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**New Reactions of
Aminofunctionalization of Alkenes**

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Summary of the Thesis (in French)

1) Introduction

Les amines aliphatiques sont au cœur de la chimie fine. Elles sont présentes dans plus de 40% des molécules pharmaceutiques mais sont également des précurseurs clés pour la construction de molécules bioactives complexes, de produits naturels et de polymères.^[1] Par conséquent, l'accès à ces composés, notamment les β -aryléthylamines (Schéma 1), représente un défi synthétique important.^[2] Actuellement, les méthodes les plus courantes pour préparer des amines primaires aliphatiques β -aryliques sont l'addition 1,4 aux nitroalcènes, l'arylation d'aziridines, et l'hydroamination anti-Markovnikov d'alcènes. Cependant, elles nécessitent souvent des substrats complexes, présentent une tolérance fonctionnelle limitée ou impliquent des étapes supplémentaires de réduction ou de déprotection qui limitent encore plus leur compatibilité fonctionnelle.

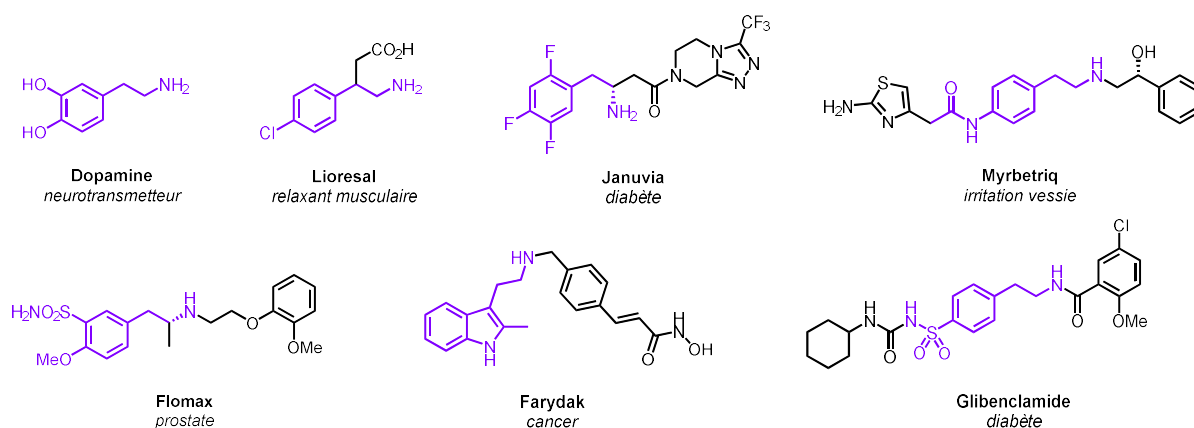


Schéma 1. Molécules bioactives incorporant un motif β -aryléthylamine

La di-fonctionnalisation des alcènes est en revanche un moyen simple de synthétiser des β -aryléthylamines en une seule étape.^[3] Ces dernières années, des méthodes élégantes ont ainsi été décrites par notamment Stephenson,^[4] Liu,^[5] et Engle.^[6] Cependant, aucune de ces stratégies ne permet d'obtenir des amines non protégées et, dans certains cas, des (hétéro)arènes pré-activés ou des groupements directeurs sont nécessaires. En outre, elles ne sont généralement pas compatibles avec plusieurs groupes fonctionnels essentiels en chimie médicinale, notamment les amides, sulfonamides, nitro, nitrile, phosphonates ou encore les NH-indoles. Pourtant, ces fonctionnalités se retrouvent dans la plupart des produits pharmaceutiques, car elles permettent des interactions clés entre les médicaments et leurs cibles biologiques. Compte

tenu de ces limitations, l'arylation des alcènes en β -aryléthylamines non protégées restait un défi en synthèse.

Dans ce contexte, l'utilisation de radicaux centrés sur l'azote est l'un des moyens les plus simples de générer des amines non protégées.^[7] Un des moyens les plus courants pour la formation de ces espèces est l'utilisation d'hydroxylamines qui ont été exploitées, par exemple, par le groupe de Morandi dans l'aminochloration, l'aminoazidation et l'aminohydroxylation des alcènes catalysées par le fer(II).^[8] L'utilisation d'(hétéro)arènes comme nucléophiles reste, elle, cependant inexplorée, ce qui peut être attribué au fait que les arènes sont facilement aminés dans ces conditions de réaction, comme l'ont montré Morandi, Jiao, Ritter ou Phipps.^[8]

Pour résoudre ce problème, nous avons ainsi envisagé un processus d'aminoarylation en un pot/deux étapes comprenant l'amination de l'alcène avec des hydroxylamines suivie de l'addition d'un nucléophile (hétéro)arène pour promouvoir l'ouverture d'un intermédiaire aziridinium (Schéma 2). En se basant sur nos études précédentes sur la réactivité des styrènes et des époxydes désactivés, nous avons émis l'hypothèse que l'utilisation de HFIP comme solvant pourrait simultanément stabiliser les intermédiaires radicalaires et cationiques tout en augmentant l'électrophilie du radical centré sur l'azote et de l'aziridinium, ce qui permettrait d'utiliser des substrats hautement désactivés dans la réaction.

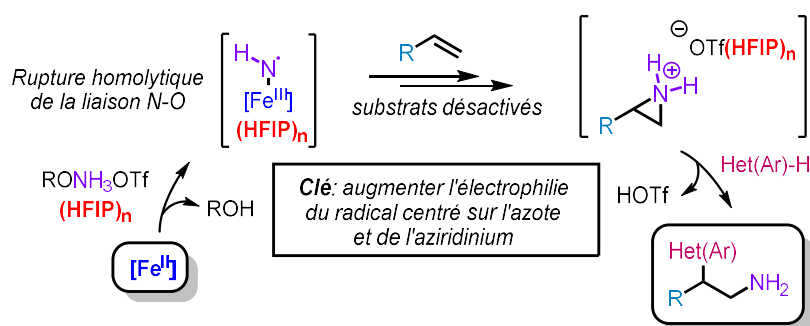


Schéma 2. Stratégie envisagée pour la synthèse de β -(hétéro)aryléthylamines non protégées

2) Résultats et discussions

Dans un premier temps, nous avons étudié l'aminoarylation 1,2 du *para*-nitrostyrène en utilisant le mésitylène comme arène nucléophile. Après une étude détaillée des conditions réactionnelles, nous avons réussi à obtenir le produit visé avec un rendement de 51% en conduisant la réaction dans HFIP (0.6 M) en présence de $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (10 mol%) comme catalyseur et $[\text{MsO-NH}_3][\text{OTf}]$ comme agent d'amination (Schéma 3).^[9]

Nous avons ensuite exploré le champ d'application de la réaction, en évaluant la réactivité de divers (hétéro)arènes riches en électrons. La réaction fonctionne ainsi sans problème avec les indoles et pyrroles pour fournir les produits correspondants avec des rendements allant jusqu'à 64%. De plus, cette séquence n'est pas limitée aux hétéroarènes mais peut également être étendue aux arènes riches en électrons, notamment les dérivés d'anisole et de naphthalène. Dans la plupart des cas, les produits ont été obtenus avec de bons rendements et une excellente régiosélectivité. Bien que des arènes moins riches en électrons comme le benzène puissent être utilisés dans la transformation, nous avons observé une diminution du rendement assez importante. Notre protocole s'est aussi avéré compatible avec une large gamme de styrènes désactivés. Les produits formés incorporent une large gamme de groupements fonctionnels essentiels en chimie médicinale mais qui n'avaient jamais été décrits jusqu'à présent, comme des cyano, amide, sulfonamide, ester sulfonate, phosphonate et morpholine. En outre, des styrènes non terminaux peuvent aussi être employés dans cette transformation. Il est important de noter que la transformation n'est pas limitée aux dérivés du styrène. Les substrats allyliques réagissent facilement avec le 2-méthylindole pour donner les composés d'aminoarylation. Cependant, nous avons remarqué une inversion de la régiosélectivité avec l'obtention d'amines aliphatiques ramifiées. Cela peut s'expliquer par la présence de groupements électroattracteurs qui réduisent l'électrophilie de la position interne de l'intermédiaire aziridinium, favorisant l'addition nucléophile en position terminale. Finalement, cette séquence réactionnelle n'est pas limitée à la préparation d'amines primaires mais peut également être employée pour introduire des amines secondaires.

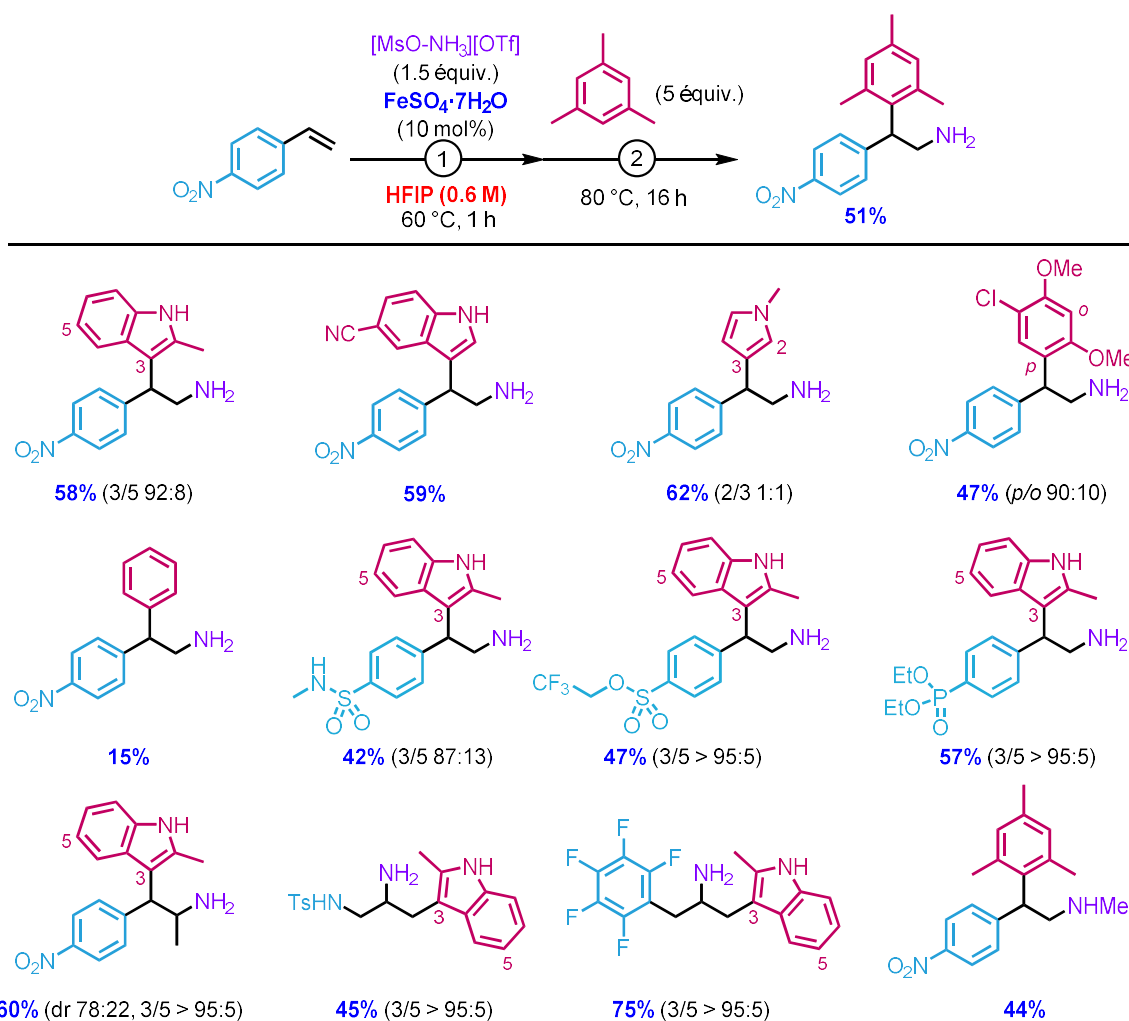


Schéma 3. Aminoarylation d'alcènes

L'utilité synthétique de cette transformation a également été mise en évidence par une série de fonctionnalisations afin d'obtenir des composés plus variés (Schéma 4). Par exemple, le groupement nitro du composé **1** a été facilement réduit avec H_2 sur Pd/C pour fournir l'aniline correspondante avec un rendement de 79%. Ce substrat a également été mis en réaction avec l'éther de 2-bromoéthyle pour installer une unité morpholine (79%). La méthylation d'Eschweiler-Clarke a permis d'obtenir la *N,N*-diméthylamine correspondante avec un rendement de 88%. Le couplage de l'amine primaire avec l'acide (*S*)-mandélique et la réduction ultérieure du groupe nitro ont fourni un composé qui peut être utilisé pour synthétiser des analogues du Myrbetriq.

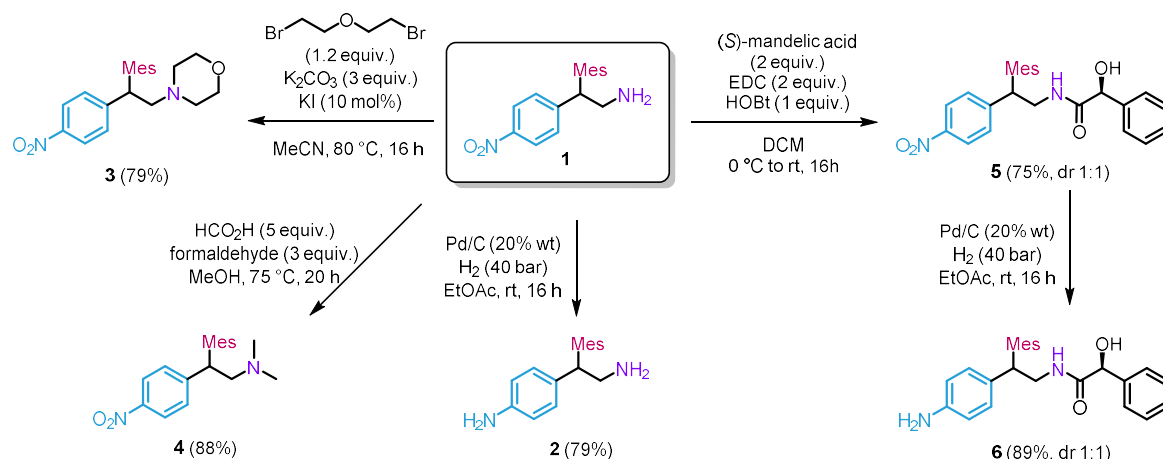


Schéma 4. Fonctionnalisations du composé **1**

Au cours de nos études sur l'(hétéro)arylation, nous avons observé que, dans le cas de la diphenylamine faiblement basique, le produit de diamination était obtenu au lieu du produit d'aminoarylation (Schéma 5). Nous avons supposé que cette observation pourrait être utilisée pour développer une 1,2-diamination générale des styrènes, indépendante de la basicité et de la nucléophilie de l'amine utilisée. Développer une telle méthode est d'autant plus intéressante que les diamines vicinales sont des motifs structuraux privilégiés dans des composés biologiquement actifs, mais ont également trouvé une large utilisation dans la catalyse par les métaux de transition et l'organocatalyse.

