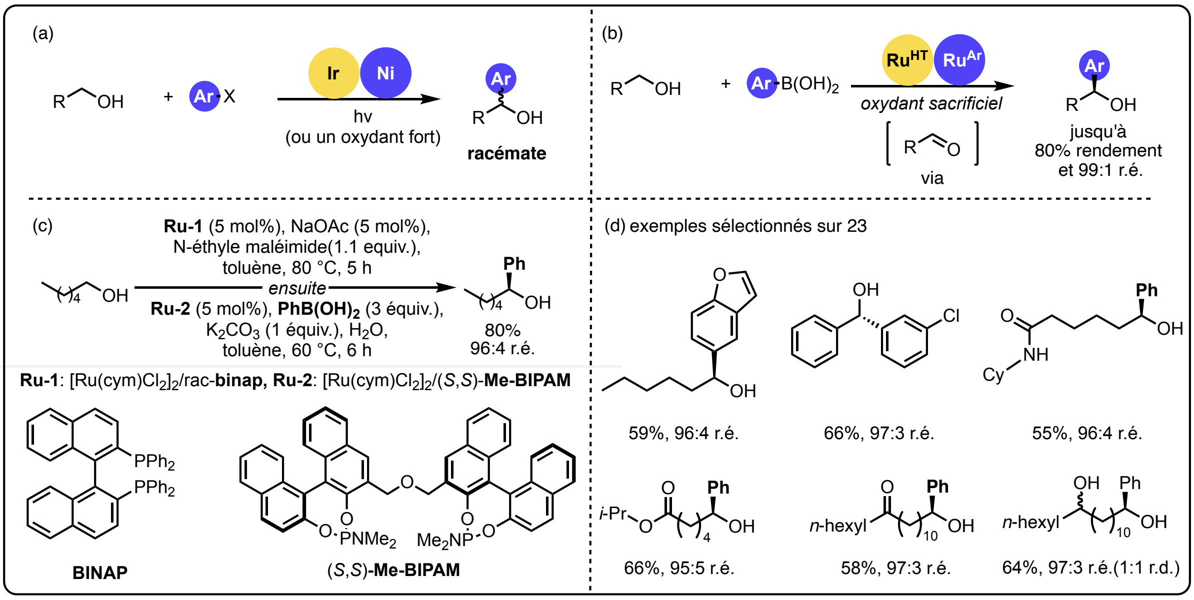


2.4 α-Arylation énantiosélective d'alcools primaires par catalyse séquentielle en un point (chapitre 4)

Comme mentionné dans la section 2.3, les alcools benzyliques secondaires énantioenrichis constituent un motif structurel important. Compte tenu de la disponibilité des alcools, la fonctionnalisation C-H directe en position α pourrait constituer une voie attrayante pour accéder aux produits souhaités. L'α-arylation directe d'alcools, à partir d'alcools aliphatiques couramment disponibles.[14,15] Cependant, les méthodes décrites dans la littérature conduisent à la formation d'un mélange racémique (**schéma 3a**).

Nous avons cherché à utiliser la multicatalyse pour accéder à des alcools benzyliques secondaires énantioenrichis directement à partir d'alcools aliphatiques primaires. Inspirés par nos travaux antérieurs sur la séquence d'isomérisation-addition des alcools allyliques (chapitre 3), nous avons conçu un relais dans lequel l'alcool subit d'abord une oxydation par transfert d'hydrogène sur un accepteur sacrificiel, suivie d'une hydroarylation énantiosélective de l'aldéhyde généré in situ (**schéma 3b**).[8]

Schéma 3. a) Arylation α-C-H établie des alcools primaires. b) Conception du système pour l'α-arylation énantiosélective des alcools primaires. c) Conditions de réaction pour l'α-arylation énantiosélective des alcools primaires. d) Exemples de champ d'application sélectionnés.



Lors du développement de la réaction, il était essentiel de s'assurer que les composants de l'étape d'oxydation n'interféreraient pas avec l'étape d'hydroarylation. Le brouillage des ligands pourrait nuire à l'énantiosélectivité de la réaction. La grande robustesse du catalyseur d'hydroarylation a été soulignée puisque la haute sélectivité de la réaction a été maintenue dans le système complet par rapport à la réaction isolée. En combinant deux catalyseurs à base de ruthénium et le N-éthyl maléimide comme accepteur d'hydrogène sacrificiel, le produit a été formé avec un rendement de 80 % et un rapport énantiomérique de 96:4.

Après avoir établi les conditions de la transformation, la tolérance des groupes fonctionnels de la méthode a été étudiée (**schéma 3c**). Au cours de l'étude, la grande sélectivité du catalyseur d'hydroarylation a été mise en évidence, car une large gamme de composés contenant un groupe carbonyle a été sélectivement arylée. Il convient de noter que la réaction a toléré un groupe d'alcool secondaire, ce qui est dû à la sélectivité du catalyseur d'oxydation vis-à-vis des alcools primaires par rapport aux alcools secondaires.

Dans l'ensemble, cette étude a démontré l'utilité du relais séquentiel multicatalytique pour réaliser l'α-arylation énantiosélective formelle d'alcools primaires. Un avantage de cette approche est qu'elle ne nécessite pas d'isolations, souvent fastidieuses, d'intermédiaires potentiellement instables.

3. Conclusion générale

L'objectif de la thèse était de développer de nouvelles méthodes de fonctionnalisation énantio- et diastéréosélective des alcools à une position non biaisée en utilisant la multicatalyse. Dans l'ensemble, plusieurs nouvelles méthodes ont été développées, qui permettent d'accéder à une large gamme d'alcools fonctionnalisés. Dans le deuxième chapitre, une méthode de β-arylation énantiosélective d'alcools primaires a été présentée. En combinant la catalyse relais et la résolution cinétique dynamique, les produits peuvent être formés en une seule étape, ce qui permet de surmonter la réactivité inhérente des matériaux de départ. Le troisième chapitre met en lumière divers aspects d'un relais séquentiel qui permet d'accéder à des alcools benzyliques secondaires énantioenrichis à partir d'alcools allyliques ou d'alcènes. Sans ou avec un minimum d'élaboration entre les deux, les méthodes fournissent des moyens d'augmenter rapidement la complexité des molécules, tout en commençant par des matériaux de départ simples et abondants. Le dernier chapitre s'appuie sur le précédent, en fournissant la même classe de produits de valeur, mais en partant directement d'alcools primaires. La transformation globale permet l'α-arylation formelle des alcools, jusqu'alors difficile à réaliser. Dans un contexte plus large, la thèse démontre les diverses opportunités qui découlent de la combinaison de plusieurs catalyseurs dans un même récipient.

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CHAPTER 1

Variable structure diversification by multicatalysis: the case of alcohols

The literature review described in this chapter was written in collaboration with K. Das.

I was responsible for conceiving the manuscript, collecting most of the necessary literature, writing the first draft, and making the figures.

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1.1 Introduction

Alcohols are ubiquitous functional groups in natural products, synthetic bioactive compounds, pharmaceuticals and agrochemicals, commercial building blocks, and many other fine and bulk chemicals.[1-4] Hence, methods enabling facile diversification of available alcohols toward libraries of structurally varied derivatives are highly sought after. Such strategies create opportunities to readily explore broad chemical space, facilitate the discovery and development of biologically relevant molecules, synthesize known valuable fine chemicals, and valorise feedstock materials.

The reactivity of alcohols is typically dictated by the lone pairs of the oxygen atom. Therefore, they often act as nucleophiles, or alternatively, as a proton source, due to the strong polarization of the O–H bond.[5] In some instances, the hydroxyl group may serve as a directing group or can be easily transformed into convenient leaving groups.[6,7] These modes of reactivity created room for the development of many useful transformations of alcohols. However, modifying alcohols at one of the neighbouring carbon positions remains cumbersome and typically requires wasteful multistep procedures. Therefore, alternative new strategies that overcome their limited inherent reactivity and enable their direct functionalization would be attractive.

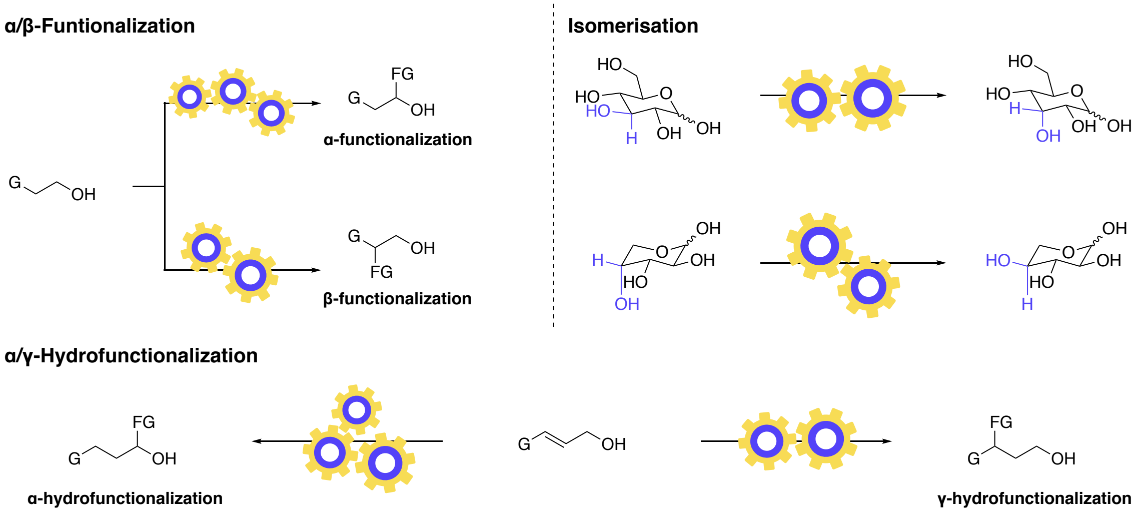
Catalysis creates an opportunity to devise novel, valuable reactions.[8,9] Carefully designed catalysts can execute transformations that modify molecules with high regio-, stereo-, and enantiocontrol under mild conditions. However, these reactions typically occur at inherently reactive and sterically accessible sites and altering compounds at sterically or electronically unbiased positions is still one of the major challenges in catalysis.[10] Usually, such transformations require changing the reactivity of the molecule by introducing either new handles, such as catalyst-directing groups, or modifying the functional groups, conducted at the expense of additional tedious synthetic steps.[11]

Recently, inspired by biological systems, a trend has emerged in the field of catalysis, which involves using multiple catalysts to execute several transformations in one vessel, increasing the general efficiency and creating new selective transformations.[12-2] For instance, multicatalysis proved to enable modifying molecules at their inherently poorly reactive sites thanks to the cooperativity between two orthogonal reactions operating in a one-pot. Also, merging multiple reactions into a one-step process makes the overall transformations more time-efficient, economical, and easier to execute for an experimenter. In general, the multicatalytic approaches have the potential to address many challenges of modern organic synthesis, unlocking new synthetic routes and novel derivatizations of molecules.

A historical example of multicatalysis outperforming traditional catalysis can be traced to the coupling of aryl halides with acetylenes. The groups of Cassar and Heck demonstrated that this reaction was possible using palladium catalysts.[23,24] However, in a simultaneous report, the group of Sonogashira demonstrated that adding copper salt as a co-catalyst allows for conducting the reaction at milder conditions.[25] Overall, the presence of two catalysts was crucial for expanding the application of the transformation.[26]

The field of multicatalysis has undergone vigorous growth over recent years, enabling a broad range of highly selective transformations for various classes of starting materials, and has been the subject of multiple reviews.[12-22] In this Feature article, we focus on different aspects of the design and development of such multicatalytic systems, their advantages, and their challenges, for modifying the structure of alcohol-containing molecules (**Figure 1.1**). More specifically, the focus will be paid to transformations of alcohols as starting materials in which the hydroxyl group remains unaltered in the product. Multicatalytic approaches, which convert the alcohol group into a different functionality, are outside of the scope of this feature article.[14,27–30]

Figure 1.1 Multicatalytic approaches to modifying alcohols: α-functionalization of alcohols, β-functionalization of alcohols, α-hydro functionalization of allylic alcohols, γ-hydro functionalization of allylic alcohols, site-selective modifications of sugars.

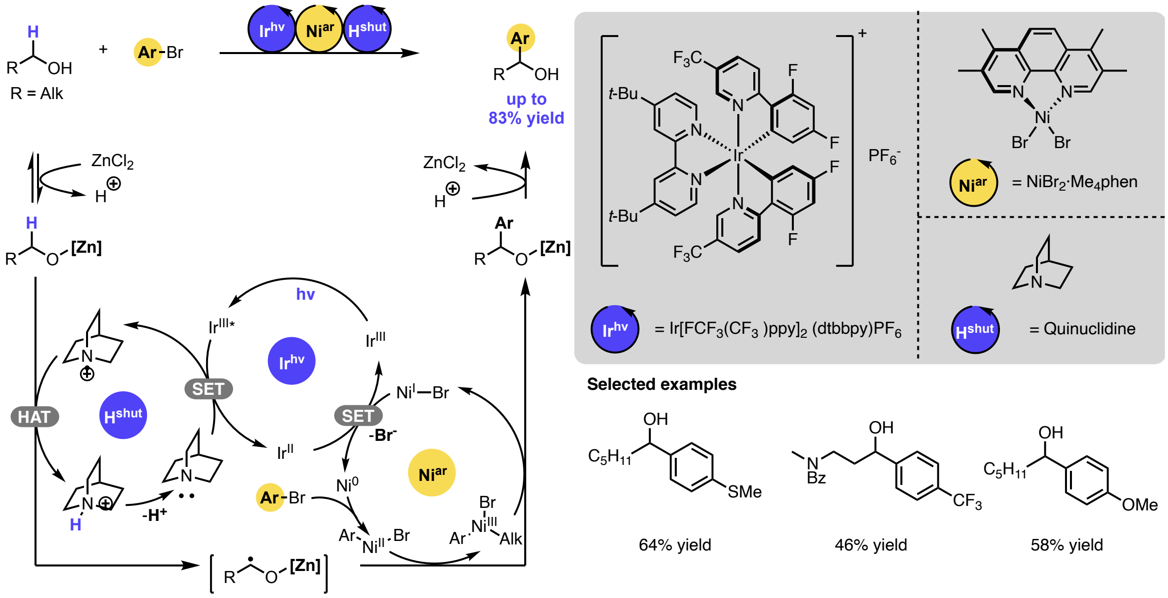


1.2 α-Functionalization of aliphatic alcohols

MacMillan and coworkers showed that the merger of nickel catalysis with photoredox catalysis enables the direct α-arylation of alcohols with aryl bromides (**Scheme 1.1**).[31] The identification of the conditions required the evaluation of various nickel catalysts, iridium photocatalysts, bases, and Lewis acids that promoted the productive pathway and suppressed side-processes. Specifically, first, the aminium radical cation, H^{shut}, needs to be generated by the oxidation of an amine with the excited iridium photocatalyst in a single electron transfer (SET). Next, the hydrogen atom transfer (HAT) occurs between H^{shut} and the alkoxide to generate an α-carbon-centered radical. The latter then adds to a nickel(ii) aryl halide complex, which is generated before through the oxidative addition of aryl bromide to a nickel (0) complex. The resulting nickel(iii) alkyl aryl intermediate undergoes reductive elimination, forming the product and a nickel(i) species. Lastly, the nickel(i) intermediate is reduced back to nickel (0) complex in a SET event oxidizing the initially reduced iridium photocatalyst, thereby regenerating all intermediates involved and closing all catalytic cycles.

The critical aspects to enabling the cooperation of the different catalysts were suppressing the competitive C–O arylation and the chemoselective formation of a radical in the α-position of the alcohols. Crucial, as it turned out, was using an appropriate Lewis acid to activate the desired position by forming a metal alkoxide. The α-C–H bond of this species has an increased hydridic character that promotes the formation of the α-carbon-centred radical by hydrogen abstraction. Also, the Lewis acid is key to preventing transmetalation of the alkoxide species with nickel(ii) aryl intermediates, the side process that could be followed by reductive elimination leading to the formation of aryl ethers.[32-34]

Scheme 1.1 α-Arylation of alcohols with aryl bromides under the Ir/Ni/amine photoredox multicatalysis.

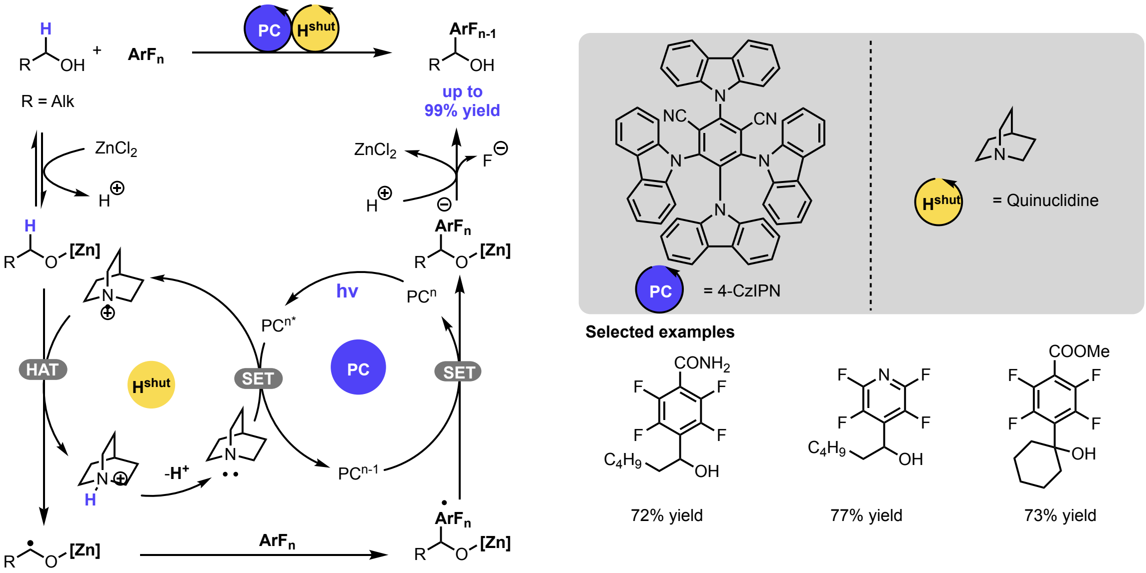


Accessing secondary benzylic alcohols *via* a dual-catalytic photoredox system is also possible, starting from α-hydroxyalkyltrifluoroborates as the radical precursor, as was demonstrated by the group of Molander.[35] Along the same lines, the α-alkylation of alcohols has recently been reported by Kanai and coworkers.[36] Here, a merger of a photocatalyst, a hydrogen atom transfer catalyst, and a Lewis acid catalyst mediates generating α-carbon-centred radical, which adds to an alkene to yield secondary alcohol.

In 2022, Wu and coworkers expanded the chemistry of radical-mediated α-arylation of alcohols with polyfluoroarenes *via* a cooperative photoredox-hydrogen atom transfer catalysis (**Scheme 1.2**).[37] A Lewis acid was involved in the initial activation of the alcohol, which upon hydrogen atom abstraction by a quinuclidine radical cation, generates an α-carbon-centered radical. The latter adds to the aryl fluoride, and a subsequent single electron transfer followed by fluoride elimination and proton exchange leads to the product.

The same type of transformation, *i.e.*, α-arylation of alcohols, can also be carried out in non-catalytic systems; however, their synthetic utility is somewhat limited when compared to the multicatalytic approach.[38,39] Having catalysts controlling each step of the transformations allows for higher selectivity compared to non-catalytic approaches, permitting higher functional group tolerance. For instance, the non-catalytic methods appear to not operate well with electron-rich aryl halides or tolerate functional groups such as amines or sulphides. Additionally, this type of transformation is also feasible in a system with only one catalyst present, as demonstrated by the nickel catalysed α-arylation of alcohols reported by the group of Newman.[40,41]

Scheme 1.2 α-Arylation of alcohols with aryl fluorides under the photoredox-hydrogen atom transfer multicatalysis.



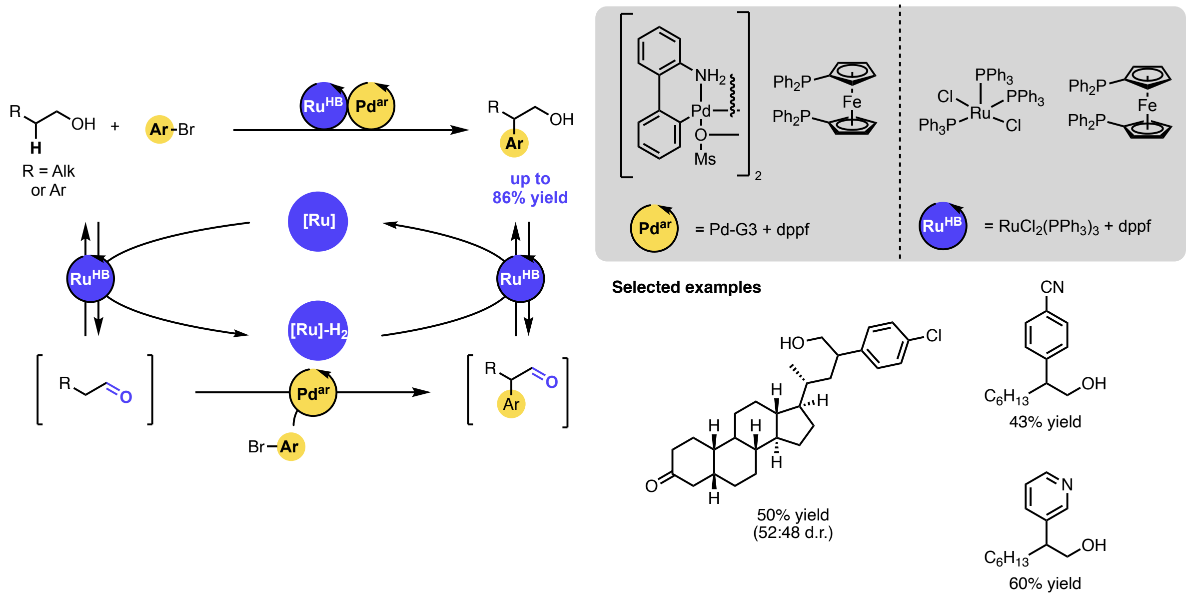
1.3 β-Functionalization of primary alcohols

Our group reported an example of an orthogonal relay that enables the direct β-arylation of primary aliphatic alcohols with aryl bromides (**Scheme 1.3**).[42] The strategy merges Ru-catalysed hydrogen borrowing reactivity,[26,27] mediating reversible activation of the alcohol to a transient aldehyde intermediate, with a Pd-catalysed arylation of the (activated) aldehyde intermediate.[43-45] Specifically, the initial oxidation of the alcohol to the aldehyde intermediate is carried out by the Ru-catalyst that temporarily stores the hydrogen. The aldehyde undergoes the arylation with aryl bromide on the Pd-catalyst. Lastly, the arylated aldehyde is reduced to the corresponding aryl alcohol by the Ru-catalyst using the borrowed and stored hydrogen.

Therefore, this protocol of β-arylation of alcohols is redox-neutral, with no stoichiometric oxidants or reductants used, despite the oxidation and reduction steps involved in the relay.

The striking differences between the above-described catalytic orthogonal relay and the isolated reactions are revealed by the kinetic features. In the Ru/Pd relay, for instance, deuterium labelling studies have demonstrated that the rate-limiting step is the enolate formation from the transient aldehyde. In contrast, for the isolated arylation of the aldehyde, kinetic studies indicate that oxidative addition of the aryl bromide to the palladium catalyst becomes the slowest step. These changes in rate-limiting steps are likely a result of operating under significantly different concentration regimes. In the relay, the transient aldehyde intermediate is present at a low concentration, which is dictated by the concentration of Ru-complex and is significantly lower than the aldehyde concentration in the isolated reaction. Hence, the rate of the enolate formation becomes slow with respect to the oxidative addition of the aryl bromide in the dual-catalytic system.

Scheme 1.3 Direct β-arylation of alcohols with aryl bromides under the dual-catalytic Ru/Pd relay.



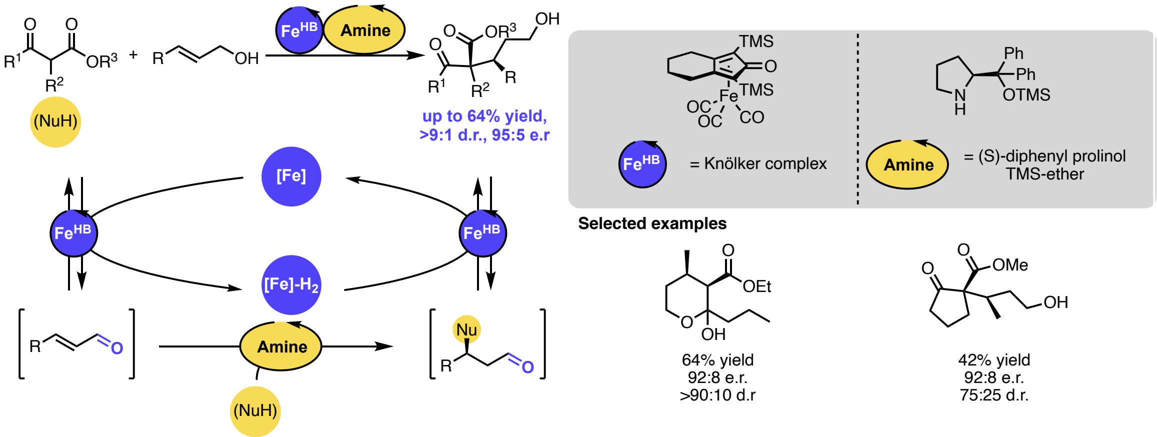
The above-discussed example demonstrates that, when devising multi-catalytic systems, it is crucial to consider the kinetics and investigate the catalysts in the entire system. The simplified analysis of the isolated components of the multicatalytic transformations might lead to faulty conclusions regarding the behaviour of the complete systems.

1.4 γ-Hydrofunctionalization of allylic alcohols

Several multicatalytic systems for selective γ-hydrofunctionalization of allylic alcohols were reported, all of which exploit the merger of the hydrogen borrowing reactivity with a range of orthogonal transformations. Common in the design is the initial oxidation of the allylic alcohol starting material to an α,β-unsaturated aldehyde or ketone intermediate with a hydrogen borrowing catalyst that temporarily stores the hydrogen. Because the oxidation step changes the reactivity of the double bond, the α,β-unsaturated carbonyl intermediate can undergo 1,4-addition with a range of nucleophiles to form a range of functionalized aldehyde intermediates, respectively. In the final stage, the latter undergo hydrogenation restoring the alcohol functionality, albeit with the double bond selectively hydrofunctionalized. Given the innate reactivity of α,β-unsaturated carbonyl compounds, the strategy does not require the use of multiple catalysts.[46-48] However, employing multiple catalysts expands the scope of available nucleophiles and introduces precise control over the reaction selectivity, as shown by the examples discussed below.

In one case, the orthogonal relay strategy was used to merge iron-based hydrogen transfer catalysis with organocatalysis to facilitate the enantioselective addition of keto-ester-based carbon nucleophiles to primary allylic alcohols (**Scheme 1.4**).[49] Here, the 1,4-addition occurs upon the formation of an iminium intermediate between the α,β-unsaturated aldehyde intermediate and the amine organocatalyst. Given that an isolated reaction of the Michael addition of the nucleophile to the α,β-unsaturated aldehyde led to the formation of the aldehyde product with the same absolute configuration and comparable enantiomeric purity as observed in the full system, the organocatalyst seems to influence the enantio- and diastereoselectivity. The kinetic investigations indicated that the iron-based catalyst is likely involved in the rate-determining step.

Scheme 1.4 Enantioselective Michael-type addition of keto-esters to allylic alcohols under the dual iron-/organocatalytic system.

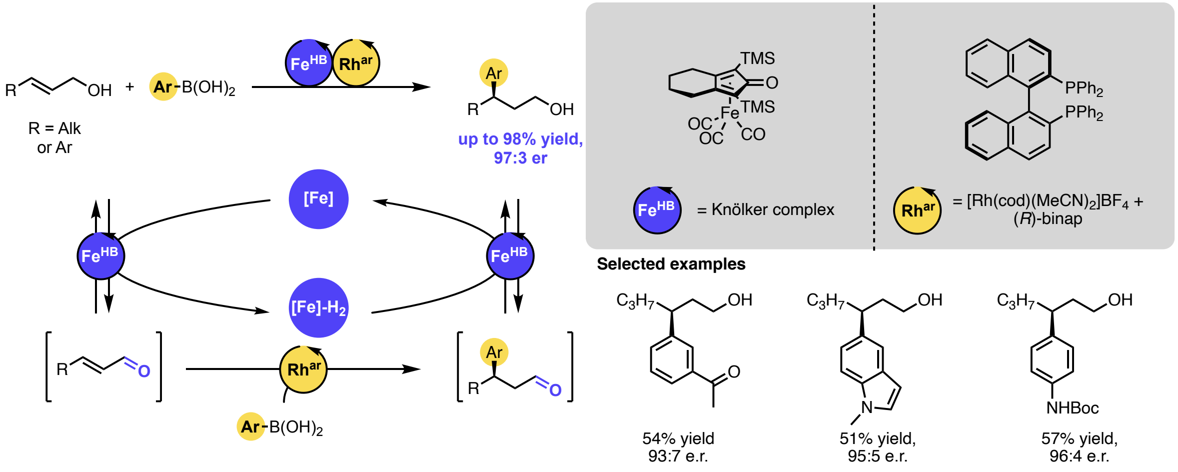


In a follow-up study, the scope of the transformation was extended by incorporating catalytic copper species, which resulted in increased rates of the overall transformation.[50] The strategy was taken even further, when the original system was combined with another reaction, enabling the direct formation of lactones from ketoesters and allylic alcohols in a one-pot procedure.[51] This work neatly demonstrated the great ability of multicatalysis to build up rapidly complex scaffolds from relatively simple starting materials. The methodology was applied for the synthesis of the key polyketide fragment of the anticancer agent Apratoxin A.[52] The application of the 1,4-addition sequence and the cascade shortened the overall synthesis to just 6 steps, a substantial improvement when compared with the previously reported syntheses counting between 12 to 20 steps.

The above-described work illustrates another advantage of multicatalysis. Although the Michael-type additions of related carbon nucleophiles to allylic alcohols were reported with a single catalyst that mediates the reversible oxidation,[53] building a dual catalytic system with a catalyst for the 1,4-addition step allows for more precise control of the reaction sequence and enables controlling its enantioselectivity.

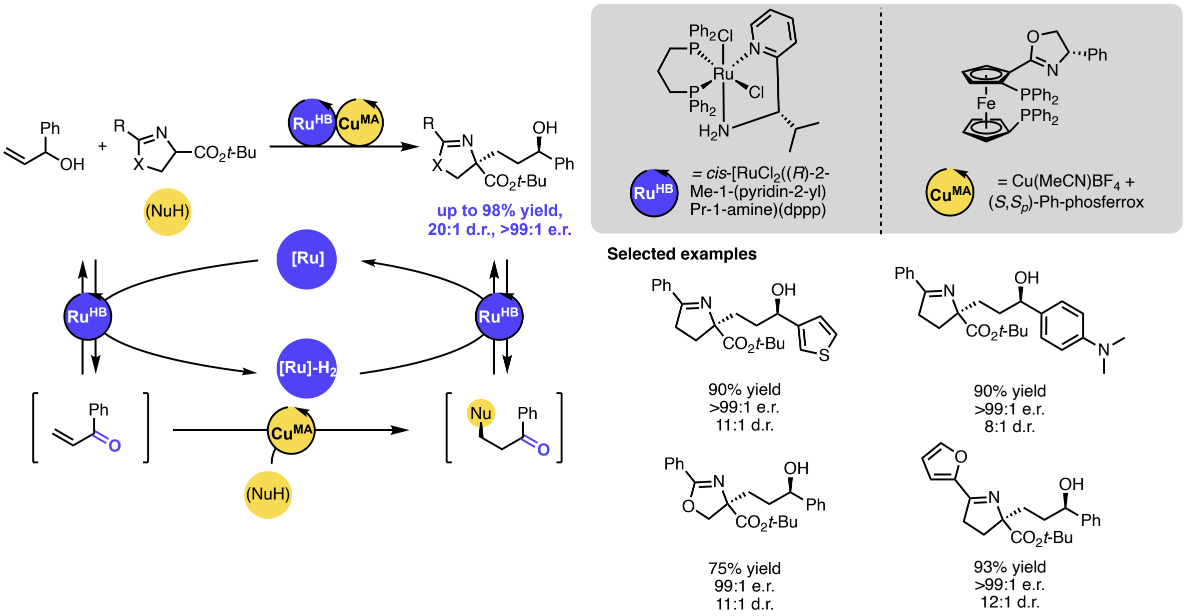
In turn, our group reported the γ-hydroarylation of allylic alcohols with aryl boronic acids under dual-catalysis (**Scheme 1.5**).[42] In contrast to the previous systems merging transition metal catalysis with organocatalysis, the reaction was driven by dual transition metal catalysis. In this case, a ruthenium or iron-based hydrogen borrowing catalyst was relayed with a rhodium-based catalyst bearing chiral (*R*)-BINAP ligand to furnish the overall transformation. The latter complex mediated the enantioselective 1,4-addition of aryl boronic acids to the transient unsaturated aldehydes. The method proved to tolerate a number of functional groups and form the target products in high yields and enantiopurity for a range of sterically and electronically-varied starting materials.

Scheme 1.5 Enantioselective Michael-type addition of boronic acids to allylic alcohols under the dual-catalytic Fe/Rh relay.



While the above-described functionalizations of primary allylic alcohols occur to form the products with one stereogenic centre, the reactions with secondary allylic alcohols may lead to the formation of products with two stereogenic centres, thereby introducing the need for another level of stereoselectivity control. Wang and coworkers recently reported a ruthenium/copper relay system for the functionalization of secondary allylic alcohols to construct alcohols bearing 1,4-adjacent stereogenic centres (**Scheme 1.6**).[54]

Scheme 1.6 Stereodivergent synthesis of alcohols bearing 1,4-stereocentres from allylic alcohols and ketimine esters under the dual-catalytic Ru/Cu system.

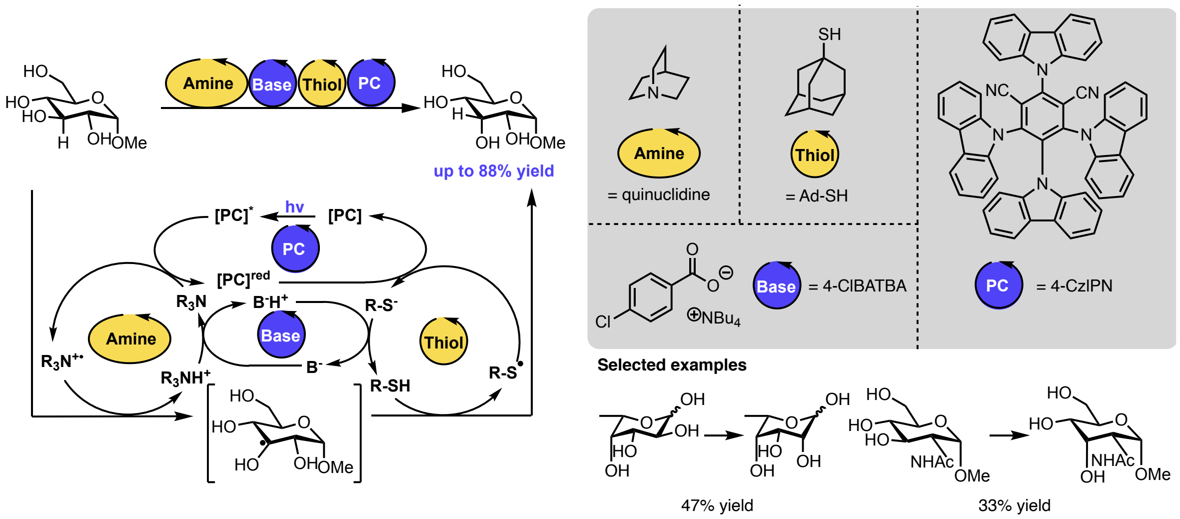


In this case, the transiently formed α,β-unsaturated ketone undergoes the enantioselective copper-catalyzed 1,4-addition of the ketimine ester nucleophile. Then, the modified ketone is stereoselectively reduced to the alcohol through the chiral Ru complex with the hydrogen borrowed in the initial step. Importantly, the employment of two different metal catalysts allows precise control over each reaction occurring within the relay. The chirality of the newly formed stereogenic centres could be controlled by using a suitable chiral copper complex during the Michael addition and the chiral ruthenium complex during the ketone reduction. Because the configurations of both newly formed stereogenic centres are strictly controlled by the distinct chiral catalysts, all possible stereoisomers of the product could be synthesized by selecting suitable enantiomers of ruthenium and copper complexes.

1.5 Site-selective isomerization of sugars

An excellent example of utilizing multicatalysis to access natural products, which are difficult to isolate from natural sources, was reported by the group of Wendlandt (**Scheme 1.7**).[55] Here, rare sugar isomers were synthesized from biomass-produced carbohydrates available in large amounts. Combining two hydrogen atom transfer processes allowed for the selective altering of the stereogenic configuration at one of the carbon positions. In this instance, the catalytic quinuclidinium radical cation abstracts the hydrogen atom from the sugar starting material. The generated radical sugar intermediate then abstracts the hydrogen atom from a thiol donor, generating the product diastereoselectively (along with a thiyl radical). A base and a cyanoarene-based photocatalyst regenerate both catalytic species – the quinuclidinium radical cation and the thiol, closing all the catalytic cycles. In such processes, it is necessary to ensure that each of the catalysts involved in the hydrogen atom transfer steps are selective since any cross-reactivity could cease the target transformation. Follow-up studies revealed that sugars and other polyols could be selectively epimerized at different positions upon fine-tuning the catalysts and the reaction conditions.[56] Similarly, photoredox catalysis and auxiliary additives allow for the epimerisation of *trans*-diols to *cis*-diols as reported by the group of MacMillan or the opposite direction – from *cis*-diols to *trans*-diols as demonstrated by the group of Wendlandt.[57,58] Overall, these studies demonstrate that leveraging two catalysts operating under photocatalytic conditions can drive thermodynamically uphill reactions, thanks to kinetic control over the product formation and the continuous supply of energy by light.

Scheme 1.7 Site-selective epimerization of sugars operating under photocatalysis with two hydrogen atom transfer processes.



1.6 Conclusion

Illustrated herein with the examples of different methods enabling diversified functionalisations of aliphatic and unsaturated alcohols, multicatalysis emerges as a dynamically developing field. Attractively, many multicatalytic strategies offer the opportunity for a rapid increase in the complexity of simple starting materials by reducing the number of tedious purification steps while maintaining high yields and, where applicable, the stereoselectivity of the overall transformation. This advantage leads to improving the cost, time, and material efficiency of the transformations. In addition, multicatalytic systems offer the possibility of directly modifying poorly reactive positions of molecules, even in the presence of other innately more reactive sites. Furthermore, multicatalysis offers the possibility of designing novel transformations, which are either tedious or impossible when performed in a non-catalytic fashion or by a classical catalytic approach. Overall, developing one-pot processes can lead to remarkable breakthroughs in the synthesis of valuable chemicals and materials.[59]

Crucial to further leveraging the potential of multicatalysis as a synthetic tool is to gain deeper mechanistic insight into the created systems. To fully capitalise on the remarkable capacity of multicatalysis, it is key to develop a different mindset when designing (multi)catalytic systems. The most productive catalysts developed for simple environments, *i.e.*, isolated reactions conducted separately, can prove to be inefficient in complex settings of reaction mixtures, *e.g.*, a network of cooperative reactions. Hence breaking down the system into simpler pieces might not be the most effective way of analysing and devising a multicatalytic system. Overall, learning how catalysts behave in complex mixtures can provide the opportunity to fine-tune them and design even more potent systems.

In a broader context, multicatalysis has the potential to unlock the nature-inspired synthesis of organic molecules. Starting from simple resources and efficiently yielding complex products is a highly attractive prospect for chemists. By further designing and investigating the systems that arise when multiple catalysts are combined, the development of even more complex systems can be facilitated. This, in turn, could lead to not only more straightforward transformations but also enable high control over the outcome, all while increasing the overall efficiency of the process, the holy grail of practical catalysis.

1.7 References

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CHAPTER 2

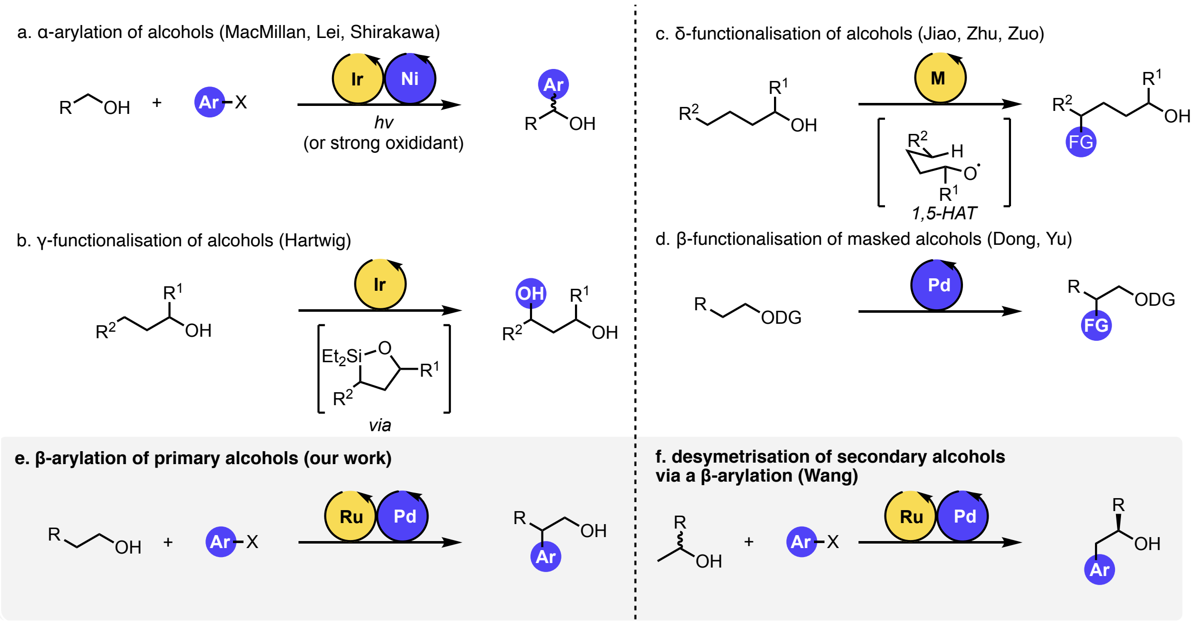
Enantioselective β-arylation of primary alcohols via a multicatalytic relay

The work in this chapter was mostly conducted by me. F. Mammadova joined in the later stages of the project and assisted with evaluating the scope of the transformation.

2.1 Introduction

Alcohols are ubiquitous in natural products, bioactive compounds, and fine and bulk chemicals.[1,2] Having methods available to diversify alcohols could lead to exploring new chemical space. Such functionalised alcohols could provide the opportunity for discovering new, value-added products. However, to preserve the hydroxyl functional group in the product it is key to develop strategies that overcome the typical reactivity of alcohols. Alcohols typically react as nucleophiles on the oxygen atom or as a proton source.[3] To date several protocols have been developed to modify alcohols at one of the carbon positions. In the case of the α-position, the proximity of it to the hydroxyl group causes the C-H bond to be active in hydrogen atom transfer (HAT) processes to generate carbon-centred radicals. This has been exploited to develop protocols enabling the direct α-arylation of alcohols (**Scheme 2.1a**).[4,5,6,7] In addition, several methods have been demonstrated to perform an α-functionalisation, proceeding via a transient aldehyde intermediate.[8,9,10,11] In turn, modifying the γ-position is possible via an Ir-catalysed reaction, proceeding via 5-membered silacycles (**Scheme 2.1b**).[12,13] Finally, the δ-position of alcohols can be activated via a 1,5-HAT process (**Scheme 2.1c**).[14,15,16]

Scheme 2.1 Approaches to modifying alcohols at the carbon positions

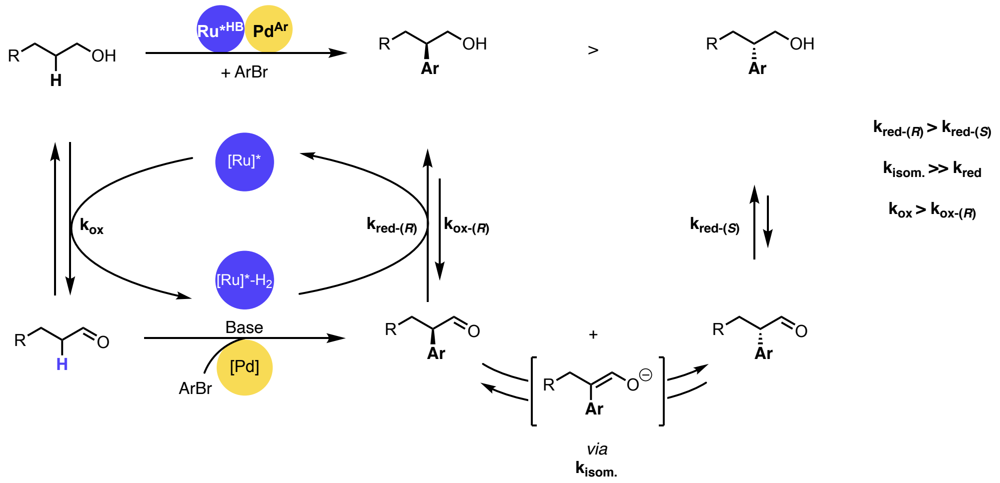


However, modifying alcohols at the β-position represents a unique challenge. Typically, it requires employing designer directing groups to guide the metal into the desired position (**Scheme 2.1d**).[17,18] Recently, our group has demonstrated that combining the hydrogen borrowing strategy with the α-arylation of aldehydes makes it possible to access β-arylated alcohols starting from primary alcohols directly (**Scheme 2.1e**).[19] The overall transformation relies on a Ru-based catalyst to oxidize the alcohol to the corresponding aldehyde whilst storing the "borrowed" hydrogen in the system.[20] This aldehyde then undergoes a Pd-catalysed arylation reaction.[21,22,23] Finally, the modified aldehyde is reduced to the β-arylated alcohol by the hydrogen temporarily stored in the system. Recently, this design has been extended to secondary alcohols, including the desymmetrization of a racemic starting alcohol via a β-arylation reaction combined with asymmetric reduction of the transient ketone (**Scheme 2.1f**).[24]

Tempted by even further expanding the utility of the hydrogen borrowing relay, we drew our attention to designing a protocol for the enantioselective β-arylation of primary alcohols. Directly incorporating an enantioselective arylation reaction is not feasible in the system as the product undergoes rapid racemisation via the enolate intermediate under reaction conditions.[25,26] However, this isomerization could be leveraged to yield the enantioenriched product via so-called dynamic kinetic resolution. In this vein, racemic α-arylated aldehydes can be asymmetrically hydrogenated to yield the enantioenriched alcohol.[27,28]

By employing a suitable chiral hydrogen transfer catalyst, we envisioned that the stored hydrogen could be selectively transferred to one of the enantiomers of the arylated aldehyde in the full arylation system (**Scheme 2.2**). For this to be possible several kinetic conditions would have to be fulfilled. Firstly, the catalyst must reduce one of the aldehyde enantiomers faster than the other one. Secondly, it is key that the rate of racemization of both aldehyde enantiomers is significantly higher than the rates of their reduction. This ensures the equilibration (or steady state) between both enantiomers is maintained. Lastly, the oxidation of the starting material should be more rapid than the oxidation of the product, which would eventually lead to the racemisation of the product. In addition to fulfilling those kinetic conditions, it is also key that no ligand scrambling occurs in the orthogonal relay, as this can cause a deterioration of the enantioselectivity of the reaction.[29]

Scheme 2.2 Envisioned system design for the enantioselective β-arylation of primary alcohols



Here, we disclose a protocol which enables the enantioselective β-arylation of primary alcohols via an orthogonal relay of reactions enabled by two catalysts. By merging a

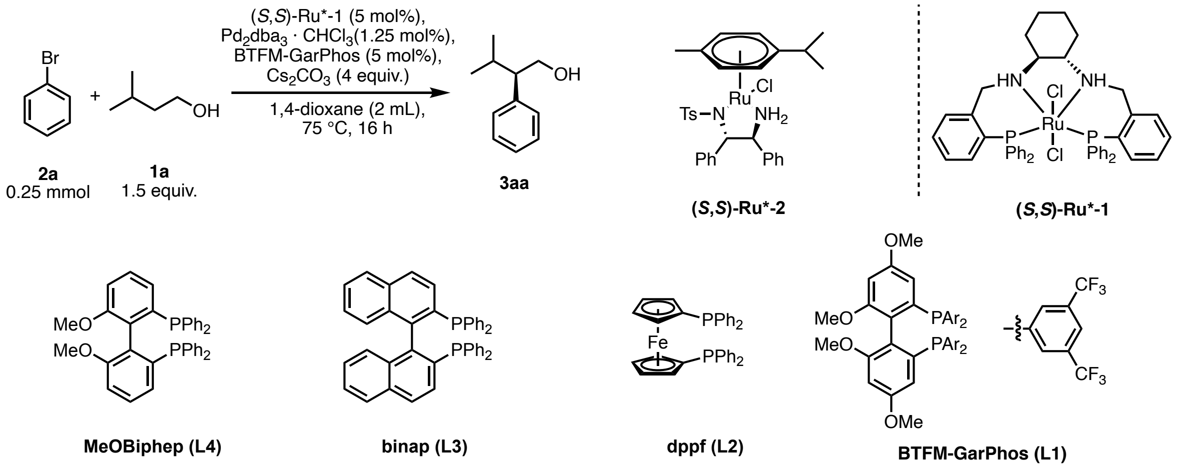
Pd-based catalyst with a chiral Ru-based catalyst the products were furnished with moderate to high yields and high enantioselectivities.