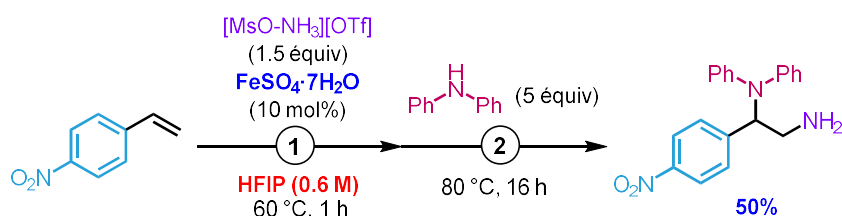


Schéma 5. Diamination du *p*-nitrostyrène

En utilisant le *p*-nitrostyrène et la benzocaïne (anesthésique) comme substrats modèles, nous avons constaté que notre séquence de réactionnelle conduisait à une diamine densément fonctionnalisée avec un rendement de 63%, incorporant trois unités azotées différentes et un ester (Schéma 6). En stoppant le processus après la première étape, nous avons pu isoler l'aziridine correspondante avec un rendement de 60%. En réengageant l'aziridine dans nos conditions standard, nous avons obtenu la diamine avec un rendement de 81%, ce qui est consistant avec son rôle d'intermédiaire dans la réaction. En revanche, la présence de la benzocaïne dès le début empêche la réaction, suggérant une réaction secondaire avec le sel d'hydroxylammonium. Dans ce cas, le *p*-nitrostyrène a été entièrement récupéré.

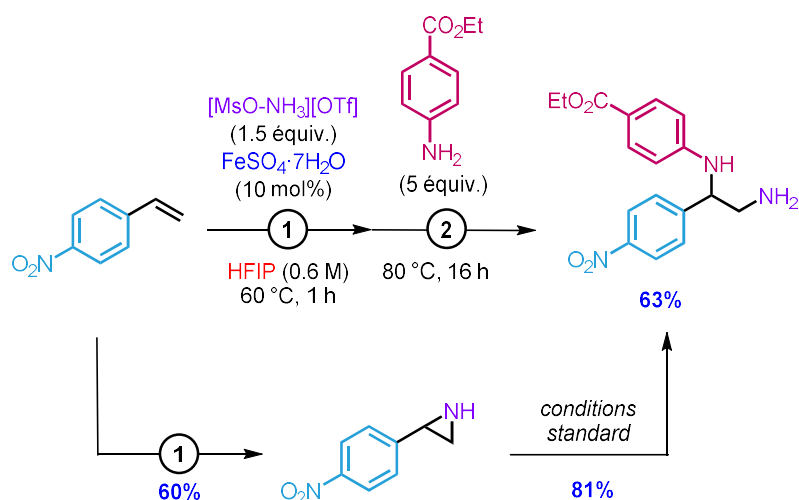


Schéma 6. Diamination du *p*-nitrostyrène avec la benzocaïne

Un des problèmes de cette approche est qu'elle n'est pas compatible avec des styrènes riches en électrons ou encore des styrènes modérément désactivés. Nous avons ainsi développé une méthodologie alternative. En l'absence de HFIP, ceci a été réalisé en combinant une étape d'aminochloruration avec [PivO-NH₃][OTf] et NaCl suivie par une substitution du chlorure par l'aniline en un pot (Schéma 7). Au cours de la seconde étape, l'utilisation d'une quantité catalytique d'acide triflique s'est avérée essentielle pour obtenir des rendements satisfaisants. Nous supposons que son rôle consiste en l'activation du groupe chlorure pour favoriser une réaction de S_N2.

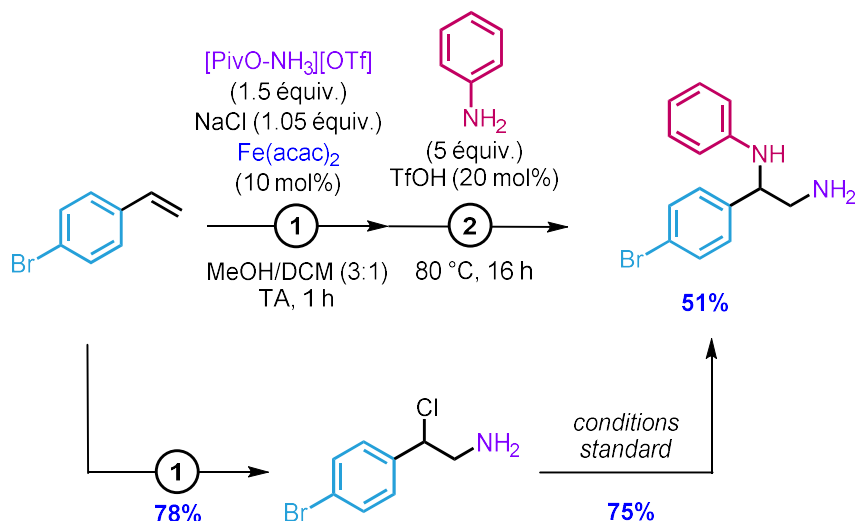


Schéma 7. Diamination du *p*-bromostyrène avec l'aniline

Après avoir démontré l'efficacité de notre protocole avec une aniline primaire, nous avons examiné sa compatibilité avec anilines diversement substituées (Schéma 7). Toutes ces anilines

ont réagi sans problème pour fournir les produits de diamination correspondants avec des rendements allant de 33 à 71%. La transformation a été aussi étendue aux naphthylamines. Nous avons ensuite examiné la réactivité des anilines secondaires, qui se sont révélées être des nucléophiles tout aussi efficaces. Une observation intéressante est que les fonctions alcène et alcyne des produits dérivés de la *N*-allylaniline et de la *N*-propargyl aniline sont restées intactes et aucun produit de cyclisation résultant de l'hydroamination n'a été observé. La benzocaïne a ensuite été choisie comme nucléophile modèle pour explorer le champ d'application de la réaction des styrènes appauvris en électrons. Notre protocole permet une construction rapide de diamines vicinales à partir d'une large gamme de styrènes désactivés avec des rendements allant de 40 à 90%, incorporant des substituants trifluorométhyle, sulfonamide, sulfonylester, amide, etc. Ici, la réaction ne s'est pas limitée aux styrènes mono-substitués mais a pu être étendue à l' α -méthylstyrènes et des styrènes internes. En revanche, aucun produit n'a été détecté dans le cas du 4-nitrostilbène. Ici, comme la 4-vinylaniline ne peut pas être utilisée directement pour cette séquence de réaction, le produit correspondant a été formellement obtenu par réduction du groupe nitro de la diamine avec un rendement quasi quantitatif (97%). Lorsque des molécules bioactives telles que la sulfadiazine (antibiotique) et le sulfaméthoxazole (antibiotique) ont été utilisées dans la séquence de réaction, les produits de diamination ont été obtenus avec des rendements de 52% et 50%, respectivement.

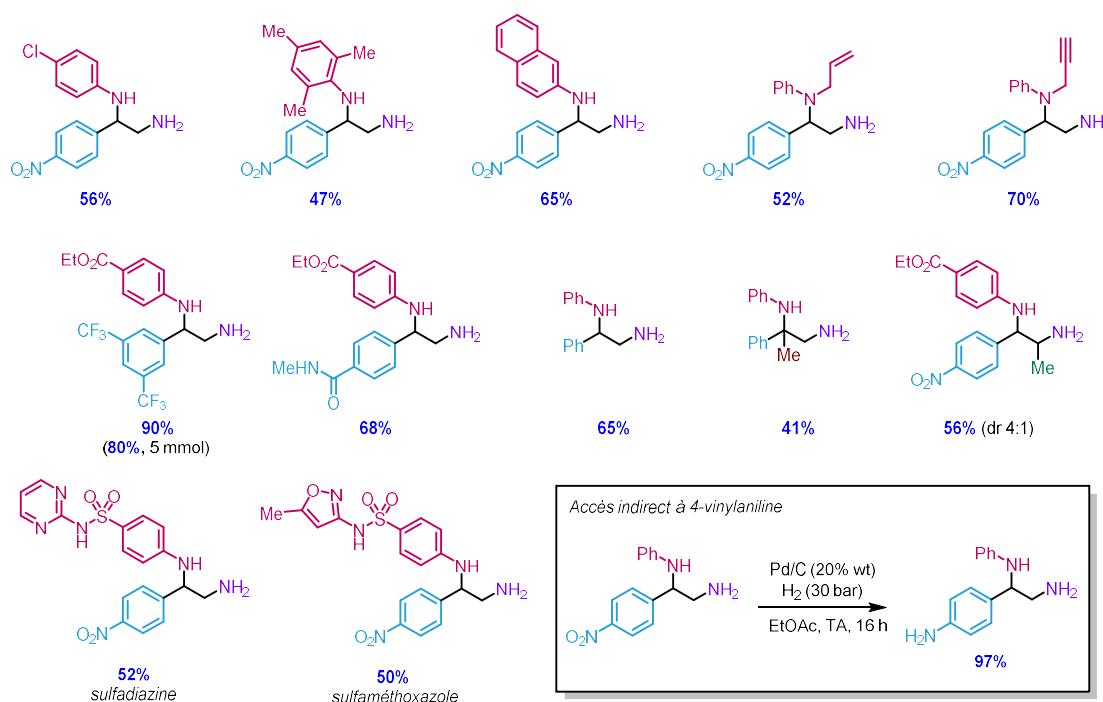


Schéma 7. Diamination de styrènes

Ensuite, nous avons étendu le protocole aux amines aliphatiques. Des amines aliphatiques primaires comme la tryptamine ou un acide aminé protégé été introduites avec succès dans le produit (Schéma 8). Dans certains cas, le produit a été isolé comme un mélange de la base libre et de son sel d'ammonium, auquel cas il a été protégé par Boc pour simplifier la caractérisation. En outre, notre protocole a permis l'incorporation d'amines secondaires d'intérêt comme l'amoxapine (antidépresseur) ou la rasagiline (traitement de la maladie de Parkinson) avec des rendements allant de 40 à 52%. Nous nous sommes ensuite demandé si des nucléophiles azotés apparentés, tels que les sulfoximines, qui sont devenus des groupes fonctionnels populaires dans la découverte de médicaments,^[10] seraient compatibles avec cette séquence de réaction. Comme ils présentent un pKa similaire à celui des anilines, nous avons considéré qu'ils devraient, en principe, présenter une réactivité similaire, ce qui a été confirmé. Les NH-hétérocycles tels que l'adénine se sont également révélés être des nucléophiles compétents pour la transformation de 1,2-diamination conçue. Dans le cas des substrats allyliques, la régiosélectivité est cependant inversée, car le groupement électroattracteur contrôle l'ouverture de cycle de l'aziridinium en faveur de l'addition en position terminale, ce qui permet d'accéder rapidement à des aminoacides non naturels β . De plus, cette séquence réactionnelle a été étendue avec succès à l'aminothioloation.

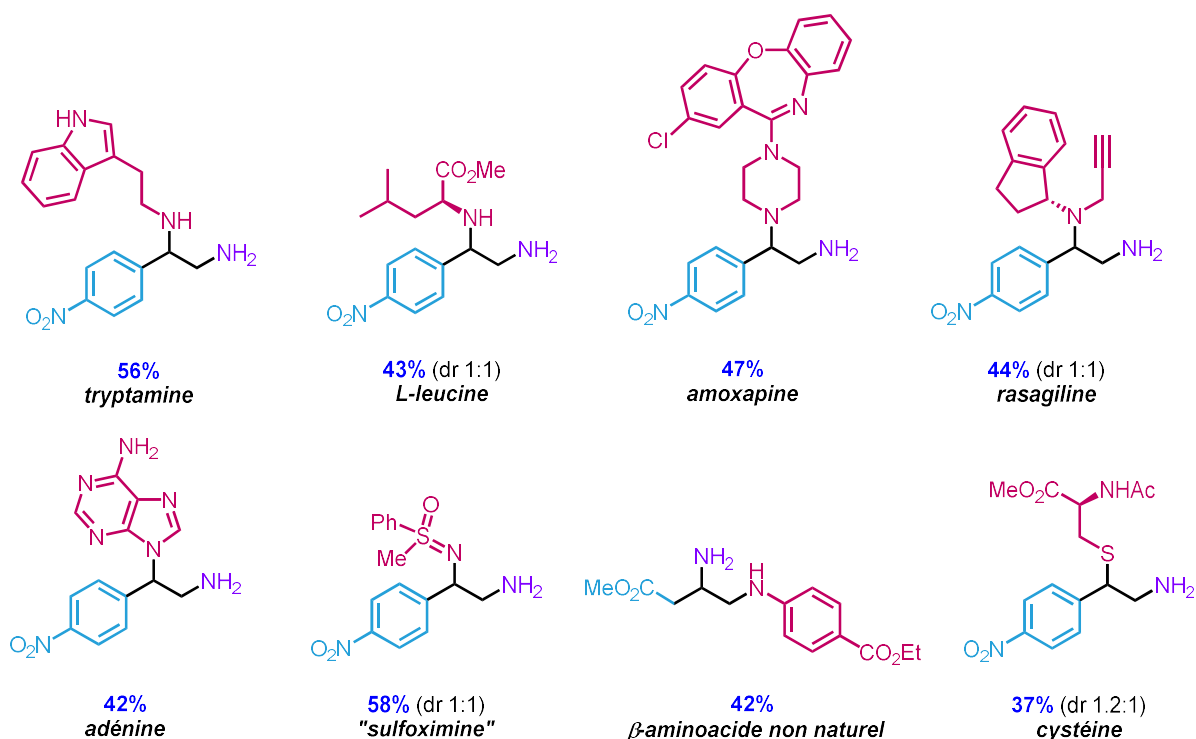


Schéma 8. Diamination de styrènes

Finalement, nous nous sommes intéressés au développement de nouveaux précurseurs de radicaux centrés sur l'azote de type O-tosylhydroxylamine qui pourraient réagir avec des alcènes pour former des tétrahydroquinolines fonctionnalisées (Schéma 9). En nous appuyant sur les propriétés uniques de HFIP, nous avons fait l'hypothèse que nous pourrions débloquent la réactivité de styrènes hautement désactivés électroniquement pour étendre le champ d'application de la réaction de Povarov classique. Notre idée de départ reposait sur l'utilisation de dérivés de type N-benzylhydroxylamine protégés par un groupement Boc et obtenus par une réaction de type Mitsunobu. Contrairement à la réaction classique de Povarov, notre méthodologie s'est montrée compatible avec des alcènes aliphatiques et déficients en électrons, élargissant ainsi l'espace chimique des molécules contenant le motif tétrahydroquinoline.

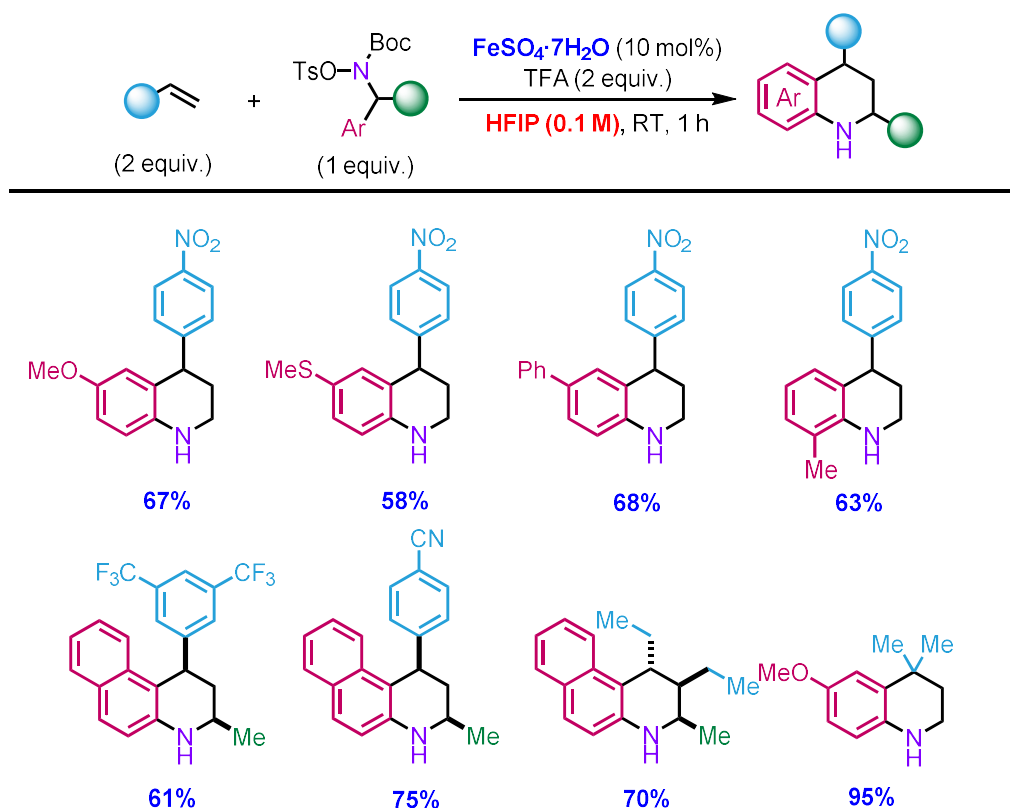


Schéma 9. Champ d'application de la synthèse des tétrahydroquinolines

3) Conclusion générale

En conclusion, nous avons développé une méthode générale pour l'accès rapide aux motifs β -aryléthylamines et 1,2-diamines avec des rendements modérés à élevés, à partir de styrènes, de sels d'hydroxylammonium et de divers nucléophiles. Contrairement aux approches précédentes, notre protocole simple en un pot/deux étapes permet une construction modulaire de diamines vicinales densément fonctionnalisées où l'une des fonctionnalités azotées est une amine

aliphatique primaire. L'une des caractéristiques de cette transformation est sa capacité à incorporer de nombreuses classes des nucléophiles (hétéro)arènes, des amines et de nucléophiles soufrés, y compris des molécules bioactives. En fonction de la nature électronique du substrat étudié, deux conditions réactionnelles différentes ont été développées, qui couvrent une grande variété de substrats avec groupement fonctionnels souvent retrouvés dans des molécules bioactives. De plus, la possibilité de facilement fonctionnaliser ces molécules permet d'obtenir des composés à haute valeur ajoutée, notamment la conception et la préparation d'analogues pour la potentielle découverte de nouveaux médicaments. Nous avons également conçu la synthèse de divers tétrahydroquinolines à partir de nouveaux précurseurs des radicaux centrés sur l'azote de type N-benzylhydroxylamine et des alcènes appauvris en électrons et avons ainsi élargi le champ d'application de la réaction de Povarov classique.

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- [10] U. Lücking, *Chem. Eur. J.* **2022**, 28, e202201993.

LISTE DES PRESENTATIONS

Pour toutes les présentations:

V. Pozhydaiev, M. Vayer, C. Fave, J. Moran, D. Lebœuf.

Synthesis of Unprotected β -Arylethylamines by Iron(II)-Catalyzed 1,2-Aminoarylation of Alkenes in Hexafluoroisopropanol

Communications par affiche:

4th Swiss Industrial Chemistry Symposium, Basel, Switzerland (01/2023)
BASF International Summer Course 2023, Ludwigshafen, Germany (08/2023)

Communications orales:

22nd European Symposium on Organic Chemistry, Ghent, Belgium (07/2023)
Swiss Summer School 2023: Organic Synthesis, Haute-Nendaz, Switzerland (08/2023)

LISTE DES PUBLICATIONS

- 1) **V. Pozhydaiev**, M. Vayer, C. Fave, J. Moran, D. Lebœuf. Synthesis of Unprotected β -Arylethylamines by Iron(II)-Catalyzed 1,2-Aminoarylation of Alkenes in Hexafluoroisopropanol. *Angew. Chem. Int. Ed.* **2023**, 62, e202215257.
- 2) **V. Pozhydaiev**, C. Muller, J. Moran, D. Lebœuf. Catalytic Synthesis of β -(Hetero)arylethylamines: Modern Strategies and Advances. *Angew. Chem. Int. Ed.* **2023**, 62, e202309289.
- 3) **V. Pozhydaiev**, A. Paparesta, J. Moran, D. Lebœuf. Iron(II)-Catalyzed 1,2-Diamination of Styrenes Installing a Terminal -NH₂ Group Alongside Unprotected Amines. *Angew. Chem. Int. Ed.* **2024**, e202411992.
- 4) **V. Pozhydaiev**, D. Al-Othman, J. Moran, D. Lebœuf. A Povarov-type reaction to access tetrahydroquinolines from N-benzylhydroxylamines and alkenes in HFIP. *Chem. Commun.* **2024**, 60, 10504-10507.

General Introduction

21st Century: The Renaissance of Radical Organic Chemistry

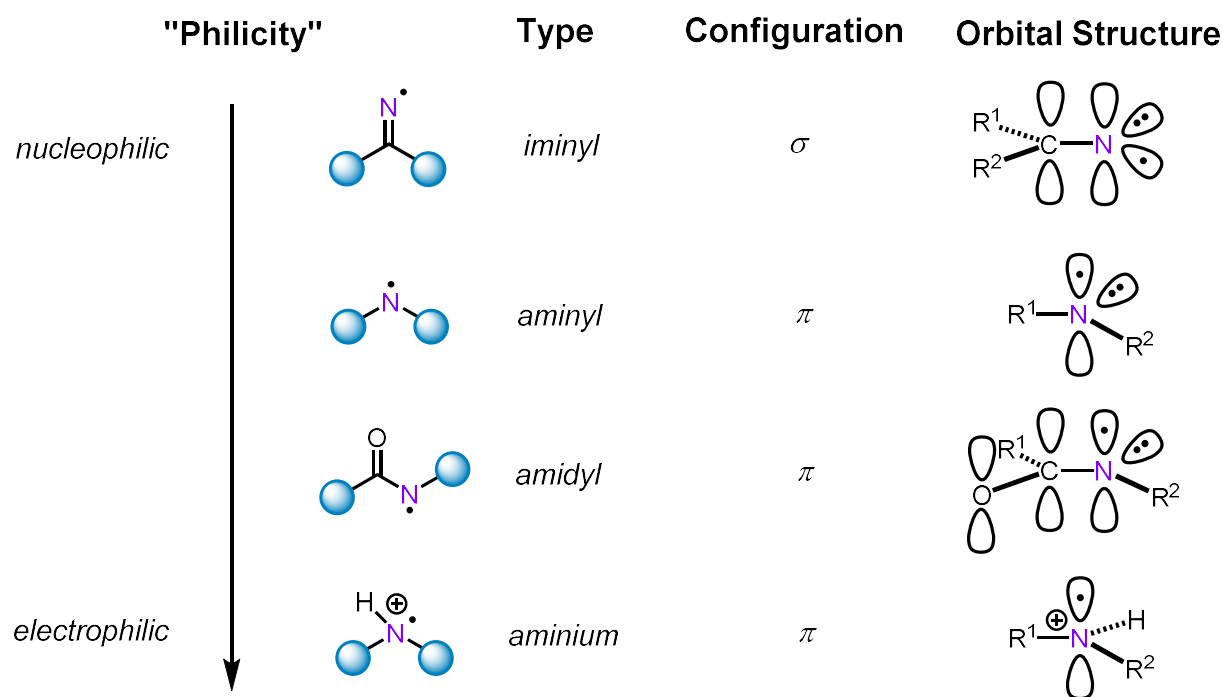
Over the past 20 years, the field of radical organic chemistry had blossomed and expanded at an unprecedented rate. The major reason behind the renaissance of this field has been the emergence of photoredox catalysis and organic electrosynthesis which turned out to be more versatile, operationally friendlier and greener alternatives for the generation of radical species. Several recent reviews exemplified the rapid development of this field and outlined future directions as well as current challenges.^[1a-d] In this context, the groups of MacMillan and Baran deserve credit for their pioneering works in the development of standardized experimental protocols and set-ups which made the field accessible to newcomers. These new approaches quickly took over more traditional methods relying on the use of radical initiators (AIBN, peroxides, etc.) and stoichiometric quantities of toxic organotin hydrides. As a positive side effect, the rising interest in radical chemistry has also spurred the development of many synthetically useful new radical precursors which could be activated either by new techniques or by other more “classical” methods e.g. thermal homolysis or single-electron redox processes with transition metals.

Radicals are open-shell species whose main reactivity pattern consists in achieving the closed-shell electronic configuration of noble gases. This property is a guiding principle for the understanding of reactivity trends and typical elementary steps of radical species. Thus, one-electron disconnections during the retrosynthetic planning enabled by radicals arise as a powerful alternative to the classical two-electron disconnections which proceed through ionic/pericyclic elementary steps. In this context, the reactivity of nitrogen-centered radicals (NCRs) can be harnessed for the construction of C–N bonds, complementing the established arsenal of ionic and transition-metal-based methods such as reductive amination, addition/reduction of cyanides or Buchwald-Hartwig cross-coupling reaction. The ubiquity of nitrogen-containing molecules in modern agrochemicals and pharmaceuticals highlights the importance of devising robust reactions for the incorporation of nitrogen atoms into organic compounds, the final goal being to expand the attainable chemical space of biologically relevant molecules.

Structure and Reactivity of N-Centered Radicals

Depending on hybridization of the nitrogen atom and its substituent pattern, NCRs can be divided into four main types: iminyl, aminyl, (sulfon)amidyl and aminium (Scheme 1).^[2a-f] NCRs can be labelled as nucleophilic or electrophilic in nature, with the iminyl radical being the most

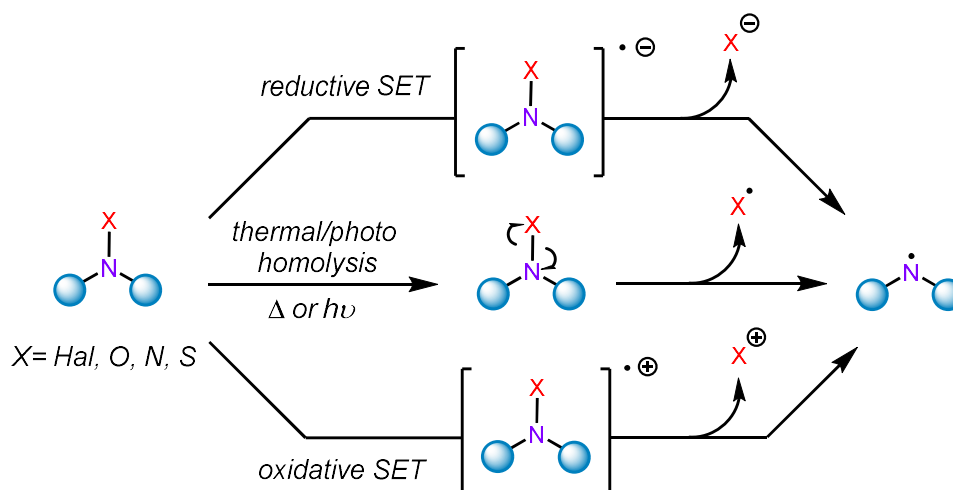
nucleophilic and aminium being the most electrophilic. The “philicity” of the radical may be used as a proxy indicator of its reactivity towards electronically diverse substrates.^[3a,b] For example, a nucleophilic NCR will usually react well with electron-deficient olefins and vice versa. Although these observations are supported by many experiments and are quite general, several exceptions exist. One of the factors which is often overlooked, yet critical, is the role of solvent, which may completely alter the reaction outcome. As it will be discussed in future chapters, hexafluoroisopropanol (HFIP) may enable reactions between electrophilic radicals and non-nucleophilic alkenes bearing strong electron-withdrawing groups, an example not falling into the classical electrophile-nucleophile reactivity scheme.



Scheme 1. Four main classes of N-centered radicals.

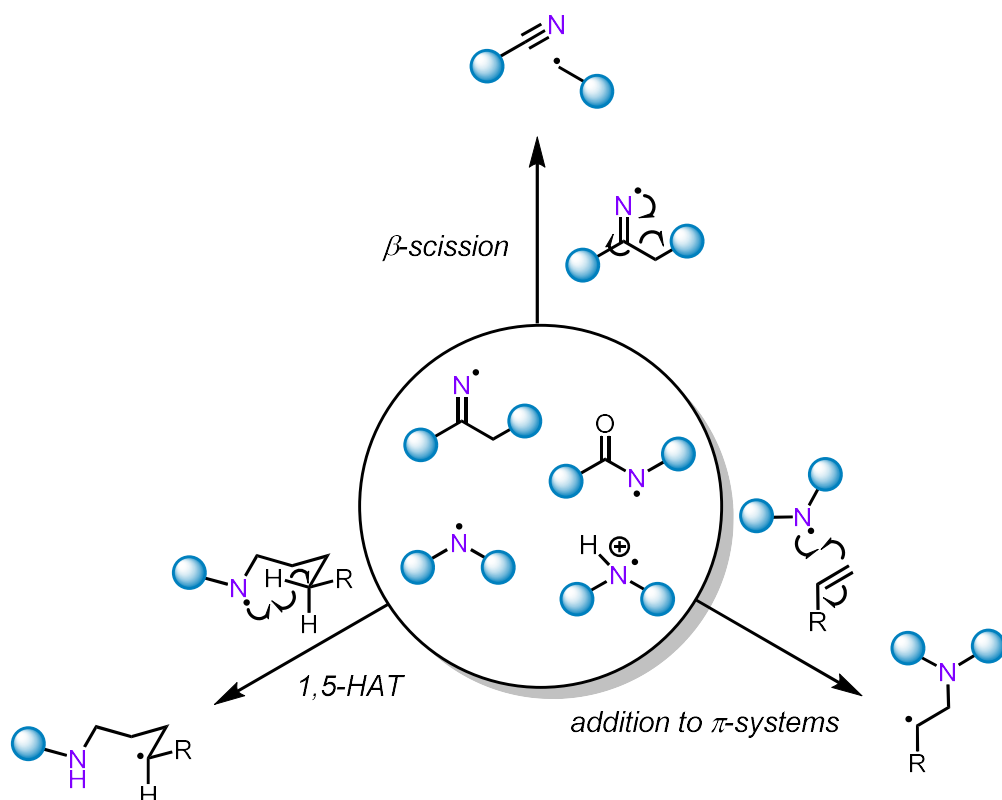
The common structural feature shared by all NCR precursors is the presence of a labile N–X bond (X = Hal, O, N, S) to facilitate an initial homolytic cleavage. The most popular ways of activating NCR precursors are thermally or photo-induced homolysis, or reductive and oxidative single-electron transfers (SET) (Scheme 2). Upon heating, higher energy vibrational states of a labile N–X bond are populated leading to homolytic cleavage. Similarly, homolysis can be achieved upon photoexcitation since the bond is weaker in the excited state, which favors its dissociation.

In the case of a reductive SET, an electron is supplied by a photocatalyst in the excited state, electrode or transition metal salt and reduces the NCR precursor to the radical anion which decomposes into the corresponding NCR and counterion. A similar principle applies to the oxidative SET.



Scheme 2. General activation schemes of N-centered radical precursors.