2.2 Results and discussion

Extensive evaluation of metal complexes and reaction conditions provided a protocol which allowed for the formation of the enantioenriched product **3aa** with 59% yield and 93:7 enantiomeric ratio starting from alcohol **1a** and the aryl bromide **2a** (**Table 2.1**, entry 1). Employing a chiral Ru-complex **(*S*,*S*)-Ru*-1** in parallel with **Pd_2dba_3•$CHCl_3$** combined with the racemic bisphosphine ligand BTFM-GarPhos (**L1**) proved to be crucial for the transformation to occur.

Varying the ligand revealed that using dppf (**L2**), which was used in the previously reported method by our group, yielded the product with only 15% yield of the product (**Table 2.1**, entry 2). Using binap (**L3**) or MeOBiphep (**L4**) caused the yield to decrease further (**Table 2.1**, entries 3 and 4). Changing the Pd-source from **Pd_2dba_3•$CHCl_3$** to **$Pd(OAc)_2$** resulted in the product being formed with lower yield and using **Pd(P(*o*-tol)$_3$)$_2$** as the precursor did not impact the yield substantially, but lowered the enantioselectivity of the reaction (**Table 2.1**, entries 5 and 6). Also, it proved to be crucial to use **Pd_2dba_3•$CHCl_3$** since the use of commercial **Pd_2dba_3** resulted in the poor reproducibility of the reaction outcome (see **Section 2.4.8** for details).[30] Changing the solvent to toluene in place of 1,4-dioxane also proved detrimental to the reaction yield (**Table 2.1**, entry 7). Noteworthy, when changing the transfer hydrogenation catalyst to **(*S*,*S*)-Ru*-2** the yield of the reaction increased, but the product formed was nearly racemic (**Table 2.1**, entry 8). Finally, swapping the base to either DIPEA or K_3PO_4 caused the reaction to not yield the target product at all (**Table 2.1**, entries 9 and 10).

Table 2.1 Reaction development[a]



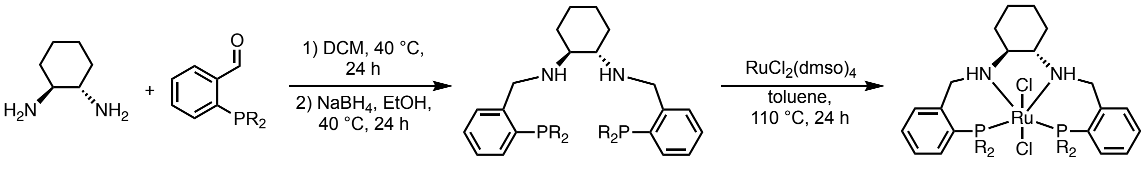
#	variations from the standard cond.	yield (%)	er
1	none	59%	93:7
2	**L2** instead of **L1**	15%	86:14
3	**L3** instead of **L1**	7%	92:8
4	**L4** instead of **L1**	< 5%	-
5	$Pd(P(o\text{-tol})_3)_2$ instead of $Pd_2dba_3{\bullet}CHCl_3$	56%	82:18
6	$Pd(OAc)_2$ instead of $Pd_2dba_3{\bullet}CHCl_3$	21%	92:8
7	Toluene instead of 1,4-dioxane	24%	-
8	**(*S*,*S*)-Ru*-2** instead of **(*S*,*S*)-Ru*-1**	78%	45:55
9	DIPEA instead of Cs_2CO_3	< 5%	-
10	K_3PO_4 instead of Cs_2CO_3	< 5%	-

[a]Standard conditions: **1a** (0.375 mmol), **2a** (0.25 mmol), **(*S*,*S*)-Ru*-1** (5 mol%), $Pd_2dba_3{\bullet}CHCl_3$ (1.25 mol %), rac-BTFM-GarPhos (5 mol%), Cs_2CO_3 (4 equiv.), 1,4-dioxane (2 mL), stirred for 16 h at 75 °C. Yields determined by ^1H NMR analysis with an internal standard; enantiomeric ratios (er; *R*:*S*) determined by SFC analysis.

While developing the reaction protocol, we prepared new ligands and complexes and evaluated their performance in facilitating the model reaction.

First, we turned our attention to varying the hydrogen borrowing catalyst sterically. Crucially, we attempted to vary the phenyl rings of **(*S*,*S*)-Ru*-1**. To do so the same route was selected as for the synthesis of **(*S*,*S*)-Ru*-1** (**Scheme 2.3**).[31,32] First, the ligand was prepared by reductive amination of various diarylphosphinobenzaldehydes. In this fashion ligands **(*S*,*S*)-L3*** and **(*S*,*S*)-L4*** were prepared, containing xylyl and p-tolyl rings respectively. Next, the corresponding complexes **(*S*,*S*)-Ru*-3** and **(*S*,*S*)-Ru*-4** were prepared, using $RuCl_2(dmso)_4$ as the ruthenium source.

Scheme 2.3 Synthesis of Ru-based complexes

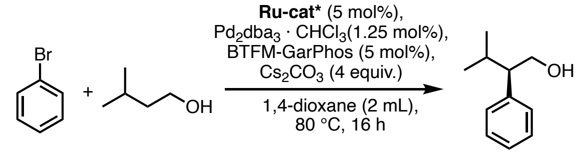


(***S,S***)-**L1***, R = Ph, 49%
(***S,S***)-**L3***, R = Xyl, 33%
(***S,S***)-**L4***, R = *p*-Tol, 34%

(***S,S***)-**Ru*-1**, R = Ph, 62%
(***S,S***)-**Ru*-3**, R = Xyl, 33%
(***S,S***)-**Ru*-4**, R = *p*-Tol, 35%

Having the new hydrogen borrowing complexes in hand, their performance in the model reaction was evaluated. Even though in both cases product **3aa** was furnished in comparable yields when using **(*S*,*S*)-Ru*-1**, the enantioselectivity was decreased when using **(*S*,*S*)-Ru*-3** and **(*S*,*S*)-Ru*-4** (**Table 2.2**). Based on those results, increasing the steric bulk of the aryl rings of the complex causes a decrease in enantioselectivity. This could provide valuable insight into potential further modifications of the ligand structure.

Table 2.2 Evaluation of synthesised Ru-based complexes in the β-arylation reaction[a]



2a 0.25 mmol

1a 1.5 equiv.

3aa

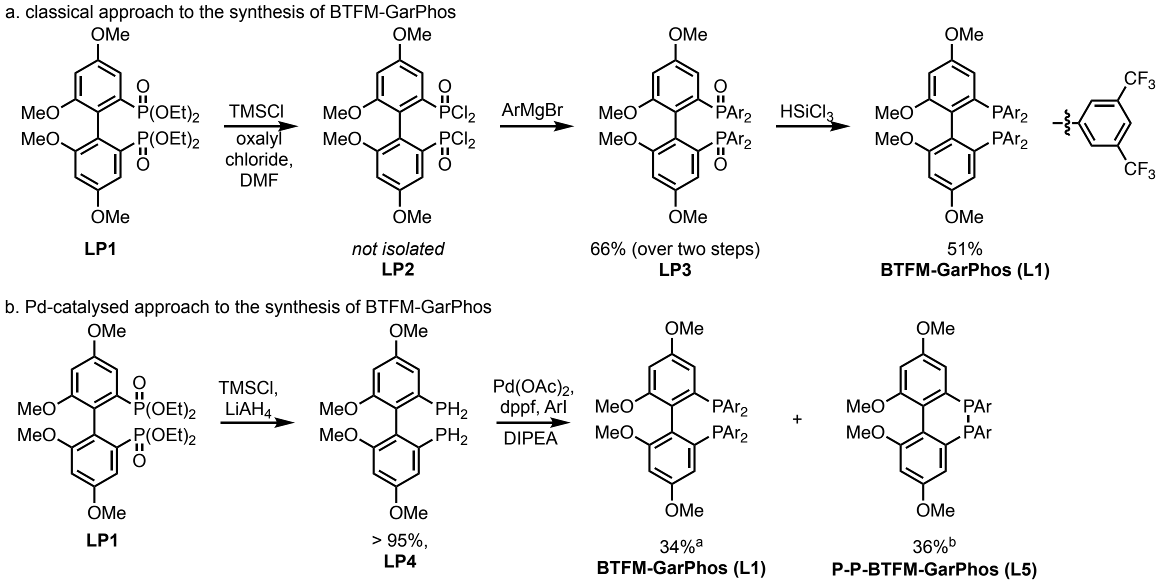
#	Ru-cat*	yield (%)	er
1	(*S*,*S*)-Ru*-1	64%	88:12
2	(*S*,*S*)-Ru*-3	70%	71:29
3	(*S*,*S*)-Ru*-4	58%	80:20

[a]Standard conditions: **1a** (0.375 mmol), **2a** (0.25 mmol), (*S*,*S*)-**Ru*-1** (5 mol%), $Pd_2dba_3{\cdot}CHCl_3$ (1.25 mol %), rac-BTFM-GarPhos (5 mol%), Cs_2CO_3 (4 equiv.), 1,4-dioxane (2 mL), stirred for 16 h at 75 °C. Yields determined by ^1H NMR analysis with an internal standard; enantiomeric ratios (er; *R*:*S*) determined by SFC analysis.

Second, we sought to vary the aldehyde arylation ligand structurally. Classically, GarPhos-type phosphine ligands are prepared from bisphosphonates in a three-step procedure via the phosphine oxide (**Scheme 2.4a**).[33] Inspired by the synthesis of MeOBiphep derivatives reported previously, we turned our attention to the possibility of preparing GarPhos derivatives from the same bisphosphonates in a two-step procedure via a reduction-coupling route (**Scheme 2.4b**).[34,35] Besides being the shorter route, utilising the metal coupling to instal the aryl rings onto the phosphine could open access to structures inaccessible via the classical approach.

Gratifyingly, the bisphosphonate precursor (**LP1**) could be converted into the phosphine (**LP4**) quantitatively. However, in the Pd-catalysed step, another product was observed. Based on the literature and NMR analysis the product of the reaction was a GarPhos analogue containing a P-P bond (P-P-BTFM-GarPhos, **L5**, **Scheme 2.4b**). After varying the reaction conditions, it was possible to obtain BTFM-GarPhos (**L1**) as the major product, by adding the phosphine precursor as a solid to the reaction mixture, instead of as a solution (see section **2.4.4** for details). This highlights the sensitivity of the coupling reaction to the concentration and should be considered if further developing the reaction. In total, this approach did not provide a clear advantage over the classical synthesis of BTFM-GarPhos (**L1**) in terms of yield.

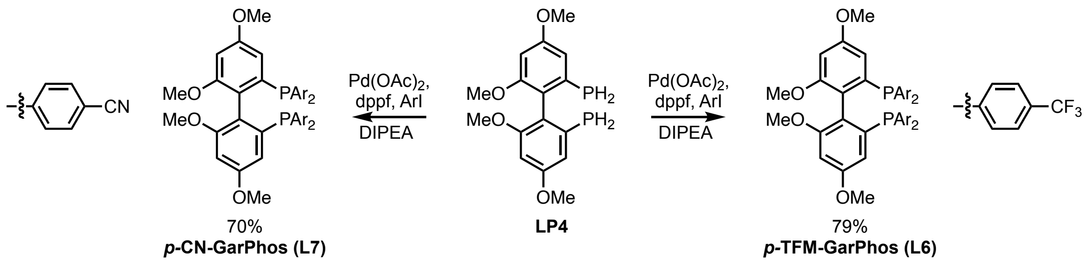
Scheme 2.4 Comparison of classical GarPhos-type ligand synthesis approach with Pd-catalysed MeOBiphep synthesis approach



[a]Isolated yield when phosphine precursor is added as solid. [b]Isolated yield when phosphine precursor is added as solution.

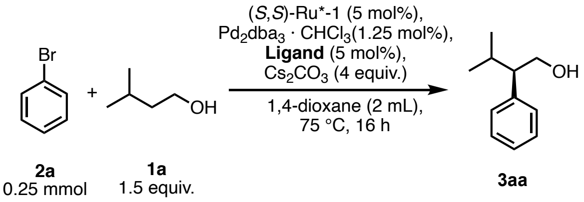
Other GarPhos-type ligands were prepared to evaluate in the β-arylation reaction. By employing the Pd-catalysed protocol *p*-TFM-GarPhos (**L6**) and *p*-CN-GarPhos (**L7**) were obtained in high yields **(Scheme 2.5**). This demonstrates an advantage of the coupling approach as cyano-containing ligands are not accessible using the traditional route, as it involves the use of Grignard reagents and strong reducing agents.

Scheme 2.5 Synthesis of GarPhos-type ligands via Pd-catalysed approach



Next, the newly obtained ligands were tested in the β-arylation system. Even though the newly synthesised ligands do not perform well in the reaction when compared to BTFM-GarPhos (**L1**), the product **3aa** can be detected (**Table 2.3**), suggesting that the ligands have potential to form active catalytic species and could be of potential interest when developing new reactions.

Table 2.3 Evaluation of synthesised ligands in the β-arylation reaction[a]



#	Ligand	yield (%)	er
1	**L1**	59%	93:7
2	**L6**	<5%	-
3	**L7**	7%	96:4
4	**L5**	-	-

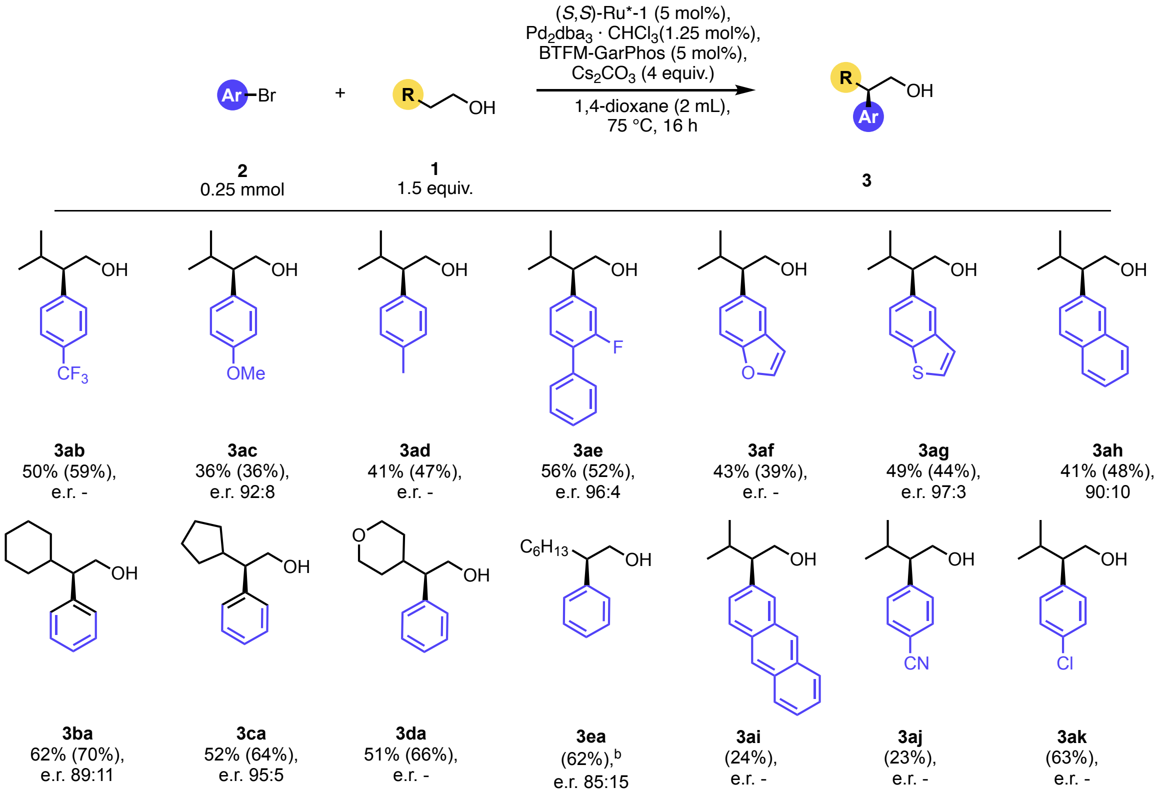
[a] Standard conditions: **1a** (0.375 mmol), **2a** (0.25 mmol), **(*S*,*S*)-Ru*-1** (5 mol%), $Pd_2dba_3•CHCl_3$ (1.25 mol %), **ligand** (5 mol%), Cs_2CO_3 (4 equiv.), 1,4-dioxane (2 mL), stirred for 16 h at 75 °C. Yields determined by ^1H NMR analysis with an internal standard; enantiomeric ratios (er; *R*:*S*) determined by SFC analysis.

Having established a protocol for the enantioselective β-arylation of primary alcohols we next focused on investigating the functional group tolerance of the developed protocol. The studies are currently ongoing.

The reaction proves to be well compatible with electron-rich (**3ac**, **3ad**) and electron-deficient aryl bromides (**3ab**, **3ae**, **3aj**, **3ak**), although the yields decrease when employing aryl bromides with electron-donating substituents. In the case of the cyano-group bearing aryl bromide **2j** the major detected product is an ether (the product of *O*-arylation of alcohol **1a**). In addition, (hetero)cyclic aryl bromides such as napthyl (**3ah**), anthracyl (**3ai**) benzofuranyl (**3af**) and benzothiophenyl (**3ag**) bromides yield the modified alcohol with moderate to low yields. A key limitation is that ortho-substituted aryl bromides are not tolerated (see **section 2.4.7**).

Alcohols bearing various cyclic carbon side chains could be arylated while maintaining high enantioselectivity (**3ba**, **3ca**). However, when a linear primary alcohol is employed in the reaction the enantiomeric ratio of the desired product is 85:15 (**3ea**). Additionally, alcohols containing a tetrahydropyranyl moiety could also be modified (**3da**).

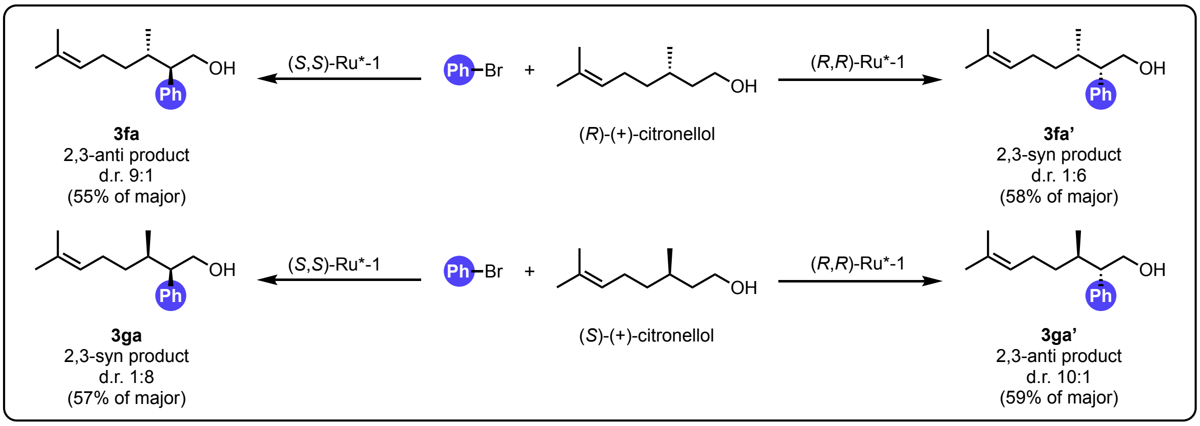
Scheme 2.6 Scope of the enantioselective β-arylation of primary alcohols[a]



[a]Standard conditions: **1** (0.375 mmol), **2** (0.25 mmol), **(*S*,*S*)-Ru*-1** (5 mol%), Pd_2dba_3•$CHCl_3$ (1.25 mol %), BTFM-GarPhos (5 mol%), Cs_2CO_3 (4 equiv.), 1,4-dioxane (2 mL), stirred for 16 h at 75 °C..Isolated yields reported. Yields determined by ^{1}H NMR analysis with an internal standard in brackets, mass confirmed with GC-MS analysis.; enantiomeric ratios (er) determined by SFC analysis. [b]Reaction run at 70 °C instead of 75 °C.

The devised reaction protocol can be successfully applied to the arylation of alcohols already bearing stereocenters. In the case of the reaction with either (*R*)- or (*S*)-citronellol (**1f** and **1g**), both diastereoisomers can be obtained and the configuration of the newly formed stereocenter is controlled by the Ru-based catalyst (**Scheme 2.7**). This underlines a key advantage of the

Scheme 2.7 Ligand controlled, diastereoselective β-arylation of alcohols bearing stereocenters[a]



[a] Standard conditions: **1f or 1g** (0.375 mmol), **2a** (0.25 mmol), **Ru*-1** (5 mol%), $Pd_2dba_3 \cdot CHCl_3$ (1.25 mol %), BTFM-GarPhos (5 mol%), Cs_2CO_3 (4 equiv.), 1,4-dioxane (2 mL), stirred for 16 h at 75 °C. Yields determined by ^1H NMR analysis with an internal standard in brackets, mass confirmed with GC-MS analysis. Diastereomeric ratios determined by ^1H NMR analysis of crude reaction mixture.

2.3 Conclusion

In conclusion, we developed a protocol which allows for the direct enantioselective β-arylation of primary alcohols. By including so-called dynamic kinetic resolution into a multicatalytic relay, we demonstrate that even if the stereocentre-forming step of the relay leads to the formation of a racemate, it is possible to obtain the enantioenriched product. Overall, this approach has the potential to be applied to other transformations, while providing a stepping-stone to the further development of multicatalytic systems.

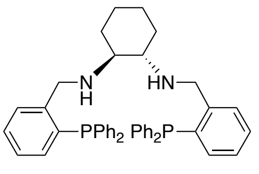
2.4 Experimental Section

2.4.1 General remarks

Unless stated otherwise, all reactions and manipulations were conducted on a laboratory bench or in a well-ventilated fume hood in air with reagent-grade solvents. Reactions under an inert gas atmosphere were carried out in oven-dried glassware in a nitrogen-filled glovebox or by standard Schlenk techniques under nitrogen.[36] Unless noted otherwise, all reagents and solvents were purchased from commercial suppliers and used without further purification. For experiments under an inert gas atmosphere, dry solvents were purchased from commercial suppliers and used as received or dried according to literature procedures and stored over molecular sieves and an inert atmosphere.[37] Column chromatography was carried out with the aid of a CombiFlash EZ Prep Chromatography System with integrated ELSD using RediSep Rf (Gold) Silica Gel Disposable Flash columns. TLC visualization was carried out with ultraviolet light (254 nm), followed by staining with a 1% aqueous $KMnO_4$ solution. NMR spectra were acquired on the 400 or 500 MHz Bruker instrument at the Institute of Science and Supramolecular Engineering (ISIS), University of Strasbourg. NMR spectra were processed using MestReNova version 14.2. Chemical shifts are reported in parts per million and referenced to residual solvent peaks or tetramethylsilane (TMS).[38] Coupling constants are reported in hertz. SFC analysis was conducted using an Agilent SFC 1260 Infinity II instrument connected to Agilent MSD XT mass spectrometry equipment. Chiral SFC separation was achieved using Chiralpak SFC {100 mm × 3 mm [inside diameter (ID)] × 3 µm} columns. GC and NMR yields were calculated using 1,3,5-trimethoxybenzene or dodecane as the internal standard.

2.4.2 Synthesis of the hydrogen borrowing ligands and complexes

(*1S*,2*S*)-*N,N'*-Bis[2-(diphenylphosphino)benzyl]cyclohexane-1,2-diamine ((*S*,*S*)-L1*)



The title compound was prepared according to the modified literature procedure.[31]

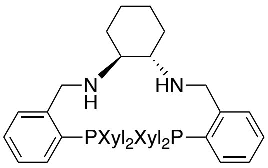
Under an inert atmosphere, (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (0.50g, 4.4 mmol), 2-(diphenylphosphino)benzaldehyde (2.5 g, 2 equiv.) and 4 A molecular sieves (0.1 g, 20 weight%) were added to an oven-dried 250 mL flask. Next, dry DCM (80 mL) was added. The mixture was allowed to stir for 24 h at 40 °C. After the reaction mixture was cooled to 25 °C, the solids were filtered off and washed with DCM (40 mL) in air. The volatiles from the combined filtrates were removed under reduced pressure. Under an inert atmosphere, the remaining solid residues were dissolved in dry ethanol (60 mL) and sodium borohydride (3.3 g, 20 equiv.) was added portion-wise. The reaction mixture was then allowed to stir for 24 h at 40 °C. The mixture was quenched by slowly adding water (20 mL). The suspension was extracted with DCM (3 x 75 mL). The combined organic fractions were then washed with saturated NH_4Cl solution (2 x 50 mL) and brine (50 mL). The organic phase was then dried over anhydrous Na_2SO_4. After filtration, the volatiles were removed under reduced pressure. The remaining residue was then subjected to column chromatography, using silica gel (60 g) and solutions of Et_3N in ethyl acetate (99:1 vol/vol) and Et_3N in petroleum ether (99:1 vol/vol) as eluents, with a gradient between 0:100 and 100:0). The fractions containing the product (as determined by TLC) were combined and the solvents were removed under reduced pressure yielding the product as a yellow powder (1.4 g, 49% yield).

The analytical data are consistent with those previously reported.[31]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.44 (m, 2H), 7.37 – 7.13 (m, 22H), 7.12 – 7.05 (m, 2H), 6.83 – 6.76 (m, 2H), 3.98 (d, *J* = 13.5 Hz, 2H), 3.80 (d, *J* = 2.1 Hz, 2H), 2.14 – 2.09 (m, 2H), 2.03 – 1.90 (m, 2H), 1.87 (bs, 2H), 1.61 – 1.52 (m, 2H), 1.12 – 0.98 (m, 2H), 0.94 – 0.71 (m, 2H).

^{31}P NMR (162 MHz, $CDCl_3$) δ -15.9.

(1*S*,2*S*)-*N,N'*-bis(2-(bis(3,5-dimethylphenyl)phosphaneyl)benzyl)cyclohexane-1,2-diamine ((*S*,*S*)-L3*)



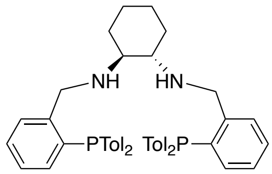
The title compound was prepared in an analogous fashion as **L1*** starting from (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (66 mg, 0.58 mmol) and 2-[bis(3,5-dimethylphenyl)phosphino]benzaldehyde (0.4 g, 2 equiv.)

The product was obtained as a yellow powder (0.15 g, 33%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.41 (m, 2H), 7.24 – 6.64 (m, 18H), 3.92 (d, *J* = 13.9 Hz, 2H), 3.85 – 3.77 (m, 2H), 2.31 – 2.19 (m, 4H), 2.15 (s, 24H), 1.95 – 1.87 (m, 2H), 1.53 (d, *J* = 8.4 Hz, 2H), 1.16 – 0.98 (m, 4H).

^{31}P NMR (202 MHz, $CDCl_3$) δ -15.95.

(1*S*,2*S*)-*N*,*N'*-bis(2-(di-*p*-tolylphosphaneyl)benzyl)cyclohexane-1,2-diamine ((*S*,*S*)-L4*)



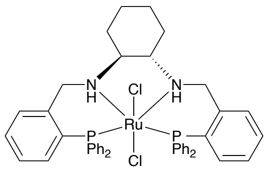
The title compound was prepared in an analogous fashion as **L1*** starting from (1*S*,2*S*)-(+)-1,2-diaminocyclohexane (50 mg, 0.44 mmol) and 2-(di-p-tolylphosphino)benzaldehyde (0.28 g, 2 equiv.).

The product was obtained as a yellow powder (0.11 g, 34% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (td, *J* = 8.4, 4.1 Hz, 2H), 7.48 – 7.08 (m, 20H), 6.94 (dtd, *J* = 10.7, 5.3, 2.5 Hz, 2H), 4.15 (d, *J* = 10.8 Hz, 2H), 3.95 (d, *J* = 13.5 Hz, 2H), 2.56 – 2.48 (m, 2H), 2.45 (s, 2H), 2.43 (d, *J* = 3.1 Hz, 12H), 2.10 (d, *J* = 12.4 Hz, 2H), 1.73 (d, *J* = 8.0 Hz, 2H), 1.28 – 0.91 (m, 4H).

^{31}P NMR (202 MHz, $CDCl_3$) δ -17.64.

Dichloro{(1*S*,2*S*)-*N*,*N'*-bis[2-(diphenylphosphino)benzyl]cyclohexane-1,2-diamine}-ruthenium(II) ((S,S)-Ru*-1)



The title compound was prepared according to the literature procedure.[32]

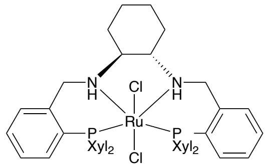
In a nitrogen-filled glovebox, **(*S*,*S*)-L1*** (700 mg, 1.1 mmol) and $Ru(dmso)_4Cl_2$ (0.51 g, 1 equiv.) were weighed in an oven-dried vial equipped with a stirring bar. Next, dry toluene (15 mL) was added, and the solution was allowed to stir at 110 °C for 24 h. Next, the reaction mixture was cooled to 25 °C. The volatiles were removed under vacuum. Next, the remaining residues were dissolved in DCM (5 mL) and deposited on a plug of silica gel (25 g), which was then washed with DCM (100 mL). The eluate was concentrated to approximately 5 mL DCM. Upon the addition of *n*-pentane (50 mL), a precipitate was formed. The precipitate was filtered off, and dried under vacuum, yielding the product as a yellow powder (0.55 g, 62% yield).

The analytical data are consistent with those previously reported.[32]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 6.83 (m, 28H), 4.66 (t, *J* = 11.2 Hz, 2H), 4.02 (d, *J* = 11.9 Hz, 2H), 3.91 (s, 2H), 2.93 (s, 2H), 2.71 (d, *J* = 11.1 Hz, 2H), 1.80 (d, *J* = 7.9 Hz, 2H), 1.30 – 1.08 (m, 4H).

^{31}P NMR (162 MHz, $CDCl_3$) δ 42.7.

Dichloro{(1*S*,2*S*)-*N*,*N'*-bis[2-(3,5-dimethylphenyl)phosphaneyl)benzyl]-cyclohexane-1,2-diamine}-ruthenium(II) ((*S*,*S*)-Ru*-3)



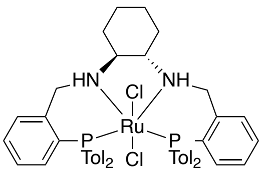
The title compound was prepared in an analogous fashion as **(S,S)-Ru*-1** starting from **(*S*,*S*)-L3*** (0.15 g, 0.19 mmol) and $Ru(dmso)_4Cl_2$ (94 mg, 1 equiv.).

The product was isolated as an orange powder. (53 mg, 33% yield)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.05 (m, 8H), 6.97 – 6.88 (m, 2H), 6.82 (s, 2H), 6.76 – 6.61 (m, 8H), 4.65 (t, *J* = 11.2 Hz, 2H), 4.02 (dt, *J* = 11.6, 4.6 Hz, 2H), 3.89 (t, *J* = 10.5 Hz, 2H), 2.94 (d, *J* = 8.7 Hz, 2H), 2.71 (d, *J* = 10.9 Hz, 2H), 1.97 (s, 12H), 1.90 (s, 12H), 1.82 – 1.75 (m, 2H), 1.25 – 1.03 (m, 4H).

^{31}P NMR (162 MHz, $CDCl_3$) δ 42.79.

Dichloro{(1*S*,2*S*)-*N*,*N'*-bis[2-(di-*p*-tolylphosphaneyl)benzyl]cyclohexane-1,2-diamine}-ruthenium(II) ((*S*,*S*)-Ru*-4)



The title compound was prepared in an analogous fashion as **(S,S)-Ru*-1** starting from **(*S*,*S*)-L4*** (0.10 g, 0.14 mmol) and Ru(dmso)$_4$Cl$_2$ (67 mg, 1 equiv.).

The product was isolated as orange crystals. (43 mg, 35% yield)

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.25 – 7.13 (m, 12H), 6.79 (dd, *J* = 16.1, 7.7 Hz, 8H), 6.67 (d, *J* = 8.0 Hz, 4H), 4.66 (t, *J* = 11.2 Hz, 2H), 3.98 (d, *J* = 11.9 Hz, 2H), 3.86 (s, 2H), 2.92 (d, *J* = 9.1 Hz, 2H), 2.70 (d, *J* = 11.7 Hz, 2H), 2.25 (s, 6H), 2.14 (s, 6H), 1.79 (s, 2H), 1.22 – 1.06 (m, 4H).

^{31}P NMR (202 MHz, CDCl$_3$) δ 41.19.

2.4.3 Synthesis of the palladium complexes

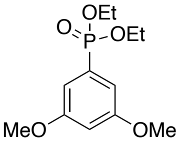
Tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (Pd$_2$dba$_3$•CHCl$_3$)

The title compound was prepared according to the literature procedure.[39]

Under an inert atmosphere, sodium acetate (2.0 g, 8.5 equiv.) and dba (2.3 g, 3.5 equiv.) were dissolved in dry MeOH (75 mL) and heated to 50 °C. Next PdCl$_2$ (500 mg, 2.8 mmol) was added, and the mixture was allowed to stir for 4 h at 40 °C. Next, the mixture was cooled to 25 °C and a precipitate formed. The precipitate was filtered off in air, and washed with water (30 mL), and acetone (30 mL). The precipitate was then dissolved in warm CHCl$_3$ (60 mL, 50 °C) and the solution was filtered through a cannula with a filter to remove any solid residues. The filtrate was then carefully layered with Et$_2$O (150 mL). The flask containing the mixture was then sealed and placed in the freezer (-20 °C) for 72 h. The solid was filtered off and washed with cold Et$_2$O (100 mL, -20 °C) and subsequently dried under vacuum to yield the product as a burgundy crystalline powder (0.96 g, 66% yield).

2.4.4 Synthesis of *rac*-GarPhos type ligands

Diethyl (3,5-dimethoxyphenyl)phosphonate (LP5)



The title compound was prepared according to the literature procedure.[33]

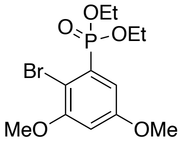
Under an inert atmosphere a solution of 1-bromo-3,5-dimethoxybenzene (20.0 g, 92.1 mmol) in dry THF (80 mL) was added dropwise to an oven-dried two-necked flask (500 mL) with magnesium turnings (2.5 g, 1.1 equiv.), I$_2$ (5 mg), and THF (140 mL) and refluxed for 2 h. Next, the solution was cooled to 25 °C, transferred to another oven-dried flask (500 mL), and cooled to -78 °C. A solution of diethyl phosphorochloridate (14.7 mL, 1.1 equiv.) in dry THF (80 mL) was added dropwise at that temperature. The mixture was slowly allowed to warm up to 25 °C and allowed to stir for 16 h. The reaction was quenched with brine (100 mL). The phases were separated, and the aqueous phase was washed with AcOEt (2 x 75 mL) and DCM (2 x 75 mL). The combined organic phases were washed with brine (2 x 150 mL) and dried over anhydrous Na$_2$SO$_4$. After filtration, the volatiles were removed under reduced pressure. The remaining residues were subjected to column chromatography on silica gel (300 g) using a gradient of ethyl acetate in petroleum ether (0:100 to 100:0) as eluent. The fractions containing the product (as determined by TLC) were combined and the solvents were removed under reduced pressure to give the desired product as a yellow oil (20.13 g, 80% yield).

The analytical data are consistent with those previously reported.[33]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (dd, *J* = 14.8, 2.3 Hz, 2H), 6.61 (t, *J* = 2.3 Hz, 1H), 4.21 – 4.00 (m, 4H), 3.82 (s, 6H), 1.33 – 1.25 (m, 6H).

^{31}P NMR (162 MHz, $CDCl_3$) δ 18.45.

Diethyl (2-bromo-3,5-dimethoxyphenyl)phosphonate (LP6)



The title compound was prepared according to the modified literature procedure.[33]

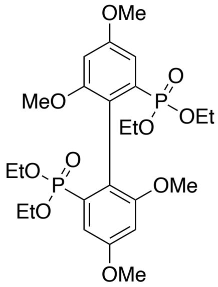
N-Bromosuccinimide (11.4 g, 1.1 equiv.), which was recrystallised from water according to literature procedure,[40] was added to a solution of **LP5** (15.9 g, 58.0 mmol) in DCM (200 mL) at 0 °C. The suspension was allowed to stir at 0 °C for 16 h. The reaction was quenched with of saturated Na_2CO_3 solution (100 mL). Next, both phases were separated, and the aqueous phase was extracted with DCM (2 x 100 mL). The combined organic phases were then washed with brine (2 x 125 mL) and dried over anhydrous Na_2SO_4. After filtration, the volatiles were removed from the filtrate under vacuum yielding the title product as a yellow oil (20.8 g, 96% yield).

The analytical data are consistent with those previously reported.[33]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 15.5, 2.8 Hz, 1H), 6.64 (d, *J* = 2.9 Hz, 1H), 4.27 – 4.03 (m, 4H), 3.89 (s, 3H), 3.85 (s, 3H), 1.41 – 1.30 (m, 6H).

^{31}P NMR (162 MHz, $CDCl_3$) δ 15.19.

Tetraethyl (4,4',6,6'-tetramethoxy-[1,1'-biphenyl]-2,2'-diyl)bis(phosphonate) (LP1)



The title compound was prepared according to the modified literature procedure.[33]

Under an inert atmosphere, copper powder (1.1 g, 3 equiv.) was added to a solution of **LP6** (2.0 g, 5.7 mmol) in dry DMF (8 mL) in an oven-dried 25 mL screw-capped vial. Next, copper (**I**) iodide (10 mg) was added. The vial was sealed and placed in a preheated aluminium block at 120 °C and the resulting suspension was allowed to stir for 4 h at 120 °C. The reaction mixture was cooled to 25 °C and the volatiles were removed under vacuum. Chloroform (15 mL) was added to the residues. The mixture was allowed to stir for 30 minutes. The solid residues were filtered off and washed with chloroform (2 x 30 mL). The combined organic phases were washed with saturated NH_4Cl (2 x 20 mL, colour of aq. phase changes to blue). The organic phase was then dried with anhydrous Na_2SO_4. The volatiles were removed under reduced pressure, and the formed residues were filtered through silica gel (40 g silica). A solution of THF in DCM (5:95 vol/vol; 200 mL) was used as an eluent to elute the side-products followed by THF in DCM (50:50 vol/vol; 200 mL) to elute the product). The volatiles were then removed under reduced pressure, and the solids were dissolved in a minimum amount of DCM at 50 °C. Next, ~20-fold excess of Et_2O was slowly layered and the layers were gently allowed to mix to precipitate a cream-coloured solid, which was filtrated and dried under vacuum yielding the title product (0.62 g, 40% yield).

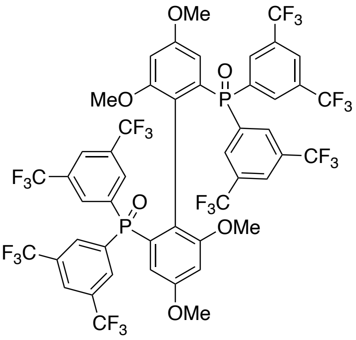
(Of note: the reaction proved to be highly temperature sensitive. When attempting to scale up the reaction, it might be necessary to modify the reaction temperature to account for the difference in the efficiency of heat transfer).

The analytical data are consistent with those previously reported.[33]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 15.4, 2.4 Hz, 2H), 6.65 (d, *J* = 2.4 Hz, 2H), 4.07 – 3.73 (m, 14H), 3.68 (s, 6H), 1.26 – 1.09 (m, 12H).

^{31}P NMR (162 MHz, $CDCl_3$) δ 17.88.

(4,4',6,6'-Tetramethoxy-[1,1'-biphenyl]-2,2'-diyl)bis(bis(3,5-bis(trifluoromethyl)-phenyl)phosphine oxide) (LP3)



The title compound was prepared according to the literature procedure.[33]

3,5-bis(trifluoromethyl)phenyl)magnesium bromide: Under inert atmosphere, an oven-dried 100 mL round bottom flask was charged with magnesium turnings (0.27 g, 12 equiv.) and iodine (5 mg), followed by the addition of dry THF (10 mL). Then, the mixture was heated to reflux. Next, a solution of 1-bromo-3,5-bis(trifluoromethyl)benzene (1.7 mL, 11 equiv.) in dry THF (10 mL) was added dropwise. The resulting mixture was allowed to stir for 3 h at reflux and then cooled down.

Under an inert atmosphere, TMSCl (0.46 mL mL, 4 equiv.) was added dropwise to a solution of **LP1** (0.50 g, 0.91 mmol) and sodium iodide (0.55 g, 4 equiv.) in dry acetonitrile (5 mL). The resulting mixture was warmed to 50 °C and allowed to stir for 16 h at that temperature. All the volatiles were removed under vacuum. The residues were suspended in dry DCM (20 mL) with DMF (0.1 mL), followed by the dropwise addition of oxalyl chloride (0.78 mL, 10 equiv.). The mixture was allowed to stir for 4 h at 40 °C. Next the mixture was cooled down to 25 °C. The suspension was filtered through a cannula with a filter and the volatiles evaporated from the filtrate. The remaining residues were dissolved in dry THF (15 mL) in an oven-dried 500 mL round bottom flask. Next, the solution was cooled to -78 °C. The freshly prepared solution of 3,5-bis(trifluoromethyl)phenyl)magnesium bromide (prepared as described above) was added dropwise. The resulting mixture was allowed to warm to 25 °C and was then allowed to stir for 1 h. Then, the reaction was quenched with a saturated, aqueous solution of NH_4Cl (15 mL). Next, water (10 mL) was added. The phases were separated, and the aqueous phase was washed with ethyl acetate (2 x 80 mL). The combined organic phases were washed with brine (2 x 80 mL) and dried over anhydrous $MgSO_4$. After filtration, the volatiles were removed under reduced pressure. The remaining residues were subjected to column chromatography on silica gel (40 g) using a gradient of ethyl acetate in petroleum ether (0:100 to 100:0) as the eluent. The fractions containing the product (as determined by TLC) were combined and the solvents were removed under reduced pressure to yield the product as a yellowish powder (0.72 g, 66% yield).

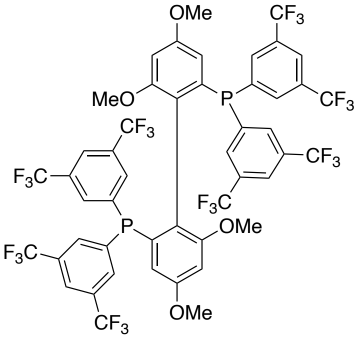
The analytical data are consistent with those previously reported.[33]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 11.2 Hz, 4H), 8.08 (d, J = 11.8 Hz, 4H), 7.94 (d, J = 41.3 Hz, 4H), 6.42 (dd, J = 15.3, 2.3 Hz, 2H), 6.21 (d, J = 2.3 Hz, 2H), 3.65 (s, 6H), 3.48 (s, 6H).

^{31}P NMR (162 MHz, $CDCl_3$) δ 23.88.

^{19}F NMR (377 MHz, $CDCl_3$) δ -62.92, -63.03.

Rac-BTFM-GarPhos (L1) – method 1



The title compound was prepared according to the literature procedure.[33]

Trichlorosilane (2.0 mL, 34 equiv.) was added dropwise to a solution of phosphine oxide **LP3** (0.72 g, 0.59 mmol) in dry toluene (50 mL) in an oven-dried 250 mL two-necked round bottom flask. Next, the mixture was allowed to stir for 36 h at 110 °C. Then cooling to room temperature, 2 M NaOH aqueous solution (50 mL) was added slowly to the reaction mixture. The phases were separated. The aqueous phase was washed with toluene (2 x 25 mL). The combined organic phases were washed with brine (2 x 30 mL) and next dried over $MgSO_4$. Upon filtration, the filtrate was concentrated to ~20 mL the solution was then subjected to column chromatography on silica gel (150 g) using a gradient of DCM in petroleum ether (0:100 to 30:70) as eluent. The fractions containing the product (as determined by TLC) were combined and the volatiles were removed under reduced pressure to yield the product as a white powder (0.36 g, 51% yield).

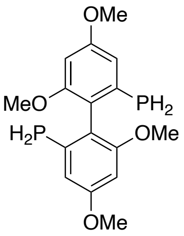
The analytical data are consistent with those previously reported.[33]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 29.8 Hz, 4H), 7.62 (d, *J* = 19.9 Hz, 8H), 6.43 (d, *J* = 2.3 Hz, 2H), 6.13 (q, *J* = 2.1 Hz, 2H), 3.65 (s, 6H), 3.41 (s, 6H).

^{31}P NMR (162 MHz, $CDCl_3$) δ -10.64.

^{19}F NMR (471 MHz, $CDCl_3$) δ -62.99, -63.18.