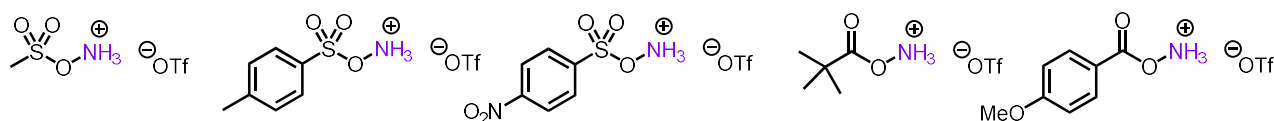
The reactivity of most NCRs falls into three main classes of elementary steps: β -scission, 1,5-hydrogen atom transfer (HAT) and addition to π -systems (Scheme 3). β -scission is akin to an E2 mechanism and is more common with iminyl radicals but can also seldom take place with aminyl radicals. It results in the formation of the corresponding nitrile/imine and C-centered radical of the fragment. In 1,5-HAT, NCR abstracts hydrogen at δ -position, provided that a chair-like 6-membered transition state can be formed, which affords a C-centered radical at δ -position. The intra- and intermolecular additions of NCRs to π -systems represent arguably the most synthetically useful class of reactions as they enable the construction of N-heterocycles or incorporation of nitrogen functionalities into larger molecules. Not surprisingly, the addition to π -systems represents the majority of transformations developed with NCRs and will be the focus of this thesis. It is noteworthy that, similarly to other radical additions to olefins, NCRs consistently give anti-Markovnikov selectivity.



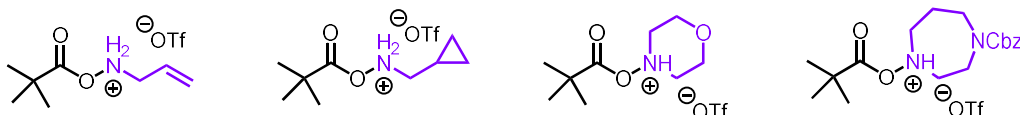
Scheme 3. Three main classes of elementary steps regarding N-centered radicals.

Among different families of N-centered radical precursors, electrophilic hydroxylamine-based derivatives deserve particular attention. Specifically, hydroxylammonium triflate salts $[\text{RO}-\text{NH}_3][\text{OTf}]$ exploited by the group of Morandi represent an ideal source of $-\text{NH}_2$ group for the amination of alkenes or arenes (Scheme 4), avoiding additional deprotection steps to obtain unprotected primary amines.^[4] One of the major strengths of these reagents is their high customizability. Depending on the nature of the leaving group $-\text{OR}$, their reactivity can be tailored to individual needs, while the substitution on the nitrogen atom can turn them into the source of an alkylamine group. Among the practical advantages of these reagents are their air and thermal stability as well as their easy scalability.^[5]

Variation of the leaving group -OR



Variation of the N-substitution



Scheme 4. Representative examples of hydroxylammonium triflate salts as precursors of aminium radicals.

Aim of the thesis

The aim of the present study is to develop new protocols for the aminofunctionalization of alkenes by leveraging the reactivity of aminium radicals formed from hydroxylammonium triflate precursors. The main idea is to combine the amination step with the introduction of another densely functionalized moiety to obtain molecules with high added value in one pot. Such strategy would enable the construction of biologically relevant scaffolds such as unprotected β -arylethylamines or differentiated 1,2-vicinal diamines in one pot, which would significantly reduce the number of necessary reaction steps. Another critical point of this thesis was to address the reactivity of strongly deactivated alkenes, substrates which remain underrepresented in this type of reactions. Since HFIP is known to enable challenging transformations with electron-deficient alkenes, we anticipated that its unique properties would be particularly beneficial for such processes. Another major goal is to expand the inventory of available hydroxylamine-based radical precursors and explore their reactivity for the synthesis of tetrahydroquinolines.

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Chapter 1: Iron(II)-Catalyzed Synthesis of Unprotected β -(Hetero)arylethylamines in Hexafluoroisopropanol (HFIP)

Introduction

Catalytic Synthesis of β -(Hetero)arylethylamines: Modern Strategies and Advances

The most common features found in the structural backbone of biologically active molecules are amines, polar groups, nitrogen heterocycles and fluorine-containing groups. Among these molecules, the (hetero)arylethylamine scaffold has become a prevalent structural motif that can be found in a large variety of pharmaceuticals, but also in neurotransmitters such as dopamine and serotonin (Figure 1).^[1-3] To date, the most common methods to access these medicinally privileged scaffolds include the reduction of cyanide, nitro or oxime groups, the Staudinger reaction, nucleophilic substitution, the decarboxylation of amino acids or the reductive amination of carbonyls. Most of these classical methods require advanced substrates and additional steps, notably reductions, that may be incompatible with broad functional group tolerance. The hydrogenation of enamide and enamine derivatives represents another convenient strategy to access β -(hetero)arylethylamines.^[4] Yet, although this approach is particularly valuable to prepare enantiopure compounds, it involves the pre-installation of all desired functionalities, which can be time-consuming when the goal is to rapidly screen compounds for biological activity. As a result, the development of efficient and versatile methods to expedite the preparation of the β -(hetero)arylethylamine framework in a step-economic and selective manner has become a never-ending quest for synthetic chemists. Recently, the development of modern strategies based on directing group assisted C–H activation, photocatalysis, electrocatalysis, and single electron transfer (SET) processes has provided creative solutions for accessing β -(hetero)arylethylamines. These approaches provide more structural complexity and diversity under milder reaction conditions from readily accessible or commercially available substrates, often enabled by practical and sustainable methods. In recent past years, punctual reviews have examined certain facets of these strategies,^[5-7] but the aim of this introduction is to provide a broader perspective on the synthesis of β -(hetero)arylethylamines and associated challenges. We cover modern approaches such as cross-coupling reactions, the ring-opening of aziridines, the hydroarylation of enamides, the anti-Markovnikov hydroamination of vinyl (hetero)arenes, the Truce-Smiles rearrangement, and the aminoarylation of alkenes that enable the simple formation of C–C and/or C–N bonds in a single step (Scheme 1). Given the massive number of reports on the preparation of (hetero)arylethylamines, we have chosen to focus on the formation of acyclic products. The main goal is not to be exhaustive but to highlight recent key examples that have shaped the field and opened new avenues for the future.

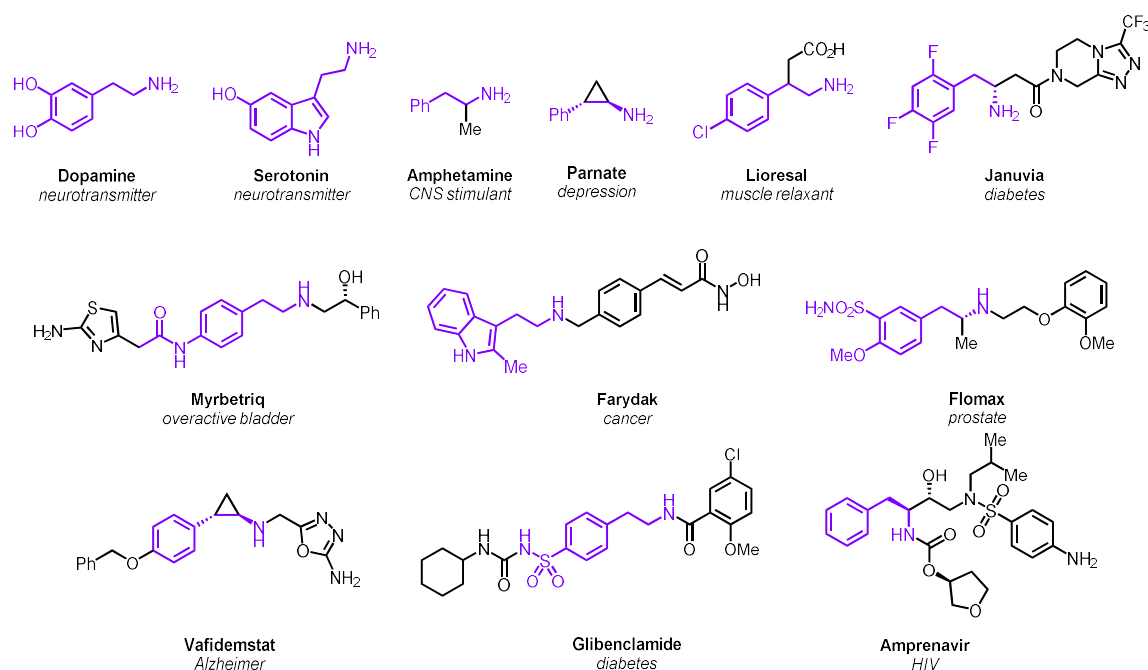
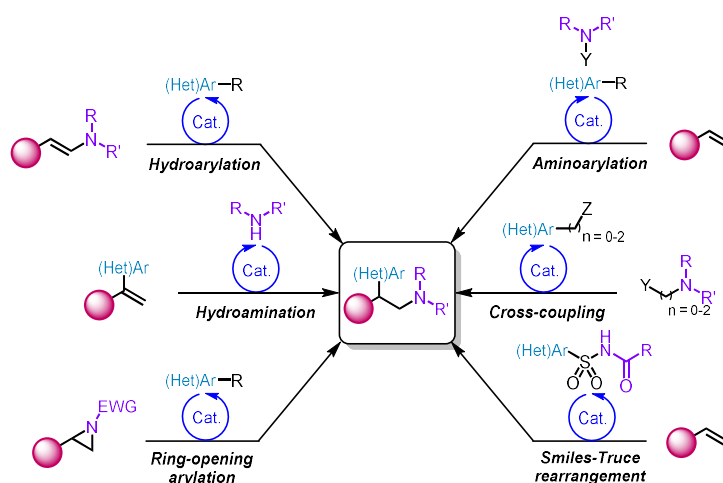


Figure 1. Selected examples of bioactive molecules incorporating β -(hetero)arylethylamine scaffolds.



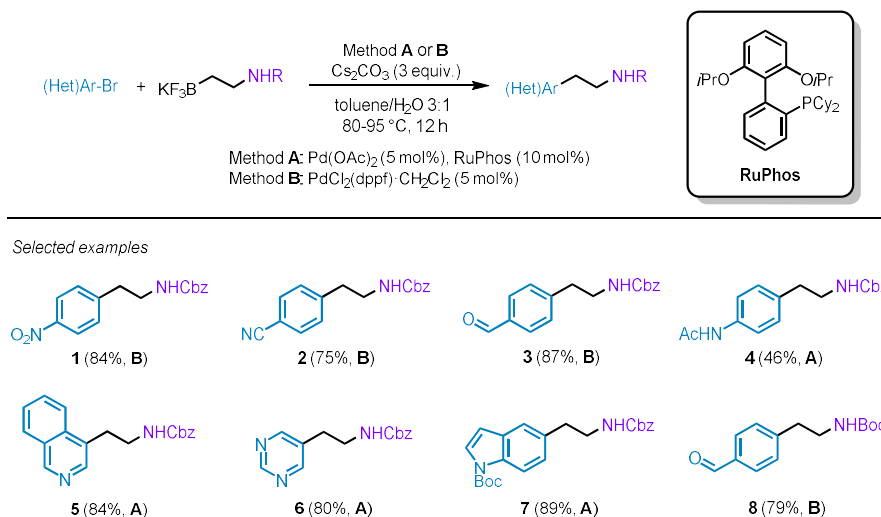
Scheme 1. Modern strategies to access β -(hetero)arylethylamines.

Transition metal-catalyzed cross-coupling reactions

Transition metal-catalyzed C–C cross-couplings are the hallmark of modern chemistry and one of the most powerful instruments in the chemists' toolbox for the preparation of molecules. This family of transformations is rightfully recognized as a general and predictable way of forging C–C bonds to generate molecular complexity, which makes it an expedient way to construct β -(hetero)arylethylamine scaffolds. From a medicinal chemistry perspective, cross-couplings are

routinely optimized using high-throughput experimentation techniques, which accelerates catalyst optimization and enables the rapid transfer of new methodology from concept to practice. As discussed below, potential disconnections go beyond common C(sp²)-C(sp³) cross-couplings to include C(sp³)-C(sp³) couplings and C(sp³)-H aminations.

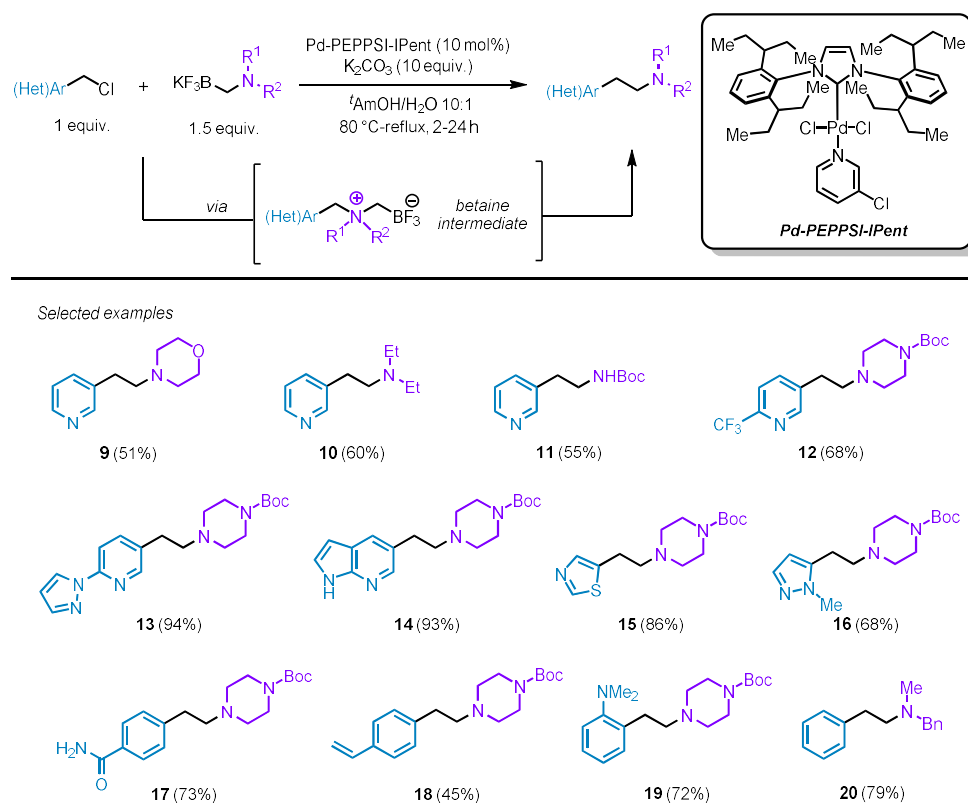
Following seminal studies by the group of Overman on the cross-coupling between (hetero)aryl halides and Cbz-protected vinyl carbamates via the formation of alkylboronic acids *in-situ*,^[8,9] the Molander group pioneered the use of bench-stable potassium organotrifluoroborate salts as an alternative to the use of sensitive alkylboronic acids for Suzuki-Miyaura reactions.^[10,11] The salt is slowly hydrolyzed in the reaction medium, which permits the gradual release of the boronic acid for cross-coupling. In the context of the synthesis of β-(hetero)arylethylamines, this approach avoids the two-step preparation of boronic acids *in-situ*, making it attractive for high-throughput experimentation and catalyst optimization workflows. Following the initial study with carbazole coupling partners,^[10] the group extensively explored the reactivity of carbamate derivatives with (hetero)aryl halides bearing substitution patterns frequently encountered in medicinal chemistry (Scheme 2).^[11] Depending on whether the (hetero)aryl halide was electron-rich or electron-deficient, two distinct promoter systems were found to be optimal, which might be ascribed to different propensities toward oxidative addition.



Scheme 2. Aminoethylation of (hetero)aryl bromides by Pd-catalyzed Suzuki-Miyaura cross-coupling.

Organotrifluoroborate salts were also successfully used by Murphy, Barrett and co-workers to synthesize β-(hetero)arylethylamines through a less common palladium-catalyzed C(sp³)-C(sp³) cross-coupling.^[12] The reaction scope was widely expanded by this new methodology, enabling incorporation of numerous nitrogen heterocycles of biological interest (Scheme 3). In addition,

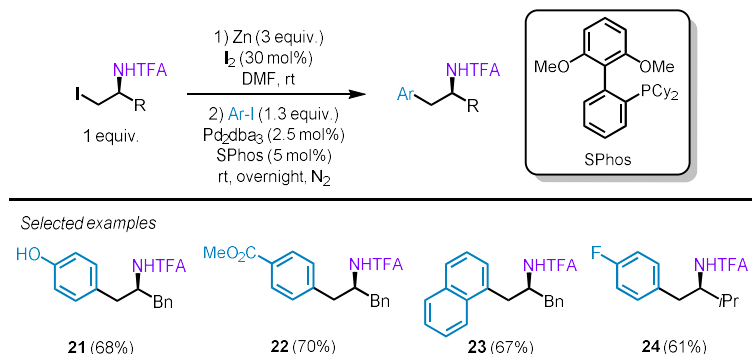
this protocol is compatible with organotrifluoroborates bearing secondary alkylamines, in contrast to earlier studies that required Cbz- and Boc-protected amines. The monitoring of the reaction by LC-MS revealed the formation of a betaine intermediate, which was observed even in the absence of the Pd catalyst, suggesting an initial S_N2 displacement of chloride by the amine. The addition of the Pd catalyst triggered the cross-coupling reaction and afforded the corresponding β-(hetero)arylethylamine in high yields, which supports the active role of the betaine in the catalytic cycle.



Scheme 3. Synthesis of β-(hetero)arylethylamines via C(sp³)–C(sp³) Pd-catalyzed Suzuki-Miyaura cross-coupling.

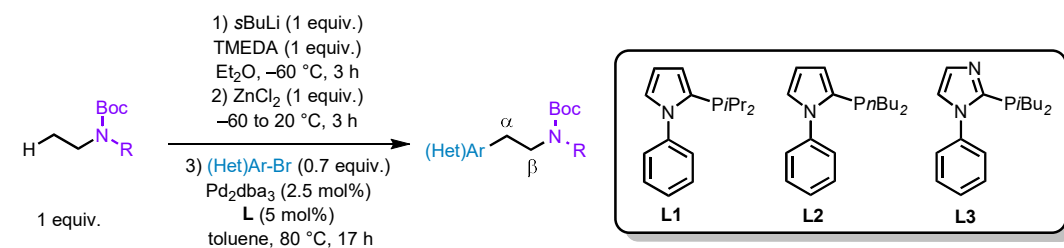
Most cross-coupling strategies for β-(hetero)arylethylamine synthesis led to products lacking substitution within the internal ‘ethylene’ moiety, thereby excluding stereochemical issues. In 2010, the group of Jackson disclosed a modified version of the Negishi cross-coupling to access chiral β-(hetero)arylethylamines (Scheme 4).^[13,14] Based on previous experimental evidence, the authors suggested that the presence of an electron-withdrawing TFA protecting group on the amine could hinder β-elimination of the Pd-alkyl intermediate, keeping the β-aminoalkyl iodide precursor’s chiral center intact in the final product. This indeed proved to be the case, but the

reaction was limited to simple aryl iodides and to benzyl and isopropyl groups at the α -position of the amine.^[31]

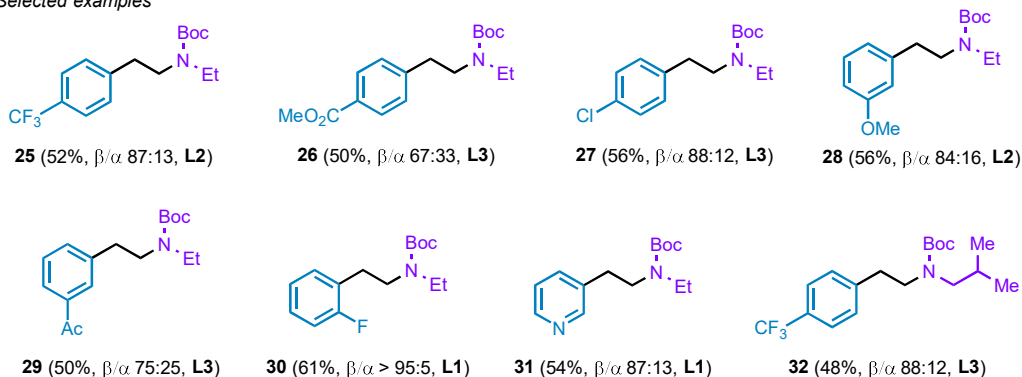


Scheme 4. Synthesis of chiral arylethylamines via Negishi cross-coupling.

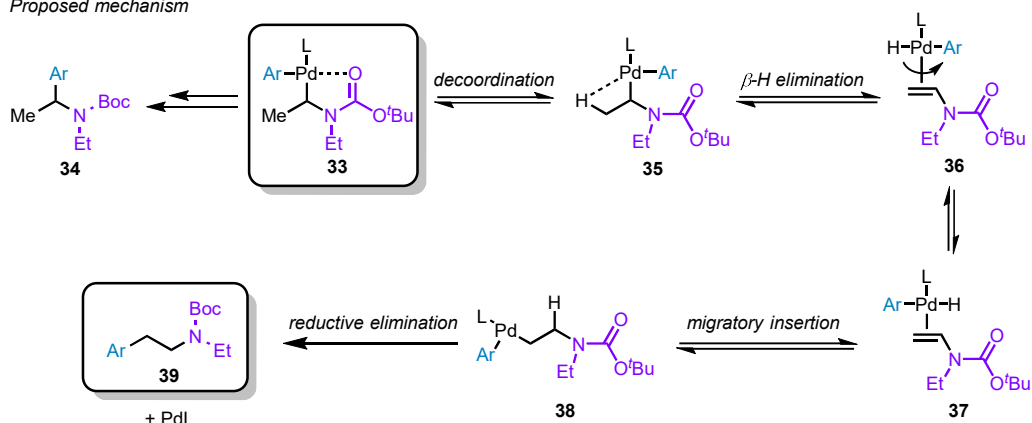
An alternative approach for the generation of alkylzinc intermediates for Negishi cross-coupling reactions, relying on simple ethylamines, was developed by the group of Baudoin (Scheme 5).^[15] The presence of a Boc protecting group enables a directed α -lithiation of ethylamine followed by transmetalation with ZnCl_2 . In a second step, a palladium pre-catalyst, an electron-rich phosphine ligand, and a (hetero)aryl bromide bearing electron-donating or -withdrawing groups were added to implement the Negishi cross-coupling, delivering a wide variety of simple β -(hetero)arylamines. Mechanistic investigations supported by density functional theory (DFT) calculations suggest that the Pd-alkyl complex **35**, formed after transmetalation with the alkylzinc substrate, undergoes β -H elimination to give a Pd-H species **36**. Following rotation of the coordinated enecarbamate, the alkene undergoes migratory insertion into the Pd-H bond to give **38**. Depending on the nature of the ligand, migratory insertion at the β -carbon site may have a lower activation barrier over the α -carbon, which would explain the observed regioselectivity. Given the yields and regioselectivities obtained, this synthetic method has large potential for further optimization and ligand tuning.



Selected examples



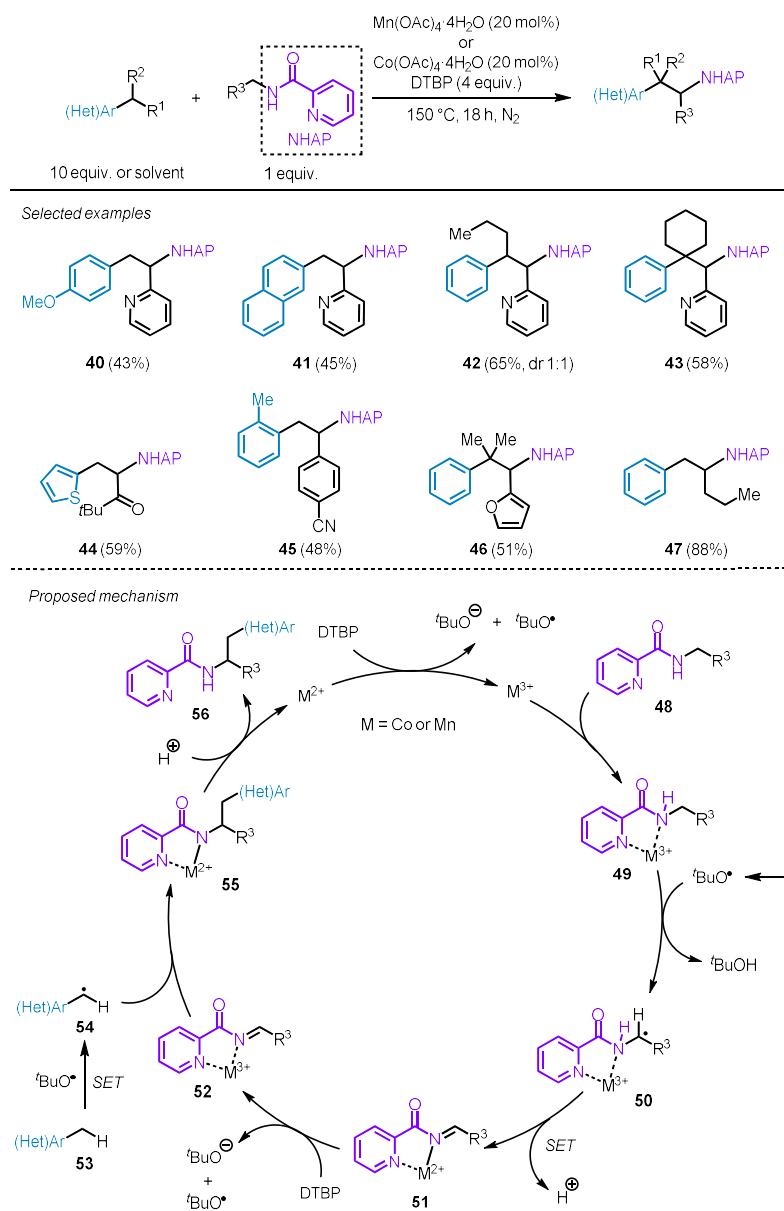
Proposed mechanism



Scheme 5. Ligand-controlled β -arylation of acyclic N-Boc amines.

Considering the previous example, the direct amination of inert $\text{C}(\text{sp}^3)\text{-H}$ bonds is a highly attractive strategy to access β -(hetero)arylethylamines. Unlike approaches based on classical cross-coupling reactions, no stoichiometric waste is generated. In this regard, the You group recently disclosed how a $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)$ disconnection can be leveraged for the synthesis of β -arylethylamines.^[16] Catalytic oxidative cross-coupling using abundant metals such as cobalt and manganese enabled the functionalization of various benzylic substrates in good yields to access α -substituted β -arylethylamines via a coordination activating strategy (Scheme 6). An excess of di-*tert*-butyl peroxide (DTBP) was used as a source of radicals for generating several key intermediates in the catalytic cycle via hydrogen atom transfer (HAT) and SET pathways. The

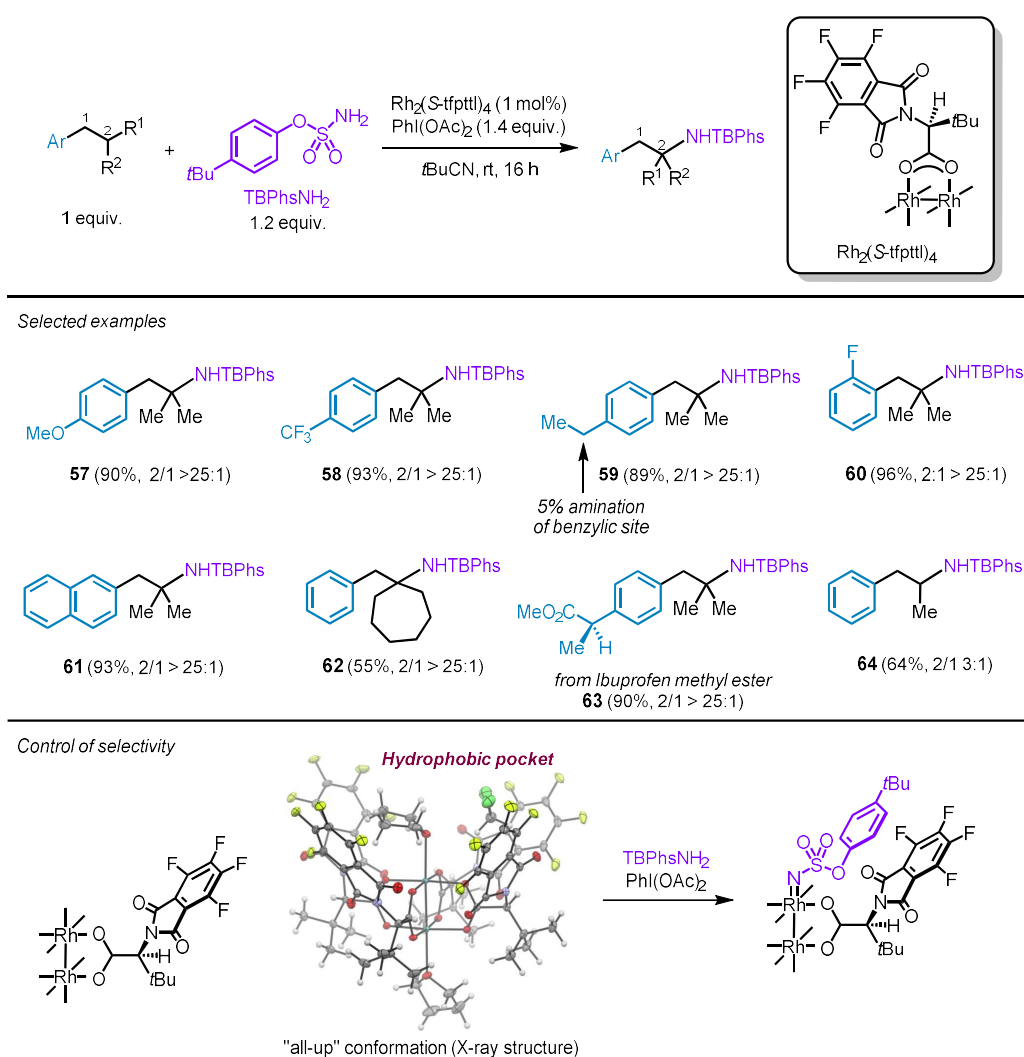
reaction is suggested to proceed via initial coordination of the pyridyl amide moiety to the metal (**49**), which would activate the substrate towards a HAT mediated by *tert*-butoxyl radical. The newly formed C-centered radical **50** would then undergo SET to afford imine intermediate **51**. Meanwhile, the *tert*-butoxyl radical would abstract a hydrogen atom from the benzylic coupling partner to give benzylic radical **54** that immediately adds across imine **52** to create the critical C(sp³)-C(sp³) bond and to construct the β-(hetero)arylethylamine scaffold. A series of control experiments corroborated the mechanistic proposal. For instance, carrying out the transformation using an amide bearing an additional methyl group did not deliver any cross-coupling product, confirming the critical role of the amide's free NH in the reaction. In the presence of radical scavengers such as 2,2,6,6-tetramethylpiperidiny-1-oxy (TEMPO) or butylated hydroxytoluene (BHT), the reactivity was suppressed, supporting the involvement of radical intermediates. When conducting a competition experiment between toluene and toluene-d₈, a significant primary kinetic isotope effect ($k_H/k_D = 6.14$ when R³ = 2-pyridyl) was observed, likely pointing towards the formation of the benzylic radical as the rate-determining step. Despite these advances, harsh reaction conditions and the need to use arene derivatives in large excess hamper the broad applicability of this methodology.