(4,4',6,6'-tetramethoxy-[1,1'-biphenyl]-2,2'-diyl)bis(phosphane) (L4)



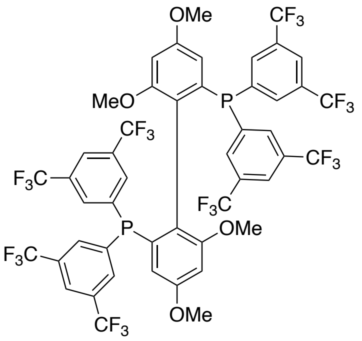
The title compound was prepared according to the literature procedure.[34]

Under an inert atmosphere, $LiAlH_4$ (1.8g, 5 equiv.) was added to an oven-dried 500 mL round bottom flask. Dry and deoxygenated THF (80 mL) was added. A solution of TMSCl (6.2 mL, 5 equiv.) in dry and deoxygenated THF (100 mL) was added dropwise whilst stirring the suspension at 0 °C. The suspension was allowed to stir for 2 h at 25 °C. Next, the solution of **LP1** (5.3 g, 9.7 mmol) in dry and deoxygenated THF (150 mL) was added dropwise at 0 °C and the reaction mixture was allowed to stir at 25 °C for 72 h. Under an inert atmosphere, the reaction was quenched by drop-wise addition of deoxygenated water (8 mL). Next, deoxygenated 1 M NaOH aqueous solution (20 mL) was added. Once the suspension became clear a whiteish precipitate formed. The solution was filtered via cannula filtration. The precipitate was washed with deoxygenated THF (3x80 mL). Next deoxygenated Et_2O (60 mL) was added to the combined organic phases. The organic phases were extracted with deoxygenated brine (2x60 mL) and then transferred to an oven-dried dried flask and dried with Na_2SO_4. After cannula filtration, the volatiles were removed under vacuum to yield the product as a white powder (3.1 g, 95% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 – 6.72 (m, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 3.84 (s, 3H), 3.82 – 3.74 (m, 1H), 3.71 (s, 3H), 3.43 – 3.33 (m, 1H).

^{31}P NMR (162 MHz, $CDCl_3$) δ -125.59 (t, *J* = 203.9 Hz).

Rac-BTFM-GarPhos (L1) – method 2



The title compound was prepared according to a modified literature procedure for preparing MeOBIPHEP-type ligands.[35]

In a nitrogen-filled glovebox, $Pd(OAc)_2$ (4.0 mg, 6 mol%) and dppf (19.7 mg, 12 mol%) were suspended in dry and degassed MeCN (1 mL) in an oven-dried dry 25 mL vial equipped with an octagonal stirring bar. The suspension was allowed to stir for 1 h. Next, DIPEA (0.41 mL, 8 equiv.) and the aryl iodide (0.31 mL, 6 equiv.) were added. The mixture was heated to 80 °C. Next, **LP4** (100 mg) was added to the reaction mixture at 80 °C, which was then allowed to stir at 80 °C for 16 h. The reaction mixture was diluted to volume of 50 mL with DCM. Then the organic phase was washed with brine (2 x 50 mL) and dried over $MgSO_4$. After filtration, the volatiles were removed under reduced pressure. The remaining residues were subjected to column chromatography on silica gel (40 g) using a gradient of DCM in petroleum ether (0:100 to 100:0) as eluent. The fractions containing the product (as determined by TLC) were combined and the solvents were removed under reduced pressure to yield the product as a white powder (117 mg, 34% yield).

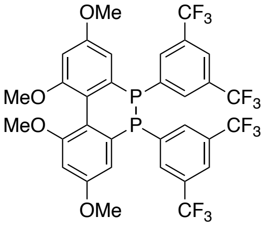
The analytical data are consistent with those previously reported.[33]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 38.3 Hz, 4H), 7.55 (d, *J* = 25.1 Hz, 8H), 6.36 (d, *J* = 2.3 Hz, 2H), 6.06 (d, *J* = 2.1 Hz, 2H), 3.59 (s, 6H), 3.34 (s, 6H).

^{31}P NMR (202 MHz, $CDCl_3$) δ -10.69.

^{19}F NMR (471 MHz, $CDCl_3$) δ -62.89, -63.26.

P-P-BTFM-GarPhos (L5)



The title compound was prepared according to a modified literature procedure for preparing MeOBIPHEP-type ligands.[35]

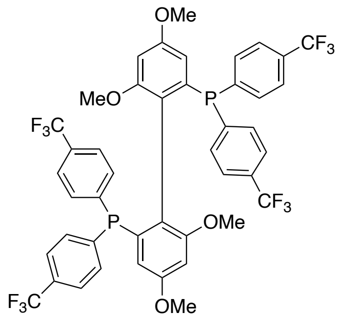
In a nitrogen-filled glovebox $Pd(OAc)_2$ (4.0 mg, 6 mol%) and dppf (19.7 mg, 12 mol%) were suspended in dry and degassed MeCN (1 mL) in an oven-dried dry 25 mL vial equipped with an octagonal stirring bar. The suspension was allowed to stir for 1 h. Next, DIPEA (0.41 mL, 8 equiv.) and the aryl iodide (0.31 mL, 6 equiv.) were added. The mixture was heated to 80 °C. Next, **LP4** (100 mg) was dissolved in dry and degassed MeCN (2 mL) and the solution was added to the reaction mixture dropwise at 80 °C. The solution was allowed to stir at 80 °C for 16 h. The reaction was diluted until 50 mL with DCM. Then the organic phase was washed with brine (2 x 50 mL), and next dried over $MgSO_4$. After filtration, the volatiles were removed under reduced pressure. The remaining residues were subjected to column chromatography on silica gel (40 g) using a gradient of DCM in petroleum ether (0:100 to 100:0) as eluent. The fractions containing the product (as determined by TLC) were combined and the solvents were removed under reduced pressure to yield the product as a white powder (121 mg, 36% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (bs, 2H), 7.49 (bs, 4H), 6.64 (td, *J* = 7.5, 2.4 Hz, 2H), 6.48 (d, *J* = 2.5 Hz, 2H), 3.77 (s, 6H), 3.71 (s, 6H).

^{31}P NMR (202 MHz, $CDCl_3$) δ -29.07, -29.11, -29.15.

^{19}F NMR (471 MHz, $CDCl_3$) δ -63.07.

Rac-p-TFM-GarPhos (L6)



The title compound was prepared according to a modified literature procedure for preparing MeOBIPHEP-type ligands.[35]

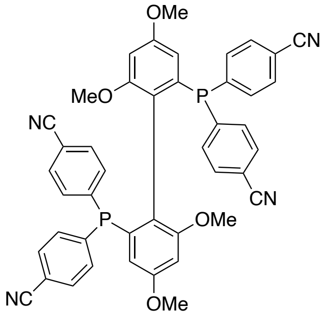
In a nitrogen-filled glovebox Pd(OAc)$_2$ (4.0 mg, 6 mol%) and dppf (19.7 mg, 12 mol%) were suspended in dry and degassed MeCN (1 mL) in an oven-dried dry 25 mL vial equipped with an octagonal stirring bar. The suspension was allowed to stir for 1 h. Next, DIPEA (0.41 mL, 8 equiv.) and the aryl iodide (0.26 mL, 6 equiv.) were added. The mixture was heated to 80 °C. Next, **LP4** (100 mg) was added to the reaction mixture as a solid at 80 °C. The solution was allowed to stir at 80 °C for 16 h. The reaction was diluted until 50 mL with DCM. Then the organic phase was washed with brine (2 x 50 mL), and next dried over MgSO$_4$. After filtration, the volatiles were removed under reduced pressure. The remaining residues were subjected to column chromatography on silica gel (40 g) using a gradient of DCM in petroleum ether (0:100 to 100:0) as eluent. The fractions containing the product (as determined by TLC) were combined and the solvents were removed under reduced pressure to yield the product as a white powder (212 mg, 79% yield).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.55 (d, *J* = 7.9 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.37 (dt, *J* = 7.5, 3.2 Hz, 2H), 7.18 (dt, *J* = 8.0, 3.1 Hz, 2H), 6.38 (d, *J* = 2.4 Hz, 1H), 6.17 (q, *J* = 2.1 Hz, 1H), 3.64 (s, 3H), 3.24 (s, 3H).

^{31}P NMR (162 MHz, CDCl$_3$) δ -12.49.

^{19}F NMR (471 MHz, CDCl$_3$) δ -62.75, -62.85.

Rac-p-CN-GarPhos (L7)



The title compound was prepared according to a modified literature procedure for preparing MeOBIPHEP-type ligands.[35]

In a nitrogen-filled glovebox Pd(OAc)$_2$ (4.0 mg, 6 mol%) and dppf (19.7 mg, 12 mol%) were suspended in dry and degassed MeCN (1 mL) in an oven-dried dry 25 mL vial equipped with an octagonal stirring bar. The suspension was allowed to stir for 1 h. Next, DIPEA (0.41 mL, 8 equiv.) and the aryl iodide (0.26 mL, 6 equiv.) were added. The mixture was heated to 80 °C. Next, **LP4** (100 mg) was added to the reaction mixture as a solid at 80 °C. The solution was allowed to stir at 80 °C for 16 h.The reaction was diluted until 50 mL with DCM. Then the organic phase was washed with brine (2 x 50 mL), and next dried over MgSO$_4$. After filtration, the volatiles were removed under reduced pressure. The remaining residues were subjected to column chromatography on silica gel (40 g) using a gradient of ethyl acetate in petroleum ether (0:100 to 100:0) as eluent. The fractions containing the product (as determined by TLC) were combined and the solvents were removed under reduced pressure to yield the product as a yellowish powder (154 mg, 70% yield).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.58 (dd, *J* = 31.1, 8.1 Hz, 8H), 7.40 – 7.32 (m, 4H), 7.23 – 7.15 (m, 4H), 6.40 (d, *J* = 2.3 Hz, 2H), 6.09 (q, *J* = 2.0 Hz, 2H), 3.66 (s, 6H), 3.28 (s, 6H).

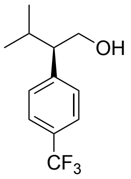
^{31}P NMR (162 MHz, CDCl$_3$) δ -9.27.

2.4.5 General procedure for the enantioselective β-arylation of primary alcohols

In a nitrogen-filled glovebox, a solution of $Pd_2dba_3 \cdot CHCl_3$ (3.3 mg, 1.25 mol%) and *rac*-GarPhos (15.0 mg, 5 mol%) in dry 1,4-dioxane (1 mL) was allowed to stir for 1 h. A solution of **(S,S)-Ru*-1** (10.5 mg, 5mol%) was prepared in dry 1,4-dioxane (0.5 mL). Cs_2CO_3 (0.33 g, 4 equiv.) was weighed in a 20 mL screw-capped vial equipped with an octagonal stirring bar (20 mm x 5 mm), followed by the addition of dry 1,4-dioxane (0.5 mL) and the alcohol (0.38 mmol, 1.5 equiv). Next, the Pd-stock solution was added followed by the Ru-stock solution. Finally, the aryl bromide (0.25 mmol) was added. Next, the vial was sealed, removed from the glovebox, and secured with electric tape. The vial was then placed in a preheated aluminium heating block at 75 °C and was allowed to stir at 800 rpm for 16 h. After cooling to room temperature, isopropanol (2 mL) was added. Next, the contents of the vials were filtered through a small plug of celite (~ 2 g). The celite plug was then washed with ethyl acetate (25 mL). The desired product was then isolated via column chromatography on silica gel (either manual column or using a CombiFlash instrument) using a mixture of petroleum ether and ethyl acetate (typically a gradient from 100:0 to 25:75) as the eluent. Fractions containing the pure product (judged by TLC and/or GC-MS analyses) were combined, and the solvents evaporated under reduced pressure to yield the pure product.

2.4.6 Scope characterisation

(*R*)-3-methyl-2-(4-(trifluoromethyl)phenyl)butan-1-ol (3ab)



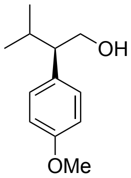
The title compound was prepared according to the general procedure by reaction of 3-methylbutan-1-ol (**1a**, 40.8 uL, 0.38 mmol) with 4-bromobenzotrifluoride (**2b**, 35.2 uL, 0.25 mmol) and isolated via column chromatography (silica gel, gradient of ethyl acetate in petroleum ether, 0:100 to 25:75) to yield the product as a yellowish oil (28.9 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.96 (dd, *J* = 10.9, 4.8 Hz, 1H), 3.88 (dd, *J* = 10.9, 8.6 Hz, 1H), 2.58 (td, *J* = 8.6, 4.8 Hz, 1H), 2.06 – 1.89 (m, 1H), 1.28 – 1.21 (m, 1H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5 (d, *J* = 1.4 Hz), 129.2, 129.1 (d, *J* = 32.3 Hz), 125.5 (q, *J* = 3.8 Hz), 124.4 (d, *J* = 271.8 Hz), 65.1, 55.8, 30.1, 21.1, 21.0.

Specific rotation: $[\alpha]_D^{23}$ -14.5° (c 0.19, $CHCl_3$) for the isolated sample. The absolute configuration was determined by analogy to compound **(*R*)-3ba** and was not further confirmed.

(*R*)-2-(4-methoxyphenyl)-3-methylbutan-1-ol (3ac)



The title compound was prepared according to the general procedure by reaction of 3-methylbutan-1-ol (**1a**, 40.8 uL, 0.38 mmol) with 4-bromoanisole (**2c**, 31.5 uL, 0.25 mmol) and isolated via column chromatography (silica gel, gradient of ethyl acetate in petroleum ether, 0:100 to 25:75) to yield the product as a yellowish oil (17.5 mg, 36%).

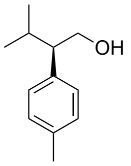
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.07 (m, 2H), 6.93 – 6.83 (m, 2H), 3.91 (dd, *J* = 10.8, 4.9 Hz, 1H), 3.80 (s, 3H), 3.77 (dd, *J* = 10.8, 9.2 Hz, 1H), 2.46 (td, *J* = 8.9, 4.9 Hz, 1H), 1.96 – 1.79 (m, 1H), 1.25 (s, 1H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 133.9, 130.1, 114.4, 65.7, 55.7, 55.4, 30.7, 21.5, 21.4.

SFC with Chiralpak IG-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(major, **(*R*)-3ac**) = 4.11 min, t(minor, **(*S*)-3ac**) = 4.77 min.

Specific rotation: $[\alpha]_D^{23}$ -9.3° (c 0.23, $CHCl_3$) for an enantiomerically enriched sample of 92:8 er. The absolute configuration was determined by comparison of the optical rotation with that reported in literature of the opposite enantiomer $[\alpha]_D^{20}$ +11.3 (c 1.0, $CHCl_3$), 97:3 er.[27]

(*R*)-3-methyl-2-(*p*-tolyl)butan-1-ol (3ad)



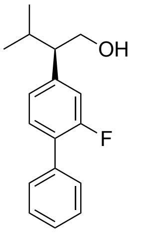
The title compound was prepared according to the general procedure by reaction of 3-methylbutan-1-ol (**1a**, 40.8 uL, 0.38 mmol) with 4-bromotoluene (**2d**, 30.9 uL, 0.25 mmol,) and isolated via column chromatography (silica gel, gradient of ethyl acetate in petroleum ether, 0:100 to 25:75) to yield the product as a yellowish oil (21.2 mg, 41%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.11 (m, 2H), 7.11 – 7.05 (m, 2H), 3.92 (dd, *J* = 10.8, 4.9 Hz, 1H), 3.80 (dd, *J* = 10.8, 9.1 Hz, 1H), 2.47 (td, *J* = 8.9, 4.8 Hz, 1H), 2.33 (s, 3H), 2.00 – 1.80 (m, 1H), 1.37 (s, 1H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 136.4, 129.4, 128.7, 65.4, 55.5, 30.2, 21.2, 21.2, 21.1.

Specific rotation: $[\alpha]_D^{23}$ -3.8° (c 0.11, $CHCl_3$) for the isolated sample. The absolute configuration was determined by comparison of the optical rotation with that reported in literature of the opposite enantiomer $[\alpha]_D^{20}$ +10.3 (c 1.1, $CHCl_3$), 96:4 er.[27]

(*R*)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)-3-methylbutan-1-ol (3ae)



The title compound was prepared according to the general procedure by reaction of 3-methylbutan-1-ol (**1a**, 40.8 uL, 0.38 mmol) with 4-bromo-2-fluorobiphenyl (**2e**, 63.1 mg, 0.25 mmol) and isolated via column chromatography (silica gel, gradient of ethyl acetate in petroleum ether, 0:100 to 25:75) to yield the product as a yellow, amorphous solid (36.3 mg, 56%).

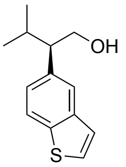
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.51 (m, 2H), 7.49 – 7.32 (m, 4H), 7.09 – 6.98 (m, 2H), 3.97 (dd, *J* = 10.9, 4.7 Hz, 1H), 3.87 (dd, *J* = 10.9, 8.8 Hz, 1H), 2.55 (td, *J* = 8.7, 4.7 Hz, 1H), 2.05 – 1.88 (m, 1H), 1.42 (s, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.92 (d, *J* = 248.2 Hz), 143.86 (d, *J* = 7.3 Hz), 135.81 (d, *J* = 1.3 Hz), 130.77 (d, *J* = 4.0 Hz), 129.08 (d, *J* = 3.0 Hz), 128.58, 127.69, 127.36 (d, *J* = 13.6 Hz), 124.91 (d, *J* = 3.2 Hz), 116.22 (d, *J* = 22.8 Hz), 65.18, 55.48 (d, *J* = 1.4 Hz), 30.18, 21.13.

SFC with Chiralpak IB-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(major, **(*R*)-3ae**) = 4.32 min, t(minor, **(*S*)-3ae**) = 4.89 min.

Specific rotation: $[\alpha]_D^{23}$ -8.3° (c 0.96, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er. The absolute configuration was determined by analogy to compound **(*R*)-3ba** and was not further confirmed.

(*R*)-2-(benzo[*b*]thiophen-5-yl)-3-methylbutan-1-ol (3ag)



The title compound was prepared according to the general procedure by reaction of 3-methylbutan-1-ol (**1a**, 40.8 uL, 0.38 mmol) with 5-bromo-benzo[b]thiophene (**2g**, 58.1 mg, 0.25 mmol) and isolated via column chromatography (silica gel, gradient of ethyl acetate in petroleum ether, 0:100 to 25:75) to yield the product as a yellowish, amorphous solid (28.1 mg, 49%).

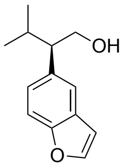
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dt, *J* = 8.4, 0.8 Hz, 1H), 7.66 (d, *J* = 1.7 Hz, 1H), 7.45 (d, *J* = 5.5 Hz, 1H), 7.31 (dd, *J* = 5.4, 0.8 Hz, 1H), 7.20 (dd, *J* = 8.3, 1.7 Hz, 1H), 4.00 (dd, *J* = 10.9, 4.8 Hz, 1H), 3.88 (dd, *J* = 10.9, 9.1 Hz, 1H), 2.63 (td, *J* = 9.0, 5.0 Hz, 1H), 2.08 – 1.91 (m, 1H), 1.26 (s, 1H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.76 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.12, 138.33, 137.92, 126.90, 125.14, 123.88, 123.87, 122.77, 65.56, 55.97, 30.45, 21.30, 21.23.

SFC with Chiralpak ID-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(major, **(*R*)-3ag**) = 5.52 min, t(minor, **(*S*)-3ag**) = 7.71 min.

Specific rotation: $[\alpha]_D^{23}$ -14.5° (c 0.44, $CHCl_3$) for an enantiomerically enriched sample of 97:3 er. The absolute configuration was determined by analogy to compound **(*R*)-3ba** and was not further confirmed.

(*R*)-2-(benzofuran-5-yl)-3-methylbutan-1-ol (3af)



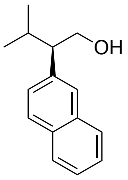
The title compound was prepared according to the general procedure by reaction of 3-methylbutan-1-ol (**1a**, 40.8 uL, 0.38 mmol) with 5-bromobenzofuran (**2f**, 31.5 uL, 0.25 mmol) and isolated via column chromatography (silica gel, gradient of ethyl acetate in petroleum ether, 0:100 to 25:75) to yield the product as a yellowish oil (24.3 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 2.2 Hz, 1H), 7.50 – 7.34 (m, 2H), 7.13 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.74 (dd, *J* = 2.2, 1.0 Hz, 1H), 3.98 (dd, *J* = 10.9, 4.8 Hz, 1H), 3.85 (dd, *J* = 10.9, 9.2 Hz, 1H), 2.60 (td, *J* = 9.0, 4.8 Hz, 1H), 1.96 (dp, *J* = 8.8, 6.6 Hz, 1H), 1.37 (s, 1H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9, 145.1, 135.8, 127.5, 124.6, 120.9, 111.2, 106.3, 65.4, 55.6, 30.3, 21.0, 20.9.

Specific rotation: $[\alpha]_D^{23}$ -10.4° (c 0.43, $CHCl_3$) for the isolated sample. The absolute configuration was determined by analogy to compound **(*R*)-3ba** and was not further confirmed.

(*R*)-3-methyl-2-(naphthalen-2-yl)butan-1-ol (3ah)



The title compound was prepared according to the general procedure by reaction of 3-methylbutan-1-ol (**1a**, 40.8 uL, 0.38 mmol) with 2-bromonaphtalene (**2h**, 52.0 mg, 0.25 mmol) and isolated via column chromatography (silica gel, gradient of ethyl acetate in petroleum ether, 0:100 to 25:75) to yield the product as a yellowish, amorphous solid (22.1 mg, 41%).

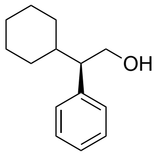
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 3H), 7.68 – 7.63 (m, 1H), 7.52 – 7.41 (m, 2H), 7.39 – 7.32 (m, 1H), 4.02 (dd, *J* = 10.9, 4.8 Hz, 1H), 3.92 (dd, *J* = 10.9, 9.1 Hz, 1H), 2.68 (td, *J* = 9.0, 4.7 Hz, 1H), 2.11 – 1.96 (m, 1H), 1.43 (s, 1H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.77 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 133.6, 132.7, 128.5, 127.9, 127.8, 126.7, 126.2, 125.7, 65.3, 56.2, 30.2, 21.4, 21.2.

SFC with Chiralpak IC-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(major, **(*R*)-3ah**) = 7.26 min, t(minor, **(*S*)-3ah**) = 6.43 min.

Specific rotation: $[\alpha]_D^{23}$ -13.2° (c 0.36, $CHCl_3$) for an enantiomerically enriched sample of 90:10 er. The absolute configuration was determined by comparison of the optical rotation with that reported in literature of the opposite enantiomer $[\alpha]_D^{20}$ +17.2 (c 1.0, $CHCl_3$), 95:5 er.[27]

(*R*)-2-cyclohexyl-2-phenylethan-1-ol (3ba)



The title compound was prepared according to the general procedure by reaction of 2-cyclohexylethan-1-ol (**1b**, 52.3 uL, 0.38 mmol) with bromobenzene (**2a** ,26.3 uL, 0.25 mmol) and isolated via column chromatography (silica gel, gradient of ethyl acetate in petroleum ether, 0:100 to 25:75) to yield the product as a yellowish oil (31.7 mg, 62%).

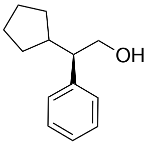
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 2H), 7.28 – 7.19 (m, 1H), 7.22 – 7.15 (m, 2H), 3.95 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.84 (dd, *J* = 10.8, 9.0 Hz, 1H), 2.57 (td, *J* = 8.9, 4.9 Hz, 1H), 1.93 – 1.84 (m, 1H), 1.80 – 1.70 (m, 1H), 1.70 – 1.53 (m, 3H), 1.48 – 1.34 (m, 3H), 1.17 – 0.95 (m, 2H), 0.92 – 0.67 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.8, 128.9, 128.7, 126.8, 65.0, 54.9, 39.9, 31.5, 31.4, 26.6, 26.5, 26.5.

SFC with Chiralpak IB-3, 2.5% iPrOH / 97.5% CO_2, 1.2 mL/min, t(major, **(*R*)-3ba**) = 6.28 min, t(minor, **(*S*)-3ba**) = 7.53 min.

Specific rotation: $[\alpha]_D^{23}$ -13.3° (c 0.30, $CHCl_3$) for an enantiomerically enriched sample of 89:11 er. The absolute configuration was determined by comparison of the optical rotation with that reported in literature of the opposite enantiomer $[\alpha]_D^{20}$ +5.6 (c 1.2, $CHCl_3$), 96:4 er.[27]

(*R*)-2-cyclopentyl-2-phenylethan-1-ol (3ca)



The title compound was prepared according to the general procedure by reaction of 2-cyclopentylethan-1-ol (**1c**, 46.5 uL, 0.38 mmol) with bromobenzene (**2a**, 26.3 uL, 0.25 mmol) and isolated via column chromatography (silica gel, gradient of ethyl acetate in petroleum ether, 0:100 to 25:75) to yield the product as a yellowish oil (24.7 mg, 52%).

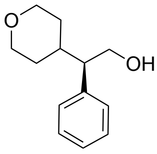
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 2H), 7.26 – 7.20 (m, 3H), 3.90 (dd, *J* = 10.9, 4.4 Hz, 1H), 3.77 (dd, *J* = 10.9, 9.0 Hz, 1H), 2.56 (td, *J* = 9.1, 4.4 Hz, 1H), 2.15 – 1.98 (m, 1H), 1.98 – 1.84 (m, 1H), 1.75 – 1.18 (m, 7H), 1.12 – 0.92 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 128.7, 128.6, 126.8, 66.8, 55.1, 42.5, 31.9, 31.5, 25.5, 24.7.

SFC with Chiralpak IC-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(major, **(*R*)-3ca**) = 3.44 min, t(minor, **(*S*)-3ca**) = 3.22 min.

Specific rotation: $[\alpha]_D^{23}$ -11.9° (c 0.66, $CHCl_3$) for an enantiomerically enriched sample of 95:5 er. The absolute configuration was determined by comparison of the optical rotation with that reported in literature of the opposite enantiomer $[\alpha]_D^{20}$ +17.5 (c 1.0, $CHCl_3$), 96:4 er.[27]

(*R*)-2-phenyl-2-(tetrahydro-2*H*-pyran-4-yl)ethan-1-ol (3da)



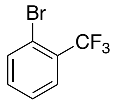
The title compound was prepared according to the general procedure by reaction of 2-tetrahydro-2H-pyran-4-ylethan-1-ol (**1d**, 49.8 uL, 0.38 mmol) with bromobenzene (**2a**, 26.3 uL, 0.25 mmol) and isolated via column chromatography (silica gel, gradient of ethyl acetate in petroleum ether, 0:100 to 25:75) to yield the product as a yellowish oil (26.6 mg, 51%).

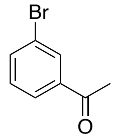
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 2H), 7.30 – 7.21 (m, 1H), 7.23 – 7.16 (m, 2H), 4.00 (dd, *J* = 11.6, 1.6 Hz, 1H), 3.94 (dd, *J* = 10.9, 4.7 Hz, 1H), 3.90 – 3.81 (m, 2H), 3.44 – 3.35 (m, 1H), 3.33 – 3.23 (m, 1H), 2.58 (td, *J* = 8.8, 4.7 Hz, 1H), 1.95 – 1.74 (m, 2H), 1.51 – 1.36 (m, 2H), 1.27 – 1.12 (m, 2H).

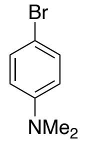
^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9, 128.9, 128.8, 127.1, 68.3, 68.0, 64.5, 54.5, 37.1, 31.6, 31.4, 29.9.

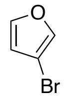
Specific rotation: $[\alpha]_D^{23}$ -12.9° (c 0.54, $CHCl_3$) for the isolated sample. The absolute configuration was determined by analogy to compound **(*R*)-3ba** and was not further confirmed.

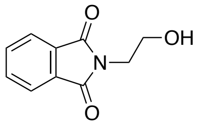
2.4.7 Unsuccesful examples

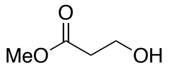


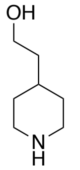




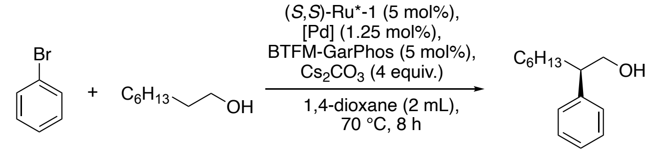








2.4.8 Reproducibility of the β-arylation reaction



2a
0.25 mmol

1e
1.5 equiv.

3ea

#	[Pd]	yield (%)[a]
1	Pd_2dba_3	44% ± 22%[b]
2	Pd_2dba_3•$CHCl_3$	38% ± 4%[c]

[a] Standard conditions: **1e** (0.375 mmol), **2a** (0.25 mmol), **(*S*,*S*)-Ru*-1** (5 mol%), [Pd] (1.25 mol %), BTFM-GarPhos (5 mol%), Cs_2CO_3 (4 equiv.), 1,4-dioxane (2 mL), stirred for 8 h at 70 °C.. Yields determined by ^1H NMR analysis with an internal standard. [b] Reported yield is the average and the reported uncertainty is the standard deviation of 3 runs. [c] Reported yield is the average and the reported uncertainty is the standard deviation of 8 runs. The runs include commercial Pd_2dba_3•$CHCl_3$ and two different, synthetized batches.

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CHAPTER 3

Multicatalytic approach to one-pot stereoselective synthesis of secondary benzylic alcohols

The work described in this chapter was performed in collaboration with A. Casnati, D. Lichosyt and L. Veth

I assisted with evaluating the scope of the metathesis-sequence part of the project and with comparing the efficiency of the sequence to the stepwise approach

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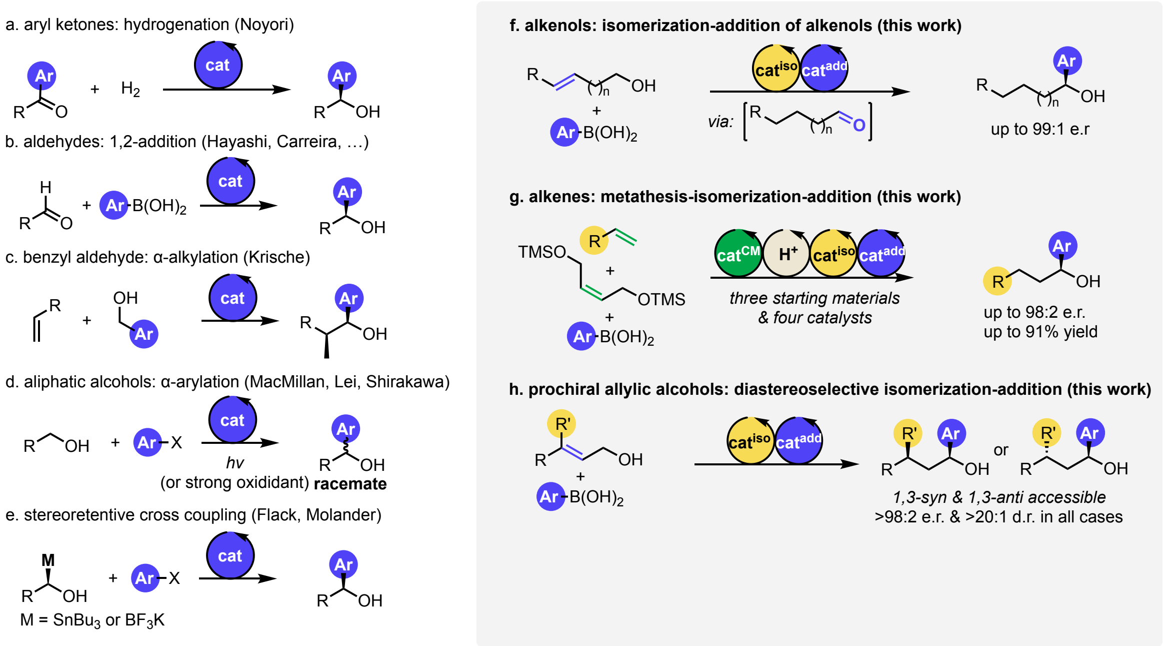
Casnati, A.; Lichosyt, D.; Lainer, B.; Veth, L.; Dydio, P. Multicatalytic Approach to One-Pot Stereoselective Synthesis of Secondary Benzylic Alcohols. *Org. Lett.* **2021**, *23* (9), 3502–3506. https://doi.org/10.1021/acs.orglett.1c00939.

3.1 Introduction

Secondary benzylic alcohols (SBAs) represent prevalent motifs of biologically active molecules and chiral building blocks for fine-chemical synthesis. Therefore, methods for their stereoselective synthesis from available starting materials are important. Asymmetric (transfer) hydrogenation proved highly effective when aryl ketones are available (**Scheme 3.1a**).[1]In turn, enantioselective addition of an aryl nucleophile to a carbonyl bond is practical for aliphatic aldehydes as starting materials (**Scheme 3.1b**).[2,3] Given the abundance of alcohols, functionalization of their C–H bonds is attractive.[4-6] In that regard, Krische reported an elegant enantio- and diastereoselective α-alkylation of alcohols with unsaturated hydrocarbons (e.g., dienes, enynes; (**Scheme 3.1c**).[7] Methods for α-arylation of aliphatic alcohols were recently reported by MacMillan, Lei, and Shirakawa (**Scheme 3.1d**),[8-10] although the enantioselective variants remain to be developed. In addition, the stereoretentive cross-couplings to form SBAs were reported by Falck and Molander (**Scheme 3.1e**).[11,12]

Scheme 3.1 Context and the current study: stereoselective synthesis of secondary benzylic alcohols (SBAs).



We envisioned that one-pot sequential catalysis could enrich the access to SBAs from other classes of readily available starting materials (**Scheme3.1f–h**). First, we conceived the enantioselective isomerization–addition sequence for aliphatic alcohols bearing an unsaturated bond (**Scheme3.1f**), which are common motifs in bioderived materials (e.g., terpenols). The strategy could be further extended to abundant alkenes (**Scheme 3.1g**), given the alkene cross-metathesis,[13] double-bond isomerization,[14] and enantioselective addition[2,3] reactions were compatible in a one-pot fashion. Also, diastereoselective synthesis of SBAs bearing two stereocenters with a 1,3-relationship could be envisioned (**Scheme 3.1h**), provided the compatibility of both chiral catalysts was ensured. Noteworthy, the execution of multicatalytic multistep synthesis in a one-pot fashion, without or with limited intermediary workup, proved enabling and highly advantageous from the efficiency standpoint.[15,16] However, the development of such protocols with multiple transition-metal-catalyzed reactions operating in one vessel remains challenging.[17] The prospective cross-reactivity is likely to hinder the required activity.[18] In asymmetric reactions, any exchange of ligands is likely to deteriorate the stereoselectivity.[19] Therefore, careful selection of catalysts and conditions is critical.

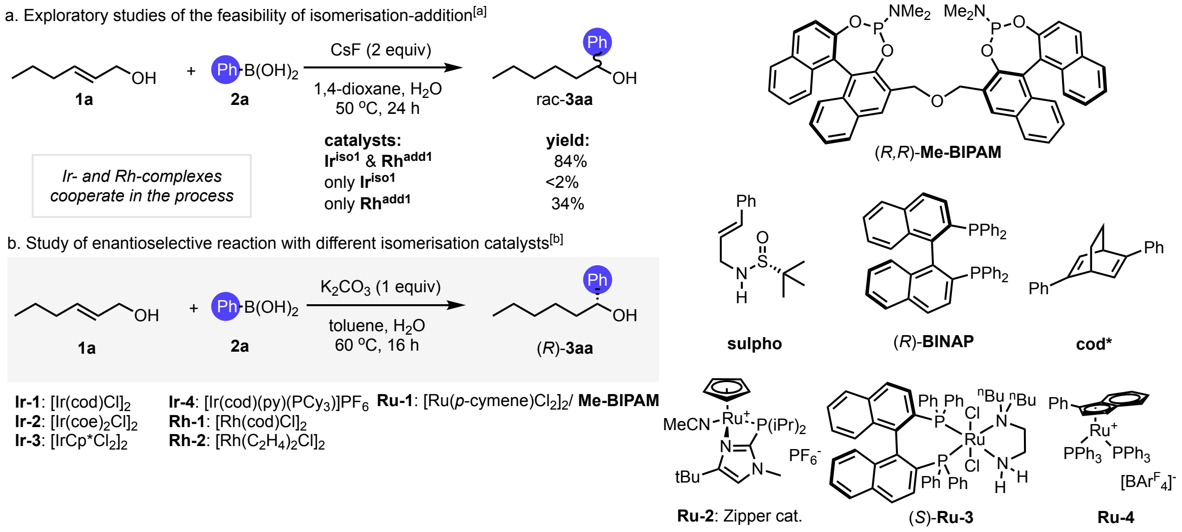
Here, we report sequential multistep protocols with up to three transition-metal complexes and a Brønsted acid that execute redox-neutral transformations for a series of alkenes, (protected) unsaturated alcohols, and aryl boronic acids, with no or with minimal intermediary workup, to furnish varied SBAs in high stereoselectivity, with up to 99:1 er, dr >20:1, and 91% yield (**Scheme 3.1f–h**). We showed that not only the protocols are operationally simpler and up to ~3-fold less resource-intensive than the stepwise synthesis but also that the overall yield of the product is increased (77% versus 43%) thanks to preventing cumulative losses of the materials during subsequent isolations and purifications of the intermediates.

3.2 Results and discussion

We initiated the study by validating the possibility to conduct in situ both the isomerization of unsaturated alcohols and the addition of aryl boronic acids to aldehyde intermediates. Model substrates, *trans*-2-hexenol **1a** and phenylboronic acid **2a**, reacted to furnish racemic alcohol **3aa**, 1-phenyl-1-hexanol in 84% yield in the presence of $[Ir(cod)Cl]_2$ (**Ir-1**), and $[Rh(cod)(CH_3CN)_2]BF_4$ (**Rh-1**) (**Table 3.1a**). The control experiments confirmed the role of both complexes. The reactivity was diminished when either complex was not present.

The enantioselective variant of the transformation required exchanging the Rh-catalyst for the Ru-complex bearing chiral Me-BIPAM (**Ru-1**, **Table 3.1b**), the latter being a privileged ligand developed by Yamamoto and Miyaura for enantioselective Rh- or Ru-catalyzed reactions, including 1,2-addition reactions.[20,21] We found that although a Rh-catalyst bearing chiral diene ligand **Rh-2/cod*** [3] proved active, product **3aa** was formed in modest enantioselectivity (70:30 er). The evaluation of other Rh-complexes bearing N-sulfinyl chiral sulfur-olefin[22] **Rh-2/sulpho** or phosphine[2]**Rh-2/BINAP** ligands, did not secure any highly enantioselective protocol. In sharp contrast, the reaction in the presence of **Ir-1** and (*R,R*)-**Ru-2**,[21] furnished product (*R*)-**3aa** in high er of 96:4, albeit in a low yield of 23%. The use of other isomerization catalysts[14] in place of **Ir-1** enabled the formation of (*R*)-**3aa** in higher yields. The reaction in the presence of **Ru-4** and (*R,R*)-**Ru-1** furnished the product in 55% yield and 96:4 er. Further experiments revealed that the presence of **Ru-1** partially inhibits the activity of **Ir-1**. Fortunately, when **1a** was shortly incubated in the presence of 0.125 mol % **Ir-1**, prior to the addition of **2a** and (*R,R*)-**Ru-1**, (*R*)-**3aa** was formed in 81% yield (78% isolated material) and 96:4 er.

Table 3.1 Figure 2. Studies toward the enantioselective conversion of allylic alcohols to SBAs.



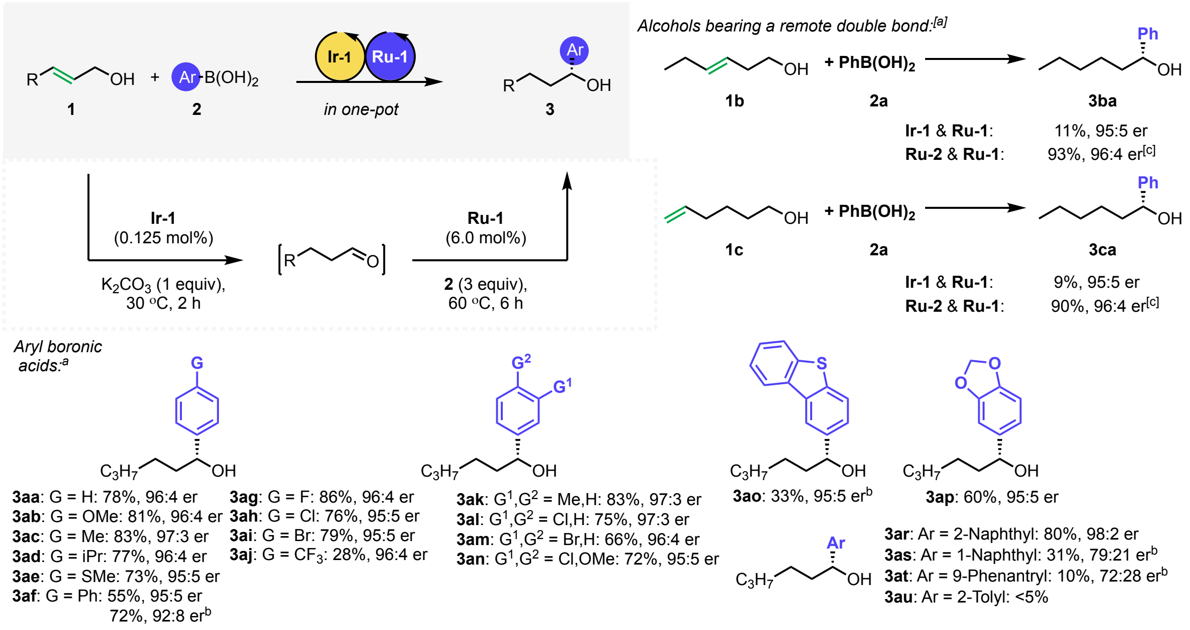
#	cat^{iso}	cat^{add}	Conversion (%)^a	e.r.^{a}
1	Ir-2/cod*	Rh-2/cod*	40	70:30
2	Ir-3	Rh-2/cod*	51	70:30
3	Ir-3	Rh-2/sulpho	40	69:31
4	Ir-2	Rh-2/(*R*)-BINAP	20	43:57
5	Ir-2	Rh-2/(*R*,*R*)-Me-BIPAM	25	50:50
6	Ir-3	Rh-2/(*R*,*R*)-Me-BIPAM	64	55:45
7	Ir-1	Ru-1	23	96:4
8	Ir-3	Ru-1	18	96:4
9	Ir-4	Ru-1	5	96:4
10	Ru-2	Ru-1	18	96:4

#	cat^{iso}	cat^{add}	Conversion (%)^{a}	e.r.^{a}
11	Ru-3	Ru-1	14	96:4
12	**Ru-4**	**Ru-1**	**55**	**96:4**
13[b]	**Ir-1**	**Ru-1**	**64**	**96:4**
14[b,c]	**Ir-1**	**Ru-1**	**81 (78)**[d]	**96:4**

(a) By NMR, GC, or SFC analysis. (b) A mixture of **1a** and **Ir-1** was kept at 30 °C for 2 h, followed by the addition of **2a** and (*R,R*)-**Ru-1** (6.0 mol %), and kept at 60 °C for 6 h. (c) 0.125 mol % **Ir-1**. (d) Yield of isolated material.

The identified protocol proved applicable to a substantial range of aryl boronic acids and alkenylic alcohols (**Scheme 3.2**). The reactions of **1a** with phenylboronic acid derivatives containing an electron-donating or an electron-withdrawing group in the para- or meta-position of the phenyl ring (**2b**–**2i**, **2k**–**2n**) as well as those with a sizable aryl moiety (**2o**–**2q**) formed the product with 92:8 to 99:1 er and up to 86% yield.

Scheme 3.2 Scope for conversion of linear alkenylic alcohols to SBAs.



(a) Reagents added to the mixture subsequently without any workup; yields of isolated material are reported (yields determined by NMR analysis are ~2–13% higher); er calculated by SFC analysis. (b) Second step at 90 °C for 24 h. (c) Yields by NMR analysis using an internal standard. (d) **Ru-2** (2 mol %).

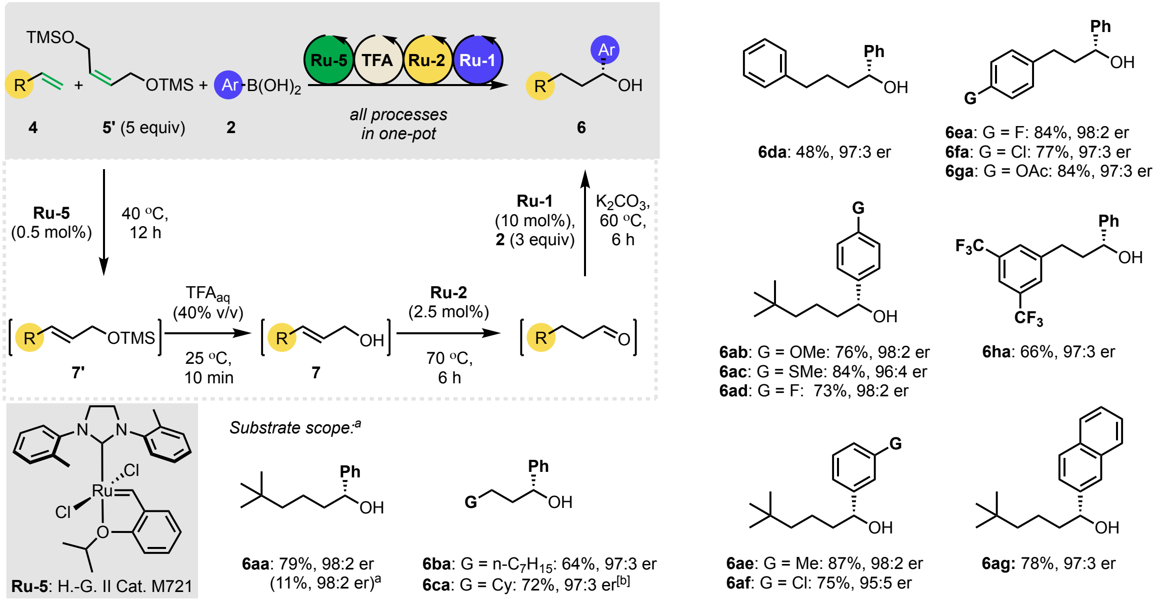
The reactions for aryl boronic acids bearing either a strongly electron-withdrawing group or steric hindrance in the ortho-position, such as **2j** and **2r**–**2t**, respectively, furnished the products in modest yields (up to 31%) and moderate enantioselectivity

(<79:21 er), indicating the limitations of the protocol. Heteroaryl derivatives, including dibenzothiophene **2o** and 1,3-benzodioxole **2p**, reacted to form the products in 95:5 er and 33–60% yields. Alcohols containing a remote double bond, such as homoallylic 3-hexenol **1b** and 5-hexenol **1c**, are suitable substrates; however, the Zipper catalyst **Ru-3**[23] was used in place of **Ir-1** to form the products in high yields (93% and 90%, respectively). It is worth noting that the presence of **Ru-3** bearing an achiral phosphine ligand does not erode the enantioselectivity of the step executed by **Ru-1** (96:4 er), demonstrating the key compatibility between the catalysts.

Because cross-metathesis represents a convenient method to install an alkenylic alcohol moiety on olefins, we next sought a protocol that would enable the direct assembly of a SBA from an alkene, a simple alkenylic alcohol, and an aryl boronic acid. Such method would be attractive due to the increase in the structural diversity of the products by using combinations of readily accessible building blocks. However, the requirement of the compatibility of three transition-metal catalysts in the series of three subsequent processes represents a challenge. Cross-inhibition issues aside, any ligand-exchange processes between a metathesis or an isomerization catalyst and a chiral catalyst that operates in the final 1,2-addition step are likely to deteriorate the stereoselectivity.