Scheme 6. Manganese/cobalt-catalyzed oxidative C(sp³)-C(sp³) cross-coupling between amines and benzylic substrates.

Another noteworthy approach for the synthesis of β -arylethylamines through site-selective amination of unactivated C(sp³)-H bonds was recently described by the group of Dauban (Scheme 7).^[17] The major advantage of the work is that the substrate does not require a directing group. It hinges on the previous discovery that the dinuclear rhodium(II) carboxylate complex derived from α -N-(phthaloyl) amino acids can adopt an “all-up” conformation with phthalimide moieties, forming a hydrophobic pocket akin to that found within calixarenes. The authors hypothesized that the use of a sterically demanding nitrene precursor would lead to the formation of a Rh-nitrene species

residing in the upper hydrophobic pocket. Meanwhile, the steric hindrance exhibited by this pocket would preclude the reaction at the benzylic position, favoring the nitrene insertion into the more accessible C(sp³)-H bond. The fine-tuning of the sulfamate nitrene precursor and the ligand's phthalimide motif allowed a successful discrimination between the benzylic and tertiary C(sp³)-H bonds for a variety of substrates, affording β -arylethylamine products in high yields with excellent regiocontrol. The catalytic system was sufficiently robust to selectively functionalize a challenging Ibuprofen methyl ester and a simple propylbenzene, albeit in a lower selectivity. This new protocol represents an expedient way of synthesizing β -arylethylamines incorporating an α -tertiary amine. Of note, the obtained products were easily deprotected with pyridine to give the free amine.



Scheme 7. Rh-catalyzed intermolecular selective C(sp³)-H amination of tertiary C-H bonds. X-ray structure reproduced from ref. [17]. Copyright (2021), with permission from American Chemical Society.

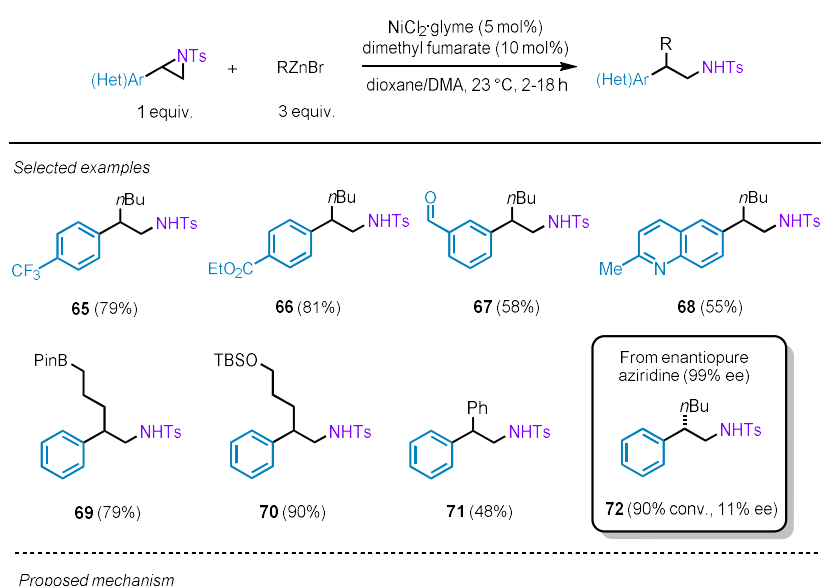
Classical transition metal-catalyzed cross-coupling reactions are a reliable and efficient tool for the synthesis of β -(hetero)arylethylamines. However, most methods capable of assembling this type of scaffold require pre-activation of the coupling partners, which generates stoichiometric waste, and are limited to producing unsubstituted ethyl scaffolds. Moreover, only a single study tackled the synthesis of β -(hetero)arylethylamines bearing a chiral center, and in this case the center was already present in the starting material. As an attractive alternative, the development of novel C(sp³)-H functionalization methodologies that alleviate the need for specifically pre-functionalized substrates (e.g. boronic acids, alkylzinc/alkyltin species) have already shown great promise and more developments to access β -(hetero)arylethylamines are certainly forthcoming thanks to recent developments in photocatalysis and electrocatalysis.

Ring-opening of aziridines

Aziridine ring-opening represents another efficient way of constructing β -(hetero)arylethylamines by directly providing the 'ethylamine' backbone. As a three membered ring, aziridine is a highly strained molecule that can be ring-opened under mild conditions, a feature that has been extensively exploited in nucleophilic additions or cross-coupling reactions.^[18] Furthermore, aziridines are readily accessible from feedstock alkenes and their reactivity can be easily fine-tuned in accordance with their substitution pattern.^[19] Over the past decade, major strides in transition metal-catalyzed ring-opening of aziridines have expanded the applications of this transformation.

Nickel catalysis holds a prominent place in this area. Owing to its capacity to participate in one- and two-electron elementary processes while accommodating several stable oxidation states, numerous nickel-catalyzed transformations have emerged, ranging from classical organometallic chemistry to photo- and electrocatalysis. In their seminal works, the groups of Hillhouse and Wolfe showed that Ni⁰ and Pd⁰ could undergo S_N2-type oxidative addition to one of the aziridine C–N bonds to form a 4-membered azametallacycle.^[20,21] However, these findings did not translate into efficient cross-coupling methodologies due to the strong preference to undergo β -elimination to form imines.^[21] A significant step forward was made in 2012 when the Doyle group reported a Ni-catalyzed Negishi cross-coupling reaction between phenylaziridines and alkylzinc reagents (Scheme 8).^[22-25] During the reaction development, classical ligands such as PPh₃, PCy₃, BINAP or 2,2'-bipyridine failed to provide the target product. Unexpectedly, the use of electron-deficient dimethyl fumarate as a ligand unlocked the desired reactivity and delivered cross-coupling ring-opening products in high yields and excellent regioselectivity for the benzylic position. The reaction exhibits broad functional group compatibility, but the scope of substrates was exclusively

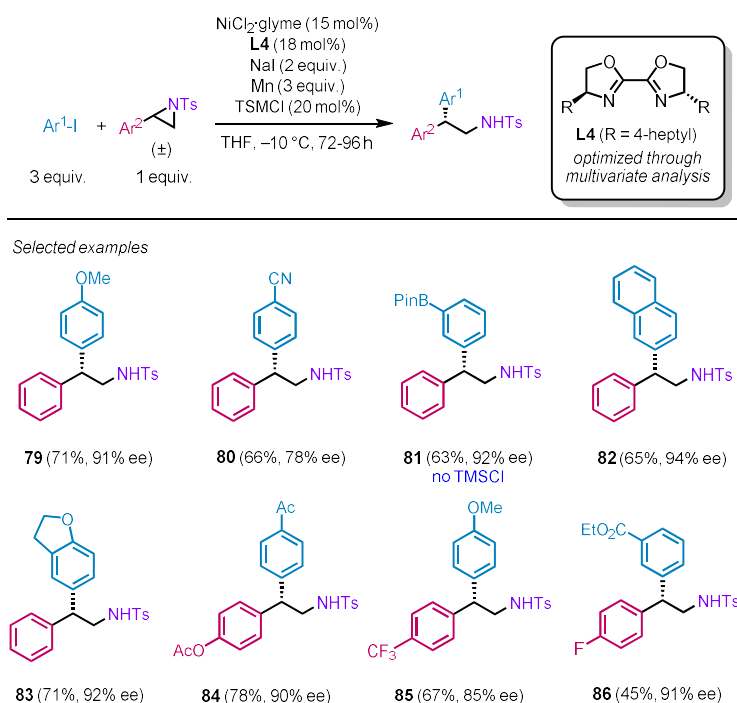
limited to phenylaziridines, as aliphatic aziridines proved unreactive. Additionally, the use of an enantiopure aziridine as a substrate revealed the scrambling of stereochemistry in the final product. These observations bring the plausibility of 2-electron elementary steps into question. The authors presumed that the initial oxidative addition might proceed via a SET reduction of aziridine **73** to form benzylic radical **74**, which then immediately recombines with the metal (**77**). Such a pathway could explain the loss of stereochemistry and why, due to the easier formation of more stable radicals, the substrate scope is limited to phenylaziridines. The electron-deficient nature of the dimethyl fumarate ligand was proposed to facilitate the challenging reductive elimination from **78** that leads to the final product.



Scheme 8. Ni-catalyzed Negishi cross-coupling between styrenyl aziridines and alkylzinc bromides.

In 2017, a breakthrough was disclosed by the groups of Sigman and Doyle regarding a stereoconvergent reductive cross-coupling of phenylaziridines with aryl iodides (Scheme 9).^[26] Compared to previous reports on Negishi cross-coupling reactions with aziridines, this new

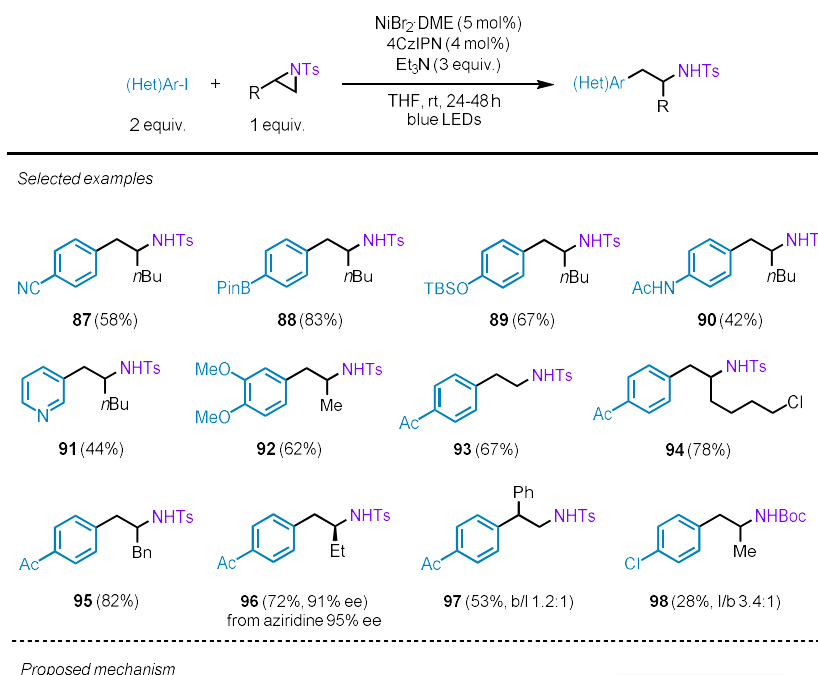
protocol enabled the use of readily available and bench-stable aryl iodides instead of sensitive zinc reagents. Moreover, by using a chiral 4-heptyl BiOx ligand, the racemic starting material could be transformed into the cross-coupling product with high enantioinduction. As the effect of the ligand on stereoselectivity was not trivial to rationalize, a multivariate analysis of ligand structure based on various molecular descriptors was performed. Long branched alkyl groups were found to have the most profound influence on ee values. The overall effect seems to originate from the bulkiness of these substituents, which disfavors the formation of the other enantiomer, and from a larger surface that facilitates non-covalent interactions with substrates. Notwithstanding these major improvements, the methodology remained limited in that β,β -diarylethylamines could be accessed only from aromatic aziridines.^[25]



Scheme 9. Ni-catalyzed enantioselective reductive cross-coupling of styrenyl aziridines with aryl iodides.

Encouraged by these results, the group of Doyle further expanded this methodology by using a cooperative approach between a dicyanoarene photocatalyst (PC) and a nickel catalyst (Scheme 10).^[28] This protocol allows the extension of the ring-opening arylation to unsubstituted aziridines or to aliphatic aziridines, with the electrophilic cross-coupling occurring at the least hindered site. A wide array of β -(hetero)arylethylamines bearing a variety of pharmaceutically relevant substituents, including amphetamine derivatives, were obtained in moderate to high yields. On the other hand, in the case of *N*-tosyl-2-phenylaziridine, a mixture of linear and branched products was obtained with a 1.2:1 l/b ratio. Importantly, starting from an enantiopure aziridine, only a slight

decrease of the enantiomeric excess was observed, which is consistent with the sole activation of the less-substituted C–N bond. Mechanistic investigations ruled out a direct SET reduction of the aziridine but pointed instead towards the formation of iodoamine intermediate **101** via a nucleophilic ring-opening. Iodoamine was detected by ^1H NMR monitoring of the reaction which, when subjected to the reaction conditions, led to the corresponding cross-coupling product. It is noteworthy that, when the reaction was carried out without nickel, the formation of sultam **99** was observed. This product is likely the result of an intramolecular cyclization of the tosyl group and alkyl radical, which is formed upon SET reduction of iodoamine. The mechanistic hypothesis is supported by the formation of the sultam in higher yields if 10 mol% of tetrabutylammonium iodide was added to the nickel-free reaction. Based on these data, the following mechanistic scenario was proposed: the excited photocatalyst triggers the SET oxidation of Et_3N to form a radical cation, which generates the $[\text{Et}_3\text{N}\cdot\text{HI}]$ species. Based on previous studies on the ring-opening of epoxides with $[\text{Et}_3\text{N}\cdot\text{HI}]$, the authors suggested that a nucleophilic addition would occur at the less hindered site to afford iodoamine **101**. Iodoamine would then undergo either a SET reduction or a halogen atom abstraction (HAA) to form alkyl radical **102**, which would immediately react with nickel complex **103** resulting from oxidative addition into the Ar–I bond. A subsequent reductive elimination would finally deliver cross-coupling product **105**. Such a mechanism explains the lack of reactivity of aryl bromides under these conditions, as the resulting bromoamine intermediate might not be sufficiently electrophilic to react with the nickel complex. Importantly, as this mechanistic scenario diverges from previous reports involving the oxidative insertion of nickel into the aziridine, protecting groups other than sulfonyl (e.g. Boc) could also be employed, albeit in a lower yield and regioselectivity. Sulfonamide protecting groups therefore appear to ease the initial oxidative addition.



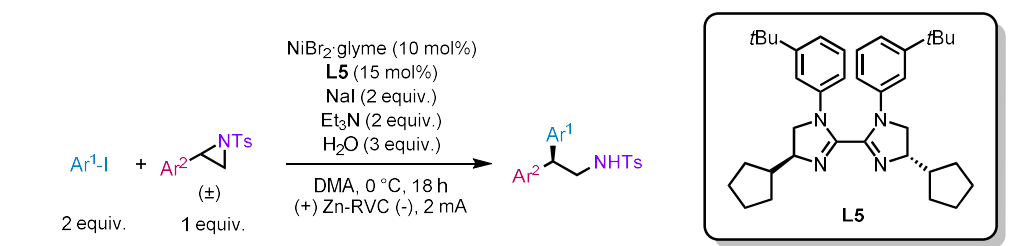
Scheme 10. Ni/Photoredox electrophilic cross-coupling of aliphatic aziridines with (hetero)aryl iodides.