Initial experiments indicated that a cross-metathesis reaction of 4,4-dimethyl-1-pentene (**4a**) and *cis*-2-butene-1,4-diol (**5**) in the presence of the *o*-tolyl Hoveyda–Grubbs catalyst M721(**Ru-5**) followed in situ by the isomerization–addition sequence with **2a**, **Ru-2**, and (*R,R*)-**Ru-1** furnished benzylic alcohol (*R*)-**6aa** in 98:2 er (**Scheme 3.3**). High stereoselectivity of the reaction confirmed the critical compatibility of chiral **Ru-1** with the other catalysts in the sequence. However, because of the limited conversion of alkene **4a** to allylic alcohol intermediate **7**, product (*R*)-**6aa** was formed in only up to 11% yield (see **section 3.4.6**). Alkene **4a** reacted more readily with **5′**, TMS-protected **5**, in the presence of **Ru-5**, forming **7′** in a high yield (>95% by GC analysis). The latter was quickly and quantitatively deprotected to form alkenol **7** in the presence of trifluoroacetic acid. The acid was washed off with an aqueous base solution, and no further workup is required for the subsequent isomerization–addition sequence. However, because the full removal of aqueous phase is essential, we noticed that drying the reaction mixture over Na_2SO_4 (and its removal) prior to the subsequent steps is beneficial for the reproducibility. Overall, such protocol that engages three different Ru-catalysts and a Brønsted acid with a minimal intermediary workup converts **4a**, **5′**, and **2a** to alcohol (*R*)-**6aa** in 88% yield (79% isolated material) and 98:2 er.

Scheme 3.3 Enantioselective sequential multicatalysis for conversion of alkenes to SBAs



(a) As in Scheme 3.2; no workup except for washing off TFA and optional drying over Na_2SO_4; (b) With *cis*-2-butene-1,4-diol.

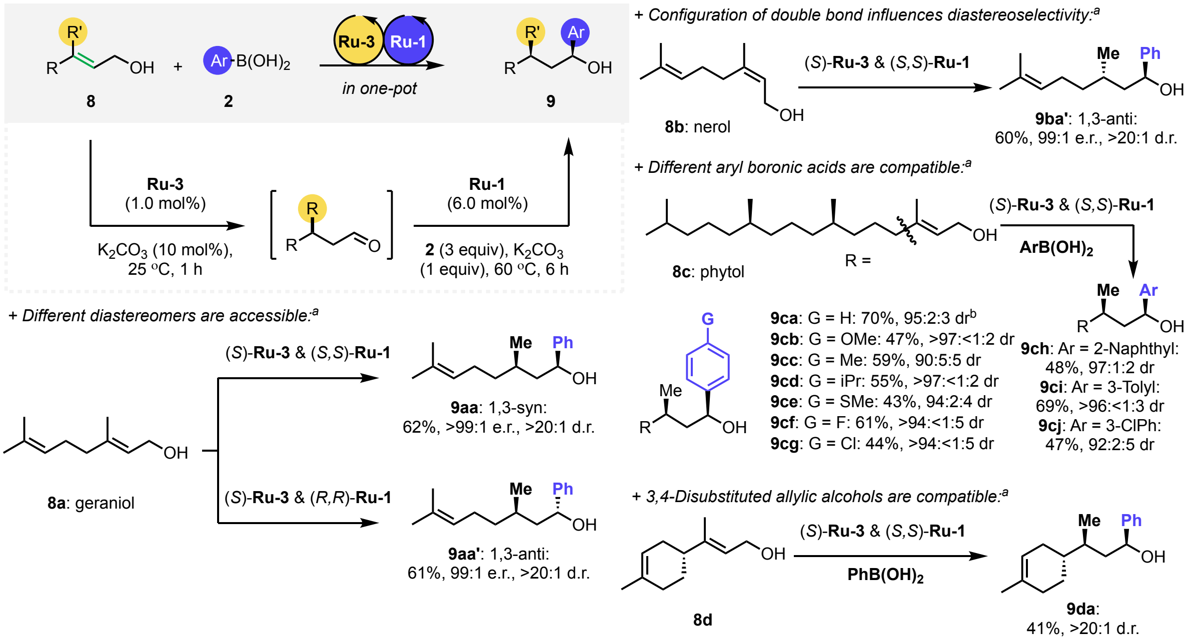
The side-by-side experiments on a 2.4 mmol scale of **4a** for the synthesis of (*R*)-**6aa** proved that not only the established protocol is faster, more operationally simple, and ~3-fold less resource-intensive than the stepwise approach, but also the final yield of the isolated material is increased, i.e., 77% versus 43%, respectively. Although the consecutive steps of the sequence occurred with similar GC yields in both cases, the sequential protocol prevented cumulative losses of the material during subsequent isolations and purifications of the intermediates, illustrating an additional advantage of the approach (for details, see **section 3.4.9**).

The established protocol integrating alkene cross-metathesis, isomerization, and enantioselective addition is broadly applicable (**Scheme 3.3**). A series of aliphatic alkenes, electron-rich or electron-deficient vinyl arenes, TMS-protected alkenol, and stereoelectronically varied aryl boronic acids reacted to form a range of SBAs in high enantioselectivities (er's > 95:5) and 48–87% yields (isolated material).

Lastly, we focused on allylic alcohols bearing a prochiral double bond. The isomerization–addition sequence for 3-substituted allylic alcohols constitutes an attractive strategy to produce the SBAs bearing two stereocenters with a 1,3-relationship. We surmised that a method utilizing two different chiral catalysts that independently construct each stereogenic center would give access to all 1,3-syn and 1,3-anti stereoisomers of the product. However, the key requirement is the independent activity of both chiral catalysts and their compatibility.

Combining suitable enantiomers of **Ru-3**, the isomerization catalyst reported by Ohkuma,[24] and **Ru-1** enables the isomerization–addition sequence to form different diastereomers of the products with high stereocontrol in a one-pot fashion (**Scheme 3.4**).

Scheme 3.4 Stereoselective conversion of substitute allylic alcohols to SBAs.



(a) As in Scheme 3.2; no workup except for removal of EtOH under vacuum; yields of the isolated major diastereomer. (b) dr of 1,3-syn (major):1,3-syn(minor):sum of 1,3-anti products.

The catalysts proved to require different solvents to operate efficiently (i.e., ethanol and toluene, respectively; for details, see **section 3.4.10**). Therefore, the medium needs to be exchanged between the steps (evaporation under vacuum); albeit no resource-intensive workup is needed. Importantly, the stereocontrol for the formation of each stereogenic center is solely determined by the catalyst involved. For instance, while the reaction of geraniol **8a** and **2a** in the presence of (*S*)-**Ru-3** and (*S,S*)-**Ru-1** furnished 1,3-syn benzylic alcohol (1*S*,3*R*)-**9aa** with >99:1 er, >20:1 dr, in 62% yield, the same reaction but with (*R,R*)-**Ru-1** in place of (*S,S*)-**Ru-1** furnished 1,3-anti diastereomeric alcohol (1*S*,3*S*)-**9aa'**, in similarly high 99:1 er, >20:1 dr, and 61% yield. The diastereoselectivity of the transformation depends on the configuration of the double bond in the starting material.[24] Under the conditions that geraniol **8a** reacted to from 1,3-syn **9aa**, nerol **8b**, the (*Z*)-analogue of geraniol **8a**, reacted to form 1,3-anti **9ba'** containing the opposite major enantiomer of **9aa'**, in 99:1 er, > 20:1 dr, and 60% yield. Noteworthy, the isolated double bonds of starting materials **8a**–**8b** remained intact in the corresponding products. Chiral phytol **8c**, reacted with varied arylboronic acids to form the products in high stereoselectivity, i.e., 90–97% of the major stereoisomer, and from 43% to 70% yield. The presence of an additional chiral center next to the allylic alcohol moiety in the starting material seems not to disturb the reaction. (+)-Limonene derivative **8d** reacted with **2a** to form **9da** in >20:1 dr, and 41% yield, expanding the scope of the system.

3.3 Conclusion

In conclusion, the herein disclosed methods enable the rapid modular stereoselective syntheses of a broad range of secondary benzylic alcohols from simple available starting materials.[25] The strategy relies on the construction of the sequences of multiple catalytic reactions occurring consecutively with no or minimal intermediary workup. The transformation is executed with the aid of up to three transition-metal catalysts and requires a single isolation and purification of the product. Overall, the approach simplifies the synthesis of target motifs, increases material efficiency, and limits cost, time, and waste associated with the standard stepwise procedures. In a greater perspective, the study highlights the synthetic potential of the multicatalytic approaches to quickly access increasingly complex architectures from simple starting materials.

3.4 Experimental section

3.4.1 General remarks

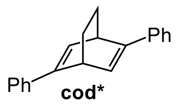
Unless stated otherwise, all reactions and manipulations were conducted on a laboratory bench or in a well-ventilated fume hood in air with reagent grade solvents. Reactions under inert gas atmosphere were carried out in the oven-dried glassware in a nitrogen-filled glovebox or by standard Schlenk techniques under nitrogen. Unless noted otherwise, all reagents and solvents were purchased from commercial suppliers and used without further purification. For experiments under inert gas atmosphere, dry solvents like dichloromethane (DCM), tetrahydrofuran (THF), toluene, hexane, and diethyl ether (Et_2O) dioxane, acetonitrile, 1,4-xylene, were purchased from commercial suppliers and used as received. Water was degassed by purging with nitrogen for 30 min. Column chromatography was carried out either with the aid of CombiFlash EZ Prep Chromatography System with integrated ELSD using the RediSep Rf (Gold) Silica Gel Disposable Flash columns or with the aid of the Biotage Isolera instrument using Merck Kieselgel 60 (230-400 mesh). TLC visualisation was carried out with ultraviolet light (254 nm), followed by staining with a 1% aqueous $KMnO_4$ solution. NMR spectra were acquired on the 400 MHz or 500 MHz Bruker instruments at the Institute of Science and Supramolecular Engineering (ISIS) or at the Department of Chemistry, University of Strasbourg, Strasbourg. NMR spectra were processed using the MestReNova 10.0 software. Chemical shifts are reported in parts per million (ppm) and referenced to residual solvent peaks or tetramethylsilane (TMS). Coupling constants are reported in hertz (Hz). SFC analysis was conducted using an Agilent SFC 1260 Infinity II instrument connected to an Agilent MSD XT mass spectrometry equipment. Chiral SFC separation was achieved using Chiralpak SFC (100 mm x 3 mm ID x 3 μm) columns. GC-FID analysis was obtained either on a Shimadzu GC-2010 Plus instrument equipped with a SH-Rxi-5MS column (25 m x 0.20 mm ID x 0.33 μm film) connected to a FID detector, or on a ThermoFisher TRACE 1300 instrument equipped with a HP-5 column (25 m x 0.20 mm ID x 0.33 μm film) for achiral analysis or with an CP-Chiralsil- Dex CB column (30m x 0.25mm x 0.25 μm film) for chiral analysis, connected to a FID detector. GC-MS analysis was obtained either on a Shimadzu QP2020 (EI) instrument equipped with a SH-Rxi-5MS column (25 m x 0.20 mm ID x 0.33 μm film) or on an Agilent 7820A (G4320) equipped with a HP-5MS UI column (30 m x 0.25 mm ID x 0.25 μm film) connected to an Agilent MSD block 5977E (G7036A). GC and NMR yields were calculated using 1,3,5-trimethoxybenzene, decane, or dodecane as the internal standards. GC yields were corrected for response factors for all compounds. Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell. High-resolution atmospheric pressure photoionization mass spectra (HR-MS APPI) were obtained on Thermo Exactive Plus EMR with a MasCom GC-APPI Interface (at ISIS).

3.4.2 Preparation and characterization of substrates, ligands and complexes

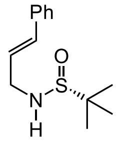
(*R,R*)- or (*S,S*)-**Me-BIPAM**[26] and **sulpho**[27] ligands, as well as, **Ru-2**, [28] (*S*)- or (*R*)-**Ru-3**, [29] **Ru-4**[30] complexes were prepared following previously reported procedures. Other ligands and complexes were purchased from common commercial suppliers and were used as received. All complexes and ligands were stored under inert atmosphere at < -20 °C.

Ir-1: $[Ir(cod)Cl]_2$
Ir-2: $[Ir(coe)_2Cl]_2$
Ir-3: $[IrCp^*Cl_2]_2$

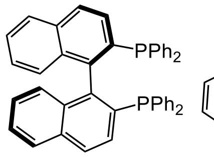
Ir-4: $[Ir(cod)(py)(PCy_3)]PF_6$
Rh-1: $[Rh(cod)Cl]_2$
Rh-2: $[Rh(C_2H_4)_2Cl]_2$



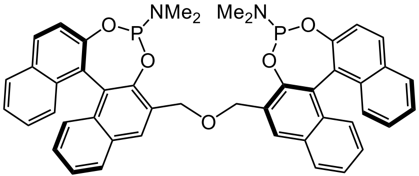
cod*



sulpho

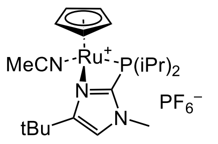


(*R*)-**BINAP**

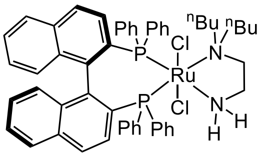


(*R,R*)-**Me-BIPAM**

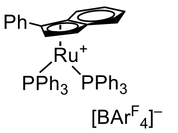
Ru-1: $[Ru(cymene)Cl_2]_2$/ **Me-BIPAM**



Ru-2: Zipper cat.

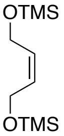


(*S*)-**Ru-3**



Ru-4

Bis-TMS protected (*Z*)-but-2-ene-1,4-diol (S1)

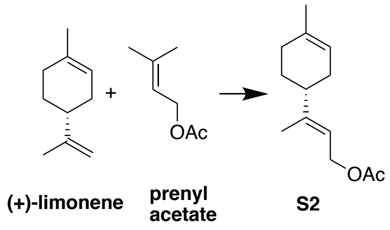


S1

Under inert atmosphere, TMSCl (4 equiv 194.31 mmol, 24.5 mL) was slowly added to a stirred solution of (*Z*)-but-2-ene-1,4-diol (1.0 equiv, 48.6 mmol, 4.0 mL) and triethylamine (6.0 equiv, 291 mmol, 40.4 mL) in dry DCM (100 mL) kept at 0 °C. The reaction mixture was allowed to warm to room temperature and then stir for an additional 4 h. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (100 mL). The organic layer was washed with $NaHCO_{3(sat.)}$ (2 x 100 mL) and brine (1 x 100 mL). The organic phase was separated and dried over anhydrous Na_2SO_4. The solid was filtered off and the volatiles from the filtrate were evaporated under reduced pressure. The residue was subjected to flash column chromatography on silica, with petroleum ether (2 x 500 mL) and a mixture of petroleum ether and ethyl acetate (95:5, 3 x 500 mL) as the eluent. Fractions containing the pure product were combined, and the solvent was removed under reduced pressure, yielding the product (9.5 g, 40.9 mmol, 84%) as a colourless liquid. The NMR data match previously reported data for the title product.[31]

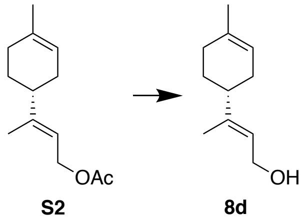
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 – 5.55 (m, 2H), 4.24 – 4.16 (m, 4H), 0.13 (s, 18H).

(*R*,E)-3-(4-methylcyclohex-3-en-1-yl)but-2-en-1-yl acetate (S2)



Product **S2** was obtained following a literature procedure,[32] with small modifications: In a nitrogen-filled glovebox, a 4 mL screw-cap vial containing a stirring bar was charged with (+)-limonene (777 mg, 925 µL, 5.70 mmol, 30.0 equiv), prenyl acetate (24.3 mg, 26.5 µL, 0.19 mmol, 1.0 equiv), 2nd gen. Hoveyda-Grubbs catalyst (6.0 mg, 0.010 mmol, 0.05 equiv), and benzene (1 mL). The vial was sealed with a Teflon-lined screw cap, removed from the glovebox, placed in a preheated aluminium block at 100 °C, and allowed to stir for 24 h. The volatiles from the mixture were removed under reduced pressure. The residue was subjected to column chromatography on silica gel, with a mixture of petroleum ether and ethyl acetate as the eluent. Fractions containing the pure product were combined (judged by TLC and GC-MS analysis), the solvent was evaporated, and the residue was used directly in the following step.

(*R*,E)-3-(4-methylcyclohex-3-en-1-yl)but-2-en-1-ol (8d)



To the above-described material containing **S2**, K_2CO_3 (26.5 mg), and dry MeOH (1 mL) were added. The reaction mixture was allowed to stir at 50°C for 16 h (when GC-MS analysis indicated full conversion of the starting material). The volatiles were removed under reduced pressure. The residue was subjected to column chromatography on silica gel, with a mixture of petroleum ether and ethyl acetate as the eluent. Fractions containing the pure product (judged by TLC analysis) were combined, and the solvent was evaporated, yielding product **8d** (ca. 14% yield over 2 steps) as light-yellow oil. The NMR data matches previously reported data for the title product.[33]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.50 – 5.15 (m, 2H), 4.18 (d, J = 6.8 Hz, 1H), 2.16 – 1.84 (m, 5H), 1.75 (m, 1H), 1.66 (s, 3H), 1.65 (s, 3H), 1.49 (m, 1H), 1.39 – 1.28 (br s, 1H).

3.4.3 One-pot isomerization and enantioselective arylation of allylic alcohols – general procedures

General procedure 1: enantioselective isomerization-arylation of linear allylic alcohols

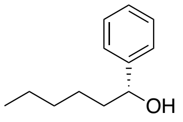
In a nitrogen-filled glovebox, an oven-dried 4 mL screw-cap scintillation vial equipped with an octagonal stir bar (2 mm x 5 mm) was charged with a stock solution of $[Ir(cod)Cl]_2$ (0.21 mg, 1.25 x 10^{-4} equiv, 3.1 x 10^{-4} mmol) in anhydrous toluene (1 mL). Then, the appropriate allylic alcohol (1.0 equiv, 0.25 mmol), K_2CO_3 (35 mg, 1.0 equiv, 0.25 mmol), and degassed H_2O (150 µL) were added. Next, the vial was sealed with a Teflon-lined screw cap, placed in a preheated aluminum block at 30 °C, and allowed to stir at 800 rpm for 2 h. After that, the vial was removed from the heating block and let to cool to room temperature. (In the meantime, a stock solution of **Ru-1** was prepared by allowing to stir a mixture of $[Ru(p\text{-}cymene)Cl_2]_2$ (4.6 mg, 0.030 equiv, 7.5 x 10^{-3} mmol) and Me-BIPAM (13 mg, 0.066 equiv, 1.65 x 10^{-2} mmol) in toluene (1 mL) for 1 h at rt). Then, the solution of **Ru-1** and arylboronic acid (3.0 equiv, 0.75 mmol) were added to the reaction mixture. The vial was re-sealed with a Teflon-lined screw cap, removed from the glovebox, placed in a preheated aluminum block at 60 °C, and allowed to stir at 800 rpm for 6 h. Next, the vial was removed from the heating block and let to cool to room temperature. (The yield was measured by GC-MS and/or NMR analysis using dodecane or 1,3,5-trimethoxybenezene as an internal standards). The volatiles were removed under reduced pressure. The residue was subjected to column chromatography on silica gel (12 g), conducted with the aid of a Combiflash instrument, using a mixture of petroleum ether and ethyl acetate (usually with gradient of 100:0 – 80:20) as the eluent. Fractions containing the pure product (judged by the TLC and/or GC analyses) were combined, and the solvent was evaporated, yielding the target product.

General procedure 2: enantioselective isomerization-arylation of linear alcohols bearing a remote double bond

In a nitrogen-filled glovebox, an oven-dried 4 mL screw-cap scintillation vial equipped with an octagonal stir bar (2 mm x 5 mm) was charged with a solution of Alkene Zipper catalyst **Ru-2** (acetonitrile(cyclopentadienyl)[2-(di-*i*-propylphosphino)-4-(*t*-butyl)-1-methyl-1*H*-imidazole]ruthenium(II) hexafluorophosphate; 3.0 mg, 0.020 equiv, 5.0 x 10^{-3} mmol) in anhydrous dichloromethane (1 mL). The appropriate allylic alcohol (1.0 equiv, 0.25 mmol) was added. Next, the vial was sealed with a Teflon-lined screw cap, placed in a preheated aluminum block at 70 °C, and allowed to stir at 800 rpm for 3 h. After that, the vial was removed from the heating block and let to cool to room temperature. (In the meantime, a stock solution of **Ru-1** was prepared by allowing to stir a mixture of [Ru(p-cymene)Cl_2]$_2$ (4.6 mg, 0.030 equiv, 7.5 x 10^{-3} mmol) and Me-BIPAM (13 mg, 0.066 equiv, 1.65 x 10^{-2} mmol) in toluene (1 mL) for 1 h at rt). Then, the solution of **Ru-1**, arylboronic acid (3.0 equiv, 0.75 mmol), and K_2CO_3 (35 mg, 1 equiv) were added to the reaction mixture. The vial was re-sealed with a Teflon-lined screw cap, removed from the glovebox, placed in a preheated aluminum block at 60 °C, and allowed to stir at 800 rpm for 6 h. Next, the vial was removed from the heating block, let to cool to room temperature. (The yield was measured by GC-MS and/or NMR analysis using dodecane or 1,3,5-trimethoxybenezene as an internal standards). The volatiles were removed under reduced pressure. The residue was subjected to column chromatography on silica gel (12 g), conducted with the aid of a Combiflash instrument, using a mixture of petroleum ether and ethyl acetate (usually with gradient of 100:0 – 80:20) as the eluent. Fractions containing the pure product (judged by the TLC and/or GC analyses) were combined, and the solvent was evaporated, yielding the target product.

3.4.5 One-pot isomerization and enantioselective arylation of allylic alcohols – full characterization of reaction products

(*R*)-1-phenylhexan-1-ol (3aa)



The compound **3aa** was prepared according to **General procedure 1** with (R,R)-**Ru-1** by reaction of (*E*)-hex-2-en-1-ol (29 µL, 0.25 mmol) with phenylboronic acid (91 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a colorless oil in 78% yield (34.6 mg); NMR yield 81%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 3.7 Hz, 4H), 7.29 – 7.24 (m, 1H), 4.65 (t, *J* = 6.8 Hz, 1H), 1.88 (d, *J* = 2.1 Hz, 1H), 1.84 – 1.75 (m, 1H), 1.74 – 1.65 (m, 1H), 1.46 – 1.36 (m, 1H), 1.34 – 1.22 (m, 5H), 0.92 – 0.82 (m, 3H).

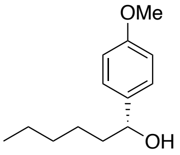
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 145.1, 128.5, 127.6, 126.0, 74.8, 39.2, 31.9, 25.6, 22.7, 14.2.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd for $C_{12}H_{17}$ 161.1325; Found 161.1326.

SFC with Chiralpak IG-3, 3% iPrOH / 97% CO_2, 1.2 mL/min, t(minor, **(*S*)-3aa**) = 3.66 min, t(major, **(*R*)-3aa**) = 4.00 min.

Specific rotation: $[\alpha]_D^{20}$ +31.6° (c 1.00, $CHCl_3$) for an enantiomerically enriched sample of 96 : 4 er. The absolute configuration was determined by comparison of the optical rotation with that reported in literature $[\alpha]_D^{23}$ +37.5° (c 0.82, $CHCl_3$), 97:3 er.[34]

(*R*)-1-(4-methoxyphenyl)hexan-1-ol (3ab)



The compound **3ab** was prepared according to **General procedure 1** with (R,R)-**Ru-1**) by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with (4-methoxyphenyl)boronic acid (114.0 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white solid, mp [43.2 – 43.7 °C], in 81% yield (42.0 mg); NMR yield 92%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 2H), 6.92 – 6.83 (m, 2H), 4.60 (t, *J* = 6.7 Hz, 1H), 3.80 (s, 3H), 1.83 (s, 1H), 1.82 – 1.75 (m, 1H), 1.73 – 1.62 (m, 1H), 1.43 – 1.34 (m, 1H), 1.33 – 1.20 (m, 5H), 0.91 – 0.83 (m, 3H).

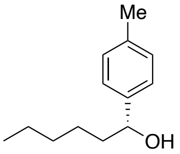
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.1, 137.2, 127.3, 113.9, 74.4, 55.4, 39.1, 31.9, 25.7, 22.7, 14.2.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd for $C_{13}H_{19}O$ 191.1430; Found 191.1432.

SFC with Chiralpak IC-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(major, **(*R*)-3ab**) = 4.38 min, t(minor, **(*S*)-3ab**) = 5.00 min.

Specific rotation: $[\alpha]_D^{20}$ +27.5° (c 1.00, $CHCl_3$) for an enantiomerically enriched sample of 96 : 4 er. The absolute configuration was determined by comparison of the optical rotation with that reported in literature $[\alpha]_D^{28}$ +18.8° (c 1.02, $CHCl_3$), 98.5:1.5 er.[35]

(*R*)-1-(p-tolyl)hexan-1-ol (3ac)



The compound **3ac** was prepared according to **General procedure 1** with (R,R)-**Ru-1** by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with *p*-tolylboronic acid (102.0 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white crystals, mp [47.8 – 48.2 °C], in 83% yield (40.0 mg); NMR yield 87%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 4.62 (t, J = 6.7 Hz, 1H), 2.35 (s, 3H), 1.88 (s, 1H), 1.84 – 1.74 (m, 1H), 1.74 – 1.63 (m, 1H), 1.47 – 1.35 (m, 1H), 1.35 – 1.20 (m, 5H), 0.94 – 0.82 (m, 3H).

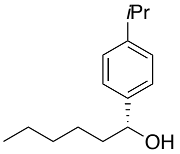
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 142.1, 137.2, 129.2, 126.0, 74.7, 39.1, 31.9, 25.7, 22.7, 21.2, 14.2.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd for $C_{13}H_{19}$ 175.1481; Found 175.1482.

SFC with Chiralpak IB N-3, 2.5% iPrOH / 97.5% CO_2, 1.2 mL/min, t(minor, **(*S*)-3ac**) = 3.21 min, t(major, **(*R*)-3ac**) = 3.46 min.

Specific rotation: $[\alpha]_D^{20}$ +28.6° (c 1.02, $CHCl_3$) for an enantiomerically enriched sample of 97 : 3 er. The absolute configuration was assigned by analogy to (*R*)-**3aa** and it was not further verified.

(*R*)-1-(4-isopropylphenyl)hexan-1-ol (3ad)



The compound **3ad** was prepared according to **General procedure 1** with (R,R)-**Ru-1** by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with (4-isopropylphenyl)boronic acid (123.0 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a colourless oil in 77% yield (42.2 mg); NMR yield 80%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 4.63 (t, J = 6.6 Hz, 1H), 2.91 (hept, J = 7.0 Hz, 1H), 1.87 – 1.75 (m, 2H), 1.74 – 1.64 (m, 1H), 1.49 – 1.39 (m, 1H), 1.35 – 1.27 (m, 5H), 1.25 (d, J = 7.0 Hz, 6H), 0.92 – 0.83 (m, 3H).

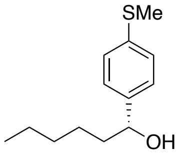
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 148.3, 142.5, 126.6, 126.0, 74.7, 39.1, 33.9, 31.9, 25.8, 24.2, 22.7, 14.2.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd for $C_{15}H_{23}$ 203.1794; Found 203.1793.

SFC with Chiralpak IB N-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(minor, **(*S*)-3ad**) = 1.96 min, t(major, **(*R*)-3ad**) = 2.17 min.

Specific rotation: $[\alpha]_D^{20}$ +26.0° (c 1.00, $CHCl_3$) for an enantiomerically enriched sample of 96 : 4 er. The absolute configuration was assigned by analogy to (*R*)-**3aa** and it was not further verified.

(*R*)-1-(4-(methylthio)phenyl)hexan-1-ol (3ae)



The compound **3ae** was prepared according to **General procedure 1** with (R,R)-**Ru-1** by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with (4-(methylthio)phenyl)boronic acid (126.0 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white solid, mp [64.1 – 64.7 °C], in 73% yield (41.1 mg); NMR yield 83%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 4H), 4.62 (dd, J = 7.5, 5.9 Hz, 1H), 2.48 (s, 3H), 1.81 (s, 1H), 1.80 – 1.73 (m, 1H), 1.71 – 1.63 (m, 1H), 1.45 – 1.34 (m, 1H), 1.34 – 1.22 (m, 5H), 0.92 – 0.82 (m, 3H).

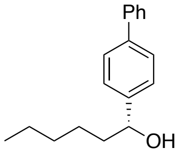
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 142.0, 137.5, 126.9, 126.6, 74.4, 39.1, 31.8, 25.6, 22.7, 16.1, 14.2.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd for $C_{13}H_{19}S$ 207.1202; Found 207.1208.

SFC with Chiralpak IG-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(minor, **(*S*)-3ae**) = 7.52 min, t(major, **(*R*)-3ae**) = 8.24 min.

Specific rotation: $[\alpha]_D^{20}$ +26.9° (c 1.01, $CHCl_3$) for an enantiomerically enriched sample of 95 : 5 er. The absolute configuration was assigned by analogy to (*R*)-**3ab** and it was not further verified.

(*R*)-1-([1,1'-biphenyl]-4-yl)hexan-1-ol (3af)



The compound **3af** was prepared according to **General procedure 1** with (R,R)-**Ru-1**) by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with [1,1'-biphenyl]-4-ylboronic acid (148.5 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a transparent oil in 55% yield (34.8 mg); NMR yield 54% or 72% if the 2nd step is performed at 90 °C for 24 hours.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.55 (m, 4H), 7.49 – 7.39 (m, 4H), 7.38 – 7.33 (m, 1H), 4.72 (t, *J* = 6.7 Hz, 1H), 1.87 (s, 1H), 1.86 – 1.80 (m, 1H), 1.79 – 1.71 (m, 1H), 1.51 – 1.40 (m, 1H), 1.37 – 1.28 (m, 5H), 0.94 – 0.84 (m, 3H).

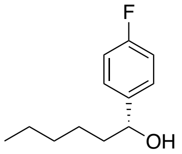
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.1, 141.0, 140.5, 128.9, 127.4, 127.3, 127.2, 126.5, 74.6, 39.2, 31.9, 25.7, 22.7, 14.2.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd for $C_{18}H_{21}$ 237.1638; Found 237.1638.

SFC with Chiralpak IG-3, 10% iPrOH / 90% CO_2, 1.2 mL/min, t(minor, **(*S*)-3af**) = 4.71 min, t(major, **(*R*)-3af**) = 5.69 min.

Specific rotation: $[\alpha]_D^{20}$ +23.4° (c 0.94, $CHCl_3$) for an enantiomerically enriched sample of 95 : 5 er. The absolute configuration was assigned by analogy to (*R*)-**3aa** and it was not further verified.

(*R*)-1-(4-fluorophenyl)hexan-1-ol (3ag)



The compound **3ag** was prepared according to **General procedure 1** with (R,R)-**Ru-1** by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with (4-fluorophenyl)boronic acid (104.9 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white solid, mp [42.8 – 43.5 °C], in 86% yield (42.1 mg); NMR yield 93%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.06 – 6.98 (m, 2H), 4.64 (dd, J = 7.6, 5.8 Hz, 1H), 1.93 (s, 1H), 1.81 – 1.72 (m, 1H), 1.71 – 1.61 (m, 1H), 1.44 – 1.34 (m, 1H), 1.34 – 1.20 (m, 5H), 0.92 – 0.82 (m, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.3 (d, J = 245.2 Hz), 140.8 (d, J = 3.1 Hz), 127.6 (d, J = 8.0 Hz), 115.4, 115.2, 74.2 (d, J = 0.6 Hz), 39.30 (d, J = 0.8 Hz), 31.8, 25.6, 22.7, 14.1.

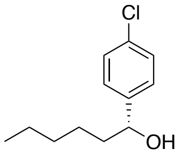
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -115.30.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd for $C_{12}H_{16}F$ 179.1231; Found 179.1233.

SFC with Chiralpak IG-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(minor, **(*S*)-3ag**) = 1.75 min, t(major, **(*R*)-3ag**) = 1.94 min.

Specific rotation: $[\alpha]_D^{20}$ +29.3° (c 1.03, $CHCl_3$) for an enantiomerically enriched sample of 96 : 4 er. The absolute configuration was assigned by analogy to (*R*)-**3aa** and it was not further verified.

(*R*)-1-(4-chlorophenyl)hexan-1-ol (3ah)



The compound **3ah** was prepared according to **General procedure 1** with (R,R)-**Ru-1** by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with (4-chlorophenyl)boronic acid (117.3 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white solid, mp [60.5 – 61 °C], in 76% yield (40.3 mg); NMR yield 83%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.27 – 7.23 (m, 2H), 4.63 (dd, J = 7.5, 5.8 Hz, 1H), 1.89 (s, 1H), 1.80 – 1.69 (m, 1H), 1.69 – 1.60 (m, 1H), 1.42 – 1.33 (m, 1H), 1.30 – 1.22 (m, 5H), 0.90 – 0.82 (m, 3H).

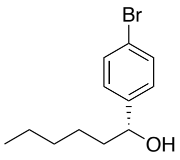
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.5, 133.2, 128.7, 127.4, 74.1, 39.3, 31.8, 25.5, 22.7, 14.1.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd for $C_{12}H_{16}Cl$ 195.0935; Found 195.0935.

SFC with Chiralpak IC-3, 2.5% iPrOH / 97.5% CO_2, 1.2 mL/min, t(major, **(*R*)-3ah**) = 3.57 min., t(minor, **(*S*)-3ah**) = 4.04 min.

Specific rotation: $[\alpha]_D^{20}$ +26.9° (c 0.99, $CHCl_3$) for an enantiomerically enriched sample of 95 : 5 er. The absolute configuration was assigned by analogy to (*R*)-**3aa** and it was not further verified.

(*R*)-1-(4-bromophenyl)hexan-1-ol (3ai)



The compound **3ai** was prepared according to **General procedure 1** with (R,R)-**Ru-1** by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with (4-bromophenyl)boronic acid (150.6 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white solid, mp [68.2 – 69.3 °C], in 79% yield (50.9 mg); NMR yield 83%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.42 (m, 2H), 7.25 – 7.18 (m, 2H), 4.63 (dd, J = 7.5, 5.8 Hz, 1H), 1.86 (s, 1H), 1.80 – 1.70 (m, 1H), 1.71 – 1.60 (m, 1H), 1.44 – 1.34 (m, 1H), 1.32 – 1.21 (m, 5H), 0.92 – 0.82 (m, 3H).

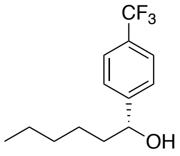
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.0, 131.6, 127.8, 121.3, 74.2, 39.2, 31.8, 25.5, 22.7, 14.1.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd for $C_{12}H_{16}Br$ 239.0430; Found 239.0433.

SFC with Chiralpak IC-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(major, **(*R*)-3ai**) = 2.46 min., t(minor, **(*S*)-3ai**) = 2.86 min.

Specific rotation: $[\alpha]_D^{20}$ +19.7° (c 0.99, $CHCl_3$) for an enantiomerically enriched sample of 95 : 5 er. The absolute configuration was assigned by analogy to (*R*)-**3aa** and it was not further verified.

(*R*)-1-(4-(trifluoromethyl)phenyl)hexan-1-ol (3aj)



The compound **3aj** was prepared according to **General procedure 1** with (R,R)-**Ru-1** by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with (4-(trifluoromethyl)phenyl)boronic acid (142 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a transparent oil in 28% yield (17 mg), NMR yield 30%.

^{1}H NMR (500 MHz, $CDCl_3$) 7.60 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 4.73 (dd, J = 7.6, 5.6 Hz, 1H), 2.03 (s, 1H), 1.82 – 1.73 (m, 1H), 1.73 – 1.64 (m, 1H), 1.46 – 1.36 (m, 1H), 1.36 – 1.23 (m, 5H), 0.92 – 0.84 (m, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.0 (q, *J* = 1.3 Hz), 129.7 (q, *J* = 32.3 Hz), 126.3, 125.5 (q, *J* = 3.8 Hz), 124.3 (*J* = 271.5 Hz), 74.2, 39.4, 31.8, 25.4, 22.7, 14.1.

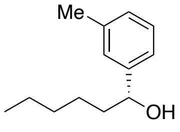
^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -62.44.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd for $C_{13}H_{16}F_3$ 229.1199; Found 229.1196.

SFC with Chiralpak IC-3, 0.5% THF / 99.5% CO_2, 1.2 mL/min, t(major, **(*R*)-3aj**) = 1.67 min., t(minor, **(*S*)-3ak**) = 1.84 min.

Specific rotation: $[\alpha]_D^{20}$ +2.4° (c 0.81, $CHCl_3$) for an enantiomerically enriched sample of ~60 : 40 er. The absolute configuration was assigned by analogy to (*R*)-**3aa** and it was not further verified.

(*R*)-1-(m-tolyl)hexan-1-ol (3ak)



The compound **3ak** was prepared according to **General procedure 1** with (R,R)-**Ru-1** by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with m-tolylboronic acid (102 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a pale yellow oil in 83% yield (40 mg), NMR yield 86%.

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30 – 7.23 (m, 1H), 7.19 (s, 1H), 7.17 – 7.08 (m, 2H), 4.65 (dd, *J* = 7.6, 5.8 Hz, 1H), 2.39 (s, 3H), 1.90 – 1.77 (m, 2H), 1.77 – 1.66 (m, 1H), 1.52 – 1.40 (m, 1H), 1.37 – 1.26 (m, 5H), 0.95 – 0.84 (m, 3H).

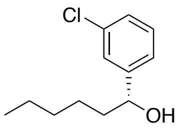
^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 145.1, 138.2, 128.4, 128.3, 126.7, 123.1, 74.9, 39.2, 31.9, 25.7, 22.7, 21.6, 14.2.

HRMS (ESI) m/z: [M+H-H$_2$O]$^+$ Calcd for C$_{13}$H$_{19}$ 175.1481; Found 175.1486.

SFC with Chiralpak ID-3, 5% iPrOH / 95% CO$_2$, 1.2 mL/min, t(major, **(*R*)-3ak**) = 1.52 min., t(minor, **(*S*)-3ak**) = 1.76 min.

Specific rotation: $[\alpha]_D^{20}$ +19.6° (c 0.32, CHCl$_3$) or $[\alpha]_D^{20}$ +13.4° (c 0.32, CH$_3$OH) for an enantiomerically enriched sample of 97 : 3 er. The absolute configuration was determined by comparison of the optical rotation measured in CH$_3$OH with that reported in literature for the opposite enantiomer $[\alpha]_D^{23}$ -16.0° (c 1.07, CH$_3$OH), 95:5.[11]

(*R*)-1-(3-chlorophenyl)hexan-1-ol (3al)



The compound **3al** was prepared according to **General procedure 1** with (R,R)-**Ru-1** by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with (3-chlorophenyl)boronic acid (117 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a transparent oil in 75% yield (39 mg), NMR yield 79%.

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35 (t, *J* = 1.9 Hz, 1H), 7.30 – 7.18 (m, 3H), 4.65 (t, *J* = 6.7 Hz, 1H), 1.87 (s, 1H), 1.82 – 1.72 (m, 1H), 1.72 – 1.64 (m, 1H), 1.46 – 1.36 (m, 1H), 1.34 – 1.24 (m, 5H), 0.92 – 0.84 (m, 3H).

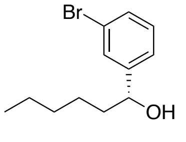
^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 147.2, 134.53, 134.49, 129.8, 127.7, 126.2, 124.2, 74.2, 39.2, 231.8, 25.5, 22.7, 14.2.

HRMS (ESI) m/z: [M+H-H$_2$O]$^+$ Calcd for C$_{12}$H$_{16}$Cl 195.0935; Found 195.0938.

SFC with Chiralpak ID-3, 5% iPrOH / 95% CO$_2$, 1.2 mL/min, t(major, **(*R*)-3al**) = 1.69 min., t(minor, **(*S*)-3al**) = 1.92 min.

Specific rotation: $[\alpha]_D^{20}$ +23.0° (c 0.43, CHCl$_3$) or $[\alpha]_D^{20}$ +21.5° (c 0.43, CH$_3$OH) for an enantiomerically enriched sample of 97 : 3 er. The absolute configuration was determined by comparison of the optical rotation measured in CH$_3$OH with that reported in literature for the opposite enantiomer $[\alpha]_D^{23}$ -25.0° (c 1.0, CH$_3$OH), 78:22.[11]

(*R*)-1-(3-bromophenyl)hexan-1-ol (3am)



The compound **3am** was prepared according to **General procedure 1** with (R,R)-**Ru-1** by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with (3-bromophenyl)boronic acid (151 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a yellow oil in 66% yield (43 mg), NMR yield 74%.

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35 (t, *J* = 1.8 Hz, 1H), 7.30 – 7.18 (m, 3H), 4.65 (dd, *J* = 7.6, 5.6 Hz, 1H), 1.86 (s, 1H), 1.81 – 1.73 (m, 1H), 1.73 – 1.63 (m, 1H), 1.46 – 1.36 (m, 1H), 1.34 – 1.26 (m, 5H), 0.93 – 0.82 (m, 3H).

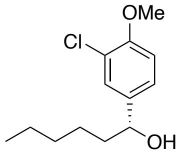
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 147.2, 134.5, 134.5, 129.8, 127.7, 126.2, 124.2, 74.2, 39.3, 31.8, 25.5, 22.7, 14.2.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd for $C_{12}H_{16}Br$ 239.0430; Found 239.0435.

SFC with Chiralpak ID-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(major, **(*R*)-3am**) = 2.04 min., t(minor, **(*S*)-3am**) = 2.50 min.

Specific rotation: $[\alpha]_D^{20}$ +15.2° (c 1.04, $CHCl_3$) for an enantiomerically enriched sample of 96 : 4 er. The absolute configuration was assigned by analogy to (*R*)-**3ak** and it was not further verified.

(*R*)-1-(3-chloro-4-methoxyphenyl)hexan-1-ol (3an)



The compound **3an** was prepared according to **General procedure 1** with (R,R)-**Ru-1** by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with (3-chloro-4-methoxyphenyl)boronic acid (139 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a pale yellow oil in 72% yield (45 mg), NMR yield 77%.

^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 2.2 Hz, 1H), 7.18 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 4.58 (dd, *J* = 7.5, 5.9 Hz, 1H), 3.89 (s, 3H), 1.84 (s, 1H), 1.81 – 1.71 (m, 1H), 1.70 – 1.61 (m, 1H), 1.44 – 1.34 (m, 1H), 1.34 – 1.20 (m, 5H), 0.91 – 0.83 (m, 3H).

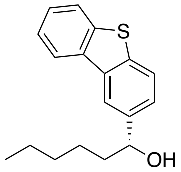
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 154.4, 138.3, 128.0, 125.4, 122.5, 112.0, 73.9, 56.3, 39.1, 31.8, 25.6, 22.7, 14.2.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd for $C_{13}H_{18}ClO$ 225.1041; Found 225.1044.

SFC with Chiralpak IC-3, 10% iPrOH / 90% CO_2, 1.2 mL/min, t(major, **(*R*)-3an**) = 2.78 min., t(minor, **(*S*)-3an**) = 3.20 min.

Specific rotation: $[\alpha]_D^{20}$ +16.2° (c 0.51, $CHCl_3$) for an enantiomerically enriched sample of 95 : 5 er. The absolute configuration was assigned by analogy to (*R*)-**3ab** and (*R*)-**3ak** and it was not further verified.

(*R*)-1-(dibenzo[b,d]thiophen-2-yl)hexan-1-ol (3ao)



The compound **3ao** was prepared according to **General procedure 1** with (R,R)-**Ru-1** by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with dibenzo[b,d]thiophen-2-ylboronic acid (171 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a yellow solid, mp [66.4 – 66.9 °C], in 33% yield (35 mg); NMR yield 42%.

^1H NMR (500 MHz, $CDCl_3$) δ 8.22 – 8.13 (m, 2H), 7.88 – 7.80 (m, 2H), 7.52 – 7.40 (m, 3H), 4.87 (td, *J* = 7.8, 7.0, 2.8 Hz, 1H), 1.97 – 1.85 (m, 2H), 1.84 – 1.77 (m, 1H), 1.51 – 1.42 (m, 1H), 1.37 – 1.28 (m, 5H), 0.93 – 0.83 (m, 3H).

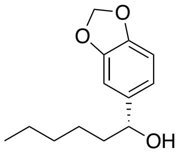
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 141.6, 140.0, 138.7, 135.8, 135.6, 126.9, 125.0, 124.5, 123.0, 122.9, 121.8, 119.0, 75.0, 39.6, 31.9, 25.7, 22.7, 14.2.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd for $C_{18}H_{19}S$ 267.1202; Found 267.1197.

SFC with Chiralpak IG-3, 20% iPrOH / 80% CO_2, 1.2 mL/min, t(major, **(*R*)-3ao**) = 3.58 min., t(minor, **(*S*)-3ao**) = 3.89 min.

Specific rotation: $[\alpha]_D^{20}$ +15.8° (c 0.83, $CHCl_3$) for an enantiomerically enriched sample of 95 : 5 er. The absolute configuration was assigned by analogy to (*R*)-**3ar** and it was not further verified.

(*R*)-1-(benzo[d][1,3]dioxol-5-yl)hexan-1-ol (3ap)



The compound **3ap** was prepared according to **General procedure 1** with (R,R)-**Ru-1** by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with benzo[d][1,3]dioxol-5-ylboronic acid (124 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white solid, mp [43.6 – 44.0 °C], in 60% yield (33 mg), NMR yield 66%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (d, *J* = 1.4 Hz, 1H), 6.79 – 6.70 (m, 2H), 5.93 (s, 2H), 4.54 (dd, *J* = 7.3, 6.1 Hz, 1H), 2.00 (s, 1H), 1.80 – 1.70 (m, 1H), 1.69 – 1.58 (m, 1H), 1.44 – 1.32 (m, 1H), 1.32 – 1.17 (m, 5H), 0.91 – 0.82 (m, 3H).

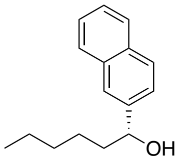
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 147.8, 146.9, 139.2, 119.4, 108.1, 106.5, 101.0, 74.6, 39.1, 31.8, 25.6, 22.7, 14.1.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd for $C_{13}H_{17}O_2$ 205.1223; Found 205.1225.

SFC with Chiralpak IC-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(major, **(*R*)-3ap**) = 3.95 min., t(minor, **(*S*)-3ap**) = 4.38 min.

Specific rotation: $[\alpha]_D^{20}$ +21.8° (c 0.38, $CHCl_3$) for an enantiomerically enriched sample of 95 : 5 er. The absolute configuration was assigned by analogy to (*R*)-**3ab** and (*R*)-**3ak** and it was not further verified.

(*R*)-1-(naphthalen-2-yl)hexan-1-ol (3aq)



The compound **3ar** was prepared according to **General procedure 1** with (R,R)-**Ru-1** by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with naphthalen-2-ylboronic acid (129 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a white solid, mp [71.3 – 72.0 °C], in 80% yield (45 mg), NMR yield 86%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.79 (m, 3H), 7.77 (s, 1H), 7.54 – 7.42 (m, 3H), 4.82 (dd, *J* = 7.4, 6.0 Hz, 1H), 2.11 (s, 1H), 1.94 – 1.84 (m, 1H), 1.84 – 1.75 (m, 1H), 1.51 – 1.39 (m, 1H), 1.37 – 1.25 (m, 5H), 0.94 – 0.83 (m, 3H).

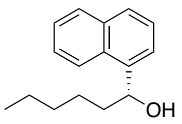
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 142.4, 133.4, 133.1, 128.3, 128.0, 127.8, 126.2, 125.9, 124.7, 124.2, 74.9, 39.0, 31.9, 25.6, 22.7, 14.2.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd for $C_{16}H_{19}$ 211.1481; Found 211.1479.

SFC with Chiralpak ID-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(major, **(*R*)-3aq**) = 3.78 min., t(minor, **(*S*)-3aq**) = 4.09 min.

Specific rotation: $[\alpha]_D^{20}$ +27.8° (c 1.43, $CHCl_3$) or $[\alpha]_D^{20}$ +21.5° (c 1.43, C_2H_5OH) for an enantiomerically enriched sample of 98 : 2 er. The absolute configuration was determined by comparison of the optical rotation measured in C_2H_5OH with that reported in literature for the opposite enantiomer $[\alpha]_D^{23}$ -23.0° (c 1.0, C_2H_5OH), 95:5.[11]

(*R*)-1-(naphthalen-1-yl)hexan-1-ol (3ar)



The compound **3as** was prepared according to **General procedure 1** with (R,R)-**Ru-1** by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with naphthalen-1-ylboronic acid (129 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a pale yellow solid, mp [66.5 – 66.9 °C], in 31% yield (18 mg), NMR yield 35%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (dd, J = 8.1, 1.6 Hz, 1H), 7.88 (dd, J = 7.6, 1.9 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.64 (dd, J = 7.2, 1.3 Hz, 1H), 7.56 – 7.41 (m, 3H), 5.45 (dd, J = 8.0, 4.7 Hz, 1H), 2.07 (s, 1H), 2.03 – 1.82 (m, 2H), 1.62 – 1.50 (m, 1H), 1.50 – 1.39 (m, 1H), 1.39 – 1.28 (m, 4H), 0.95 – 0.87 (m, 3H).

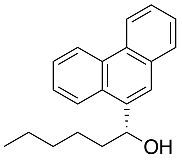
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 140.8, 133.9, 130.6, 129.0, 128.0, 126.0, 125.6, 125.5, 123.3, 122.9, 71.4, 38.5, 31.9, 26.1, 22.8, 14.2.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd for $C_{16}H_{19}$ 211.1481; Found 211.1484.

SFC with Chiralpak IC-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(minor, **(*S*)-3ar**) = 5.53 min, t(major, **(*R*)-3ar**) = 7.49 min.

Specific rotation: $[\alpha]_D^{20}$ +18.5° (c 0.4, $CHCl_3$) or $[\alpha]_D^{20}$ +30.7° (c 0.4, C_2H_5OH) for an enantiomerically enriched sample of 79 : 21 er. The absolute configuration was determined by comparison of the optical rotation measured in C_2H_5OH with that reported in literature for the opposite enantiomer $[\alpha]_D^{23}$ -45.0° (c 1.0, C_2H_5OH), 95:5.[36]

(*R*)-1-(phenanthren-9-yl)hexan-1-ol (3as)



The compound **3as** was prepared according to **General procedure 1** with (R,R)-**Ru-1** by reaction of (E)-hex-2-en-1-ol (29 µL, 0.25 mmol) with phenanthren-9-ylboronic acid (166 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a white solid, mp [81.9 – 82.6 °C], in 10% yield (7 mg), NMR yield 15%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.67 (d, *J* = 8.1 Hz, 1H), 8.16 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.96 – 7.85 (m, 2H), 7.73 – 7.53 (m, 4H), 5.49 (dt, *J* = 7.8, 3.6 Hz, 1H), 2.11 – 2.01 (m, 1H), 1.99 (d, *J* = 3.5 Hz, 1H), 1.97 – 1.86 (m, 1H), 1.68 – 1.46 (m, 2H), 1.44 – 1.28 (m, 4H), 0.96 – 0.85 (m, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.9, 131.6, 130.9, 130.1, 129.8, 128.9, 126.9, 126.7 x 2, 126.4, 124.0, 123.6, 123.5, 122.6, 71.7, 38.2, 31.9, 26.2, 22.8, 14.2.

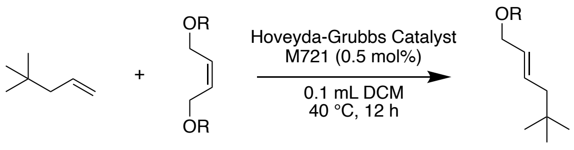
HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd for $C_{20}H_{21}$ 261.1638; Found 261.1637.

SFC with Chiralpak IG-3, 20% iPrOH / 80% CO_2, 1.2 mL/min, t(major, **(*R*)-3as**) = 4.57 min., t(minor, **(*S*)-3as**) = 5.67 min.

Specific rotation: $[\alpha]_D^{20}$ +30.3° (c 0.15, $CHCl_3$) for an enantiomerically enriched sample of 72 : 28 er. The absolute configuration was assigned by analogy to (*R*)-**3ar** and it was not further verified.

3.4.6 Multi-catalytic enantioselective conversion of alkenes to secondary benzylic alcohols - optimization of the reaction conditions and control experiments

Table 3.4.1. Metathesis optimization

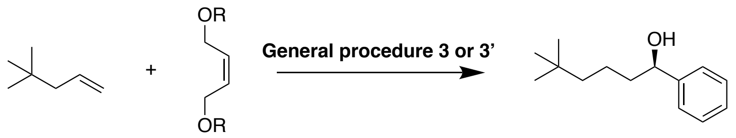


0.25 mmol x equiv. **CM product**

Entry	x	R	CM product yield[a]
1	1	H	38%
2	1.5	H	50%
3	5	H	73%
4	5	TMS	> 95%

[a] Determined by GC analysis.

Table 3.4.2. Full sequence optimization



0.25 mmol x equiv. **6aa**

Entry	x	R	6aa yield[a]
1[b]	1	H	9%
2[b]	1.5	H	11%
3[b]	5	H	< 5%
4[c]	5	TMS	88%

[a] Determined by ^{1}H NMR with TMB (1,3,5-Trimethoxybenzene) as an internal standard.

[b] Performed using **General procedure 3'** (see below).

[c] Performed using **General procedure 3** (see below).

3.4.7 Multi-catalytic enantioselective conversion of alkenes to secondary benzylic alcohols - general procedures

General procedure 3: Multi-catalytic enantioselective conversion of alkenes to secondary benzylic alcohols

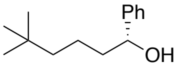
All following operations were performed in a nitrogen-filled glovebox. A 4 ml vial equipped with stirring bar (2 mm x 5 mm) was charged with an alkene (0.25 mmol, 1 equiv), bis-TMS protected (*Z*)-butenodiol **S1** (290.6 mg, 5 equiv, 1.25 mmol), and a solution of Hoveyda-Grubbs Catalyst® M721 (0.71 mg, 0.5 mol% in 100 µL DCM). Next, the vial was sealed with a Teflon-lined screw cap, placed in a preheated aluminum block at 40 °C, and allowed to stir at 800 rpm for 12 h. After that, the vial was removed from the heating block and let to cool to room temperature. A degassed solution of trifluoroacetic acid in water (40% v/v; 50 µL) was added, the vial was sealed, shaken, and let to stir vigorously for 10 min. A degassed saturated water solution of $NaHCO_3$ (0.5 mL) was added, and the mixture was allowed to stir for 10 min with free evolution of CO_2. A portion of DCM (0.4 mL) was added, the vial was sealed and shaken. Upon phase separation, the aqueous phase was separated off by either (i) gently removing the top aqueous layer with the aid of a syringe equipped with a needle, or (ii) carefully transferring the bottom organic layer to a new vial with the aid of a syringe equipped with a needle. Albeit the first procedure was faster, it was found to be less reproducible on a small scale. Therefore, the latter procedure was used preferably. In such a case, the aqueous phase was washed additionally with DCM (0.4 mL). Then, organic fractions were combined, dried over anhydrous Na_2SO_4 (~200 mg), filtered (Na_2SO_4 was washed with an additional portion of DCM (~0.4 mL)), and followed by the removal of the volatiles from the filtrate under reduced pressure. The solution of Alkene Zipper catalyst **Ru-2** (acetonitrile(cyclopentadienyl)[2-(di-*i*-propylphosphino)-4-(*t*-butyl)-1-methyl-1*H*-imidazole]ruthenium(**II**) hexafluorophosphate; 3.8 mg, 0.025 equiv, 6.3 x 10^{-3} mmol in 1 ml DCM) was added to the residue, the reaction mixture was placed in a preheated aluminum block at 70 °C and was allowed to stir for 6 h. After that, the vial was removed from the heating block and let to cool to room temperature. (In the meantime, a stock solution of **Ru-1** was prepared by allowing to stir a mixture of $[Ru(p\text{-cymene})Cl_2]_2$ (7.7 mg, 0.050 equiv, 1.25 x 10^{-2} mmol) and Me-BIPAM (20.9 mg, 0.11 equiv, 2.75 x 10^{-2} mmol) in toluene (1 mL) for 1 h at rt). Then, the solution of **Ru-1**, the solution of K_2CO_3 (34.6 mg, 1.0 equiv, 0.25 mmol) in degassed water (150 µL), and arylboronic acid (3.0 equiv, 0.75 mmol) were added to the reaction mixture. The vial was resealed with a Teflon-lined screw cap, removed from the glovebox, placed in a preheated aluminum block at 60 °C, and allowed to stir at 800 rpm for 6 h. Next, the vial was removed from the heating block. (The yield was measured by GC-MS and/or NMR analysis using dodecane or 1,3,5-trimethoxybenezene as an internal standards). The reaction mixture was diluted with ethyl acetate, Celite (~2 g) was added, and the volatiles were removed under reduces pressure. The residue was subjected to column chromatography on silica gel (24 g), conducted with the aid of a Combiflash instrument, using a mixture of petroleum ether and ethyl acetate (usually with gradient of 100:0 – 85:15) as the eluent. Fractions containing the pure product (judged by the TLC and/or GC analyses) were combined, and the solvent was evaporated, yielding the target product.

General procedure 3’: Multi-catalytic enantioselective conversion of alkenes to secondary benzylic alcohols

All following operations were performed in a nitrogen-filled glovebox. A 4 ml vial equipped with stirring bar (2 mm x 5 mm) was charged with alkene (0.25 mmol, 1 equiv), appropriate amount of (Z)-butenodiol (1 – 5 equiv) and a solution of Hoveyda-Grubbs Catalyst® M721 (0.71 mg, 0.5 mol% in 100 µL DCM). Next, the vial was sealed with a Teflon-lined screw cap, placed in a preheated aluminum block at 40 °C, and allowed to stir at 800 rpm for 12 h. After that, the vial was removed from the heating block and let to cool to room temperature. The solution of Alkene Zipper catalyst **Ru-2** (acetonitrile(cyclopentadienyl)[2-(di-*i*-propylphosphino)-4-(*t*-butyl)-1-methyl-1*H*-imidazole]ruthenium(**II**) hexafluorophosphate; 3.8 mg, 0.025 equiv, 6.3 x 10^{-3} mmol in 1 ml DCM) was added, the reaction mixture was placed in a preheated aluminum block at 70 °C and allowed to stir for 6 h. After that, the vial was removed from the heating block and let to cool to room temperature. (In the meantime, a stock solution of **Ru-1** was prepared by allowing to stir a mixture of $[Ru(p\text{-cymene})Cl_2]_2$ (7.7 mg, 0.050 equiv, 1.25 x 10^{-2} mmol) and Me-BIPAM (20.9 mg, 0.11 equiv, 2.75 x 10^{-2} mmol) in toluene (1 mL) for 1 h at rt). Then, the solution of **Ru-1**, the solution of K_2CO_3 (34.6 mg, 1 equiv, 0.25 mmol) in degassed water (150 µL), and arylboronic acid (3.0 equiv, 0.75 mmol) were added to the reaction mixture. The vial was resealed with a Teflon-lined screw cap, removed from the glovebox, placed in a preheated aluminum block at 60 °C, and allowed to stir at 800 rpm for 6 h. Next, the vial was removed from the heating block. The reaction mixture was diluted with ethyl acetate, Celite (~2 g) was added, and the volatiles were removed under reduces pressure. (The yield was measured by GC-MS and/or NMR analysis using dodecane or 1,3,5-trimethoxybenezene as an internal standards). The residue was subjected to column chromatography on silica gel (24 g), conducted with the aid of a Combiflash instrument, using a mixture of petroleum ether and ethyl acetate (usually with gradient of 100:0 – 85:15) as the eluent. Fractions containing the pure product (judged by the TLC and/or GC analyses) were combined, and the solvent was evaporated, yielding the target product.

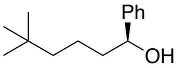
3.4.8 Multi-catalytic enantioselective conversion of alkenes to secondary benzylic alcohols - full characterization of reaction products

(*R*)-5,5-dimethyl-1-phenylhexan-1-ol (6aa)



The compound (R)-**6aa** was prepared according to **General procedure 3** with (*R,R*)-**Ru-1** by reaction of 4,4-dimethylpent-1-ene (24.6 mg, 0.25 mmol) with phenylboronic acid (91.5 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white solid in 79% yield (40.6 mg); NMR yield 88%. The enantiomeric ratio for the isolated material was determined to be 98:2 (R:S).

(*S*)-5,5-dimethyl-1-phenylhexan-1-ol (6aa) – 2.44 mmol scale reaction



The compound (S)-**6aa** was prepared on a big scale according to **General procedure 3**, with minor modifications detailed below in section **III**, using (*S,S*)-**Ru-1** by reaction of 5,5-dimethylpent-1-ene (240 mg, 2.44 mmol, 1.0 equiv), bis-TMS protected Z-butenodiol (**S1**, 2.84 g, 12.2 mmol, 5 equiv), and phenylboronic acid (893 mg, 7.32 mmol, 3 equiv), and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a yellowish solid, mp [52.7 – 53.2 °C], in 77% (389 mg). The enantiomeric ratio for the isolated material was determined to be 96:4 (S:R).

The NMR data for the isolated material from the small scale and the big scale reactions matched.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 4H), 7.31 – 7.26 (m, 1H), 4.68 (dd, *J* = 7.9, 5.5 Hz, 1H), 1.82 – 1.72 (m, 2H), 1.72 – 1.61 (m, 1H), 1.53 – 1.35 (m, 1H), 1.35 – 1.12 (m, 3H), 0.86 (s, 9H).

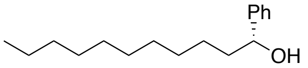
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 145.2, 128.6, 127.6, 126.0, 74.9, 44.2, 40.2, 30.5, 29.5, 21.1.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd. for $C_{14}H_{21}$ 189.1638; Found 189.1640

SFC with Chiralpak ID-3, 2% iPrOH / 98% CO_2, 1.2 mL/min, t(**(*R*)-6aa**) = 2.03 min., t(**(*S*)-6aa**) = 2.40 min.

Specific rotation: $[\alpha]_D^{20}$ -25.3° (c 1.02, $CHCl_3$) for an enantiomerically enriched sample with (*S*)-**6aa** enantiomer as a major with 96 : 4 er. The absolute configuration was assigned by analogy to (*R*)-**3aa** and it was not further verified.

(*R*)-1-phenylundecan-1-ol (6ba)



The compound **6ba** was prepared according to **General procedure 3** with (*R,R*)-**Ru-1** by reaction of dec-1-ene (35.07 mg, 0.25 mmol) with phenylboronic acid (91.5 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a colorless oil in 64% yield (39.7 mg); NMR yield 65%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 4H), 7.32 – 7.26 (m, 1H), 4.66 (dd, *J* = 7.6, 5.8 Hz, 1H), 1.85 – 1.65 (m, 3H), 1.51 – 1.37 (m, 1H), 1.37 – 1.14 (m, 15H), 0.88 (t, *J* = 6.9 Hz, 3H).

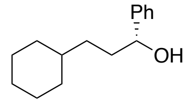
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 145.1, 128.6, 127.6, 126.0, 74.9, 39.3, 32.0, 29.74, 29.73, 29.69, 29.67, 29.5, 26.0, 22.8, 14.3.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd. for $C_{17}H_{27}$ 231.2107; Found 231.2111

SFC with Chiralpak IG-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(minor, **(*S*)-6ba**) = 3.38 min., t(major, **(*R*)-6ba**) = 3.66 min.

Specific rotation: $[\alpha]_D^{20}$ +20.0° (c 1.02, $CHCl_3$) for an enantiomerically enriched sample of 97 : 3 er. The absolute configuration was determined by comparison of the optical rotation with that reported in literature for the opposite enantiomer $[\alpha]_D^{23}$ -21.2° (c 3.00, $CHCl_3$), 98 : 2.[37]

(*R*)-3-cyclohexyl-1-phenylpropan-1-ol (6ca)



The compound **6ca** was prepared according to **General procedure 3** with (*R,R*)-**Ru-1** by reaction of vinylcyclopetroleum ether (27.6 mg, 0.25 mmol) with phenylboronic acid (91.5 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white solid, mp [73.2 – 73.9 °C], in 72% yield (39.1 mg); NMR yield 72%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 4H), 7.31 – 7.27 (m, 1H), 4.63 (dd, *J* = 7.5, 5.8 Hz, 1H), 1.92 – 1.52 (m, 8H), 1.44 – 1.27 (m, 1H), 1.26 – 1.03 (m, 5H), 0.96 – 0.80 (m, 2H).

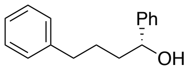
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 145.1, 128.6, 127.6, 126.1, 75.2, 37.8, 36.6, 33.5, 33.4, 26.8, 26.5.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd. for $C_{15}H_{21}$ 201.1638; Found 201.1639

SFC with Chiralpak ID-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(minor, **(*S*)-6ca**) = 2.70 min., t(major, **(*R*)-6ca**) = 2.90 min.

Specific rotation: $[\alpha]_D^{20}$ +26.6° (c 1.00, $CHCl_3$) for an enantiomerically enriched sample of 97 : 3 er. The absolute configuration was assigned by analogy to (*R*)-**3aa** and it was not further verified.

(*R*)-1,4-diphenylbutan-1-ol (6da)



The compound **6da** was prepared according to **General procedure 3** with (*R,R*)-**Ru-1** by reaction of allylbenzene (29.6 mg, 0.25 mmol) with phenylboronic acid (91.5 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a colorless oil in 48% yield (26.9 mg), NMR yield 53%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 4H), 7.28 – 7.20 (m, 3H), 7.17 – 7.10 (m, 3H), 4.66 (t, *J* = 7.4, 4.9 Hz, 1H), 2.61 (t, *J* = 7.3 Hz, 2H), 2.03 – 1.66 (m, 4H), 1.59 (dd, *J* = 10.6, 7.7 Hz, 1H).

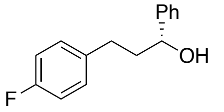
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 144.7, 142.3, 128.5, 128.4, 128.3, 127.6, 125.9, 125.8, 74.6, 38.6, 35.8, 27.6.

HRMS (ESI) m/z: $[M-H]^+$ Calcd. for $C_{16}H_{27}$ 225.1274; Found 225.1271

SFC with Chiralpak IB N-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(major, **(*R*)-6da**) = 7.25 min., t(minor, **(*S*)-6da**) = 8.40 min.

Specific rotation: $[\alpha]_D^{20}$ +16.4° (c 0.98, $CHCl_3$) for an enantiomerically enriched sample of 97 : 3 er. T The absolute configuration was assigned by analogy to (*R*)-**3aa** and it was not further verified.

(*R*)-3-(4-fluorophenyl)-1-phenylpropan-1-ol (6ea)



The compound was prepared according to **General procedure 3** with (*R,R*)-**Ru-1** by reaction of 1-fluoro-4-vinylbenzene (30.5 mg, 0.25 mmol) with phenylboronic acid (91.5 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white solid, mp [48.4 – 49.0 °C], in 84% yield (45.4 mg); NMR yield 84%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 4H), 7.22 – 7.18 (m, 1H), 7.08 – 7.02 (m, 2H), 6.91 – 6.84 (m, 2H), 4.58 (dd, J = 7.9, 5.2 Hz, 1H), 2.64 (ddd, J = 15.1, 9.8, 5.7 Hz, 1H), 2.56 (ddd, J = 14.0, 9.6, 6.6 Hz, 1H), 2.06 – 1.97 (m, 1H), 1.94 – 1.88 (m, 1H), 1.79 (bs, 1H).

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 161.4 (d, *J* = 243.3 Hz), 144.6, 137.5 (d, *J* = 3.2 Hz), 129.9 (d, *J* = 7.8 Hz), 128.7, 127.9, 126.0, 115.2 (d, *J* = 21.1 Hz), 73.9, 40.7 (d, *J* = 1.0 Hz), 31.4 (d, *J* = 0.6 Hz).

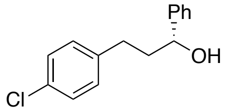
^{19}F NMR (471 MHz, $CDCl_3$) δ -117.66 – -117.76 (m).

HRMS (ESI) m/z: $[M-H]^+$ Calcd. for $C_{15}H_{13}F$ 229.1034; Found 229.1031

SFC with Chiralpak IA-3, 2.5% iPrOH / 97.5% CO_2, 1.2 mL/min, t(major, **(*R*)-6ea**) = 9.12 min., t(minor, **(*S*)-6ea**) = 9.12 min.

Specific rotation: $[\alpha]_D^{20}$ +25.5° (c 1.01, $CHCl_3$) for an enantiomerically enriched sample of 98 : 2 er. The absolute configuration was assigned by analogy to (*R*)-**3aa** and it was not further verified.

(*R*)-3-(4-chlorophenyl)-1-phenylpropan-1-ol (6fa)



The compound **6fa** was prepared according to **General procedure 3** with (*R,R*)-**Ru-1** by reaction of 1-chloro-4-vinylbenzene (34.7 mg, 0.25 mmol) with phenylboronic acid (91.5 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give white crystals, mp [66.8 – 67.3 °C], in 77% yield (47.6 mg); NMR yield 81%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 4H), 7.23 – 7.12 (m, 3H), 7.06 – 7.00 (m, 2H), 4.58 (dd, *J* = 7.9, 5.2 Hz, 1H), 2.68 – 2.51 (m, 2H), 2.11 – 1.83 (m, 2H), 1.72 (s, 1H).

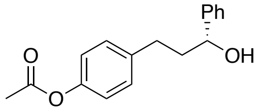
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 144.5, 140.3, 131.7, 129.9, 128.7, 128.6, 127.9, 126.0, 73.8, 40.4, 31.5.

HRMS (ESI) m/z: $[M-H]^+$ Calcd. for $C_{15}H_{13}Cl$ 245.0728; Found 245.0725

SFC with Chiralpak ID-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(major, **(*R*)-6fa**) = 4.52 min., t(minor, **(*S*)-6fa**) = 5.13 min.

Specific rotation: $[\alpha]_D^{20}$ +17.3° (c 1.02, $CHCl_3$) for an enantiomerically enriched sample of 97 : 3 er. The absolute configuration was assigned by analogy to (R)-**3aa** and it was not further verified.

(*R*)-4-(3-hydroxy-3-phenylpropyl)phenyl acetate (6ga)



The compound **6ga** was prepared according to **General procedure 3** with (*R,R*)-**Ru-1** by reaction of 4-vinylphenyl acetate (40.6 mg, 0.25 mmol) with phenylboronic acid (91.5 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 60:40) to give a colorless oil in 84% yield (56.7 mg); NMR yield 90%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.33 (m, 4H), 7.33 – 7.23 (m, 1H), 7.22 – 7.16 (m, 2H), 7.04 – 6.95 (m, 2H), 4.69 (dd, *J* = 7.9, 5.3 Hz, 1H), 2.80 – 2.56 (m, 2H), 2.29 (s, 3H), 2.22 – 1.92 (m, 2H), 1.83 (s, 1H).

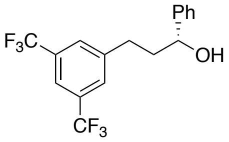
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.8, 148.9, 144.6, 139.5, 129.5, 128.7, 127.9, 126.1, 121.5, 73.9, 40.5, 31.6, 21.3.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd. for $C_{17}H_{17}O_2$ 253.1223; Found 253.1224.

SFC with Chiralpak IG-3, 10% iPrOH / 90% CO_2, 1.2 mL/min, t(major, **(*R*)-6ga**) = 3.57 min., t(minor, **(*S*)-6ga**) = 4.06 min.

Specific rotation: $[\alpha]_D^{20}$ +13.5° (c 0.99, $CHCl_3$) for an enantiomerically enriched sample of 97 : 3 er. The absolute configuration was assigned by analogy to (*R*)-**3aa** and it was not further verified.

(*R*)-3-(3,5-bis(trifluoromethyl)phenyl)-1-phenylpropan-1-ol (6ha)



The compound **6ha** was prepared according to **General procedure 3** with (*R,R*)-**Ru-1** by reaction of 1,3-bis(trifluoromethyl)-5-vinylbenzene (60 mg, 0.25 mmol) with phenylboronic acid (91.5 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give colorless crystals, mp [41.3 – 41.7 °C], in 66% yield (57.7 mg); NMR yield 79%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.63 (d, *J* = 1.7 Hz, 2H), 7.46 – 7.29 (m, 5H), 4.71 (dd, *J* = 7.9, 5.1 Hz, 1H), 3.02 – 2.66 (m, 2H), 2.28 – 1.96 (m, 2H), 1.88 (s, 1H).

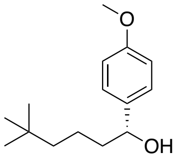
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.3 (d, *J* = 37.1 Hz), 131.7 (q, *J* = 33.0 Hz), 128.9, 128.8 – 128.7 (m), 128.2, 126.0, 123.6 (d, *J* = 272.5 Hz), 120.7 – 119.6 (m), 73.8, 40.0, 31.9.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd. for $C_{17}H_{13}F_6$ 331.0916; Found 331.0916.

SFC with Chiralpak IB N-3, 2.5% iPrOH / 97.5% CO_2, 1.2 mL/min, t(minor, **(*S*)-6ha**) = 2.94 min., t(major, **(*R*)-6ha**) = 3.31 min.

Specific rotation: $[\alpha]_D^{20}$ +23.2° (c 1.00, $CHCl_3$) for an enantiomerically enriched sample of 97 : 3 er. The absolute configuration was assigned by analogy to (*R*)-**3aa** and it was not further verified.

(*R*)-1-(4-methoxyphenyl)-5,5-dimethylhexan-1-ol (6ab)



The compound **6ab** was prepared according to **General procedure 3** with (*R,R*)-**Ru-1** by reaction of 4,4-dimethylpent-1-ene (24.6 mg, 0.25 mmol) with (4-methoxyphenyl)boronic acid (114 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white solid, mp [59.1 – 59.5 °C], in 76% yield (45.2 mg); NMR yield 84%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.63 (dd, *J* = 7.7, 5.8 Hz, 1H), 3.81 (s, 3H), 1.82 – 1.71 (m, 2H), 1.71 – 1.60 (m, 1H), 1.44 – 1.33 (m, 1H), 1.30 – 1.15 (m, 3H), 0.85 (s, 9H).

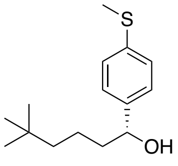
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.0, 137.2, 127.1, 113.8, 74.3, 55.3, 44.1, 40.0, 30.4, 29.4, 21.1.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd. for $C_{15}H_{23}O$ 219.1743; Found 219.1742

SFC with Chiralpak ID-3, 2% iPrOH / 98% CO_2, 1.2 mL/min, t(major, **(*R*)-6ab**) = 4.01 min., t(minor, **(*S*)-6ab**) = 4.43 min.

Specific rotation: $[\alpha]_D^{20}$ +22.4° (c 0.98, $CHCl_3$) for an enantiomerically enriched sample of 98 : 2 er. The absolute configuration was assigned by analogy to (*R*)-**3ab** and it was not further verified.

(*R*)-5,5-dimethyl-1-(4-(methylthio)phenyl)hexan-1-ol (6ac)



The compound **6ae** was prepared according to **General procedure 3** with (*R,R*)-**Ru-1** by reaction of 4,4-dimethylpent-1-ene (24.6 mg, 0.25 mmol) with (4-(methylthio)phenyl)boronic acid (126 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white solid, mp [66.9 – 67.7 °C], in 84% yield (53.1 mg); NMR yield 87%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.13 (m, 4H), 4.64 (dd, *J* = 7.8, 5.6 Hz, 1H), 2.48 (s, 3H), 1.80 – 1.69 (m, 2H), 1.69 – 1.59 (m, 1H), 1.44 – 1.33 (m, 1H), 1.30 – 1.10 (m, 3H), 0.85 (s, 9H).

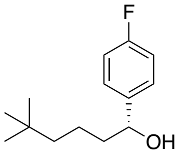
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 142.0, 137.4, 126.8, 126.5, 74.3, 44.0, 40.0, 30.4, 29.4, 21.0, 16.0.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd. for $C_{15}H_{23}S$ 235.1515; Found 235.1515

SFC with Chiralpak IC-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(major, **(*R*)-6ac**) = 4.76 min., t(minor, **(*S*)-6ac**) = 5.85 min.

Specific rotation: $[\alpha]_D^{20}$ +21.8° (c 0.98, $CHCl_3$) for an enantiomerically enriched sample of 96 : 4 er. The absolute configuration was assigned by analogy to (*R*)-**3ab** and it was not further verified.

(*R*)-1-(4-fluorophenyl)-5,5-dimethylhexan-1-ol (6ad)



The compound **6ag** was prepared according to **General procedure 3** with (*R,R*)-**Ru-1** by reaction of 4,4-dimethylpent-1-ene (24.6 mg, 0.25 mmol) with (4-fluorophenyl)boronic acid (105 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white solid, mp [69.7 – 70.4 °C], in 73% yield (41.2 mg); NMR yield 85%.

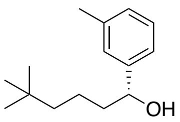
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.20 (m, 2H), 7.00 – 6.90 (m, 2H), 4.60 (dd, *J* = 7.8, 5.6 Hz, 1H), 1.73 – 1.62 (m, 2H), 1.61 – 1.51 (m, 1H), 1.37 – 1.25 (m, 1H), 1.23 – 1.07 (m, 3H), 0.78 (s, 9H).

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 162.1 (d, *J* = 245.1 Hz), 140.7 (d, *J* = 3.1 Hz), 127.5 (d, *J* = 8.0 Hz), 115.2 (d, *J* = 21.3 Hz), 74.1 (d, *J* = 0.6 Hz), 44.0, 40.1 (d, *J* = 0.8 Hz), 30.4, 29.4, 20.9.

^{19}F NMR (471 MHz, $CDCl_3$) δ -115.28 (q, *J* = 7.5, 5.4 Hz).**HRMS** (ESI) m/z: $[M+H-H_2O]^+$ Calcd. for $C_{14}H_{20}F$ 207.1544; Found 207.1545
SFC with Chiralpak IG-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(minor, **(*S*)-6ad**) = 1.81 min., t(major, **(*R*)-6ad**) = 1.95 min.

Specific rotation: $[\alpha]_D^{20}$ +23.7° (c 1.00, $CHCl_3$) for an enantiomerically enriched sample of 98 : 2 er. The absolute configuration was assigned by analogy to (*R*)-**3aa** and it was not further verified.

(*R*)-5,5-dimethyl-1-(m-tolyl)hexan-1-ol (6ae)



The compound **6ak** was prepared according to **General procedure 3** with (*R,R*)-**Ru-1** by reaction of 4,4-dimethylpent-1-ene (24.6 mg, 0.25 mmol) with *m*-tolylboronic acid (102 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a colorless oil in 87% yield (48.1 mg); NMR yield 91%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (t, *J* = 7.5 Hz, 1H), 7.09 (s, 1H), 7.08 – 6.98 (m, 2H), 4.57 (dd, *J* = 8.0, 5.3 Hz, 1H), 2.29 (s, 3H), 1.88 – 1.64 (m, 2H), 1.62 – 1.52 (m, 1H), 1.43 – 1.28 (m, 1H), 1.28 – 1.02 (m, 3H), 0.79 (s, 9H).

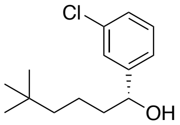
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 145.2, 138.2, 128.5, 128.3, 126.7, 123.0, 74.8, 44.2, 40.2, 30.5, 29.5, 21.6, 21.2.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd. for $C_{15}H_{23}$ 203.1794; Found 203.1795

SFC with Chiralpak ID-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(major, **(*R*)-6ae**) = 1.29 min., t(minor, **(*S*)-6ae**) = 1.48 min.

Specific rotation: $[\alpha]_D^{20}$ +22.9° (c 0.71, $CHCl_3$) for an enantiomerically enriched sample of 98 : 2 er. The absolute configuration was assigned by analogy to (*R*)-**3ak** and it was not further verified.

(*R*)-1-(3-chlorophenyl)-5,5-dimethylhexan-1-ol (6af)



The compound **6al** was prepared according to **General procedure 3** with (*R,R*)-**Ru-1** by reaction of 4,4-dimethylpent-1-ene (24.6 mg, 0.25 mmol) with (3-chlorophenyl)boronic acid (117.28 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a colorless oil in 75% yield (45.3 mg); NMR yield 80%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 1H), 7.31 – 7.18 (m, 3H), 4.67 (dd, *J* = 7.9, 5.3 Hz, 1H), 1.95 – 1.70 (m, 2H), 1.69 – 1.54 (m, 1H), 1.47 – 1.34 (m, 1H), 1.33 – 1.09 (m, 3H), 0.86 (s, 9H).

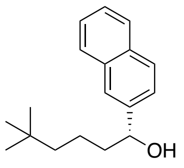
$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 147.2, 134.5, 129.8, 127.7, 126.2, 124.1, 74.2, 44.1, 40.2, 30.5, 29.5, 21.0.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd. for $C_{14}H_{20}Cl$ 223.1248; Found 223.1246

SFC with Chiralpak IA-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(major, **(*R*)-6af**) = 2.53 min., t(minor, **(*S*)-6af**) = 2.85 min.

Specific rotation: $[\alpha]_D^{20}$ +16.8° (c 1.00, $CHCl_3$) for an enantiomerically enriched sample of 95 : 5 er. The absolute configuration was assigned by analogy to (*R*)-**3ak** and it was not further verified.

(*R*)-5,5-dimethyl-1-(naphthalen-2-yl)hexan-1-ol (6ag)



The compound **6ar** was prepared according to **General procedure 3** with (*R,R*)-**Ru-1** by reaction of 4,4-dimethylpent-1-ene (24.6 mg, 0.25 mmol) with naphthalen-2-ylboronic acid (129 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white solid in 78% yield (49.8 mg); NMR yield 90%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 – 7.80 (m, 3H), 7.80 – 7.77 (m, 1H), 7.55 – 7.42 (m, 3H), 4.86 (dd, *J* = 7.7, 5.5 Hz, 1H), 1.94 – 1.82 (m, 2H), 1.81 – 1.66 (m, 1H), 1.61 – 1.37 (m, 1H), 1.37 – 1.16 (m, 3H), 0.86 (s, 9H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 142.5, 133.4, 133.1, 128.4, 128.1, 127.8, 126.2, 125.9, 124.7, 124.2, 74.9, 44.2, 40.1, 30.5, 29.5, 21.2.

HRMS (ESI) m/z: $[M+H-H_2O]^+$ Calcd. for $C_{18}H_{23}$ 239.1794; Found 239.1792

SFC with Chiralpak ID-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(major, **(*R*)-6ag**) = 3.05 min., t(minor, **(*S*)-6ar**) = 3.43 min.

Specific rotation: $[\alpha]_D^{20}$ +21.9° (c 0.53, $CHCl_3$) for an enantiomerically enriched sample of 97 : 3 er. The absolute configuration was assigned by analogy to (*R*)-**3ag** and it was not further verified.

3.4.9 Comparison of one-pot and stepwise synthesis of enantiomerically enriched 5,5-dimethyl-1-phenylhexan-1-ol - stepwise synthesis of (*S*)-5,5-dimethyl-1-phenylhexan-1-ol ((*S*)-6aa)

Stepwise synthesis of (*S*)-5,5-dimethyl-1-phenylhexan-1-ol ((*S*)-6aa)

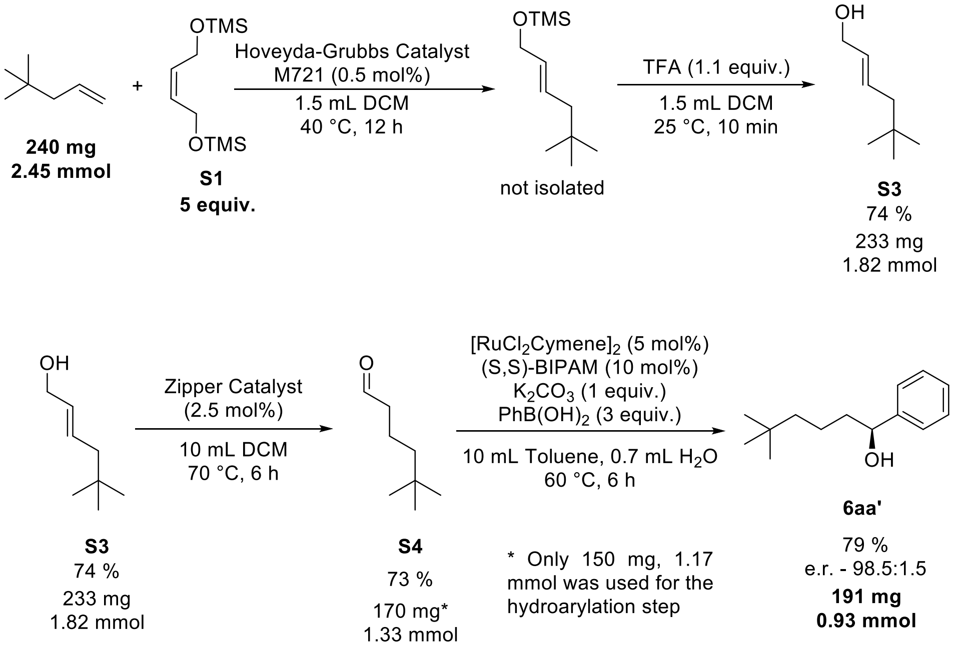


Table 3.4.3

Step	Solvents used stepwise approach	Step	Solvents used one-pot approach
Cross-Metathesis + deprotection	1.4 L	One-pot sequence	1.8 L
Isomerization	1.5 L		
Hydroarylation	1.8 L		
Total	**4.7 L**	**Total**	**1.8 L**

Table 3.4.4

Step	Yield of isolated material (Analytical yield)	Step	Yield of isolated material (Analytical yield)
Cross-Metathesis + deprotection	74% (>95% by GC analysis)	One-pot sequence	77% (86% by ^{1}H NMR analysis)
Isomerization	73% (>90% conversion by GC analysis)		
Hydroarylation	79% (81% by ^{1}H NMR analysis)		
Total	**43%**	**Total**	**77%**

(E)-5,5-Dimethylhex-2-en-1-ol (S3)

In a nitrogen filled glovebox, a 20 mL vial equipped with an octagonal stirring bar (20 mm x 5 mm) was charged with 5,5-dimethylpent-1-ene (240 mg, 2.44 mmol, 1.00 equiv) and bis-TMS protected (Z)-but-2-ene-1,4-diol (2.84 g, 5.00 equiv, 12.2 mmol). Next, a solution of Hoveyda-Grubbs catalyst M721 (0.0050 equiv, 7.0 mg, 0.012 mmol in 1 mL DCM) was added. The vial was sealed with a Teflon-lined screw cap, and the reaction mixture was allowed to stir at 800 rpm at 40 °C for 12 h. After that, the vial was removed from the heating block and let to cool to room temperature. A degassed solution of trifluoroacetic acid in water (40% v/v; 1 mL) was added, the vial was sealed, shaken, and let to stir vigorously for 10 min. A degassed saturated water solution of $NaHCO_3$ (5 mL) was added, and the mixture was allowed to stir for 10 min with free evolution of CO_2. DCM (4 mL) was added to the mixture, the vial was sealed and shaken. Upon phase separation, the bottom organic layer was transferred to a new vial with the aid of a syringe equipped with a needle. The aqueous phase was washed additionally with DCM (4 mL). The organic fractions were combined, dried over anhydrous Na_2SO_4 (3 g) and filtered. (The yield was measured by GC-FID analysis using dodecane as an internal standards). The volatiles from the filtrate were removed under reduced pressure. The residue was subjected to column chromatography on silica gel (40 g), conducted with the aid of a Combiflash instrument, using a gradient of Et_2O:DCM (0:100 to 10:90). The fractions containing the product (based on GC-MS and/or TLC) were combined. The solvent was carefully evaporated under reduced pressure to yield the product as a **volatile**, colourless liquid in 74% yield (233 mg, 1.82 mmol). The NMR data match previously reported data for the title compound.[38]

^{1}H NMR (500 MHz, CDCl$_3$) δ 5.77 – 5.67 (m, 1H), 5.70 – 5.57 (m, 1H), 4.11 (dd, *J* = 5.8, 1.1 Hz, 2H), 1.93 (dd, *J* = 7.3, 1.1 Hz, 2H), 1.33 (bs, 1H), 0.88 (s, 9H).

5,5-Dimethylhexanal (S4)

In a nitrogen-filled glovebox, a 20 mL vial equipped with an octagonal stirring bar (20 mm x 5 mm) was charged with (E)-5,5-Dimethylhex-2-en-1-ol (S1) (233 mg, 1.82 mmol). Next a solution of Alkene Zipper catalyst **Ru-2** (acetonitrile(cyclopentadienyl)[2-(di-*i*-propylphosphino)-4-(*t*-butyl)-1-methyl-1*H*-imidazole]ruthenium(II)hexafluorophosphate; 0.025 equiv, 27.6 mg, 0.045 mmol in 10 mL DCM) was added. The vial was sealed with a Teflon-lined screw cap, and the reaction mixture was allowed to stir at 800 rpm for 6 h at 70 °C. Upon cooling to room temperature, the mixture was concentrated to ~0.3-0.5 mL. The remaining liquid was subjected to flash chromatography on silica (40 g), conducted with the aid of a Combiflash instrument, using a gradient of DCM:n-pentane (0:100 to 50:50). The fractions containing the product (based on GC-MS and/or TLC) were combined and filtered through a short plug of neutral alumina,* filtered through a Teflon-coated syringe filter, and carefully concentrated under reduced pressure to yield the product as a **volatile**, colourless liquid in 73% yield (170 mg, 1.33 mmol). The product should be stored under inert atmosphere. (Full decomposition was observed overnight when stored under air at room temperature). The NMR data match previously reported data for the title compound.[39]

*We noted that it was crucial to filter 5,5-dimethylhexan-1-al through a plug of neutral alumina for the subsequent reaction. If this step was omitted, the hydroarylation reaction did not occur.

^{1}H NMR (500 MHz, CDCl$_3$) δ 9.77 (t, *J* = 1.8 Hz, 1H), 2.40 (td, *J* = 7.4, 1.8 Hz, 2H), 1.65 – 1.56 (m, 2H), 1.22 – 1.16 (m, 2H), 0.89 (s, 9H).

(*S*)-5,5-Dimethyl-1-phenylhexan-1-ol (6aa)

Under inert conditions of a nitrogen-filled glovebox, in a 20 mL vial equipped with a 20 mm x 5 mm stirring bar, a solution of [Ru[cymene]Cl$_2$]$_2$ (0.005 equiv, 38 mg, 0.060 mmol) and (S,S)-BIPAM (0.10 equiv, 95 mg, 0.12 mmol) in toluene (10 mL) was allowed to stir for 30 min at room temperature. In order, 5,5-dimethylhexanal* (160 mg, 1.25 mmol), a degassed aqueous solution of K$_2$CO$_3$ (1.8 M, 0.70 mL, 1.0 equiv), and phenyl boronic acid (456 mg, 3.00 equiv, 3.75 mmol) were added. The vial was sealed with a Teflon-coated cap, and the reaction mixture was allowed to stir with 800 rpm at 60 °C for 6 h. After cooling to room temperature, the reaction mixture was diluted with DCM (20 mL). (The yield was measured by GC-MS and/or NMR analysis using dodecane or 1,3,5-trimethoxybenezene as an internal standards). Celite (10 g) was added to the reaction mixture, and the volatile were removed under reduced pressure. The solid residue was subjected to column chromatography on silica gel (40 g), conducted with the aid of a Combiflash instrument, using a gradient of petroleum ether and ethyl acetate (100:0 to 85:15) as the eluent. Fractions containing the pure product (judged by the TLC and/or GC analyses) were combined, and the solvent was evaporated, yielding product **6aa** (191 mg, 0.93 mmol, 79% yield) as a yellowish solid. The NMR data match the above-described data for compound **6aa**. The enantiomeric ratio in the isolated material was determined to be 98.5:1.5.

*We noted that it was crucial to filter 5,5-dimethylhexan-1-al through a plug of neutral alumina. If this step was omitted, the hydroarylation reaction did not occur.

One-pot synthesis of (S)-5,5-dimethyl-1-phenylhexan-1-ol ((S)-6aa)

All following operations were performed in the nitrogen-filled glovebox. A 20 ml vial equipped with a stirring bar (20 mm x 5 mm) was charged with 5,5-dimethylpent-1-ene (240 mg, 2.44 mmol, 1.0 equiv), bis-TMS protected Z-butenodiol (**S1**, 2.84 g, 12.2 mmol, 5 equiv), and a solution of Hoveyda-Grubbs Catalyst® M721 (7.0 mg, 0.005 equiv, 0.012 mmol in 1 mL of DCM). Next, the vial was sealed with a Teflon-lined screw cap, placed in a preheated aluminum block at 40 °C, and allowed to stir at 800 rpm for 12 h. After that, the vial was removed from the heating block and let to cool to room temperature. A degassed solution of trifluoroacetic acid in water (40% v/v; 1 mL) was added, the vial was sealed, shaken, and let to stir vigorously for 10 min. A degassed saturated water solution of $NaHCO_3$ (5 mL) was added, and the mixture was allowed to stir for 10 min with free evolution of CO_2. The reaction mixture was diluted with DCM (6 mL), the vial was sealed and shaken. Upon phase separation, the bottom organic layer was transferred to a new vial with the aid of a 10 mL syringe equipped with a needle. The aqueous phase was washed additionally with DCM (6 mL). Then combined organic fractions were dried over anhydrous Na_2SO_4 (3 g), filtered, and the volatiles from the filtrate were removed under reduced pressure. The solution of Alkene Zipper catalyst **Ru-2** (acetonitrile(cyclopentadienyl)[2-(di-*i*-propylphosphino)-4-(*t*-butyl)-1-methyl-1*H*-imidazole]ruthenium(II) hexafluorophosphate; 38 mg, 0.025 mmol, 0.061 mmol in 5 ml DCM) was added, and the mixture was allowed to stir at 70 °C for 6 h. (In the meantime, a stock solution of **Ru-1** was prepared by allowing to stir a mixture of $[Ru(p\text{-cymene})Cl_2]_2$ (73 mg, 0.05 equiv, 0.12 mmol) and (S,S)-BIPAM (0.1 equiv, 186 mg, 0.24 mmol) in toluene (20 mL) for 0.5 h at rt). After cooling to room temperature, the reaction mixture was transferred to an oven-dried 100 mL round-bottom flask. Then, the solution of **Ru-1**, the aqueous solution of K_2CO_3 (1.5 mL, 1.6 M, 1 equiv), and phenylboronic acid (893 mg, 7.32 mmol, 3 equiv,) were added to the reaction mixture. The flask was sealed with a Teflon-lined cap, removed from the glovebox, placed in a preheated oil bath at 60 °C, and allowed to stir at 800 rpm for 6 h. After cooling to room temperature, the reaction mixture was diluted with DCM (20 mL). (The yield was measured by NMR analysis using dodecane or 1,3,5-trimethoxybenezene as an internal standards). Celite (10 g) was added, and the volatile were removed under reduced pressure. The solid residue was subjected to column chromatography on silica gel (40 g), conducted with the aid of a Combiflash instrument, using a gradient of petroleum ether and ethyl acetate (100:0 to 85:15) as the eluent. Fractions containing the pure product (judged by the TLC and/or GC analyses) were combined, and the solvent was evaporated, yielding product **6aa** (389 mg, 1.89 mmol, 77% yield) as a yellowish solid. The NMR data match the above-described data for compound **6aa**. The enantiomeric ratio in the isolated material was determined to be 96:4.