Inspired by the Doyle group's reaction design, the groups of Milo and Mei devised an electrochemical enantioselective nickel-catalyzed reductive cross-coupling (Scheme 11).^[29] This transformation enables electrophilic cross-coupling of arylaziridines with (hetero)aryl iodides at the benzylic position to afford β -(hetero)arylethylamines in synthetically useful yields (40-95%) and enantiomeric excesses up to 94%. Mechanistic studies with cyclic voltammetry suggest that under their standard reaction conditions, a Ni^0 species can undergo oxidative addition with aryl iodides but not with aziridines. A control experiment without electric current completely halted the reaction. This result indicates that the electrochemical reduction of the Ni^{I} species at the cathode

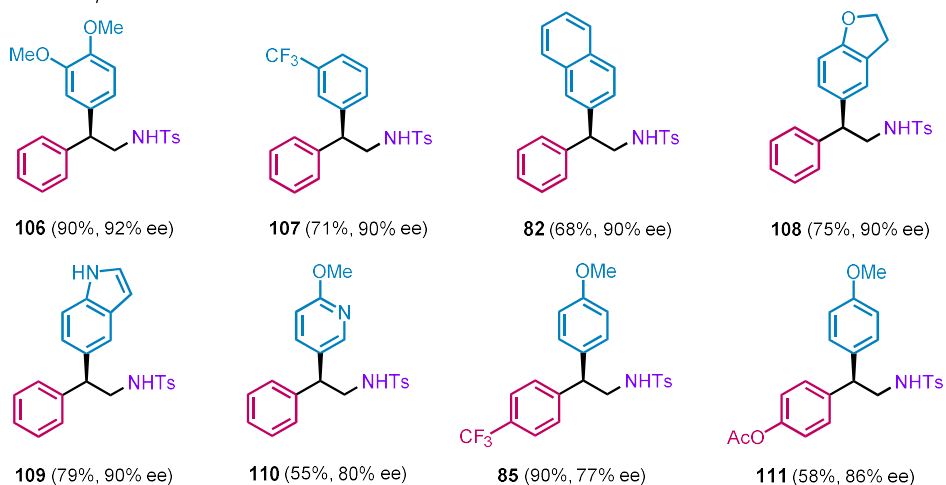
is responsible for the turnover of the catalytic cycle. The formation and potential involvement of iodoamine species in the cross-coupling was also probed. Aziridines were indeed ring-opened by the iodide at the benzylic position and the isolated iodoamine delivered the cross-coupling product when subjected to the reaction conditions. Based on these findings and the earlier report from the Doyle group, a plausible mechanism would rely on anodic

oxidation of Et_3N to a radical cation followed by formation of $[\text{Et}_3\text{N}\cdot\text{HI}]$. Nucleophilic ring-opening addition of aziridine **112** would then occur to form the corresponding iodoamine **113** which, upon SET reduction, would give benzylic radical **114** that directly engages in the nickel catalytic cycle. The formation of benzylic radical species was corroborated by two control experiments using radical scavengers, namely TEMPO and B_2Pin_2 , in which case no cross-coupling product was obtained.

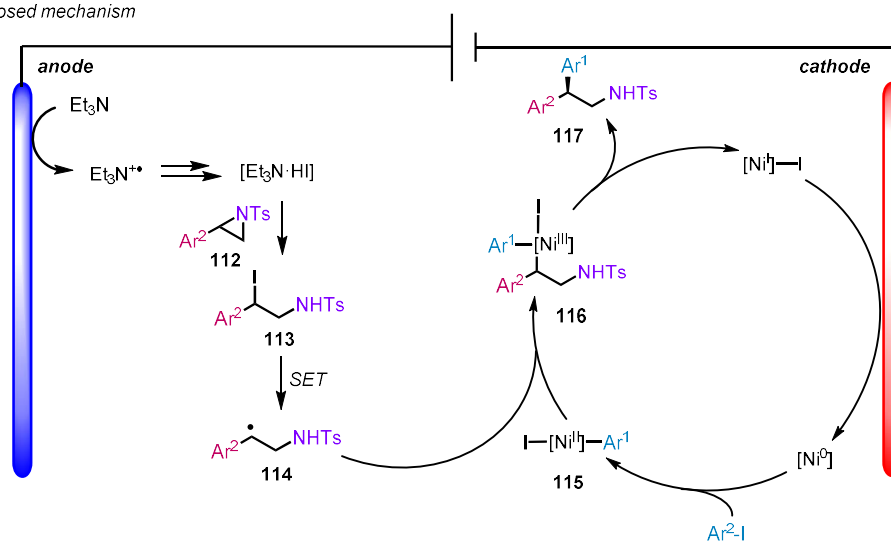
A multivariate regression analysis of the ligand structure provided insights into the origin of enantioinduction. The authors applied the same set of molecular descriptors used by the Doyle group for the photocatalytic cross-coupling of styrene oxides and aryl iodides to biimidazole ligands.^[30] The comparison between the two models revealed profound differences in the way the ligand induced enantioselectivity in electrochemical and photocatalytic cross-coupling reactions. In the case of the electrochemical reaction, the model with the best statistical fit indicates that steric factors have a determining influence on the value of $\Delta\Delta G^\ddagger$, favoring one enantiomer over another. In contrast, the model established for the photocatalytic reaction shows a strong dependency on the electronics on the metal center (e.g. natural charges on Ni from a natural population analysis (NPA)). The wider spread of enantioselectivities observed in the electrochemical reaction are therefore explained by the greater importance of the steric environment surrounding the catalyst in enantioinduction. This result exemplifies that the optimal ligand for reactions with seemingly similar mechanisms may be guided by completely different rationale.



Selected examples



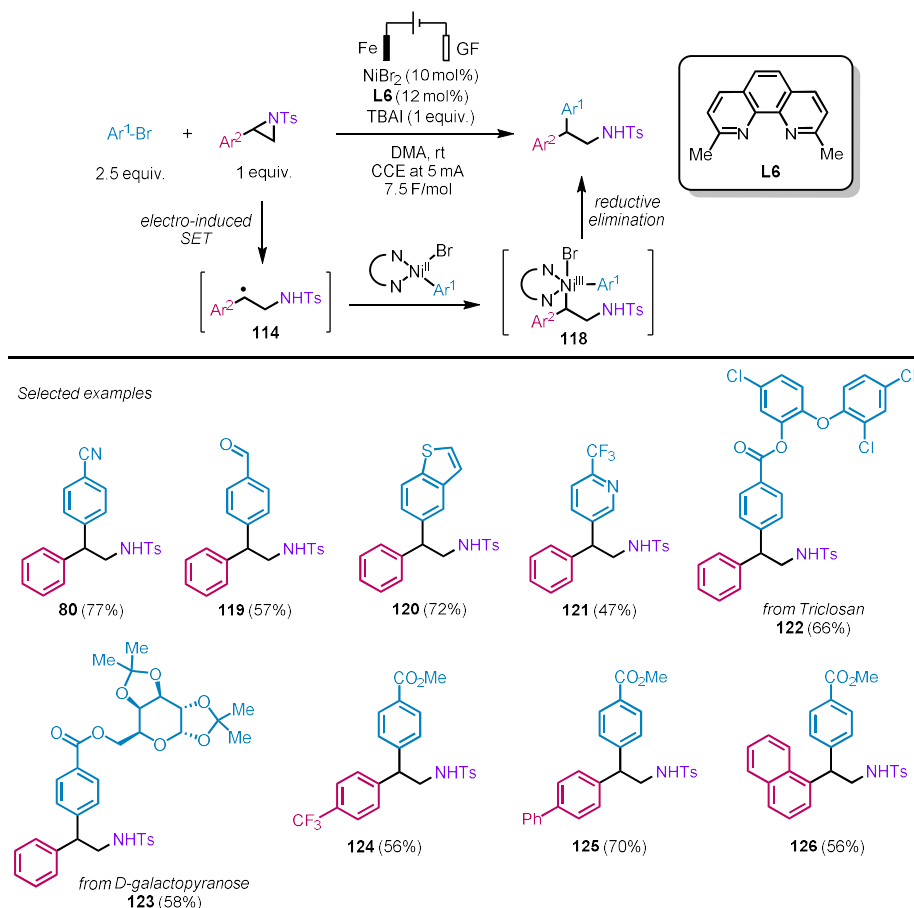
Proposed mechanism



Scheme 11. Ni/biimidazole-catalyzed electrochemical enantioselective reductive cross-coupling of styrenyl aziridines with aryl iodides.

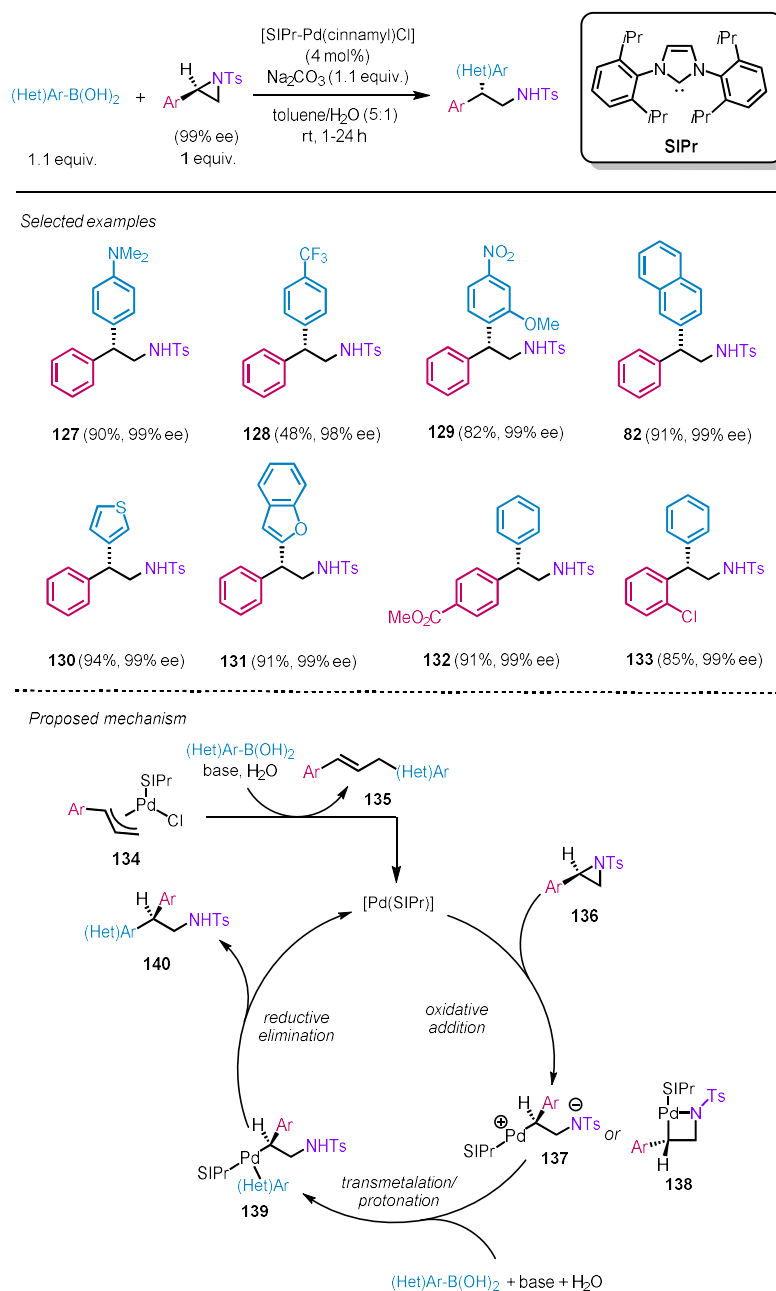
The Qiu group disclosed a similar electroreductive nickel-catalyzed cross-coupling of aziridines with aryl bromides (Scheme 12).^[31,32] The protocol was compatible with a large variety of electron-deficient (hetero)aryl bromides incorporating cyano, trifluoromethyl, aldehyde, ester, amide, and halide groups. Although oxidative addition into electron-rich aryl halides is known to be slower,

the presence of electron-donating substituents on the phenyl ring was well-tolerated to afford the ring-opening products in high yields. Similarly, the reaction was compatible with electron-rich and -deficient styrenyl aziridines. The utility of the new transformation was successfully demonstrated in the late-stage functionalization of Triclosan derivative and protected carbohydrates. In contrast with methods that involve the formation of an iodoamine, the reaction is suggested to operate via an initial SET reduction of the aziridine to directly form benzylic radical **114**, which is then trapped by a Ni complex in a catalytic cycle similar to the one described in Scheme 11. Several control experiments were carried out to evaluate the proposed mechanism. Conducting the reaction in the presence of tetrabutylammonium tetrafluoroborate (TBABF₄), rather than tetrabutylammonium iodide (TBAI), did not prevent the formation of the product, indicating that an iodoamine was not an intermediate. The use of an enantiopure *N*-tosyl-2-phenylaziridine in the reaction led to racemic product, which is consistent with the formation of a benzylic radical intermediate.



Scheme 12. Ni-catalyzed electroreductive electrophilic cross-coupling of styrenyl aziridines with aryl bromides.

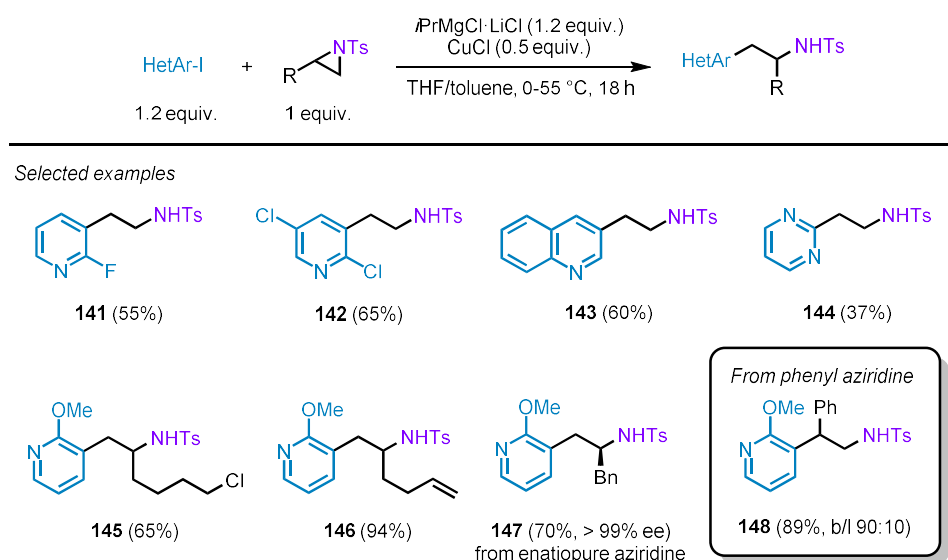
Complementing the rapid emergence of Ni-catalyzed coupling reactions, Pd-catalyzed transformations have also received attention. For instance, following the Michael group's seminal work on the Pd-catalyzed Suzuki-Miyaura cross-coupling of aliphatic aziridines with aryl boronic acids,^[33] the group of Minaka reported in 2014 a stereospecific version between styrenyl aziridines and readily available and bench-stable (hetero)arylboronic acids (Scheme 13).^[34] This methodology proved to be general, tolerating both electron-rich and -deficient arylboronic acids to afford coupling products in yields ranging from 46 to 96%. Besides aryl groups, benzofuran and thiophene moieties could also be introduced in high yields. Unlike the method of Michael, reaction conditions were compatible with the presence of a tosyl protecting group on the nitrogen. The authors suggested that an agnostic bonding of *i*Pr substituents of the NHC ligand coordinatively saturates the metal center, thus preventing a β -elimination as a side reaction. The reaction is proposed to proceed via initial S_N2-type oxidative addition with inversion at the benzylic carbon (**137** or **138**), followed by transmetalation (**139**) and reductive elimination with retention of stereochemistry (**140**).



Scheme 13. Pd/NHC-catalyzed enantiospecific arylation of styrenyl aziridines with (hetero)arylboronic acids.