3.4.10 Enantioselective isomerization and arylation of prochiral allylic alcohols - optimization of the reaction conditions and control experiments

Typical procedure: In a nitrogen-filled glovebox, an oven-dried 4 mL screw-cap scintillation vial equipped with an octagonal stir bar (2 mm x 5 mm) was charged with (E)-3,7-dimethylocta-2,6-dien-1-ol (27 µL, 0.25 mmol, 1 equiv), K_2CO_3 (3.5 mg, 0.10 equiv), **Ru-3**, and degassed ethanol. Next, the vial was sealed with a Teflon-lined screw cap and the solution was allowed to stir at the indicated temperature for the indicated time. The reaction mixture was then analyzed with the aid of GC-MS equipment. Yields were measured by GC-MS analysis using 1,3,5-trimethoxybenezene as an internal standard.

The initial experiments indicated the step of enantioselective isomerization of prochiral allylic alcohols occurs selectively in protic solvents (EtOH, MeOH), while the arylation steps occurs selectively in aromatic solvents (toluene, xylene). With the aim to avoid the need for exchange of the solvent between the isomerization and arylations steps, the experiments were performed in order to identify conditions for the isomerization with the minimal amount of solvent, which would be compatible with the arylation step (upon dilution with aromatic solvent) - Figures S1-S4. However, the high reaction concentration resulted in unselective isomerization with formation of substantial amounts of side-products. Overall, the highest-yielding reactions were performed with 0.2 M solution of the starting material (0.25 mmol of

(E)-3,7-dimethylocta-2,6-dien-1-ol in 1.25 mL of EtOH*), 10 mol% of K_2CO_3, and 2 mol% of **Ru-3**. Under these conditions, formation of byproducts was suppressed, and the aldehyde intermediate was formed in 85% yield.

* Reactions performed in MeOH afforded the product in similar yields, but the reproducibility of these reactions was lower than those in EtOH.

Figure 3.4.1. Isomerization of (E)-3,7-dimethylocta-2,6-dien-1-ol - influence of time and temperature.

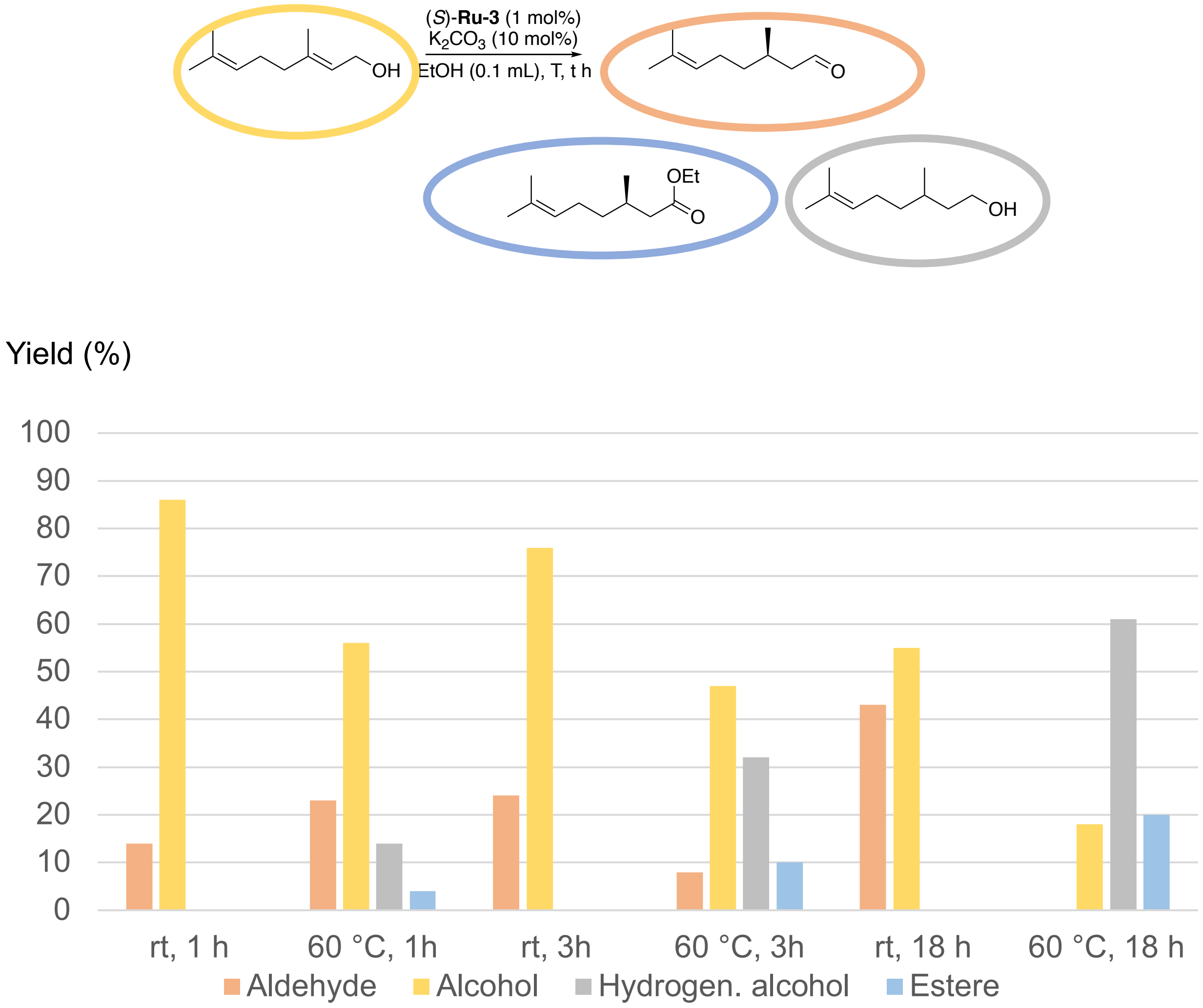


Figure 3.4.2. Isomerization of (E)-3,7-dimethylocta-2,6-dien-1-ol – influence of temperature and catalyst loading.

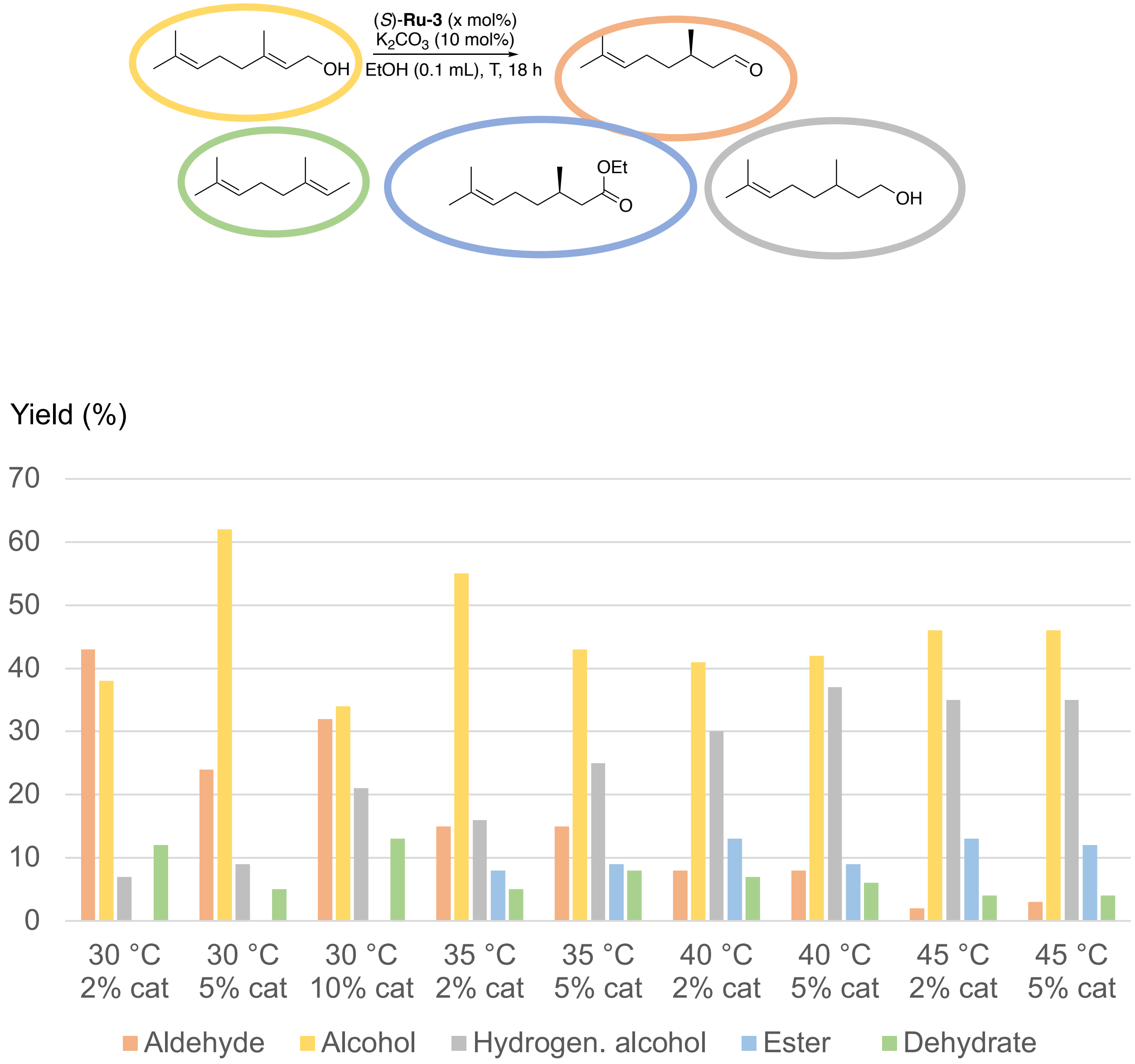
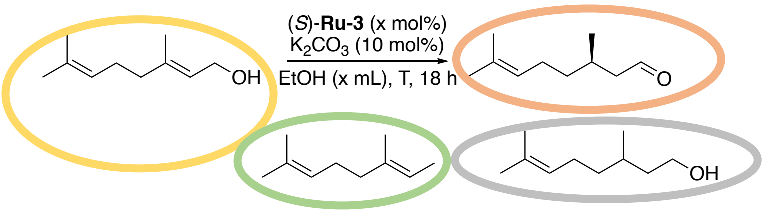


Figure 3.4.3. Enantioselective isomerization of (E)-3,7-dimethylocta-2,6-dien-1-ol – influence of concentration, catalyst loading, and temperature.



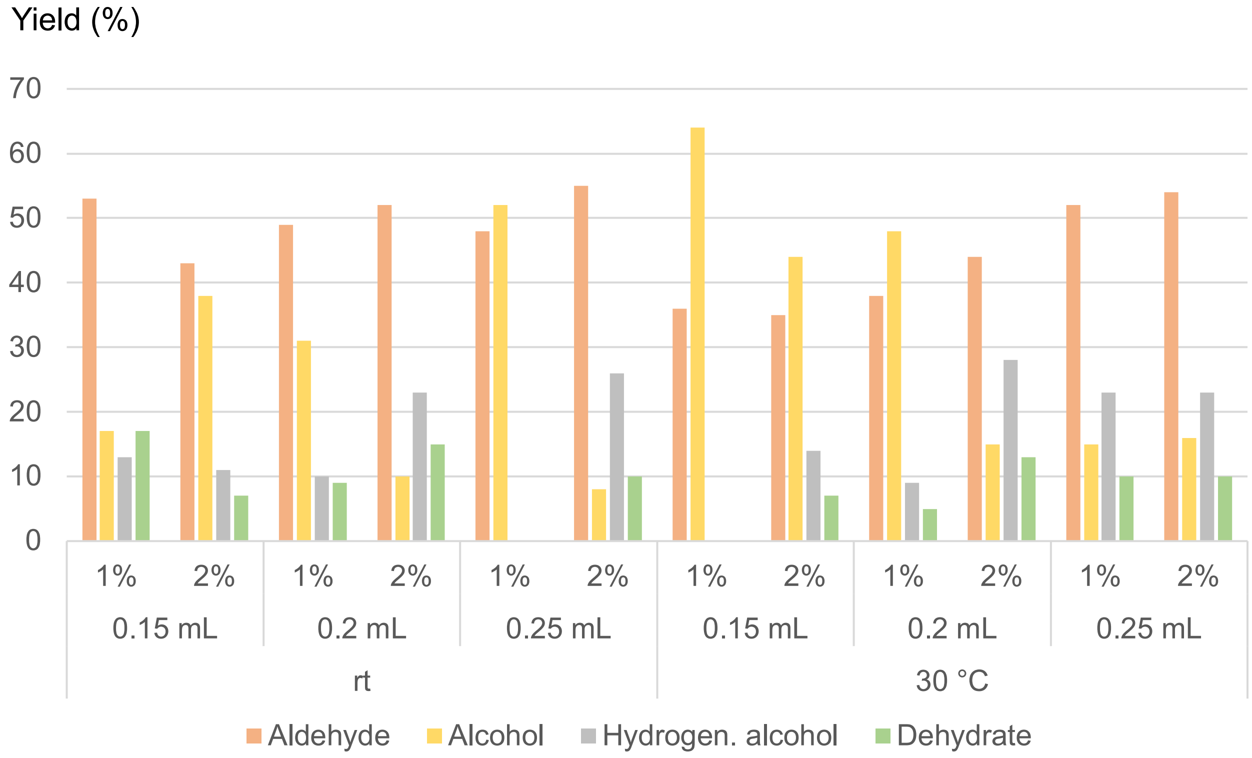


Figure 3.4.4. Enantioselective isomerization of (E)-3,7-dimethylocta-2,6-dien-1-ol – influence of concentration.

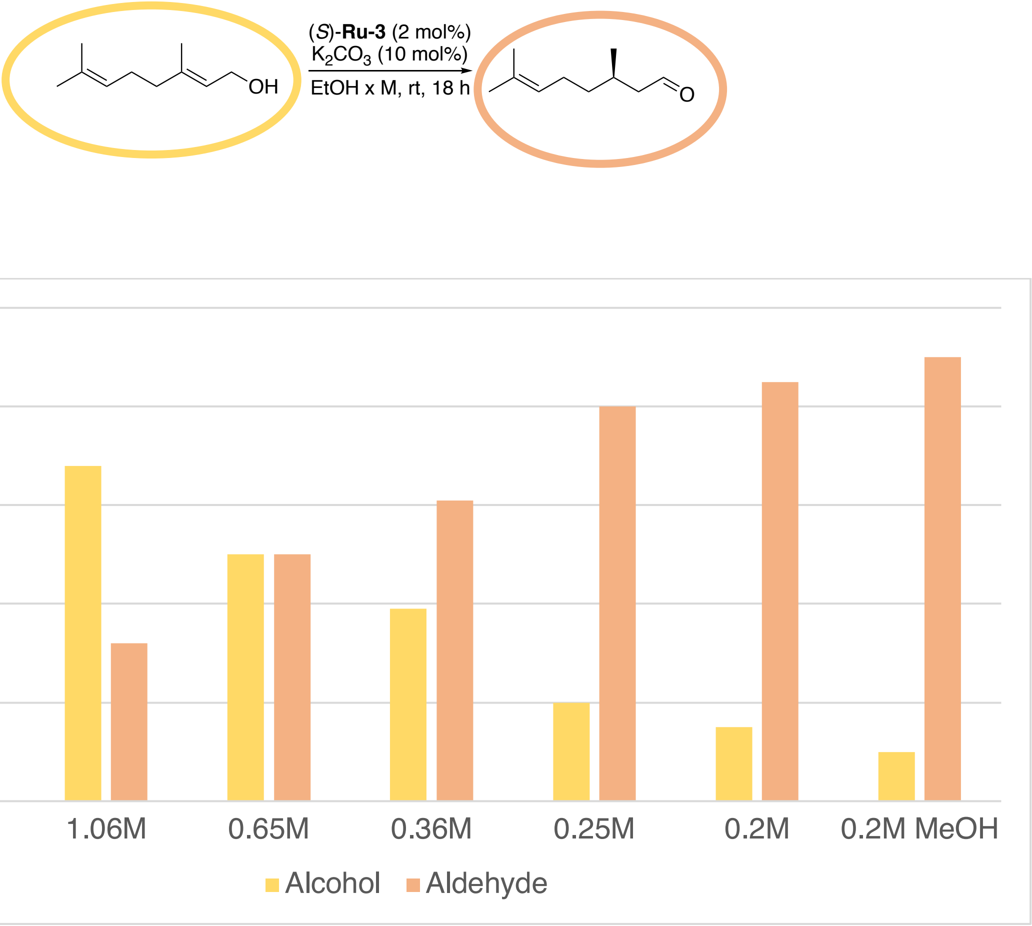


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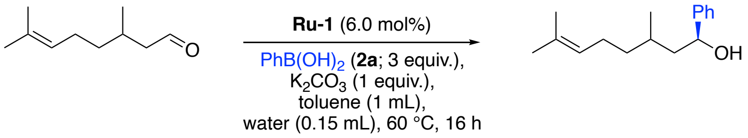
Table 3.4.5. Arylation of 3,7-dimethyloct-6-enal – influence of conditions and additives.

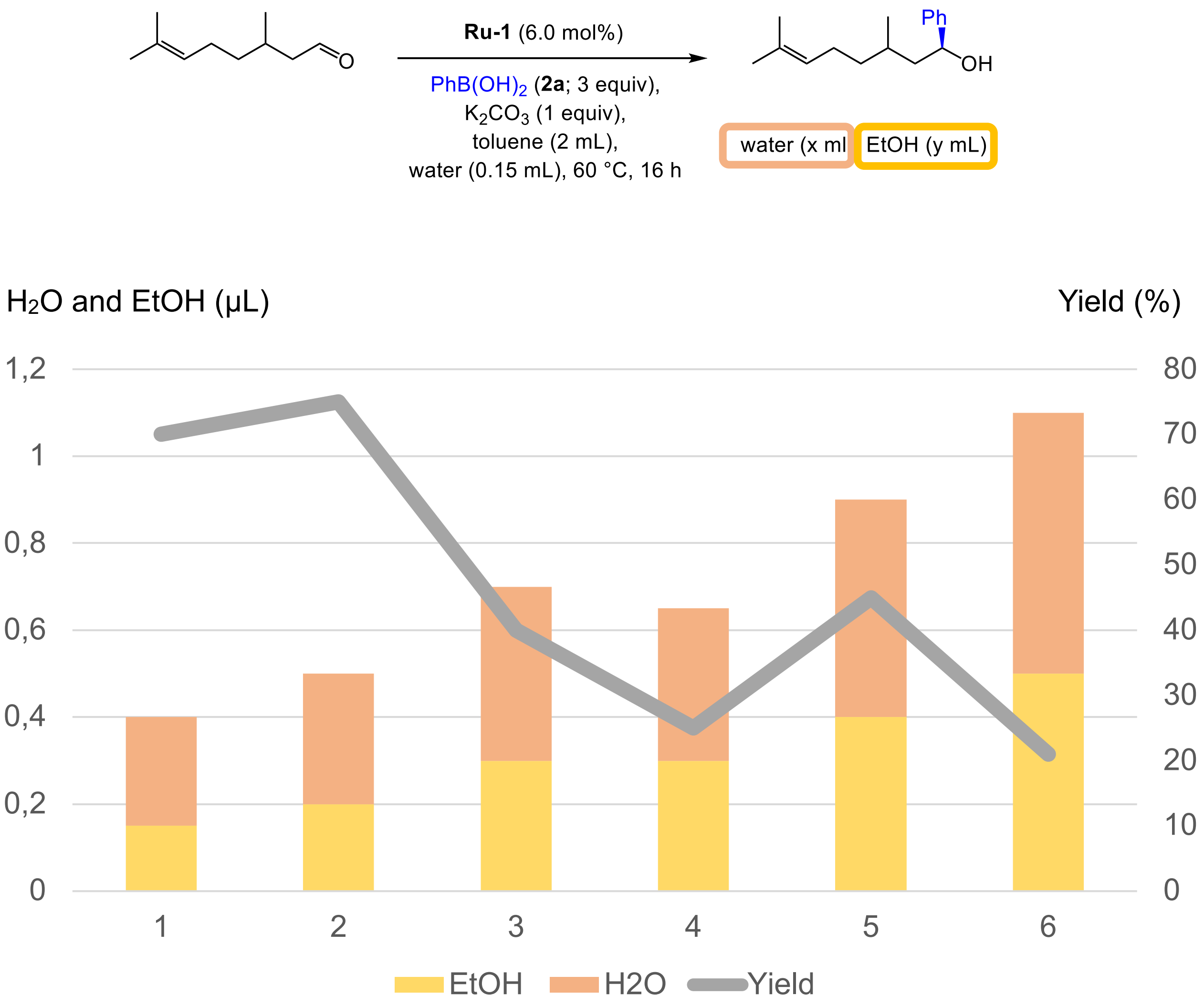


In a nitrogen-filled glovebox, a stock solution of **Ru-1** was prepared by allowing to stir a mixture of [Ru(p-cymene)$Cl_2]_2$ (4.6 mg, 0.030 equiv, 7.5 x 10^{-3} mmol) and Me-BIPAM (13 mg, 0.066 equiv, 1.65 x 10^{-2} mmol) in toluene (2 mL) for 1 h at rt. Then, a 4 mL screw-cap scintillation vial equipped with an octagonal stir bar (2 mm x 5 mm) was charged with 3,7-dimethyloct-6-enal (27 µL, 0.25 mmol, 1.0 equiv), the solution of **Ru-1**, phenyl boronic acid (91 mg, 0.75 mmol, 3.0 equiv), K_2CO_3 (35 mg, 1.0 equiv), and degassed H_2O (150 µL). The vial was sealed with a Teflon-lined screw cap, removed from the glovebox, placed in a preheated aluminum block at 60 °C and allowed to stir at 800 rpm for 16 h. Next, the vial was removed from the heating block, let to cool to room temperature. The reaction mixture was then analyzed with the aid of GC-MS equipment. Yields were measured by GC-MS analysis with 1,3,5-trimethoxybenezene as an internal standard.

Changes from the above procedure	Yield (%)
None	Quant.
30 °C	Quant.
90 °C	94%
1 mL toluene	Quant.
3 mL toluene	93%
0.1 mL water	Quant.
0.3 mL water	Quant.
2 equiv K_2CO_3	Quant.
4 equiv K_2CO_3	Quant.
4 equiv $PhB(OH)_2$	Quant.
2 equiv $PhB(OH)_2$	Quant.

Changes from the above procedure	**Yield (%)**
1% Ru-3	Quant.
2 x **Ru-1**	Quant.
+ 6 mol% Me-BIPAM	Quant.
½ x **Ru-1**	Quant.
6 h	Quant.
+ 0.10 mL EtOH	84%

Figure 3.4.5. Arylation of 3,7-dimethyloct-6-enal – influence of co-solvent and water.



3.4.11 Enantioselective isomerization and arylation of prochiral allylic alcohols – general procedures

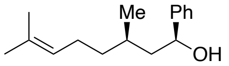
General procedure 4: enantioselective isomerization and arylation of prochiral allylic alcohols

In a nitrogen-filled glovebox, an oven-dried 4 mL screw-cap scintillation vial equipped with an octagonal stir bar (2 mm x 5 mm) was charged with an allylic alcohol (0.25 mmol, 1 equiv), K_2CO_3 (3.5 mg, 0.10 equiv), **Ru-3** (2.7 mg, 0.010 equiv) and degassed ethanol (1.25 mL). Next, the vial was sealed with a Teflon-lined screw and the solution was allowed to stir at room temperature (25 – 28 °C) for 1 h. Then, the volatiles were removed under reduced pressure at room temperature (with the aid of a vacuum line installed inside of the glovebox).* As soon as the volatiles were removed, dry toluene (1 mL) was added to the residue. (In the meantime, a stock solution of **Ru-1** was prepared by allowing to stir a mixture of $[Ru(p\text{-}cymene)Cl_2]_2$ (4.6 mg, 0.030 equiv, 7.5 x 10^{-3} mmol) and Me-BIPAM (13 mg, 0.066 equiv, 1.65 x 10^{-2} mmol) in toluene (1 mL) for 1 h at rt). Then, the solution of **Ru-1**, K_2CO_3 (35 mg, 1 equiv), arylboronic acid (3.0 equiv, 0.75 mmol) and degassed H_2O (150 μL) were added to the reaction mixture. The vial was resealed with a Teflon-lined screw cap, removed from the glovebox, placed in a preheated aluminum block at 60 °C, and allowed to stir at 800 rpm for 18 h. Next, the vial was removed from the heating block, let to cool to room temperature, and the volatiles were removed under reduced pressure. The residue was subjected to flash column chromatography on silica gel (12 g), conducted with the aid of a Combiflash instrument, using a mixture of petroleum ether and ethyl acetate (usually with gradient of 100:0 – 80:20) as the eluent. Fractions containing the pure product (judged by the TLC and/or GC analyses) were combined, and the solvent was evaporated, yielding the target product.

* EtOH needs to be removed carefully because even a small amount (~0.1-0.2 mL) can affect the subsequent step, as observed in control experiments (Table S5 and Figure S5). It is also important to evaporate the solvent at room temperature – we observed formation of aldol condensation products when the evaporation was performed at elevated temperatures.

3.4.12 Enantioselective isomerization and arylation of prochiral allylic alcohols – full characterization of products

(1*S*,3*R*)-3,7-dimethyl-1-phenyloct-6-en-1-ol (9aa)



The compound **9aa** was prepared according to **General procedure 4** with (S,S)-**Ru-1** and (S)-**Ru-3** by reaction of (E)-3,7-dimethylocta-2,6-dien-1-ol (27 µL, 0.25 mmol) with phenylboronic acid (91 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a transparent oil in 62% yield (36 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 4H), 7.30 – 7.24 (m, 1H), 5.16 – 5.04 (m, 1H), 4.78 (dd, *J* = 9.3, 4.4 Hz, 1H), 2.07 – 1.92 (m, 2H), 1.87 – 1.77 (m, 2H), 1.71 – 1.64 (m, 3H), 1.60 (s, 3H), 1.48 – 1.34 (m, 2H), 1.29 – 1.15 (m, 2H), 0.97 (d, *J* = 6.6 Hz, 3H).

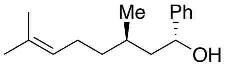
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 145.7, 131.4, 128.6, 127.6, 125.9, 124.9, 72.6, 47.0, 37.8, 29.4, 25.8, 25.6, 19.4, 17.8.

HRMS (ESI) m/z: $[M-H]^+$ Calcd for $C_{16}H_{23}O$ 231.1743; Found 231.1742.

SFC with Chiralpak ID-3, 1% iPrOH / 99% CO_2, 1.2 mL/min, t (major, (1S,3R)-**9aa**) = 3.29 min, t(minor, (1R,3S)-**9aa**) = 3.93 min

Specific rotation: $[\alpha]_D^{20}$ -6.5° (c 0.44, $CHCl_3$) for an enantiomerically enriched sample of 99 : 1 er. The absolute configuration of C3 was assigned according to the previously reported selectivity of **Ru-3** in isomerization of geraniol;[4] the absolute configuration of C1 was assigned by analogy to the selectivity of the reaction observed with linear aldehydes (see above). The absolute configuration was not further verified. It is worth noting that the configuration of C3 has no observable effect on the selectivity of the reaction at C1 center, as implied from the experiments to prepare **9aa** and **9aa’.**

(1*R*,3*R*)-3,7-dimethyl-1-phenyloct-6-en-1-ol (9aa’)



The compound **9aa’** was prepared according to **General procedure 4** with (R,R)-**Ru-1** and (S)-**Ru-3** by reaction of (E)-3,7-dimethylocta-2,6-dien-1-ol (27 µL, 0.25 mmol) with phenylboronic acid (91 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a transparent oil in 61% yield (36 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 4.0 Hz, 4H), 7.31 – 7.25 (m, 1H), 5.11 – 5.00 (m, 1H), 4.77 (t, J = 7.0 Hz, 1H), 2.02 – 1.88 (m, 2H), 1.81 (s, 1H) 1.71 – 1.64 (m, 4H), 1.62 – 1.54 (m, 3H), 1.51 – 1.38 (m, 2H), 1.32 – 1.23 (m, 1H), 1.20 – 1.12 (m, 1H), 0.95 (d, J = 6.6 Hz, 3H).

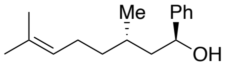
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 145.1, 131.4, 128.6, 127.7, 126.1, 124.8, 73.0, 46.5, 36.9, 29.5, 25.8, 25.4, 20.2, 17.8.

HRMS (ESI) m/z: $[M-H]^+$ Calcd for $C_{16}H_{23}O$ 231.1743; Found 231.1743.

SFC with Chiralpak IB N-3, 2% MeOH / 98% CO_2, 1.2 mL/min, t(major, (1R,3R)-**9aa'**) = 2.66 min, t(minor, (1S,3S)-**9aa'**) = 2.84 min

Specific rotation: $[\alpha]_D^{20}$ +19.5° (c 0.60, $CHCl_3$) for an enantiomerically enriched sample of 99 : 1 er. The absolute configuration was assigned by an analogous approach to that for **9aa**. The absolute configuration was not further verified.

(1*S*,3*S*)-3,7-dimethyl-1-phenyloct-6-en-1-ol (9ba')



The compound **9ba'** was prepared according to **General procedure 4** with (S,S)-**Ru-1** and (S)-**Ru-3** by reaction of (Z)-3,7-dimethylocta-2,6-dien-1- ol (27 µL, 0.25 mmol) with phenylboronic acid (91 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a transparent oil in 60% yield (35 mg).

^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 4.0 Hz, 4H), 7.31 – 7.25 (m, 1H), 5.11 – 5.00 (m, 1H), 4.77 (t, J = 7.0 Hz, 1H), 2.02 – 1.88 (m, 2H), 1.81 (s, 1H) 1.71 – 1.64 (m, 4H), 1.62 – 1.54 (m, 3H), 1.51 – 1.38 (m, 2H), 1.32 – 1.23 (m, 1H), 1.20 – 1.12 (m, 1H), 0.95 (d, J = 6.6 Hz, 3H).

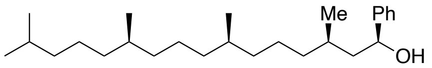
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 145.1, 131.4, 128.6, 127.7, 126.1, 124.8, 73.0, 46.5, 36.9, 29.5, 25.8, 25.4, 20.2, 17.8.

HRMS (ESI) m/z: $[M-H]^+$ Calcd for $C_{16}H_{23}O$ 231.1743; Found 231.1745.

SFC with Chiralpak IB N-3, 2% MeOH / 98% CO_2, 1.2 mL/min, t(minor, (1R,3R)-**9ba'**) = 2.66 min, t(major, (1S,3S)-**9ba'**) = 2.84 min.

Specific rotation: $[\alpha]_D^{20}$ -19.8° (c 0.62, $CHCl_3$) for an enantiomerically enriched sample of 99 : 1 er. The absolute configuration was assigned by an analogous approach to that for **9aa**. The absolute configuration was not further verified.

(1*S*,3*R*,7*R*,11*R*)-3,7,11,15-tetramethyl-1-phenylhexadecan-1-ol (9ca)



The compound **9ca** was prepared according to **General procedure 4** with (S,S)-**Ru-1** and (S)-**Ru-3** by reaction of (2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-en-1-ol (86 µL, 0.25 mmol) with phenylboronic acid (91 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a pale-yellow oil in 70% yield (65 mg). The SFC analysis revealed that besides (1S,3R,7R,11R)-**9ca** product, the isolated material contained 1.5% of the other 1,3-syn diastereomers of the product, i.e., (1R,3S,7R,11R)-**9ca**. Independent synthesis of (1R,3S,7R,11R)-**9ca** as major diastereomer showed that both 1,3-syn diastereomers are indistinguishable by ^1H and ^{13}C NMR spectroscopy.

^1H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 4H), 7.32 – 7.24 (m, 1H), 4.78 (dd, *J* = 9.4, 4.3 Hz, 1H), 1.82 (td, *J* = 9.3, 4.7 Hz, 1H), 1.70 – 1.62 (m, 1H), 1.53 (dp, *J* = 13.3, 6.6 Hz, 1H), 1.46 – 1.34 (m, 3H), 1.35 – 1.21 (m, 10H), 1.22 – 1.10 (m, 4H), 1.11 – 1.01 (m, 4H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.90 – 0.81 (m, 12H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 145.7, 128.6, 127.6, 125.9, 72.6, 47.1, 39.6, 38.1, 37.7, 37.5, 37.5, 33.1, 33.0, 29.7, 28.2, 25.0, 24.7, 24.5, 22.9, 22.8, 19.93, 19.88, 19.5.

HRMS (ESI) m/z: $[M-H]^+$ Calcd for $C_{26}H_{45}O$ 373.3465; Found 373.3468.

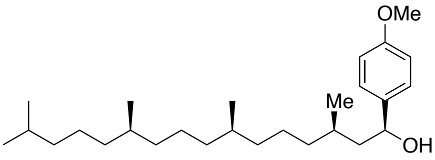
SFC with Chiralpak IG-3, 2% MeOH / 98% CO_2, 1.2 mL/min, t(major, (1S,3R,7R,11R)-**9ca**) = 4.56 min, t(minor, (1R,3S,7R,11R)-**9ca**) = 5.88 min

Specific rotation: $[\alpha]_D^{20}$ -21.8° (c 0.58, $CHCl_3$) for a sample containing a 98.5 : 1.5 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9ca** :(1R,3S,7R,11R)-**9ca**)).

Specific rotation: $[\alpha]_D^{20}$ +5.9° (c 0.51, $CHCl_3$) for a sample containing a 4 : 96 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9ca** : (1R,3S,7R,11R)-**9ca**)).

The absolute configuration was assigned by analogy to **9aa**. The absolute configuration was not further verified.

(1*S*,3*R*,7*R*,11*R*)-1-(4-methoxyphenyl)-3,7,11,15-tetramethylhexadecan-1-ol (9cb)



The compound **9cb** was prepared according to **General procedure 4** with (S,S)-**Ru-1** and (S)-**Ru-3** by reaction of (2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-en-1-ol (86 µL, 0.25 mmol)with (4-methoxyphenyl)boronic acid (107 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a pale yellow oil in 47% yield (47 mg). The SFC analysis revealed that besides (1S,3R,7R,11R)-**9cb** product, the isolated material contained 1% of the other 1,3-syn diastereomers of the product, i.e., (1R,3S,7R,11R)-**9cb**. Independent synthesis of (1R,3S,7R,11R)-**9cb** as major diastereomer showed that both 1,3-syn diastereomers are indistinguishable by ^1H and ^{13}C NMR spectroscopy.

^1H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 6.91 – 6.85 (m, 2H), 4.73 (dd, *J* = 9.2, 4.6 Hz, 1H), 3.81 (s, 3H), 1.86 – 1.77 (m, 1H), 1.68 – 1.59 (m, 1H), 1.52 (dp, *J* = 13.3, 6.7 Hz, 1H), 1.40 – 1.35 (m, 3H), 1.31 – 1.20 (m, 10H), 1.18 – 1.11 (m, 4H), 1.09 – 1.02 (m, 4H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.87 (dd, *J* = 6.7, 0.8 Hz, 6H), 0.84 (dd, *J* = 6.7, 1.8 Hz, 6H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.1, 137.8, 127.2, 114.0, 72.1, 55.4, 46.8, 39.5, 38.0, 37.6, 37.5, 37.4, 33.0, 32.9, 29.7, 28.1, 25.0, 24.6, 24.4, 22.9, 22.8, 19.92, 19.89, 19.5.

HRMS (ESI) m/z: $[M-H]^+$ Calcd for $C_{27}H_{47}O_2$ 403.3571; Found 403.3575.

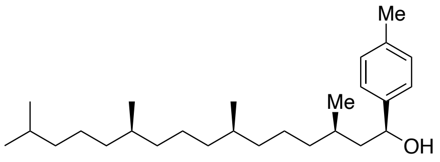
SFC with Chiralpak ID-3, 3% MeOH / 97% CO_2, 1.2 mL/min, t(major, (1S,3R,7R,11R)-**9cb**) = 2.66 min, t(minor, (1R,3S,7R,11R)-**9cb**)= 3.28 min

Specific rotation: $[\alpha]_D^{20}$ -22.4° (c 0.64, $CHCl_3$) for a sample containing a 99 : 1 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9cb** :(1R,3S,7R,11R)-**9cb**)).

Specific rotation: $[\alpha]_D^{20}$ +20.8° (c 0.51, $CHCl_3$) for a sample containing a 1 : 99 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9cb** :(1R,3S,7R,11R)-**9cb**)).

The absolute configuration was assigned by analogy to **9aa**. The absolute configuration was not further verified.

(1*S*,3*R*,7*R*,11*R*)-3,7,11,15-tetramethyl-1-(p-tolyl)hexadecan-1-ol (9cc)



The compound **9cc** was prepared according to **General procedure 4** with (S,S)-**Ru-1** and (S)- **Ru-3** by reaction of (2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-en-1-ol (86 µL, 0.25 mmol) with *p*-tolylboronic acid (102 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a transparent oil in 59% yield (57 mg). The SFC analysis revealed that besides (1S,3R,7R,11R)-**9cc** product, the isolated material contained 5% of the other 1,3-syn diastereomers of the product, i.e., (1R,3S,7R,11R)-**9cc**. Independent synthesis of (1R,3S,7R,11R)-**9cc** as major diastereomer showed that both 1,3-syn diastereomers are indistinguishable by ^{1}H and ^{13}C NMR spectroscopy.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 4.76 (dd, *J* = 9.3, 4.4 Hz, 1H), 2.37 (s, 3H), 1.87 – 1.80 (m, 1H), 1.77 (s, 1H), 1.71 – 1.62 (m, 1H), 1.55 (dp, *J* = 13.2, 6.6 Hz, 1H), 1.46 – 1.37 (m, 3H), 1.34 – 1.24 (m, 10H), 1.23 – 1.14 (m, 4H), 1.13 – 1.04 (m, 4H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.92 – 0.84 (m, 12H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 142.7, 137.2, 129.3, 125.9, 72.4, 47.0, 39.5, 38.0, 37.64, 37.63, 37.5, 33.0, 32.9, 29.6, 28.1, 25.0, 24.6, 24.4, 22.9, 22.8, 21.3, 19.94, 19.91, 19.4.

HRMS (ESI) m/z: [M-H]$^+$ Calcd for $C_{27}H_{47}O$ 387.3621; Found 387.3620.

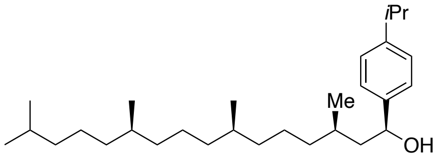
SFC with Chiralpak IC-3, 2% MeOH / 98% CO_2, 1.2 mL/min, t(major, (1S,3R,7R,11R)-**9cc**) = 2.01 min, t(minor, (1R,3S,7R,11R)-**9cc**)= 3.01 min

Specific rotation: $[\alpha]_D^{20}$ -16.9° (c 0.57, $CHCl_3$) for a sample containing a 95 : 5 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9cc** :(1R,3S,7R,11R)-**9cc**)).

Specific rotation: $[\alpha]_D^{20}$ +18.4° (c 0.64, $CHCl_3$) for a sample containing a 3 : 97 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9cc** :(1R,3S,7R,11R)-**9cc**)).

The absolute configuration was assigned by analogy to **9aa**. The absolute configuration was not further verified.

(1*S*,3*R*,7*R*,11*R*)-1-(4-isopropylphenyl)-3,7,11,15-tetramethylhexadecan-1-ol (9cd)



The compound **9cd** was prepared according to **General procedure 4** with (S,S)-**Ru-1** and (S)- **Ru-3** by reaction of (2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-en-1-ol (86 µL, 0.25 mmol) with (4-isopropylphenyl)boronic acid (128 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a yellow oil in 55% yield (57 mg). The SFC analysis revealed that besides (1S,3R,7R,11R)-**9cd** product, the isolated material contained 0.5% of the other 1,3-syn diastereomers of the product, i.e., (1R,3S,7R,11R)-**9cd**. Independent synthesis of (1R,3S,7R,11R)-**9cd** as major diastereomer showed that both 1,3-syn diastereomers are indistinguishable by ^{1}H and ^{13}C NMR spectroscopy.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 4.75 (dd, *J* = 9.4, 4.2 Hz, 1H), 2.91 (p, *J* = 6.9 Hz, 1H), 1.87 – 1.79 (m, 1H), 1.74 (s, 1H), 1.71 – 1.64 (m, 1H), 1.53 (dp, *J* = 13.2, 6.6 Hz, 1H), 1.45 – 1.35 (m, 4H), 1.33 – 1.22 (m, 14H), 1.22 – 1.11 (m, 4H), 1.11 – 1.02 (m, 4H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.92 – 0.81 (m, 12H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 148.3, 143.1, 126.6, 125.9, 72.3, 46.9, 39.5, 38.1, 37.64, 37.61, 37.5, 34.0, 33.0, 32.9, 29.6, 28.1, 25.0, 24.6, 24.4, 24.2, 22.9, 22.8, 19.92, 19.87, 19.4.

HRMS (ESI) m/z: $[M-H]^+$ Calcd for $C_{29}H_{51}O$ 415.3934; Found 415.3937.

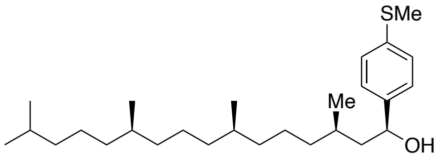
SFC with Chiralpak IG-3, 3% MeOH / 97% CO_2, 1.2 mL/min, t(minor, (1R,3S,7R,11R)-**9cd**)= 5.62 min, t(major, (1S,3R,7R,11R)-**9cd**) = 6.36 min.

Specific rotation: $[\alpha]_D^{20}$ -20.7° (c 0.66, $CHCl_3$) for a sample containing a 99.5 : 0.5 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9cd** :(1R,3S,7R,11R)-**9cd**)).

Specific rotation: $[\alpha]_D^{20}$ +18.3° (c 0.71, $CHCl_3$) for a sample containing a 0.5 : 99.5 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9cd** :(1R,3S,7R,11R)-**9cd**)).

The absolute configuration was assigned by analogy to **9aa**. The absolute configuration was not further verified.

(1*S*,3*R*,7*R*,11*R*)-3,7,11,15-tetramethyl-1-(4-(methylthio)phenyl)hexadecan-1-ol (9ce)



The compound **9ce** was prepared according to **General procedure 4** with (S,S)-**Ru-1** and (S)- **Ru-3** by reaction of (2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-en-1-ol (86 µL, 0.25 mmol)with (4-(methylthio)phenyl)boronic acid (126 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a yellow oil in 43% yield (45 mg). The SFC analysis revealed that besides (1S,3R,7R,11R)-**9ce** product, the isolated material contained 4% of the other 1,3-syn diastereomers of the product, i.e., (1R,3S,7R,11R)-**9ce**. Independent synthesis of (1R,3S,7R,11R)-**9ce** as major diastereomer showed that both 1,3-syn diastereomers are indistinguishable by ^1H and ^{13}C NMR spectroscopy.

^1H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.18 (m, 4H), 4.76 (dd, *J* = 9.3, 4.4 Hz, 1H), 2.50 (s, 3H), 1.81 (ddd, *J* = 13.9, 9.3, 4.7 Hz, 1H), 1.72 – 1.60 (m, 2H), 1.54 (dq, *J* = 13.3, 6.6 Hz, 1H), 1.45 – 1.35 (m, 3H), 1.33 – 1.22 (m, 10H), 1.22 – 1.11 (m, 4H), 1.12 – 1.02 (m, 4H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.91 – 0.83 (m, 12H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 142.6, 137.5, 127.0, 126.5, 72.1, 47.0, 39.5, 38.0, 37.61, 37.60, 37.4, 32.95, 32.93, 29.6, 28.1, 25.0, 24.6, 24.4, 22.9, 22.8, 19.91, 19.87, 19.4, 16.2.

HRMS (ESI) m/z: $[M-H]^+$ Calcd for $C_{27}H_{47}OS$ 419.3342; Found 419.3345.

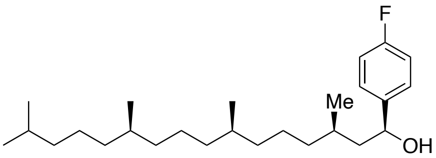
SFC with Chiralpak IC-3, 5% MeOH / 95% CO_2, 1.2 mL/min, t(minor, (1R,3S,7R,11R)-**9ce**)= 2.94 min, t(major, (1S,3R,7R,11R)-**9ce**) = 3.29 min.

Specific rotation: $[\alpha]_D^{20}$ -19.8° (c 0.68, $CHCl_3$) for a sample containing a 96 : 4 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9ce** :(1R,3S,7R,11R)-**9ce**)).

Specific rotation: $[\alpha]_D^{20}$ 24.3° (c 0.47, $CHCl_3$) for a sample containing a 4 : 96 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9ce** :(1R,3S,7R,11R)-**9ce**)).

The absolute configuration was assigned by analogy to **9aa**. The absolute configuration was not further verified.

(1*S*,3*R*,7*R*,11*R*)-1-(4-fluorophenyl)-3,7,11,15-tetramethylhexadecan-1-ol (9cf)



The compound **9cf** was prepared according to **General procedure 4** with (S,S)-**Ru-1** and (S)- **Ru-3** by reaction of (2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-en-1-ol (86 µL, 0.25 mmol)with (4-fluorophenyl)boronic acid (105 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a transparent oil in 61% yield (60 mg). The SFC analysis revealed that besides (1S,3R,7R,11R)-**9cf** product, the isolated material contained 1% of the other 1,3-syn diastereomers of the product, i.e., (1R,3S,7R,11R)-**9cf**. Independent synthesis of (1R,3S,7R,11R)-**9cf** as major diastereomer showed that both 1,3-syn diastereomers are indistinguishable by ^{1}H and ^{13}C NMR spectroscopy.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.06 – 6.98 (m, 2H), 4.76 (dd, *J* = 9.3, 4.4 Hz, 1H), 1.90 – 1.73 (m, 2H), 1.67 – 1.59 (m, 1H), 1.53 (dp, *J* = 13.2, 6.6 Hz, 1H), 1.41 – 1.34 (m, 3H), 1.31 – 1.22 (m, 10H), 1.20 – 1.12 (m, 4H), 1.10 – 1.01 (m, 4H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.89 – 0.83 (m, 12H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.2 (d, *J* = 245.2 Hz), 141.4 (d, *J* = 3.1 Hz), 127.5 (d, *J* = 8.0 Hz), 115.4 (d, *J* = 21.3 Hz), 71.9 (d, *J* = 3.1 Hz), 47.2 (d, *J* = 0.8 Hz), 39.5, 38.0, 37.6, 37.44, 37.41, 33.0, 32.9, 29.6, 28.1, 25.0, 24.6, 24.4, 22.9, 22.8, 19.93, 19.89, 19.4.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -115.37.

HRMS (ESI) m/z: $[M-H]^+$ Calcd for $C_{26}H_{44}FO$ 391.3371; Found 391.3368.

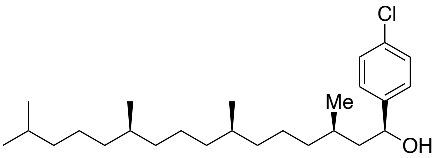
SFC with Chiralpak IG-3, 2% MeOH / 98% CO_2, 1.2 mL/min, t(major, (1S,3R,7R,11R)-**9cf**) = 3.32 min, t(minor, (1R,3S,7R,11R)-**9cf**)= 4.04 min.

Specific rotation: $[\alpha]_D^{20}$ -11.2° (c 0.55, $CHCl_3$) for a sample containing a 99 : 1 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9cf** :(1R,3S,7R,11R)-**9cf**)).

Specific rotation: $[\alpha]_D^{20}$ +14.6° (c 0.55, $CHCl_3$) for a sample containing a 2 : 98 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9cf** :(1R,3S,7R,11R)-**9cf**)).

The absolute configuration was assigned by analogy to **9aa**.

(1*S*,3*R*,7*R*,11*R*)-1-(4-chlorophenyl)-3,7,11,15-tetramethylhexadecan-1-ol (9cg)



The compound **9cg** was prepared according to **General procedure 4** with (S,S)-**Ru-1** and (S)- **Ru-3** by reaction of (2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-en-1-ol (86 µL, 0.25 mmol) with (4-chlorophenyl)boronic acid (110 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a transparent oil in 44% yield (45 mg). The SFC analysis revealed that besides (1S,3R,7R,11R)-**9cg** product, the isolated material contained <1% of the other 1,3-syn diastereomers of the product, i.e., (1R,3S,7R,11R)-**9cg**. Independent synthesis of (1R,3S,7R,11R)-**9cg** as major diastereomer showed that both 1,3-syn diastereomers are indistinguishable by ^{1}H and ^{13}C NMR spectroscopy.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 4H), 4.76 (dd, *J* = 9.4, 4.3 Hz, 1H), 1.82 – 1.72 (m, 2H), 1.68 – 1.61 (m, 1H), 1.54 – 1.47 (m, 1H), 1.41 – 1.34 (m, 3H), 1.32 – 1.21 (m, 10H), 1.21 – 1.11 (m, 4H), 1.10 – 1.00 (m, 4H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.91 – 0.80 (m, 12H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.1, 133.2, 128.7, 127.3, 71.9, 47.1, 39.5, 38.0, 37.63, 37.58, 37.4, 33.0, 32.9, 29.6, 28.1, 25.0, 24.6, 24.4, 22.9, 22.8, 19.86, 19.91, 19.4.

HRMS (ESI) m/z: $[M-H]^+$ Calcd for $C_{26}H_{44}ClO$ 407.3075; Found 407.3073.

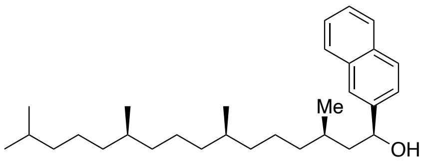
SFC with Chiralpak IG-3, 3% MeOH / 97% CO_2, 1.2 mL/min, t(minor, (1R,3S,7R,11R)-**9cg**)= 4.94 min, t(major, (1S,3R,7R,11R)-**9cg**) = 5.40 min.

Specific rotation: $[\alpha]_D^{20}$ -9.4° (c 0.59, $CHCl_3$) for a sample containing a >99 : <1 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9cg** :(1R,3S,7R,11R)-**9cg**)).

Specific rotation: $[\alpha]_D^{20}$ +10.5° (c 0.51, $CHCl_3$) for a sample containing a 2 : 98 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9cg** :(1R,3S,7R,11R)-**9cg**)).

The absolute configuration was assigned by analogy to **9aa**. The absolute configuration was not further verified.

(1*S*,3*R*,7*R*,11*R*)-3,7,11,15-tetramethyl-1-(naphthalen-2-yl)hexadecan-1-ol (9ch)



The compound **9ch** was prepared according to **General procedure 4** with (S,S)-**Ru-1** and (S)- **Ru-3** by reaction of (2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-en-1-ol (86 µL, 0.25 mmol)with naphthalen-2-ylboronic acid (129 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a white solid in 48% yield (51 mg). The SFC analysis revealed that besides (1S,3R,7R,11R)-**9ch** product, the isolated material contained 1% of the other 1,3-syn diastereomers of the product, i.e., (1R,3S,7R,11R)-**9ch**. Independent synthesis of (1R,3S,7R,11R)-**9ch** as major diastereomer showed that both 1,3-syn diastereomers are indistinguishable by ^{1}H and ^{13}C NMR spectroscopy.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 – 7.81 (m, 3H), 7.80 (s, 1H), 7.51 – 7.44 (m, 3H), 4.95 (dd, *J* = 9.3, 4.4 Hz, 1H), 1.95 – 1.81 (m, 2H), 1.74 – 1.66 (m, 1H), 1.59 – 1.47 (m, 3H), 1.35 – 1.22 (m, 10H), 1.21 – 1.11 (m, 4H), 1.10 – 1.01 (m, 4H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.91 – 0.79 (m, 12H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.0, 133.5, 133.1, 128.4, 128.0, 127.8, 126.3, 125.9, 124.4, 124.2, 72.7, 47.0, 39.5, 38.1, 37.6, 37.44, 37.38, 33.0, 32.9, 29.7, 28.1, 25.0, 24.6, 24.4, 22.9, 22.8, 19.93, 19.91, 19.5.

HRMS (ESI) m/z: $[M-H]^+$ Calcd for $C_{30}H_{47}O$ 423.3621; Found 423.3619.

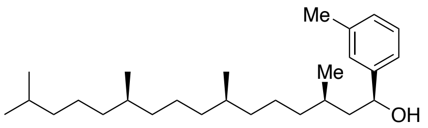
SFC with Chiralpak IG-3, 5% iPrOH / 95% CO_2, 1.2 mL/min, t(major, (1S,3R,7R,11R)-**9ch**) = 5.43 min, t(minor, (1R,3S,7R,11R)-**9ch**)= 6.35 min.

Specific rotation: $[\alpha]_D^{20}$ -20.0° (c 0.6, $CHCl_3$) for a sample containing a 99 : 1 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9ch** :(1R,3S,7R,11R)-**9ch**)).

Specific rotation: $[\alpha]_D^{20}$ +20.0° (c 0.74, $CHCl_3$) for a sample containing a 1 : 99 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9ch** :(1R,3S,7R,11R)-**9ch**)).

The absolute configuration was assigned by analogy to **9aa**. The absolute configuration was not further verified.

(1*S*,3*R*,7*R*,11*R*)-3,7,11,15-tetramethyl-1-(m-tolyl)hexadecan-1-ol (9ci)



The compound **9ci** was prepared according to **General procedure 4** with (S,S)-**Ru-1** and (S)- **Ru-3** by reaction of (2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-en-1-ol (86 µL, 0.25 mmol) with *m*-tolylboronic acid (102 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a transparent oil in 69% yield (67 mg). The SFC analysis revealed that besides (1S,3R,7R,11R)-**9ci** product, the isolated material contained <1% of the other 1,3-syn diastereomers of the product, i.e., (1R,3S,7R,11R)-**9ci**. Independent synthesis of (1R,3S,7R,11R)-**9ci** as major diastereomer showed that both 1,3-syn diastereomers are indistinguishable by ^{1}H and ^{13}C NMR spectroscopy.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (t, *J* = 7.5 Hz, 1H), 7.19 – 7.12 (m, 2H), 7.09 (d, *J* = 7.4 Hz, 1H), 4.75 (dd, *J* = 9.4, 4.2 Hz, 1H), 2.36 (s, 3H), 1.85 – 1.72 (m, 2H), 1.70 – 1.62 (m, 1H), 1.53 (dp, *J* = 13.3, 6.6 Hz, 1H), 1.44 – 1.35 (m, 3H), 1.32 – 1.23 (m, 10H), 1.20 – 1.11 (m, 4H), 1.11 – 1.01 (m, 4H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.89 – 0.82 (m, 12H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 145.7, 138.3, 128.5, 128.3, 126.6, 122.9, 72.5, 47.1, 39.5, 38.1, 37.61, 37.56, 37.4, 33.0, 32.9, 29.6, 28.1, 25.0, 24.6, 24.4, 22.9, 22.8, 21.6, 19.91, 19.86, 19.4.

HRMS (ESI) m/z: $[M-H]^+$ Calcd for $C_{27}H_{47}O$ 387.3621; Found 387.3625.

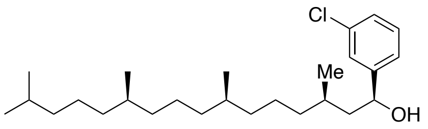
SFC with Chiralpak IG-3, 3% MeOH / 97% CO_2, 1.2 mL/min, t(major, (1S,3R,7R,11R)-**9ci**) = 2.70 min, t(minor, (1R,3S,7R,11R)-**9ci**)= 4.52 min.

Specific rotation: $[\alpha]_D^{20}$ -26.1° (c 0.86, $CHCl_3$) for a sample containing a >99 : <1 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9ci** :(1R,3S,7R,11R)-**9ci**)).

Specific rotation: $[\alpha]_D^{20}$ +20.8° (c 0.65, $CHCl_3$) for a sample containing a <1 : >99 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9ci** :(1R,3S,7R,11R)-**9ci**)).

The absolute configuration was assigned by analogy to **9aa**. The absolute configuration was not further verified.

(1*S*,3*R*,7*R*,11*R*)-1-(3-chlorophenyl)-3,7,11,15-tetramethylhexadecan-1-ol (9cj)



The compound **9cj** was prepared according to **General procedure 4** with (S,S)-**Ru-1** and (S)- **Ru-3** by reaction of (2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-en-1-ol (86 µL, 0.25 mmol) with (3-chlorophenyl)boronic acid (110 mg, 0.75 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a pale yellow oil in 47% yield (48 mg). The SFC analysis revealed that besides (1S,3R,7R,11R)-**9cj** product, the isolated material contained 1.5% of the other 1,3-syn diastereomers of the product, i.e., (1R,3S,7R,11R)-**9cj**. Independent synthesis of (1R,3S,7R,11R)-**9cj** as major diastereomer showed that both 1,3-syn diastereomers are indistinguishable by ^{1}H and ^{13}C NMR spectroscopy.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, *J* = 1.9 Hz, 1H), 7.25 – 7.17 (m, 3H), 4.73 (dd, *J* = 9.5, 4.1 Hz, 1H), 1.85 – 1.70 (m, 2H), 1.67 – 1.59 (m, 1H), 1.50 (dp, *J* = 13.3, 6.6 Hz, 1H), 1.40 – 1.32 (m, 3H), 1.30 – 1.19 (m, 10H), 1.19 – 1.09 (m, 4H), 1.08 – 0.98 (m, 4H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.83 (dd, *J* = 11.1, 6.6 Hz, 12H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 147.8, 134.5, 129.9, 127.6, 126.1, 124.0, 71.9, 47.1, 39.5, 38.0, 37.61, 37.60, 37.4, 33.0, 32.9, 29.6, 28.1, 25.0, 24.6, 24.4, 22.9, 22.8, 19.91, 19.87, 19.4.

HRMS (ESI) m/z: $[M-H]^+$ Calcd for $C_{26}H_{44}ClO$ 407.3075; Found 407.3080.

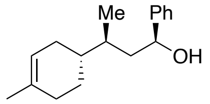
SFC with Chiralpak IA-3, 3% MeOH / 97% CO_2, 1.2 mL/min, t(minor, (1R,3S,7R,11R)-**9cj**)= 3.86 min, t(major, (1S,3R,7R,11R)-**9cj**) = 4.38 min.

Specific rotation: $[\alpha]_D^{20}$ -22.6° (c 0.58, $CHCl_3$) for a sample containing a 98.5 : 1.5 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9cj** :(1R,3S,7R,11R)-**9cj**)).

Specific rotation: $[\alpha]_D^{20}$ +18.2° (c 0.53, $CHCl_3$) for a sample containing a 0.5 : 99.5 mixture of 1,3-syn diastereomers ((1S,3R,7R,11R)-**9cj** :(1R,3S,7R,11R)-**9cj**)).

The absolute configuration was assigned by analogy to **9aa**. The absolute configuration was not further verified.

(1*S*,3*S*)-3-((*R*)-4-methylcyclohex-3-en-1-yl)-1-phenylbutan-1-ol (9da)



The compound **9da** was prepared was prepared according to **General procedure 4** with (S,S)-**Ru-1** and (S)- **Ru-3** (the reaction time of the isomerization step is 2 h) by reaction of (E)-3-(4-methylcyclohex-3-en-1-yl)but-2-en-1-ol (21 mg, 0.125 mmol) with phenylboronic acid (45 mg, 0.375 mmol) and was isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 90:10) to give a transparent oil in 41% yield (13 mg) with dr > 20:1.*

*No other diasteromers were observed by the GC-MS and ^{1}H NMR analyses for either the isolated material or in the reaction mixture.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 4H), 7.29 – 7.26 (m, 1H), 5.37 (bs, 1H), 4.77 (dt, J = 9.8, 3.5 Hz, 1H), 2.00 – 1.83 (m, 3H), 1.83 – 1.77 (m, 1H), 1.77 – 1.66 (m, 3H), 1.63 (s, 3H), 1.48 – 1.37 (m, 2H), 1.35 – 1.22 (m, 2H), 0.94 (d, J = 6.9 Hz, 3H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 145.9, 134.2, 128.6, 127.6, 125.9, 121.1, 72.6, 44.5, 39.2, 33.9, 31.2, 27.9, 27.1, 23.6, 15.8.

HRMS (ESI) m/z: $[M-H]^+$ Calcd for $C_{17}H_{23}O$ 243.1743; Found 243.1753.

Specific rotation: $[\alpha]_D^{20}$ +2° (c 0.27, $CHCl_3$) for a sample containing a single diastereomer (> dr 20:1 by the GC-MS and ^{1}H NMR analyses).

The absolute configuration was assigned by analogy to **9aa**.

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CHAPTER 4

Enantioselective α-arylation of primary alcohols under sequential one-pot catalysis

The work described in this chapter was performed in collaboration with. D. Lichosyt and M. Aleksandrova

I developed the method, evaluated about 90% of the scope and performed the competition studies.

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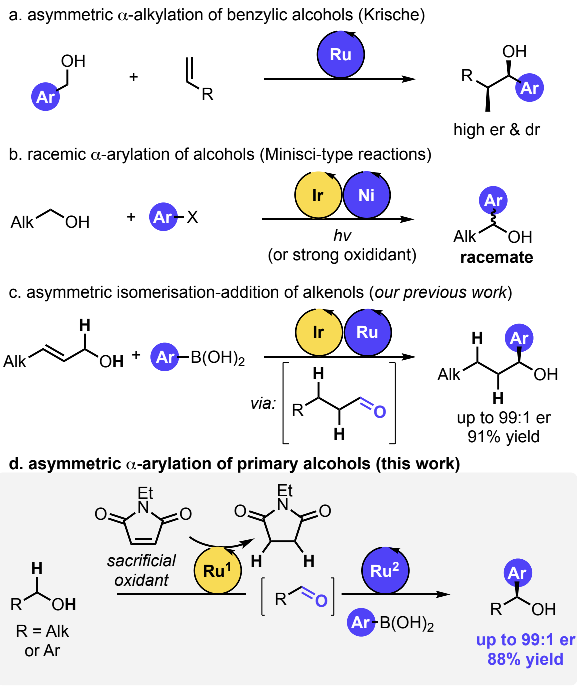
. Lainer, B.; Lichosyt, D.; Aleksandrova, M.; Dydio, P. Enantioselective α-Arylation of Primary Alcohols under Sequential One-Pot Catalysis. *J. Org. Chem*. **2021**, 86 (13), 9253–9262. https://doi.org/10.1021/acs.joc.1c00983

4.1 Introduction

Secondary benzylic alcohols (SBAs) and diarylmethanols (DAMs) constitute valuable synthetic intermediates and prevalent structural motifs of numerous natural products and bioactive compounds.[1,2]Therefore, protocols for their stereoselective synthesis from various accessible starting materials have attracted much attention over the years. Common approaches include potent asymmetric (transfer) hydrogenation of ketones[1,3,4] or 1,2-addition of aryl nucleophiles to aldehydes,[5,6] which is particularly useful for fine-chemical synthesis when such starting materials are available and do not require additional synthetic steps.

Because aliphatic alcohols represent a class of abundant starting materials, an increasing attention has been devoted to developing methods for their valorization through selective C–H bond functionalization.[7-9] In the context of SBAs, an elegant strategy for the enantioselective alkylation of α-C–H bonds of primary benzylic alcohols with unsaturated hydrocarbons (e.g., dienes and enynes) was devised by Krische and co-workers (**Scheme 4.1a**).[10,11] The methods of the arylation of α-C–H bonds of aliphatic alcohols in the Minisci-type reactions were also established (**Scheme 4.1b**).[12-17] Unfortunately, these methods lead to racemic products, leaving the enantioselective α-C–H arylation of alcohols unexplored.

Scheme 4.1 Synthesis of Secondary Benzylic Alcohols from Simple Alcohols in the Context of This Work



We have recently reported an enantioselective synthesis of SBAs from unsaturated alcohols and aryl boronic acids under sequential catalysis (**Scheme 4.1c**).[18] The one-pot sequence of an Ir-catalyzed isomerization of the starting material and a Ru-catalyzed nucleophilic addition of an aryl boronic acid to the aldehyde intermediate provided a convenient synthetic method with a broad scope and functional group tolerance.

Intrigued by the prospect of employing a multicatalytic sequential approach to the enantioselective synthesis of SBAs from readily available primary alcohols, we considered utilizing an intermolecular hydrogen transfer[19] between the starting material and a sacrificial acceptor (in place of the intramolecular isomerization step) followed by a stereoselective 1,2-addition step (**Scheme 4.1d**). Attractively, hydrogen transfer catalysis enables selective oxidation of one of multiple alcohol moieties in the presence of other functional groups, giving it utility in the late-stage modifications of complex molecules.[19,20]

Here we report, established by the design described above, a dual-catalytic method for the enantioselective α-arylation of primary aliphatic or benzylic alcohols with aryl boronic acids as nucleophiles. The protocol integrates a Ru-catalyzed hydrogen transfer oxidation with an enantioselective Ru-catalyzed 1,2-addition of an aryl nucleophile in a one-pot fashion to form either secondary benzylic alcohols or chiral diarylmethanols in an up to 99:1 enantiomeric ratio (er) and 88% yields (**Scheme 4.1d**).

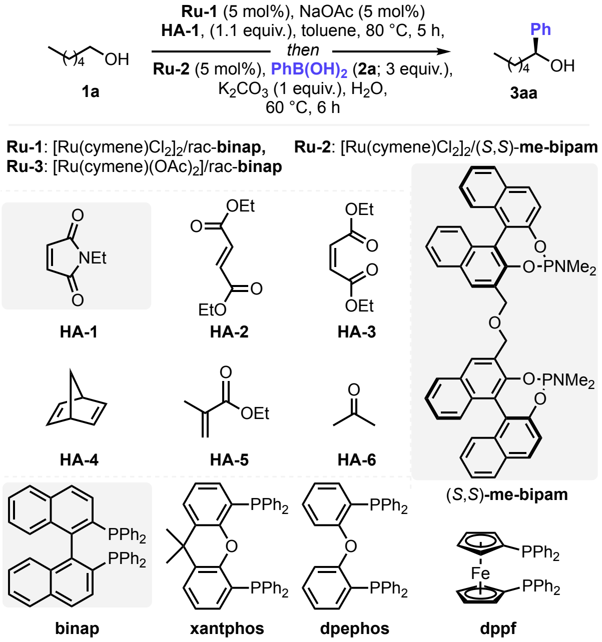
4.2 Results and discussion

The development of a multicatalytic system that executes the envisioned sequential transformation required careful balancing of the conditions to ensure compatibility between the catalysts, reagents, and intermediates of the consecutive steps.[21-25] Special attention must be paid to the selection of the catalysts, considering that any cross-reactivity or any ligand scrambling is likely not only to decrease the required activity but also to be detrimental for the overall stereoselectivity.[26,27] The Ru catalyst containing **me-bipam**, a chiral phosphoramidite ligand developed by Yamamoto and Miyaura, proved previously to be both highly enantioselective in the arylation of aldehydes[28,29] and compatible with a series of phosphine–Ru complexes,[18] which represent prospective hydrogen transfer catalysts.[19,20] Therefore, a Ru complex bearing **me-bipam** was selected as a catalyst of choice for the 1,2-addition step, and the main efforts for method development were focused on identifying a phosphine-Ru-based hydrogen transfer catalyst and a sacrificial hydrogen acceptor (**HA**). While typically used in a large excess,[19,20] a suitable hydrogen acceptor would be preferably used in stoichiometric amounts, preventing secondary oxidation reactions or any cross-reactivity in the subsequent 1,2-addition step.

Extensive experimentation of the model reaction of 1-hexanol **1a** with phenylboronic acid **2a** identified that hydrogen transfer between the alcohol and *N*-ethylmaleimide **HA-1**, used as a sacrificial hydrogen acceptor (1.1 equiv), in the presence of the Ru complex bearing *rac*-**binap** (**Ru-1**) that is followed by the 1,2-addition of the aryl nucleophile in the presence of the Ru complex bearing (*S,S*)-**me-bipam** (**Ru-2**) furnished product **3aa** in 96:4 er (*S*:*R*) and 88% yield [80% isolated yield (**Table 4.1,**

entry 1)]. The reaction mixture contained 10% of unreacted alcohol **1a**, while all of the aldehyde intermediate was converted, indicating the excellent efficiency of **Ru-2** in the second step. Control experiments confirmed the role and the required reactivity of both complexes. First, we observed that the stereoselectivity of the product is not influenced by **Ru-1** (**entry 2**), and the complex with a racemic mixture of **binap** can be used. In addition, no product was formed when **Ru-2** was omitted (**Section 4.4.6, entry 14**), indicating that **Ru-1** is completely inactive in the second step of the reaction. Similarly, no product was formed when **Ru-1** was omitted and **Ru-2** was employed in both steps, indicating that **Ru-2** is completely inactive in the oxidation step, even for benzylic alcohols that are typically easily dehydrogenated (**Section 4.4.6, entry 15**).

Table 4.1. Reaction Development[a]



#	variations from the standard cond.	yield (%)	e.r.
1	none	88 (80)[b]	96:4
2	(*R*)- or (*S*)-**binap** used	90-91	96:4
3	**xantphos** instead of **binap**	5	-
4	**dpephos** instead of **binap**	39	96:4
5	**dppf** instead of **binap**	20	94:6
6	no NaOAc	<2	-
7	25 mol% NaOAc	20	-

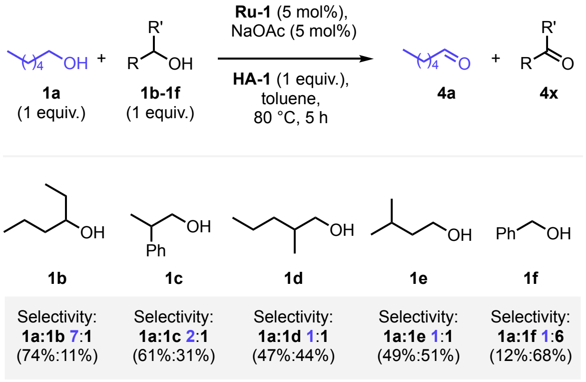
#	variations from the standard cond.	yield (%)	e.r.
8	**Ru-3** instead of **Ru-1**	<2	-
9	**Ru-3** + 10 mol% TBACl (no **Ru-1**)	50	96:4
10	no **HA-1**	<2	-
11	**HA-2** instead of **HA-1**	33	96:4
12	**HA-3** instead of **HA-1**	32	97:3
13	**HA-4** instead of **HA-1**	<2	-
14	**HA-5** instead of **HA-1**	<2	-
15	**HA-6** instead of **HA-1**	<2	-

(a) Standard conditions: **1a** (0.25 mmol), **HA-1** (1.1 equiv), **Ru-1** (5 mol % Ru site, 2.5 mol % Ru dimer), NaOAc (5 mol %), toluene (1 mL), stirred for 5 h at 80 °C (step 1); then **2a** (3 equiv), K_2CO_3 (1 equiv.) in H_2O (0.15 mL), (*S,S*)-**Ru-2** (5 mol % Ru site, 2.5 mol % Ru dimer) in toluene (1 mL) added and stirred for 6 h at 80 °C (step 2). Yields determined by ^1H NMR analysis with an internal standard; enantiomeric ratios (er; *S*:*R*) determined by SFC analysis. (b) Yield of isolated material.

In turn, reactions in the presence of other ligands in place of **binap**, such as **xantphos**, **dpephos**, or **dppf**, occurred in substantially lower yields (≤39%), albeit high enantioselectivity was maintained (**entries 3–5**), underscoring the robustness of catalyst **Ru-2**. It is noteworthy that the presence of sodium acetate in a 1:1 ratio per Ru site is key for the hydrogen transfer activity of **Ru-1**. No reaction or substantially decreased activity was observed in its absence or when the amount was 5-fold increased (**entries 6 and 7**). Similarly, no reaction was observed when **Ru-3**, an analogue of **Ru-1** bearing acetate ligands in place of chloride anions, was used, but the reactivity of **Ru-3** was partially recovered in the presence of additives bearing chloride anions (**entries 8 and 9**). These observations suggest that a mixed-ligand Ru complex might be the active species;[30,31] however, further studies are required to verify this hypothesis. *N*-Ethylmaleimide **HA-1** proved to be by far the most efficient as a sacrificial hydrogen acceptor among those tested. Up to 33% of **3aa** was formed when diethyl maleate or fumarate was used instead, and no reactions occurred with norbornadiene, ethyl methacrylate, or acetone (**entries 11–15**). The lack of an inert atmosphere, other solvents, or lower loadings of the catalysts results in lower yields of the reaction (**Section 4.4.6**).

The hydrogen transfer activity of **Ru-1** was found to be selective toward primary aliphatic alcohols over secondary alcohols, creating the attractive possibility for α-functionalization of primary alcohol moieties in the presence of other alcohol functions. Specifically, the competition experiments between linear **1a** and a series of branched aliphatic alcohols **1b–e** revealed 7:1 kinetic selectivity for the reaction of primary **1a** over (α-branched) secondary **1b** and nearly no selectivity over other primary alcohols, β-branched **1c** and **1d** or γ-branched **1e** (**Scheme 4.2**). In sharp contrast, primary benzylic alcohol **1f** reacted selectively over primary aliphatic alcohol **1a** (6:1 ratio), revealing the highest reactivity of **1f** among alcohols **1a–f**.

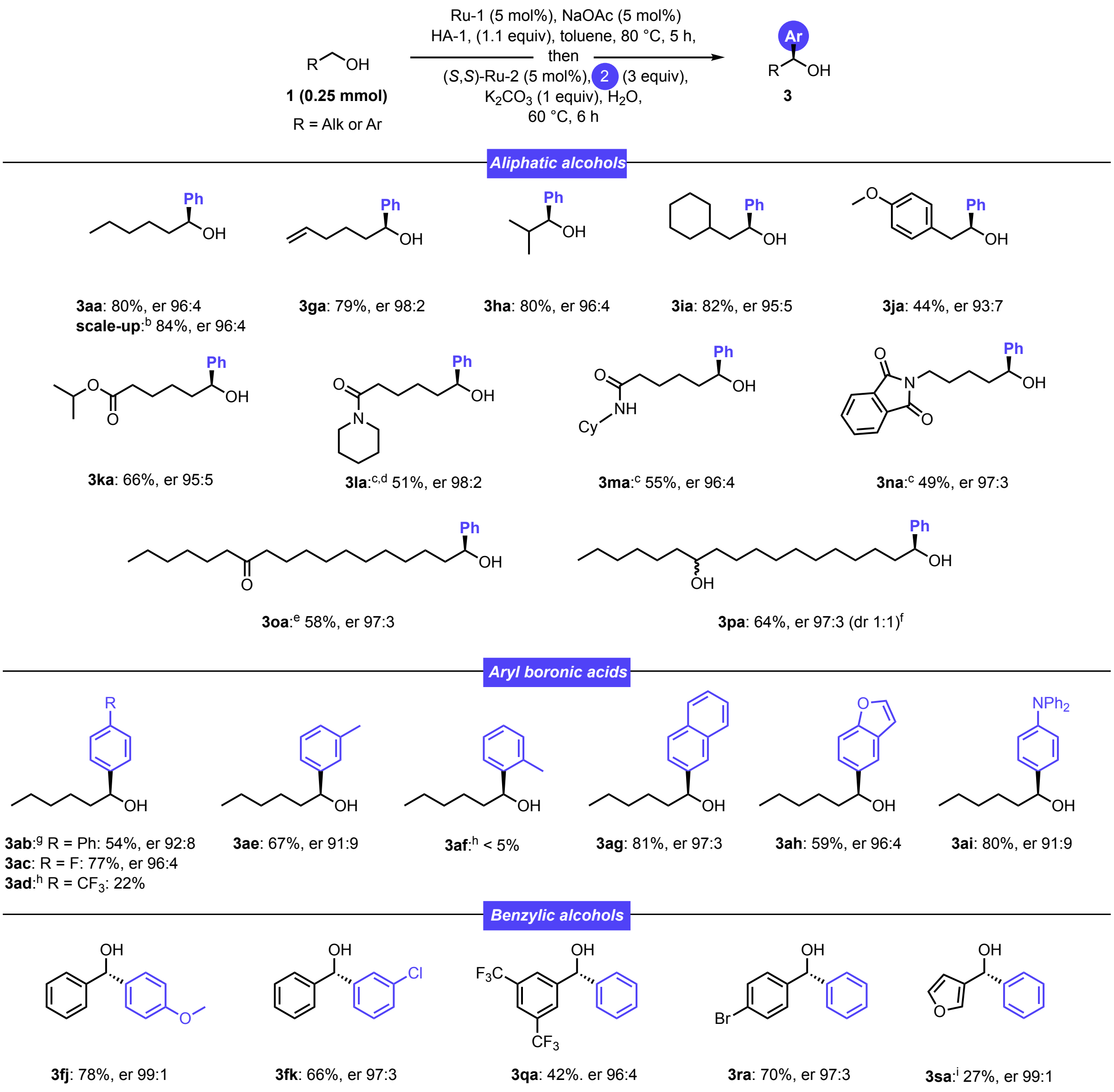
Scheme 4.2 Competition Experiments Revealing the Selectivity of the Hydrogen Transfer from Varied Alcohols by **Ru-1**[a]



(a) Reactions under the standard conditions of step 1 described in footnote a of Table 4.1 (For detail see section 4.4.8); conversions were determined by GC-FID analysis with dodecane as an internal standard.

The established dual-Ru/Ru-catalytic protocol is easily scalable, broadly applicable, and tolerant to many common functional groups (**Scheme 4.3**). A range of primary aliphatic alcohols were converted to SBAs with 93:7–98:2 er and 44–82% yields of isolated material. Reactions for alcohol **1a** on standard (0.25 mmol) and larger (1.75 mmol) scales furnished product **3aa** with the same selectivity (96:4 er) and similar yields (80–84%). Besides **1a**, unsaturated **1g** aliphatic alcohol, β,β-disubstituted alcohol **1h**, and ethanol β-substituted with a cyclohexyl group (**1i**) or an aryl group (**1j**) reacted to form the target products. Starting materials bearing common functional groups, such as a carboxylic ester **1k**, a tertiary amide **1l**, or an NH-containing amide **1m**, are tolerated. Alcohols containing free NH amines or terminal alkynes as well as (homo)allylic alcohols are not compatible (**Section 4.4.7**), due to either side reactions or no conversion in the presence of **Ru-1**. However, the reaction for alcohol-bearing *N*-phthalimide-protected amine **1n** furnished the target product. Most noteworthy are reactions of primary alcohols bearing a ketone **1o** or a secondary alcohol **1o** function, which were not hampered by either competitive 1,2-addition or oxidation but formed the target products in 58–64% yields and with 97:3 stereoselectivity for the formation of the new stereogenic center (racemic diol **1p** was used; hence, product **3pa** was formed as a 1:1 mixture of diastereomers with 97:3 er).

Scheme 4.3 Scope of the Enantioselective Synthesis of Secondary Benzylic Alcohols and Diarylmethanols from Primary Alcohols[a]



(a) For reaction conditions, see footnote (a) of Table 4.1; yields correspond to the isolated material. (b) Reaction conducted on a 1.75 mmol scale. (c) Double loading of **Ru-2** (10 mol % Ru). (d) With alcohol **1** (0.20 mmol), **2** (0.60 mmol). eWith alcohol **1** (0.13 mmol), **2** (0.39 mmol). (f) Racemic diol **1o** was used as the starting material. (g) At 90 °C in step 2. (h) Yield determined by 1H NMR analysis using an internal standard. (i) Sixteen hours in step 1.

The scope of aryl boronic acids for the devised method reflects the previously disclosed reactivity of **Ru-2**,[18,29] indicating no noticeable effect of the **Ru-1** catalyst on the 1,2-addition step. Specifically, a range of aryl boronic acid derivatives bearing either electron-donating or electron-withdrawing substituents in the *para* or *meta* position of the aryl ring reacted to deliver the target products with 91:9–97:3 er and 54–81% yields of isolated material. Noteworthy are previously undisclosed examples of benzofuran **2h** and triphenylamine derivatives **2i** that reacted to form the products with 96:4–91:9 er and 59–80% yields. Reactions for aryl boronic acids bearing either a strongly electron-withdrawing group or steric hindrance in the *ortho* position, such as **2d** or **2f**, respectively, furnished the products in modest yields, indicating the limitations of the protocol imposed by the inherent limitations of **Ru-2**;[18] no additional limitations related to the presence of **Ru-1** were encountered in the 1,2-addition step. Lastly, intrigued by the high reactivity of benzylic alcohol **1f** in hydrogen transfer reactivity mediated by **Ru-2**, we evaluated the established protocol toward enantioselective α-arylation of benzylic alcohols to form diarylmethanols (DAMs), which are known to exhibit potent biological and medicinal properties.[2] Pleasingly, **1f** reacted with electron-rich **2j** or electron-deficient **2k** aryl boronic acids under standard conditions to form chiral DAMs with >97:3 er and 66–78% yields of isolated material. In addition, electron-deficient benzyl alcohols **1q** and **1r** and electron-rich 3-furanmethanol **1s** reacted with **2a** to form the target products with >96:4 er and 27–70% yields of isolated material.

4.3 Conclusion

In conclusion, the disclosed dual-catalytic protocol enables the formal enantioselective arylation of the α-C–H bond of primary aliphatic and benzylic alcohols with varied aryl boronic acids. Importantly, the method tolerates starting materials and nucleophilic reagents bearing a range of common functional groups, including secondary alcohols and ketones. The one-pot strategy offers advantages over tedious and wasteful stepwise approaches,[32-35] especially for sequences occurring through the aldehyde intermediates that are often prone to side reactions. In a greater perspective, the study demonstrates that sequential catalysis complements current strategies for the functionalization of strong C–H bonds that require enforcing conditions with limited applicability in fine-chemical synthesis or those that are burdened with limited control of chemo-, regio-, or stereoselectivity.

4.4 Experimental section

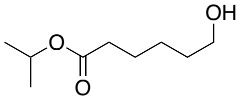
4.4.1 General information

Unless stated otherwise, all reactions and manipulations were conducted on a laboratory bench or in a well-ventilated fume hood in air with reagent grade solvents. Reactions under an inert gas atmosphere were carried out in oven-dried glassware in a nitrogen-filled glovebox or by standard Schlenk techniques under nitrogen. Unless noted otherwise, all reagents and solvents were purchased from commercial suppliers and used without further purification. (*S*,*S*)-BIPAM was prepared according to the literature procedure.[36,37] Ru(*p*-cymene)(OAc)$_2$ was prepared according to the literature procedure.[38]For experiments under an inert gas atmosphere, dry solvents like dichloromethane (DCM), tetrahydrofuran (THF), toluene, hexane, diethyl ether (Et$_2$O), dioxane, acetonitrile, and 1,4-xylene were purchased from commercial suppliers and used as received. Water was degassed by being purged with nitrogen for 30 min. Column chromatography was carried out with the aid of a CombiFlash EZ Prep Chromatography System with integrated ELSD using RediSep Rf (Gold) Silica Gel Disposable Flash columns. TLC visualization was carried out with ultraviolet light (254 nm), followed by staining with a 1% aqueous KMnO$_4$ solution. NMR spectra were acquired on the 400 or 500 MHz Bruker instrument at the Institute of Science and Supramolecular Engineering (ISIS), University of Strasbourg. NMR spectra were processed using MestReNova version 14.2. Chemical shifts are reported in parts per million and referenced to residual solvent peaks or tetramethylsilane (TMS). Coupling constants are reported in hertz. SFC analysis was conducted using an Agilent SFC 1260 Infinity II instrument connected to Agilent MSD XT mass spectrometry equipment. Chiral SFC separation was achieved using Chiralpak SFC {100 mm × 3 mm [inside diameter (ID)] × 3 µm} columns. GC-FID analysis was performed either on a Shimadzu GC-2010 Plus instrument equipped with a SH-Rxi-5MS column [25 m × 0.20 mm (ID) × 0.33 µm film] connected to a FID detector or on a ThermoFisher TRACE 1300 instrument equipped with a HP-5 column [25 m × 0.20 mm (ID) × 0.33 µm film] for achiral analysis or with an CP-Chiralsil-Dex CB column (30 m × 0.25 mm × 0.25 µm film) for chiral analysis, connected to a FID detector. GC-MS analysis was performed on a Shimadzu QP2020 (EI) instrument equipped with a SH-Rxi-5MS column [25 m × 0.20 mm (ID) × 0.33 µm film]. GC and NMR yields were calculated using 1,3,5-trimethoxybenzene or dodecane as the internal standard. GC yields were corrected for response factors for all compounds. Optical rotations were measured on a PerkinElmer Precisely/model-341 polarimeter operating at the sodium D line with a 100 mm path length cell. Electrospray ionization high-resolution mass spectra (ESI-HRMS) were recorded on a ThermoFisher Ultimate3000 instrument with a Scientific Vanquish Flex UHPLC instrument with a ThermoFisher Orbitrap: Exactive Plus with Extend Mass Range: Source HESI II (at ISIS).

4.4.2 Starting materials

Starting materials **1a–j** and **1q–s** were purchased from common chemical suppliers and used without further purification. Other starting materials were prepared and characterized as described below.

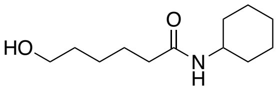
Isopropyl 6-Hydroxyhexanoate (1k)



Compound **1k** was prepared from caprolactone and isopropanol according to the literature procedure.[9] The NMR data match those of the reported molecule.[9]

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.94 (hept, *J* = 6.3 Hz, 1H), 3.58 (t, *J* = 6.5 Hz, 2H), 2.21 (t, *J* = 7.5 Hz, 2H), 1.63–1.48 (m, 4H), 1.43–1.24 (m, 3H), 1.16 (d, *J* = 6.2 Hz, 6H).

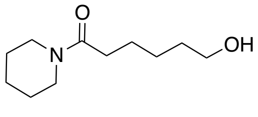
N-Cyclohexyl-6-hydroxyhexanamide (1l)



Compound **1l** was prepared from cyclohexylamine and caprolactone according to the literature procedure. [9] The NMR data match those of the reported molecule.[9]

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.20 (bs, 1H), 3.76–3.64 (m, 1H), 3.59 (t, *J* = 6.5 Hz, 2H), 2.08 (t, *J* = 7.5 Hz, 2H), 1.88–1.80 (m, 2H), 1.68–1.47 (m, 8H), 1.41–1.27 (m, 4H), 1.14–0.94 (m, 3H).

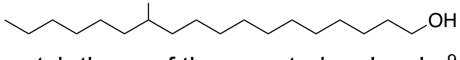
6-Hydroxy-1-(piperidin-1-yl)hexan-1-one (1m)



Compound **1m** was prepared from piperidine and caprolactone according to the literature procedure. [9] The NMR data match those of the reported molecule.[9]

^{1}H NMR (400 MHz, **$CDCl_3$**): δ 3.63–3.56 (m, 2H), 3.51–3.45 (m, 2H), 3.35–3.29 (m, 2H), 2.26 (t, *J* = 7.5 Hz, 2H), 1.64–1.42 (m, 11H), 1.40–1.30 (m, 2H).

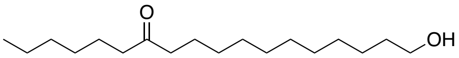
rac-Octadecane-1,12-diol (1p)



Compound **1p** was prepared according to the literature procedure from *rac*-12-hydroxystearic acid. [9] The NMR data match those of the reported molecule.[9]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (t, *J* = 6.6 Hz, 2H), 3.62–3.56 (m, 1H), 1.67–1.51 (m, 2H), 1.51–1.20 (m, 30H), 1.00–0.82 (m, 3H).

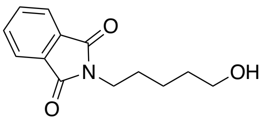
18-Hydroxyoctadecan-7-one (1o)



Compound **1o** was prepared from **1p** according to the literature procedure[9] The NMR data match those of the reported molecule.[9]

^{1}H NMR (500 MHz, $CDCl_3$**)**: δ 3.57 (t, *J* = 6.7 Hz, 2H), 2.31 (t, *J* = 7.4 Hz, 4H), 1.68–1.35 (m, 9H), 1.35–1.07 (m, 18H), 0.94–0.66 (m, 3H).

2-(5-Hydroxypentyl)isoindoline-1,3-dione (1n)



Compound **1n** was prepared from phthalic anhydride and 5-aminopentan-1-ol according to the literature procedure.[39] The NMR data match those of the reported molecule.[39]

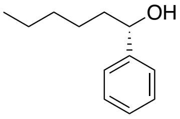
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.64 (dd, *J* = 5.5, 3.1 Hz, 2H), 3.63 (t, *J* = 7.2 Hz, 2H), 3.57 (t, *J* = 6.5 Hz, 2H), 1.72–1.60 (m, 2H), 1.60–1.50 (m, 2H), 1.43–1.30 (m, 3H).

4.4.3 General procedure for α-arylation of alcohols

In a nitrogen-filled glovebox, a solution of **Ru-1** and sodium acetate was prepared by allowing $[Ru(p\text{-cymene})Cl_2]_2$ (0.025 equiv, 0.0063 mmol, 3.8 mg), *rac*-**binap** (0.05 equiv, 0.013 mmol, 7.8 mg), and sodium acetate (0.05 equiv, 0.013 mmol, 1.0 mg) to stir in toluene (1 mL) at 80 °C for 1 h. Next, a 4 mL screw cap vial equipped with a stirring bar was charged with *N*-ethylmaleimide (34.4 mg, 1.1 equiv, 0.275 mmol), the solution of **Ru-1** and sodium acetate, and an alcohol (1 equiv, 0.25 mmol). The vial was then sealed with a Teflon-lined screw cap and placed in a preheated heating block at 80 °C, and the contents were allowed to stir for 5 h at 800 rpm. {In the meantime, a solution of **Ru-2** was prepared by allowing $[Ru(p\text{-cymene})Cl_2]_2$ (0.025 equiv, 0.0063 mmol, 3.8 mg) and **me-bipam** (0.055 equiv, 0.0138 mmol, 10.5 mg) to stir in toluene (1 mL) for 0.5 h at room temperature. Also, a solution of K_3CO_3 (1 equiv, 0.25 mmol, 34.5 mg) in water (150 µL) was prepared.} Upon cooling to room temperature, the vial was opened, and the solution of **Ru-2**, the solution of K_3CO_3, and an aryl boronic acid (3 equiv, 0.75 mmol) were added. The vial was then resealed with the screw cap, removed from the glovebox, and placed in a preheated heating block at 60 °C, and the contents were allowed to stir for 6 h at 800 rpm. The reaction mixture was allowed to cool to room temperature. The mixture was diluted with DCM (50 mL), followed by the addition of Celite (5 g). The volatiles were removed under reduced pressure. The solid residue was subjected to flash column chromatography on silica gel (12 g), conducted with the aid of a CombiFlash EZ Pack instrument using a mixture of petroleum ether and ethyl acetate (typically with a gradient from 100:0 to 85:15) as the eluent. The fractions containing the product (based on TLC and/or GC analysis) were combined, and the solvent was evaporated, yielding the product.

4.4.4 Characterization of products

(*S*)-1-Phenylhexan-1-ol (3aa)



Compound **3aa** was prepared according to the general procedure with (*S,S*)-**me-bipam** by reaction of hexan-1-ol (0.25 mmol, 31.4 µL) with phenyl boronic acid (0.75 mmol, 91.4 mg) and isolated by column chromatography (silica gel, petroleum ether/ethyl acetate from 100:0 to 85:15) to give a volatile colorless oil in 80% yield (35.6 mg). The analytical data are consistent with those previously reported.[18]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.32 (m, 4H), 7.32–7.23 (m, 1H), 4.67 (dd, J = 7.6, 5.8 Hz, 1H), 1.86–1.65 (m, 3H), 1.49–1.35 (m, 1H), 1.34–1.28 (m, 5H), 0.96–0.81 (m, 3H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 145.0, 128.5, 127.5, 125.9, 74.8, 39.1, 31.8, 25.6, 22.6, 14.1.

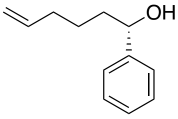
HRMS (ESI$^+$-Orbitrap) calcd for $C_{12}H_{17}$: *m/z* 161.1325 $[M + H – H_2O]^+$, found *m/z* 161.1327.

SFC (Chiralpak IG-3, 3:97 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 3.18 min [major, (*S*)-**3aa**], 3.51 min [minor, (*R*)-**3aa**].

Specific rotation: $[\alpha]_D^{23}$ −28.8° (*c* 0.98, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er. The absolute configuration was determined by comparison of the sign and the value of the optical rotation with those reported in the literature for the opposite enantiomer [$[\alpha]_D^{20}$ +31.6° (*c* 1.0, $CHCl_3$), 96:4].[18]

For scale-up, compound **3aa** was also prepared on a 1.75 mmol scale according to the general procedure with (*S,S*)-**me-bipam** by reaction of hexan-1-ol (1.75 mmol, 219.6 µL) with phenyl boronic acid (5.25 mmol, 640.1 mg) and isolated by column chromatography (silica gel, petroleum ether/ethyl acetate from 100:0 to 85:15) to give a volatile colorless oil in 84% yield (262.4 mg) with the same NMR data and 96:4 er.

(*S*)-1-Phenylhex-5-en-1-ol (3ga)



Compound **3ga** was prepared according to the general procedure with (*S,S*)-**me-bipam** by reaction of hexen-1-ol (0.25 mmol, 30.0 µL) with phenyl boronic acid (0.75 mmol, 91.4 mg) and isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a volatile colorless oil in 79% yield (35.0 mg). The analytical data are consistent with those previously reported.[40]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.31 (m, 4H), 7.31–7.24 (m, 1H), 5.84–5.72 (m, 1H), 5.03–4.91 (m, 2H), 4.68 (dd, J = 7.6, 5.7 Hz, 1H), 2.14–2.03 (m, 2H), 1.89–1.67 (m, 3H), 1.62–1.47 (m, 1H), 1.45–1.33 (m, 1H).

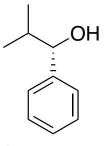
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 144.8, 138.6, 128.5, 127.6, 125.9, 114.7, 74.6, 38.5, 33.6, 25.1.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{12}H_{15}$: *m/z* 159.1168 $[M + H – H_2O]^+$, found *m/z* 159.1172.

SFC (Chiralpak IG-3, 5:95 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 2.44 min [major, (*S*)-**3ga**], 2.65 min [minor, (*R*)-**3ga**].

Specific rotation: $[\alpha]_D^{23}$ −41.2° (*c* 1.0, $CHCl_3$) for an enantiomerically enriched sample of 98:2 er. The absolute configuration was determined by comparison of the sign and the value of the optical rotation with those reported in the literature for the opposite enantiomer [$[\alpha]_D^{20}$ +38.0° (*c* 1.1, $CHCl_3$), 92:8].[40]

(*S*)-2-Methyl-1-phenylpropan-1-ol (3ha)



Compound **3ha** was prepared according to the general procedure with (*S,S*)-**me-bipam** by reaction of 2-methylpropan-1-ol (0.25 mmol, 23.1 µL) with phenyl boronic acid (0.75 mmol, 91.4 mg) and isolated by column chromatography (silica gel, *n*-pentane to dichloromethane) to give a volatile colorless oil in 80% yield (35.0 mg). The analytical data are consistent with those previously reported.[41]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.30 (m, 4H), 7.29–7.27 (m, 1H), 4.37 (d, J = 6.9 Hz, 1H), 1.96 (dq, J = 13.4, 6.7 Hz, 1H), 1.78 (bs, 1H), 1.01 (d, J = 6.7 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H).

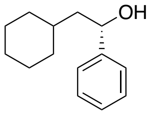
^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): δ 143.6, 128.2, 127.5, 126.6, 80.1, 35.3, 19.0, 18.3.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{10}H_{13}$: *m*/*z* 133.1012 [M + H – H_2O]$^+$, found *m*/*z* 133.1019.

SFC (Chiralpak IG-3, 2.5:97.5 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 3.44 min [major, (*S*)-**3ha**], 3.19 min [minor, (*R*)-**3ha**].

Specific rotation: $[\alpha]_D^{23}$ −39.4° (*c* 0.97, Et_2O) for an enantiomerically enriched sample of 96:4 er. The absolute configuration was determined by comparison of the sign and the value of the optical rotation with those reported in the literature for the opposite enantiomer [$[\alpha]_D^{25}$ +39.3° (*c* 1.25, Et_2O), 94:6].[41]

(*S*)-2-Cyclohexyl-1-phenylethan-1-ol (3ia)



Compound **3ia** was prepared according to the general procedure with (*S,S*)-**me-bipam** by reaction of 2-cyclohexylethan-1-ol (0.25 mmol, 34.9 µL) with phenyl boronic acid (0.75 mmol, 91.4 mg) and isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white amorphous solid in 82% yield (42.0 mg). The analytical data are consistent with those previously reported.[42]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.31 (m, 4H), 7.31–7.24 (m, 1H), 4.79 (dd, *J* = 8.8, 5.1 Hz, 1H), 1.86–1.75 (m, 1H), 1.78–1.48 (m, 7H), 1.46–1.34 (m, 1H), 1.30–1.09 (m, 3H), 1.03–0.86 (m, 2H).

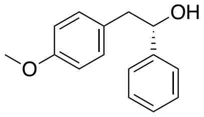
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 145.4, 128.5, 127.5, 125.8, 72.1, 47.1, 34.3, 34.0, 32.9, 26.6, 26.3, 26.2.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{14}H_{19}$: *m*/*z* 187.1481 [M + H – H_2O]$^+$, found *m*/*z* 187.1438.

SFC (Chiralpak IA-3, 5:95 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 4.15 min [major, (*S*)-**3ia**], 4.85 min [minor, (*R*)-**3ia**].

Specific rotation: $[\alpha]_D^{23}$ −21.7° (*c* 1.0, $CHCl_3$) for an enantiomerically enriched sample of 95:5 er. The absolute configuration was determined by analogy to compound (*S*)-**3aa**.

(*S*)-2-(4-Methoxyphenyl)-1-phenylethan-1-ol (3ja)



Compound **3ja** was prepared according to the general procedure with (*S,S*)-**me-bipam** by reaction of 2-(4-methoxyphenyl)ethan-1-ol (0.25 mmol, 34.6 µL) with phenyl boronic acid (0.75 mmol, 91.4 mg) and isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white solid in 44% yield (25.3 mg). The analytical data are consistent with those previously reported.[43]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.33 (m, 4H), 7.31–7.27 (m, 1H), 7.14–7.08 (m, 2H), 6.88–6.81 (m, 2H), 4.86 (dd, *J* = 8.5, 4.8 Hz, 1H), 3.80 (s, 3H), 3.03–2.89 (m, 2H), 1.63–1.46 (br, 1H).

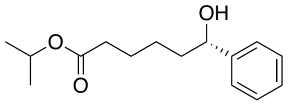
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 158.4, 143.9, 130.5, 130.0, 128.4, 127.6, 125.9, 114.0, 75.4, 55.3, 45.2.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{15}H_{15}O$: *m*/*z* 211.1117 [M + H – H_2O]$^+$, found *m*/*z* 211.1119.

SFC (Chiralpak IH-3, 5:95 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 5.96 min [major, (*S*)-**3ja**], 7.47 min [minor, (*R*)-**3ja**].

Specific rotation: $[\alpha]_D^{23}$ −2.8° (*c* 0.87, $CHCl_3$) for an enantiomerically enriched sample of 93:7 er. The absolute configuration was determined by comparison of the sign and the value of the optical rotation with those reported in the literature for the opposite enantiomer [$[\alpha]_D^{22}$ +3.8° (*c* 1.4, $CHCl_3$), 94:6].[43]

(*S*)-Isopropyl 6-Hydroxy-6-phenylhexanoate (3ka)



Compound **3ka** was prepared according to the general procedure with (*S,S*)-**me-bipam** by reaction of isopropyl 6-hydroxyhexanoate (**1k**, 0.25 mmol, 43.6 mg) with phenyl boronic acid (0.75 mmol, 91.4 mg) and isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:25) to give a white, amorphous solid in 66% yield (41.1 mg).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.32 (m, 4H), 7.31–7.27 (m, 1H), 4.98 (hept, *J* = 6.3 Hz, 1H), 4.68 (dd, *J* = 7.6, 5.7 Hz, 1H), 2.25 (t, *J* = 7.5 Hz, 2H), 1.93–1.78 (m, 1H), 1.73–1.53 (m, 4H), 1.51–1.39 (m, 2H), 1.28–1.17 (m, 6H).

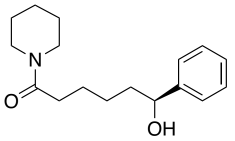
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 173.4, 144.8, 128.6, 127.7, 126.0, 74.5, 67.6, 38.8, 34.7, 25.4, 25.0, 22.0.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{15}H_{22}O_2$: *m*/*z* 233.1536 [M + H – H_2O]$^+$, found *m*/*z* 233.1541.

SFC (Chiralpak IC-3, 5:95 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 6.55 min [major, (*S*)-**3ka**], 7.24 min [minor, (*R*)-**3ka**].

Specific rotation: $[\alpha]_D^{23}$ −19.6° (*c* 1.02, $CHCl_3$) for an enantiomerically enriched sample of 95:5 er. The absolute configuration was determined by analogy to compound (*S*)-**3aa**.

Hydroxy-6-phenyl-1-(piperidin-1-yl)hexan-1-one (3la)



Compound **3la** was prepared according to the general procedure with (*S,S*)-**me-bipam**, except the loading of **Ru-2** was doubled, by reaction of 6-hydroxy-1-(piperidin-1-yl)hexan-1-one (**1l**, 0.20 mmol, 39.8 mg) with phenyl boronic acid (0.60 mmol, 73.2 mg) and isolated by column chromatography (silica gel, petroleum ether to ethyl acetate) to give a greenish oil in 51% yield (28.3 mg).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.31 (m, 4H), 7.30–7.26 (m, 1H), 4.70 (dd, *J* = 8.0, 5.5 Hz, 1H), 3.52 (t, *J* = 5.5 Hz, 2H), 3.36 (t, *J* = 5.4 Hz, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.20 (s, 1H), 1.90–1.58 (m, 6H), 1.56–1.42 (m, 5H), 1.41–1.27 (m, 1H).

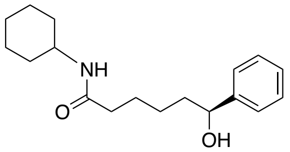
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 171.3, 145.0, 128.4, 127.4, 125.9, 74.1, 46.7, 42.7, 38.9, 33.2, 26.5, 25.7, 25.6, 25.0, 24.6.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{17}H_{24}NO$: *m*/*z* 258.1852 [M + H – H_2O]$^+$, found *m*/*z* 258.1857.

SFC (Chiralpak IA-3, 13:87 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 6.79 min [major, (*S*)-**3la**], 7.15 min [minor, (*R*)-**3la**].

Specific rotation: $[\alpha]_D^{23}$ −12.6° (*c* 1.02, $CHCl_3$) for an enantiomerically enriched sample of 98:2 er. The absolute configuration was determined by analogy to compound (*S*)-**3aa**.

(*S*)-*N*-Cyclohexyl-6-hydroxy-6-phenylhexanamide (3ma)



Compound **3ma** was prepared according to the general procedure with (*S,S*)-**me-bipam**, except the loading of **Ru-2** was doubled, by reaction of *N*-cyclohexyl-6-hydroxyhexamide (**1m**, 0.25 mmol, 53.3 mg) with phenyl boronic acid (0.75 mmol, 91.4 mg) and isolated by column chromatography (silica gel, petroleum ether to ethyl acetate) to give a greenish amorphous solid in 55% yield (39.6 mg).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.31 (m, 4H), 7.31–7.23 (m, 1H), 5.24 (d, *J* = 8.3 Hz, 1H), 4.68 (dd, *J* = 7.7, 5.6 Hz, 1H), 3.88–3.59 (m, 1H), 2.18–2.06 (m, 2H), 2.04–1.52 (m, 11H), 1.52–1.28 (m, 3H), 1.21–0.87 (m, 3H).

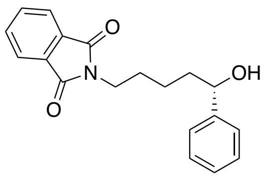
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 171.9, 144.8, 128.5, 127.5, 125.9, 74.3, 48.1, 38.7, 36.9, 33.3, 25.6, 25.5, 25.4, 24.9.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{18}H_{26}NO$: *m*/*z* 272.2009 $[M + H – H_2O]^+$, found *m*/*z* 272.2011.

SFC (Chiralpak IC-3, 20:80 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 6.69 min [major, (*S*)-**3ma**], 8.15 min [minor, (*R*)-**3ma**].

Specific rotation: $[\alpha]_D^{23}$ −16.8° (*c* 1.0, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er. The absolute configuration was determined by analogy to compound (*S*)-**3aa**.

(*S*)-2-(5-Hydroxy-5-phenylpentyl)isoindoline-1,3-dione (3na)



Compound **3na** was prepared according to the general procedure with (*S,S*)-**me-bipam**, except the loading of **Ru-2** was doubled, by reaction of 2-(5-hydroxypentyl)isoindoline-1,3-dione (**1n**, 0.25 mmol, 58.3 mg) with phenyl boronic acid (0.75 mmol, 91.4 mg) and isolated by column chromatography (silica gel, petroleum ether to ethyl acetate) to give a greenish amorphous solid in 49% yield (37.7 mg).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87–7.79 (m, 2H), 7.75–7.66 (m, 2H), 7.39–7.29 (m, 4H), 7.29–7.21 (m, 1H), 4.76–4.59 (m, 1H), 3.76–3.58 (m, 2H), 2.02–1.63 (m, 5H), 1.59–1.29 (m, 2H).

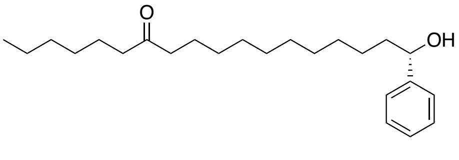
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 168.5, 144.7, 133.9, 132.1, 128.5, 127.5, 125.8, 123.2, 74.3, 38.5, 37.8, 28.4, 23.1.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{19}H_{18}NO_2$: *m*/*z* 292.1332 $[M + H – H_2O]^+$, found *m*/*z* 292.1333.

SFC (Chiralpak IC-3, 10:90 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 6.73 min [major, (*S*)-**3na**], 7.13 min [minor, (*R*)-**3na**].

Specific rotation: $[\alpha]_D^{23}$ −14.5° (*c* 1.0, $CHCl_3$) for an enantiomerically enriched sample of 97:3 er. The absolute configuration was determined by analogy to compound (*S*)-**3aa**.

(*S*)-18-Hydroxy-18-phenyloctadecan-7-one (3oa)



Compound **3oa** was prepared according to the general procedure with (*S,S*)-**me-bipam** by reaction of 18-hydroxyhexadecan-7-one (**1o**, 0.13 mmol, 37.0 mg) with phenyl boronic acid (0.39 mmol, 47.6 mg) and isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:25) to give a white amorphous solid in 58% yield (27.1 mg).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.31 (m, 4H), 7.30–7.27 (m, 1H), 4.66 (dd, *J* = 7.6, 5.8 Hz, 1H), 2.37 (td, *J* = 7.5, 2.4 Hz, 4H), 2.04–1.62 (m, 2H), 1.67–1.52 (m, 4H), 1.47–1.37 (m, 1H), 1.34–1.10 (m, 20H), 0.95–0.72 (m, 3H).

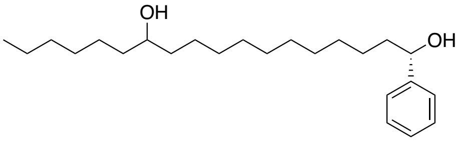
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 211.9, 145.0, 128.4, 127.5, 125.9, 74.7, 42.8, 42.8, 39.1, 31.6, 29.5, 29.5, 29.5, 29.4, 29.4, 29.3, 29.0, 25.8, 23.9, 23.9, 22.5, 14.1.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{24}H_{39}O$: *m*/*z* 343.2995 [M + H – H_2O]$^+$, found *m*/*z* 343.2998.

SFC (Chiralpak IA-3, 8.5:91.5 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 6.41 min [major, (*S*)-**3oa**], 6.01 min [minor, (*R*)-**3oa**].

Specific rotation: $[\alpha]_D^{24}$ −12.0° (*c* 0.99, $CHCl_3$) for an enantiomerically enriched sample of 97:3 er. The absolute configuration was determined by analogy to compound (*S*)-**3aa**.

(1*S*,12*R*/*S*)-1-Phenyloctadecane-1,12-diol (3pa)



Compound **3pa** was prepared according to the general procedure with (*S,S*)-**me-bipam** by reaction of *rac*-octadecane-1,12-diol (*rac*-**1p**, 0.25 mmol, 71.6 mg) with phenyl boronic acid (0.75 mmol, 91.4 mg) and isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:25) to give a white amorphous solid in 64% yield (58.0 mg). The isolated material contains both diastereomers that cannot be distinguished by ^{1}H and ^{13}C NMR spectroscopy. The diastereomeric ratio, which reflects the stereoselectivity of the formation of the new stereogenic center, was determined by SFC analysis for the diester of the *p*-nitrobenzoic acid derivative of **3pa** [**3pa′**, 1-phenyloctadecane-1,12-diylbis(4-nitrobenzoate)], which was prepared following a literature procedure.[44]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.32 (m, 4H), 7.31–7.26 (m, 1H), 4.66 (dd, *J* = 7.6, 5.8 Hz, 1H), 3.62–3.54 (m, 1H), 2.01–1.63 (m, 2H), 1.55–1.36 (m, 7H), 1.36–1.17 (m, 23H), 0.97–0.77 (m, 3H).

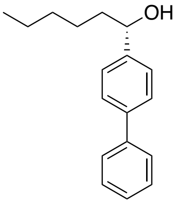
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 145.0, 128.4, 127.5, 125.9, 74.7, 72.1, 39.1, 37.5, 37.5, 31.9, 29.7, 29.6, 29.6, 29.6, 29.5, 29.5, 29.4, 25.8, 25.7, 25.6, 22.6, 14.1.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{24}H_{41}O$: *m*/*z* 327.3046 [M + H – H_2O]$^+$, found *m*/*z* 327.3046.

SFC of diester derivative (Chiralpak IA-3, 20:80 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 254 nm): t_R = 2.44 min [major, (*S*)-**3pa′**], 2.65 min [minor, (*R*)-**3pa′**].

Specific rotation: $[\alpha]_D^{24}$ −14.1° (*c* 1.01, $CHCl_3$) for a sample containing a 97:3 mixture of (1*S*,12*R*/*S*)-**3pa** and (1*R*,12*R*/*S*)-**3pa**. The absolute configuration of the newly formed stereocenter was determined by analogy to compound (*S*)-**3aa**.

(*S*)-1-([1,1′-Biphenyl]-4-yl)hexan-1-ol (3ab)



Compound **3ab** was prepared according to the general procedure with (*S,S*)-**me-bipam**, except the reaction mixture was heated to 90 °C during the hydroarylation step instead of 60 °C, by reaction of hexan-1-ol (0.25 mmol, 31.4 μL) with 2 4-biphenylboronic acid (0.75 mmol, 148.5 mg) and isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white amorphous solid in 54% yield (32.4 mg). The analytical data are consistent with those previously reported.[18]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68–7.53 (m, 4H), 7.51–7.40 (m, 4H), 7.39–7.31 (m, 1H), 4.72 (t, *J* = 6.7 Hz, 1H), 1.91–1.67 (m, 3H), 1.46 (m, 1H), 1.37–1.22 (m, 5H), 0.88 (m, 3H).

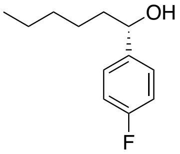
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 144.0, 140.9, 140.4, 128.8, 127.3, 127.2, 127.1, 126.4, 74.5, 39.1, 31.8, 25.6, 22.6, 14.1.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{18}H_{21}$: *m*/*z* 237.1638 [M + H – H_2O]$^+$, found *m*/*z* 237.1637.

SFC (Chiralpak IG-3, 10:90 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 4.52 min [major, (*S*)-**3ab**], 5.65 min [minor, (*R*)-**3ab**].

Specific rotation: $[\alpha]_D^{23}$ −17.7° (*c* 1.0, $CHCl_3$) for an enantiomerically enriched sample of 92:8 er. The absolute configuration was determined by comparison of the sign and the value of the optical rotation with those reported in the literature for the opposite enantiomer [$[\alpha]_D^{20}$ +23.4° (*c* 0.94, $CHCl_3$), 95:5].[18]

(*S*)-1-(4-Fluorophenyl)hexan-1-ol (3ac)



Compound **3ac** was prepared according to the general procedure with (*S,S*)-**me-bipam** by reaction of hexan-1-ol (0.25 mmol, 31.4 μL) with 4-fluorophenyl boronic acid (0.75 mmol, 104.9 mg) and isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white amorphous solid in 77% yield (37.9 mg). The analytical data are consistent with those previously reported.[18]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.28 (m, 2H), 7.07–6.98 (m, 2H), 4.65 (dd, *J* = 7.5, 5.9 Hz, 1H), 1.87–1.73 (m, 2H), 1.71–1.59 (m, 1H), 1.47–1.35 (m, 1H), 1.29 (dt, *J* = 7.0, 3.7 Hz, 5H), 0.92–0.82 (m, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 162.1 (d, *J* = 245.1 Hz), 140.6 (d, *J* = 3.1 Hz), 127.5 (d, *J* = 8.0 Hz), 115.2 (d, *J* = 21.3 Hz), 74.1 (d, *J* = 0.7 Hz), 39.2 (d, *J* = 0.8 Hz), 31.7, 25.5, 22.6, 14.0.

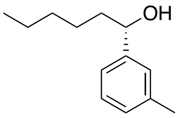
^{19}F NMR (471 MHz, $CDCl_3$): δ −115.25, −–115.34 (m).

HRMS (ESI$^+$-Orbitrap) calcd for $C_{12}H_{16}F$: *m*/*z* 179.1231 [M + H – H_2O]$^+$, found *m*/*z* 179.1230.

SFC (Chiralpak IG-3, 5:95 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 1.83 min [major, (*S*)-**3ac**], 2.03 min [minor, (*R*)-**3ac**].

Specific rotation: $[\alpha]_D^{23}$ −26.6° (*c* 0.98, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er. The absolute configuration was determined by comparison of the sign and the value of the optical rotation with those reported in the literature for the opposite enantiomer [$[\alpha]_D^{20}$ +29.3° (*c* 1.03, $CHCl_3$), 96:4 er].[18]

(*S*)-1-(3-Methylphenyl)hexan-1-ol (3ae)



Compound **3ae** was prepared according to the general procedure with (*S,S*)-**me-bipam** by reaction of hexan-1-ol (0.25 mmol, 31.4 µL) with 3-methylphenyl boronic acid (0.75 mmol, 109.5 mg) and isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a volatile colorless oil in 67% yield (32.4 mg). The analytical data are consistent with those previously reported.[18]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (t, *J* = 7.6 Hz, 1H), 7.11–6.88 (m, 3H), 4.56 (dd, *J* = 7.6, 5.7 Hz, 1H), 2.29 (s, 3H), 1.80–1.44 (m, 3H), 1.41–1.31 (m, 1H), 1.28–1.14 (m, 5H), 0.84–0.77 (m, 3H).

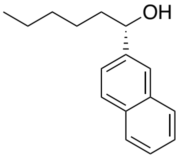
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 145.0, 138.1, 128.3, 128.2, 126.6, 123.0, 74.8, 39.1, 31.8, 25.6, 22.6, 21.5, 14.1.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{13}H_{19}$: *m/z* 175.1481 $[M + H – H_2O]^+$, found *m/z* 175.1486.

SFC (Chiralpak ID-3, 5:95 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 1.72 min [major, (*S*)-**3ae**], 1.47 min [minor, (*R*)-**3ae**].

Specific rotation: $[\alpha]_D^{24}$ −17.2° (*c* 0.91, $CHCl_3$) for an enantiomerically enriched sample of 91:9 er. The absolute configuration was determined by comparison of the sign and the value of the optical rotation with those reported in the literature for the opposite enantiomer [$[\alpha]_D^{20}$ +19.6° (*c* 0.32, $CHCl_3$), 97:3].[18]

(*S*)-1-(Naphthalen-2-yl)hexan-1-ol (3ag)



Compound **3ag** was prepared according to the general procedure with (*S,S*)-**me-bipam** by reaction of hexan-1-ol (0.25 mmol, 31.4 µL) with 2-naphthyl boronic acid (0.75 mmol, 129.0 mg) and isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white amorphous solid in 81% yield (46.0 mg). The analytical data are consistent with those previously reported.[18]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92–7.66 (m, 4H), 7.52–7.42 (m, 3H), 4.84 (dd, *J* = 7.4, 5.9 Hz, 1H), 1.94–1.75 (m, 3H), 1.59–1.37 (m, 1H), 1.37–1.29 (m, 5H), 0.96–0.82 (m, 3H).

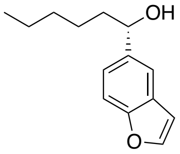
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 142.3, 133.3, 133.0, 128.3, 127.9, 127.7, 126.1, 125.8, 124.6, 124.1, 74.8, 39.0, 31.8, 25.5, 22.6, 14.1.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{16}H_{19}$: *m/z* 211.1481 $[M + H – H_2O]^+$, found *m/z* 211.1488.

SFC (Chiralpak ID-3, 5:95 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 4.05 min [major, (*S*)-**3ag**], 3.85 min [minor, (*R*)-**3ag**].

Specific rotation: $[\alpha]_D^{23}$ −23.9° (*c* 1.0, $CHCl_3$) for an enantiomerically enriched sample of 97:3 er. The absolute configuration was determined by comparison of the sign and the value of the optical rotation with those reported in the literature for the opposite enantiomer [$[\alpha]_D^{20}$ +27.8° (*c* 1.43, $CHCl_3$), 98:2].[18]

(*S*)-1-(Benzofuran-5-yl)hexan-1-ol (3ah)



Compound **3ah** was prepared according to the general procedure with (*S,S*)-**me-bipam** by reaction of hexan-1-ol (0.25 mmol, 31.4 µL) with benzofuran-5-yl boronic acid (0.75 mmol, 121.5 mg) and isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white amorphous solid in 59% yield (32.4 mg).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 2.2 Hz, 1H), 7.58 (d, *J* = 1.8 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.29 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.76 (dd, *J* = 2.2, 1.0 Hz, 1H), 4.76 (dd, *J* = 7.5, 6.0 Hz, 1H), 1.97–1.67 (m, 3H), 1.49–1.36 (m, 1H), 1.36–1.22 (m, 5H), 0.94–0.83 (m, 3H).

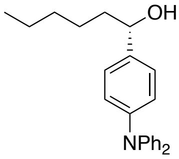
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 154.5, 145.4, 139.7, 127.4, 122.5, 118.5, 111.3, 106.6, 74.9, 39.4, 31.8, 25.6, 22.6, 14.1.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{14}H_{17}O$: *m*/*z* 201.1274 [M + H – H_2O]$^+$, found *m*/*z* 201.1275.

SFC (Chiralpak IC-3, 5:95 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 4.28 min [major, (*S*)-**3ah**], 3.86 min [minor, (*R*)-**3ah**].

Specific rotation: $[\alpha]_D^{23}$ −24.0° (*c* 0.99, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er. The absolute configuration was determined by analogy to compound (*S*)-**3aa**.

(*S*)-1-[4-(Diphenylamino)phenyl]hexan-1-ol (3ai)



Compound **3ai** was prepared according to the general procedure with (*S,S*)-**me-bipam** by reaction of hexan-1-ol (0.25 mmol, 31.4 µL) with 4-(diphenylamino)phenyl boronic acid (0.75 mmol, 216.9 mg) and isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a red oil in 80% yield (69.2 mg).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26–7.18 (m, 6H), 7.10–7.04 (m, 6H), 7.03–6.93 (m, 2H), 4.65–4.58 (m, 1H), 1.89–1.76 (m, 1H), 1.74 (d, *J* = 3.3 Hz, 1H), 1.73–1.64 (m, 1H), 1.48–1.40 (m, 1H), 1.39–1.24 (m, 5H), 0.94–0.82 (m, 3H).

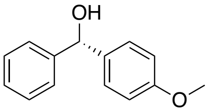
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 147.8, 147.2, 139.1, 129.2, 126.9, 124.2, 123.9, 122.7, 74.4, 38.9, 31.8, 25.7, 22.6, 14.1.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{24}H_{26}N$: *m*/*z* 328.2060 [M + H – H_2O]$^+$, found *m*/*z* 328.2066.

SFC-MS (Chiralpak IG-3, 15:85 iPrOH:CO_2, flow rate of 1.2 mL/min, m/z = 345, 346, and 368 ([M]+, [M+H]+, and [M+H]+, respectively)) tR = 2.48 min (major, (S)-3ai), 2.27 min (minor, (R)-3ai).

Specific rotation: $[\alpha]_D^{23}$ −36.8° (*c* 0.95, $CHCl_3$) for an enantiomerically enriched sample of 91:9 er. The absolute configuration was determined by analogy to compound (*S*)-**3aa**.

(*S*)-(4-Methoxyphenyl)phenylmethanol (3fj)



Compound **3fj** was prepared according to the general procedure with (*S,S*)-**me-bipam** by reaction of benzyl alcohol (0.25 mmol, 25.7 µL) with 4-methoxyphenyl boronic acid (0.75 mmol, 114.0 mg) and isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a colourless oil in 78% yield (41.8 mg). The analytical data are consistent with those previously reported.[28]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41–7.31 (m, 4H), 7.31–7.21 (m, 3H), 6.90–6.82 (m, 2H), 5.82 (s, 1H), 3.79 (s, 3H), 2.16 (d, *J* = 8.4 Hz, 1H).

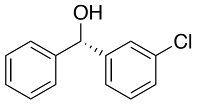
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.1, 144.0, 136.2, 128.5, 127.9, 127.5, 126.4, 113.9, 75.8, 55.3.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{14}H_{13}O$: *m*/*z* 197.0961 [M + H – H_2O]$^+$, found *m*/*z* 197.0966.

SFC (Chiralpak IC-3, 5:95 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 8.41 min [major, (*S*)-**3fj**], 7.66 min [minor, (*R*)-**3fj**].

Specific rotation: $[\alpha]_D^{23}$ −11.3° (*c* 0.99, $CHCl_3$) for an enantiomerically enriched sample of 99:1 er. The absolute configuration was determined by comparison of the sign and the value of the optical rotation with those reported in the literature [$[\alpha]_D^{22}$ −14.8° (*c* 0.81, $CHCl_3$), 96:4 er].[28]

(*S*)-(3-Chlorophenyl)phenylmethanol (3fk)



Compound **3fk** was prepared according to the general procedure with (*S,S*)-**me-bipam** by reaction of benzyl alcohol (0.25 mmol, 25.7 μL) with 3-chlorophenyl boronic acid (0.75 mmol, 117.3 mg) and isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a colorless oil in 66% yield (36.4 mg). The analytical data are consistent with those previously reported.[28]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, *J* = 2.0 Hz, 1H), 7.29–7.23 (m, 4H), 7.19 (ddd, *J* = 8.2, 4.1, 1.8 Hz, 1H), 7.17–7.07 (m, 3H), 5.71 (d, *J* = 3.2 Hz, 1H), 2.13 (d, *J* = 3.4 Hz, 1H).

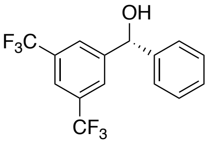
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 145.7, 143.2, 134.4, 129.8, 128.7, 128.0, 127.7, 126.6, 126.6, 124.6, 75.7.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{13}H_{10}Cl$: *m*/*z* 201.0466 [M + H – H_2O]$^+$, found *m*/*z* 201.0469.

SFC (Chiralpak IB-3, 5:95 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 7.38 min [major, (*S*)-**3fk**], 6.76 min [minor, (*R*)-**3fk**].

Specific rotation: $[\alpha]_D^{23}$ +33.0° (*c* 1.0, $CHCl_3$) for an enantiomerically enriched sample of 97::3 er. The absolute configuration was determined by comparison of the sign and the value of the optical rotation with those reported in the literature [$[\alpha]_D^{22}$ +33.1° (*c* 0.37, $CHCl_3$), 98:2 er].[28]

(*R*)-[3,5-Bis(trifluoromethyl)phenyl]phenylmethanol (3qa)



Compound **3qa** was prepared according to the general procedure with (*S,S*)-**me-bipam** by reaction of 3,5-bis(trifluoromethyl)phenylmethanol (0.25 mmol, 61.0 mg) with phenyl boronic acid (0.75 mmol, 91.4 mg) and isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white amorphous solid in 42% yield (33.9 mg). The analytical data are consistent with those previously reported.[45]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 2H), 7.78 (s, 1H), 7.43–7.31 (m, 5H), 5.94 (d, *J* = 3.1 Hz, 1H), 2.37 (d, *J* = 3.2 Hz, 1H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 146.1, 142.4, 131.7 (q, *J* = 33.3 Hz), 129.1, 128.7, 126.7, 126.5 (m), 123.3 (d, *J* = 272.7 Hz), 121.8–121.1 (m), 75.3.

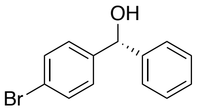
^{19}F NMR (471 MHz, $CDCl_3$): δ −62.79.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{15}H_9F_6$: *m*/*z* 303.0603 [M + H – H_2O]$^+$, found *m*/*z* 303.0610.

SFC (Chiralpak IB-3, 0.5:99.5 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 5.45 min [major, (*R*)-**3qa**], 4.98 min [minor, (*S*)-**3qa**].

Specific rotation: $[\alpha]_D^{24}$ −34.1° (*c* 0.84, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er. The absolute configuration was determined by comparison of the sign and the value of the optical rotation with those reported in the literature [$[\alpha]_D^{20}$ −38.6° (*c* 0.80, $CHCl_3$), 90:10 er].[45]

(*R*)-(4-Bromophenyl)phenylmethanol (3ra)



Compound **3ra** was prepared according to the general procedure with (*S,S*)-**me-bipam** by reaction of 4-bromophenylmethanol (0.25 mmol, 46.5 mg) with phenyl boronic acid (0.75 mmol, 91.4 mg) and isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white amorphous solid in 70% yield (46.0 mg). The analytical data are consistent with those previously reported.[28]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49–7.43 (m, 2H), 7.38–7.31 (m, 4H), 7.30–7.25 (m, 3H), 5.81 (d, *J* = 3.3 Hz, 1H), 2.19 (d, *J* = 3.5 Hz, 1H).

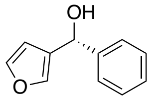
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 143.4, 142.7, 131.6, 128.7, 128.2, 127.9, 126.5, 121.4, 75.7.

HRMS (ESI$^+$-Orbitrap) calcd for $C_{13}H_{10}Br$: *m*/*z* 244.9960 [M + H – H_2O]$^+$, found *m*/*z* 244.9965.

SFC (Chiralpak IC-3, 5:95 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 5.15 min [major, (*R*)-**3ra**], 5.62 min [minor, (*S*)-**3ra**].

Specific rotation: $[\alpha]_D^{23}$ −15.5° (*c* 0.98, $CHCl_3$) for an enantiomerically enriched sample of 97:3 er. The absolute configuration was determined by comparison of the sign and the value of the optical rotation with those reported in the literature for the opposite enantiomer [$[\alpha]_D^{22}$ +18.2° (*c* 0.3, $CHCl_3$), 96:4 er].[28]

(*R*)-Furan-3-yl(phenyl)methanol (3sa)



Compound **3sa** was prepared according to the general procedure with (*S,S*)-**me-bipam**, except that during the oxidation step the reaction mixture was stirred for 16 h, by reaction of furan-3-ylmethanol (0.25 mmol, 21.6 µL) with phenyl boronic acid (0.75 mmol, 91.4 mg) and isolated by column chromatography (silica gel, petroleum ether to petroleum ether/ethyl acetate 85:15) to give a white amorphous solid in 27% yield (11.8 mg). The analytical data are consistent with those previously reported.[2]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45–7.34 (m, 5H), 7.34–7.28 (m, 2H), 6.34 (d, *J* = 1.8 Hz, 1H), 5.78 (s, 1H), 2.16 (s, 1H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 143.5, 143.0, 139.8, 128.9, 128.6, 127.9, 126.4, 109.2, 69.5.

HRMS (ESI$^+$-Orbitrap):calcd for $C_{11}H_9O$: *m*/*z* 157.0648 [M + H – H_2O]$^+$, found *m*/*z* 157.0651.

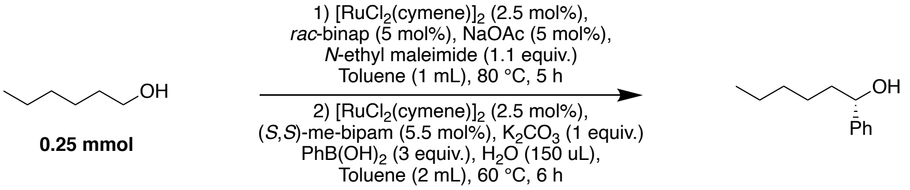
SFC (Chiralpak IC-3, 2.5:97.5 iPrOH:CO_2, flow rate of 1.2 mL/min, λ = 210 nm): t_R = 4.26 min [major, (*R*)-**3sa**], 4.82 min [minor, (*S*)-**3sa**].

Specific rotation: $[\alpha]_D^{24}$ −3.4° (*c* 0.49, $CHCl_3$) for an enantiomerically enriched sample of 99:1 er. The absolute configuration was determined by comparison of the sign and the value of the optical rotation with those reported in the literature [$[\alpha]_D^{20}$ −2.7° (*c* 0.833 $CHCl_3$), 97:3 er].[2]

4.4.5 Competition experiments

In a nitrogen-filled glovebox, a solution of **Ru-1** and sodium acetate was prepared by allowing [Ru(*p*-cymene)Cl_2]$_2$ (0.025 equiv, 0.0063 mmol, 3.8 mg), *rac*-**binap** (0.05 equiv, 0.013 mmol, 7.8 mg), and sodium acetate (0.05 equiv, 0.013 mmol, 1.0 mg) to stir in toluene (1 mL) at 80 °C for 1 h. Next, a 4 mL screw cap vial equipped with a stirring bar was charged with *N*-ethylmaleimide (31.3.4 mg, 1.0 equiv, 0.25 mmol), the solution of **Ru-1** and sodium acetate, 1-hexanol (1 equiv, 0.25 mmol, 31.3 µL), and the competing alcohol (1 equiv, 0.25 mmol). The vial was then sealed with a Teflon-lined screw cap, removed from the glovebox, and placed in a preheated heating block at 80 °C, and the contents were allowed to stir for 5 h at 800 rpm. After that, the reaction mixture was cooled, a known amount of dodecane was added, and the reaction mixture was analyzed by GC-FID. GC conversions were corrected for response factors for all compounds.

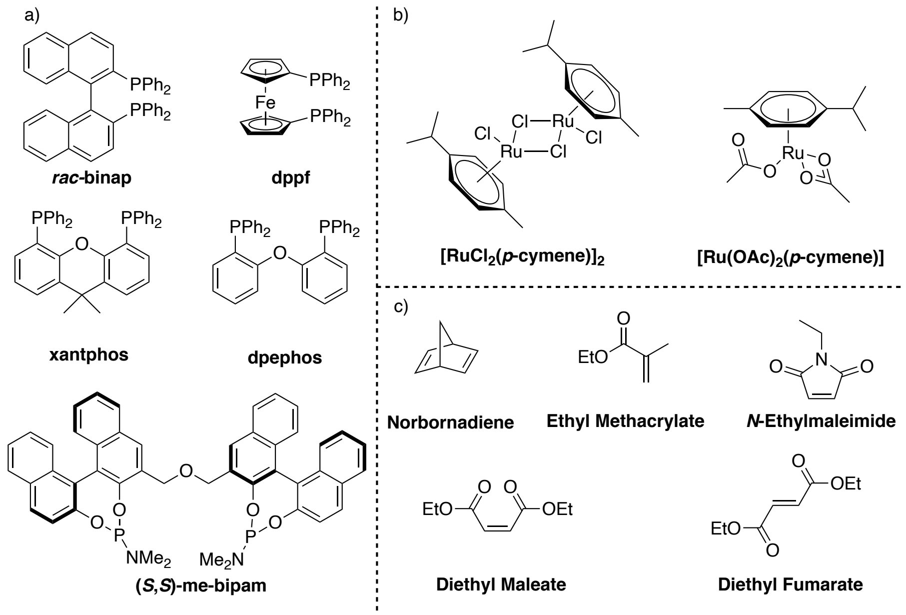
4.4.6 Detailed optimization of reaction conditions and control experiments



Entry	Deviation from standard conditions	Conversion (%)[a]	Yield (%)[b]	e.r..[c]
1	none	90	88	96:4
2	No *N*-ethylmaleimide	10	0	-
3	Norbornadiene instead of *N*-ethylmaleimide	0	0	-
4	Acetone instead of *N*-ethylmaleimide	0	0	-
5	Ethyl methacrylate instead of *N*-ethylmaleimide	6	0	-
6	Diethyl fumarate instead of *N*-ethylmaleimide	27	33	96:4
7	Diethyl maleate instead of *N*-ethylmaleimide	26	32	97:3
8	0.25 equiv sodium acetate	22	20	-
9	1 equiv sodium acetate	12	8	-
10	0.05 equiv NaOH instead of sodium acetate	18	0	-
11	No sodium acetate	9	0	-
12	5 mol% $[Ru(OAc)_2$(*p*-cymeme)] instead of $RuCl_2(cymene)]_2$ and NaOAc	0	0	-
13	5 mol% $[Ru(OAc)_2$(*p*-cymeme)] and 10 mol% TBA-Cl instead of $RuCl_2(cymene)]_2$ and NaOAc	52	52	96:4
14	(*R*)-**binap** (5 mol%) instead of *rac*-**binap**; no $RuCl_2(cymene)]_2$ and (*S*,*S*)-me-bipam in step 2)	86	0	-
15	5.5 mol% (*S*,*S*)-me-bipam in step 1) instead of *rac*-**binap** and NaOAc; benzyl alcohol instead of hexan-1-ol; 4-methoxyphenylboronic acid instead of phenylboronic acid	0	0	-
16	PPh_3 (10 mol%) instead of *rac*-**binap**	36	30	58:42
17	**dppf** (5 mol%) instead of *rac*- **binap**	31	20	94:6
18	**xantphos** (5 mol%) instead of *rac*-**binap**	5	5	-
19	**dpephos** (5 mol%) instead of *rac*-**binap**	46	39	96:4
20	(*R*)-**binap** (5 mol%) instead of *rac*-**binap**	87	91	96:4
21	(*S*)-**binap** (5 mol%) instead of *rac*-**binap**	89	90	96:4
22	1,4-dioxane instead of toluene in step 1)	27	0	-
23	THF instead of toluene in step 1)	73	0	-
24	Hexane instead of toluene in step 1)	28	0	-
25	DCM instead of toluene in step 1)	80	58	95:5

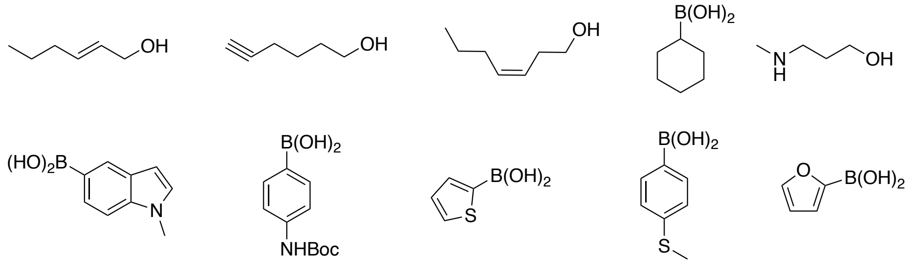
26	1.25 mol% Ru[Cl$_2$(cymene)]$_2$, 2.75 mol% (*S*,*S*)-me-bipam in step 2)	88	77	96:4
27	0.5 mol% Ru[Cl$_2$(cymene)]$_2$, 1.1 mol% (*S*,*S*)-me-bipam in step 2)	89	68	96:4
28	1.25 mol% Ru[Cl$_2$(cymene)]$_2$, 2.5 mol% *rac*-**binap**, 2.5 mol% NaOAc in step 1)	54	50	96:4
29	1.25 mol% Ru[Cl$_2$(cymene)]$_2$, 2.5 mol% *rac*-**binap**, 2.5 mol% NaOAc in step 1), 1.25 mol% Ru[Cl$_2$(cymene)]$_2$, 2.75 mol% (*S*,*S*)-me-bipam in step 2)	45	43	96:4
30	0.5 mol% Ru[Cl$_2$(cymene)]$_2$, 1 mol% *rac*-**binap**, 1 mol% NaOAc in step 1)	12	13	-
31	0.5 mol% Ru[Cl$_2$(cymene)]$_2$, 1 mol% *rac*-**binap**, 1 mol% NaOAc in step 1), 0.5 mol% Ru[Cl$_2$(cymene)]$_2$, 1.1 mol% (*S*,*S*)-me-bipam in step 2)	12	11	-

[a] Conversions determined by GC-FID analysis with dodecane as an internal standard. GC conversions were corrected for response factors for all compounds (See section V. Calibration Curves for GC Analysis). [b] Yields determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard. [c] Enantiomeric ratios determined by SFC analysis on a chiral stationary phase.



a) Structures of evaluated ligands. b) Structure of used metal sources. c) Structures of evaluated sacrificial hydrogen acceptors.

4.4.7 Unsuccessful examples



Examples of starting materials of the unsuccessful reactions.

4.5. References

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A multicatalytic approach to enantio-, and diastereoselective arylation of alcohols

Résumé

Les groupements alcooliques sont présents dans une grande diversité de produits chimiques fins précieux issus de la nature et de la synthèse, c'est pourquoi les méthodes permettant leur diversification structurelle sont recherchées. Cependant, la modification de la structure des alcools à certaines positions non réactives, même avec l'aide de la catalyse, reste un défi ou nécessite des procédures multi-étapes fastidieuses et souvent coûteuses. Récemment, une attention accrue a été accordée à la multicatalyse, qui combine plusieurs catalyseurs au sein d'un même système, ce qui permet de découvrir des réactivités auparavant inaccessibles ou d'accroître l'efficacité globale des transformations en plusieurs étapes. Les méthodes décrites ici permettent l'α- et la β-arylation diastéréo- et énantiosélective d'alcools. En combinant des catalyseurs à base de Ru et de Pd, il est possible de réaliser une β-arylation énantiosélective (et diastéréodivergente dans le cas d'alcools portant déjà des stéréocentres) sans précédent d'alcools primaires. En outre, dans le cadre d'une catalyse relais séquentielle, il est possible d'obtenir des alcools benzyliques secondaires enrichis enantioénergie à partir de divers produits de départ disponibles, tels que des alcools primaires ou des alcools portant une double liaison. Dans l'ensemble, ces protocoles démontrent le potentiel de la multicatalyse en tant qu'outil synthétique pour diversifier les alcools. Dans un contexte plus large, cette thèse ouvre la voie à la conception de nouvelles stratégies et méthodes multicatalytiques pour une synthèse efficace.

Mots clés : multicatalyse, arylation, catalyse énantiosélective, fonctionnalisation C-H, alcools, emprunt d'hydrogène, catalyse one-pot, catalyse relais

Abstract

Alcohol moieties are present in a great diversity of valuable fine chemicals from nature and synthesis, therefore methods enabling their structural diversification are sought after. However, modifying the structure of alcohols at certain unreactive positions, even with the aid of catalysis, remains a challenge or requires tedious often wasteful multistep procedures. Recently, increased attention has been paid to multicatalysis, which combines multiple catalysts within one system, enabling the discovery of previously inaccessible reactivities or increasing the overall efficiency of multistep transformations. Described within are methods which enable the diastereo-, and enantioselective α-, and β-arylation of alcohols. By combining Ru- and Pd-based catalysts the unprecedented, enantioselective (and diastereodivergent in the case of alcohols already bearing stereocenters) β-arylation of primary alcohols can be carried out. Also, under sequential relay catalysis enantioenriched secondary benzylic alcohols can be obtained from a variety of available starting materials, such as primary alcohols, or alcohols bearing a double bond. Overall, these protocols demonstrate the potential of multicatalysis as a synthetic tool for diversifying alcohols. In a broader context, this thesis sets the stage for devising novel, multicatalytic strategies and methods for efficient synthesis.

Keywords: multicatalysis, arylation, enantioselective catalysis, C-H functionalisation, alcohols, hydrogen borrowing, one-pot catalysis, relay catalysis