Key structural motifs in drug discovery, such as pyridines, remain underrepresented in transition metal-catalyzed approaches due to their tendency to coordinate the catalyst, thereby decreasing regioselectivities and yields. However, pharmaceutical company Boehringer Ingelheim has recently addressed these issues by developing a copper-catalyzed regioselective and stereospecific ring-opening of aziridines (Scheme 14).^[35,36] The overall reaction design consists

of the preparation of pyridyl organocuprates *in-situ* from a pyridyl iodide, which then reacts with the corresponding aziridine. In the first step, a pyridyl Grignard is obtained via metal-halogen exchange between a pyridyl iodide and a turbo Grignard reagent (*i*PrMgCl·LiCl) before undergoing transmetalation with CuCl to provide the reactive organocuprate. The new protocol displayed broad functional group tolerance on the pyridyl ring and even a pyrimidine moiety could be used. It also allowed aliphatic aziridines to give the corresponding linear products. In the case of aryl aziridines, the regioselectivity was reverted in favor of the branched product. On the other hand, unlike pyridyl fluorides and chlorides, the reaction was not compatible with pyridyl bromides, as these substrates formed dimers or underwent debromination under the reaction conditions.



Scheme 14. Cu-catalyzed regioselective and stereospecific ring-opening arylation of aziridines with pyridyl Grignard reagents.

These examples illustrate that the past decade has witnessed tremendous advances in nickel- and palladium-catalyzed cross-couplings of aziridines, which were previously deemed challenging. Many recent methodologies accommodate all types of substitution patterns encountered in medicinal chemistry, which together with stereospecific and enantioselective protocols, make these methods appealing for synthesis. Nickel catalysis coupled with photocatalysis, or electrochemistry backed by statistical modelling of ligands has proven to be a promising direction for the rational design of related transformations. Strategies based on C–H activation are also popular but they impose the presence of specific functional groups in the final product.^[37–39] In the context of synthesizing β -(hetero)arylethylamine scaffolds, several other shortcomings should be mentioned. Aziridines are evidently not as easily accessible as enamides or styrenes, especially with densely functionalized precursors, which adds additional steps in the

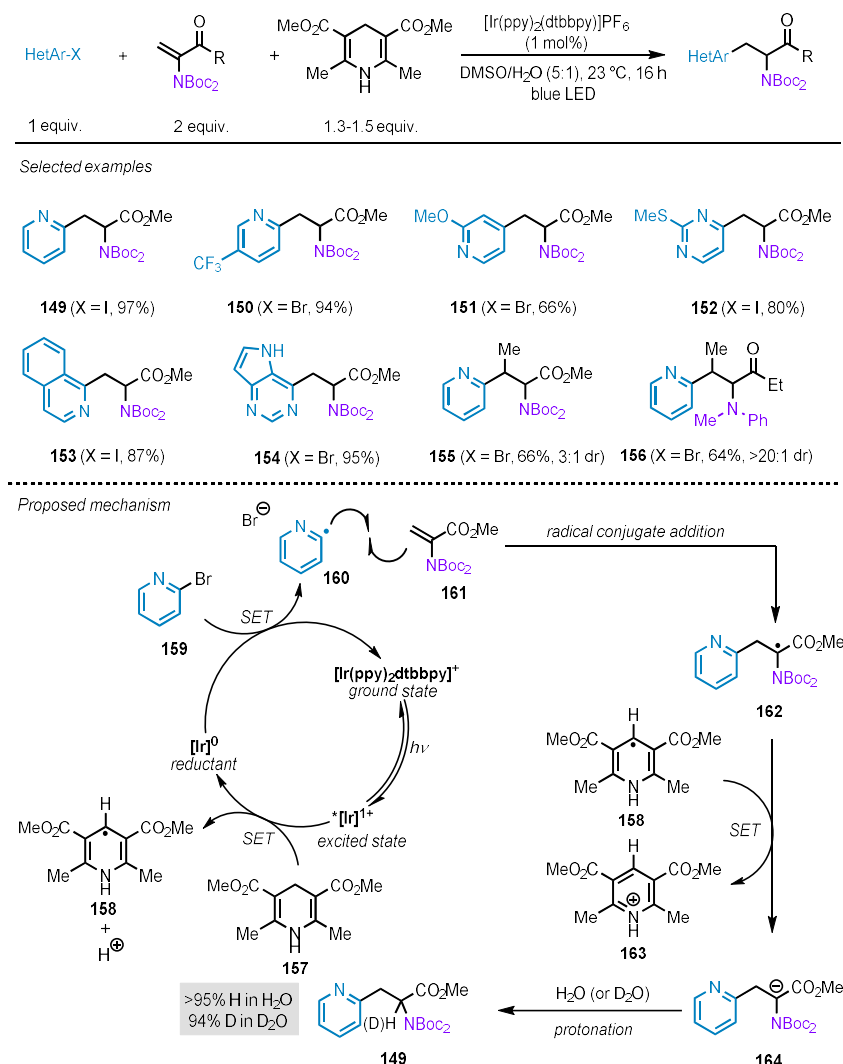
synthesis of β -(hetero)arylethylamines. Secondly, most of the current strategies require a sulfonyl protecting group on the amine to prevent catalyst poisoning or to facilitate oxidative addition. Yet, the chemoselective deprotection of sulfonamides is not always straightforward and can be incompatible with several functional groups. Developing methods compatible with a broader range of protecting groups, or avoiding them altogether, would clearly open new avenues for ring-opening functionalization of aziridines.

Hydroarylation of enamides

When it comes to the construction of the β -(hetero)arylethylamine scaffold, the hydroarylation of enamides still remains surprisingly underdeveloped. The main reason is the challenge associated with the selective anti-Markovnikov addition of the (hetero)aryl group to the double bond. Yet, enamides are well-suited to this goal because of their ease of synthesis, their diversity, and their stability.^[40] Taken together with the ready availability of (hetero)aryl halides, the hydroarylation of enamides provides a straightforward platform to rapidly assess the impact of a variety of (hetero)aryl, amine, and ethyl moieties on bioactivity.

In 2017, the group of Jui pioneered the hydroarylation of enamides using a photoredox process. The use of $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (2-phenylpyridine = ppy; 4,4'-di-tert-butyl-2,2'-bipyridine = dtbbpy) as a photosensitizer along with stoichiometric quantities of Hantzsch ester in aqueous DMSO enabled the synthesis of a variety of azatyrosine unnatural amino acid derivatives in high yields under mild conditions from Boc-protected dehydroalanine (Scheme 15).^[41] Pyridyl bromides and iodides were chosen as the sources of heteroaryl radicals, as these nitrogen heterocycles can modify the solubility, metabolic stability, and binding affinity of the compounds in which they are embedded. Here, the photoredox approach involving a radical conjugate addition has the advantage of being highly chemoselective while usually displaying a large functional group tolerance. Apart from pyridyl halides, the methodology was compatible with other *N*-heterocycles such as isoquinolines, 1,3-pyrimidines, and pyrrolopyrimidines, providing an alternative approach to unnatural amino acids that were difficult to access by other means. Aniline and ketone moieties could also be introduced instead of Boc protecting groups and esters. Control experiments in the absence of the photocatalyst, light, or a redox quencher did not afford any product, supporting the initial hypothesis of a photocatalytic pathway. Interestingly, replacing water with its deuterated analog led to a 94% deuteration at the α -carbonyl position. This finding suggests that the role of the Hantzsch ester is likely limited to the SET regeneration of the photocatalyst and the reduction of a transient α -carbonyl radical, which can then capture a proton from water. Based on these mechanistic experiments, the authors proposed the following mechanism: upon irradiation of the

cyclometalated iridium complex, the reductive quenching of the excited photocatalyst by the Hantzsch ester takes place to generate the Hantzsch ester radical **158**. Meanwhile, pyridyl bromide **159** undergoes SET with the photocatalyst to yield pyridyl radical **160**, which reacts with α -dehydroamino ester **161** via a radical conjugate addition process to form the corresponding α -carbonyl radical **162**. Subsequent SET with the Hantzsch ester radical **158** and protonation by water delivers unnatural amino acids bearing nitrogen-containing heterocycles.



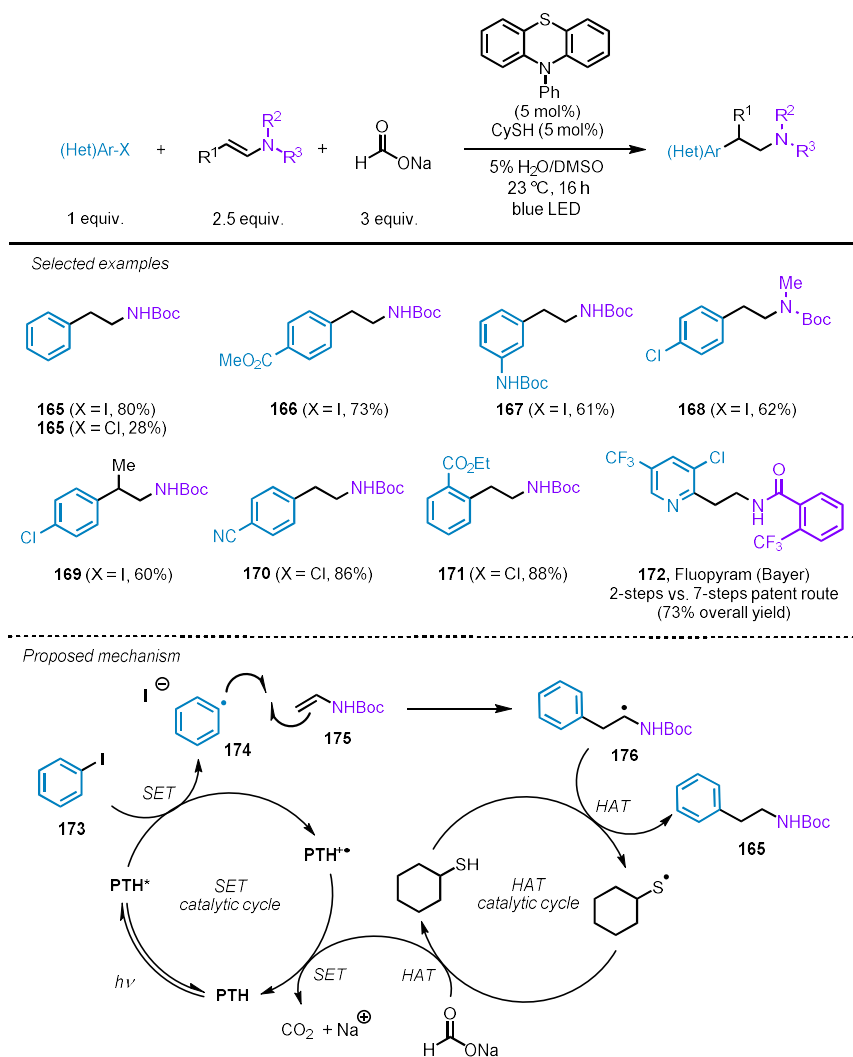
Scheme 15. Synthesis of β -heteroarylethylamine derivatives via photocatalytic radical conjugate addition.

Although remarkable, this seminal report lacks generality, as only the use of electron-deficient heteroaryl bromides and iodides was reported and substrates incorporated ester groups to facilitate the radical conjugate addition. Aryl halides are prone to undergo fast competitive HAT upon generation of the aryl radical, instead of adding to the double bond. Aryl chlorides, for

example, display high reduction potentials (≤ 2.0 V) and strong bond dissociation energies (> 95 kcal/mol), making their utilization elusive. Given that aryl chlorides constitute the large bulk of commercially available aryl halides, this represents a major synthetic limitation.

In 2019, the group of Jui designed a new and inexpensive photocatalytic system to address these limitations, featuring a highly reducing photocatalyst (*N*-phenylphenothiazine = PTH) and cyclohexanethiol (CySH) as a HAT catalyst in the presence of sodium formate (Scheme 16).^[42] The authors hypothesized that the use of CySH would preclude undesired HAT reduction of the photogenerated aryl radicals, a process which interferes with the desired addition of the aryl radical to the enamide. The reaction mechanism would initially proceed through the formation of a neutral phenyl radical **174** from phenyl iodide **173** and its subsequent anti-Markovnikov addition to enamide **175** to form α -carbamoyl radical **176**. This electrophilic intermediate would finally undergo a HAT from the electrophilic cyclohexanethiol to deliver the corresponding β -(hetero)arylethylamine. Here, the excess sodium formate would regenerate the photocatalyst and thiol species (CyS $\cdot$) by reductive SET and HAT processes.

An important feature of this method is its compatibility with aryl chlorides, which have the advantage of being cheaper than aryl iodides. The reaction is efficient with aryl chlorides incorporating electron-withdrawing groups such as nitriles or esters ($E_{1/2}^0 = -2.0$ V and -2.1 V, respectively vs SCE), but a significant drop in yield was observed with substrates that are more challenging to reduce, such as chlorobenzene ($E_{1/2}^0 = -2.8$ V vs SCE). The hydroarylation protocol, coupled with a Boc-deprotection, enabled the direct synthesis of several natural neuromodulators such as tyramine, hordenine, and dopamine. The synthetic utility of the new protocol was illustrated by the synthesis of the fungicide Fluopyram (Bayer) in only 2 steps, compared to a 7-step patented route. A series of Fluopyram analogs varied on both sides of the scaffold was prepared in high yields (up to 92%), demonstrating the utility of this method to deliver bioactive molecules based on the β -(hetero)arylethylamine skeleton.

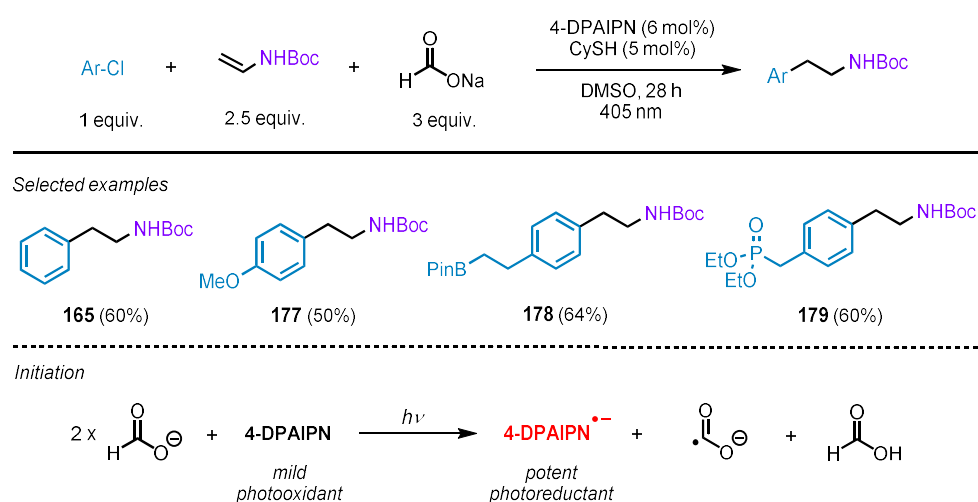


Scheme 16. Synthesis of β -(hetero)arylethylamine via dual-catalytic radical hydroarylation of enamides.

As it was emphasized by the group of Jui during their investigations, operating with aryl halides having reduction potentials inferior to -2.0 V vs SCE, as it is the case with aryl chlorides, is a challenging task under traditional photoredox catalysis. The group of Wickens approached the problem from a different angle by using electron-primed photocatalysis to generate aryl radicals from aryl chlorides (Scheme 17).^[43] The highlight of this strategy is that, upon first excitation, the photocatalyst is reduced to a radical anion which in turn undergoes a second excitation. This excited radical anion can be a highly potent reducing agent due to a very negative redox potential of the PC/PC^{•-} couple such that the reduction of challenging aryl chlorides is unlocked. Using commercially available 2,4,5,6-tetrakis(diphenylamino)isophthalonitrile (4-DPAIPN) as a photocatalyst, along with the cyclohexanethiol/sodium formate system introduced earlier by the group of Jui, this method enabled a wide range of hydroarylations of vinyl carbamates to afford

Boc-protected β -arylethylamines bearing medicinally relevant functional groups from aryl chloride precursors possessing $E_{1/2}$ around -2.8 V vs SCE.

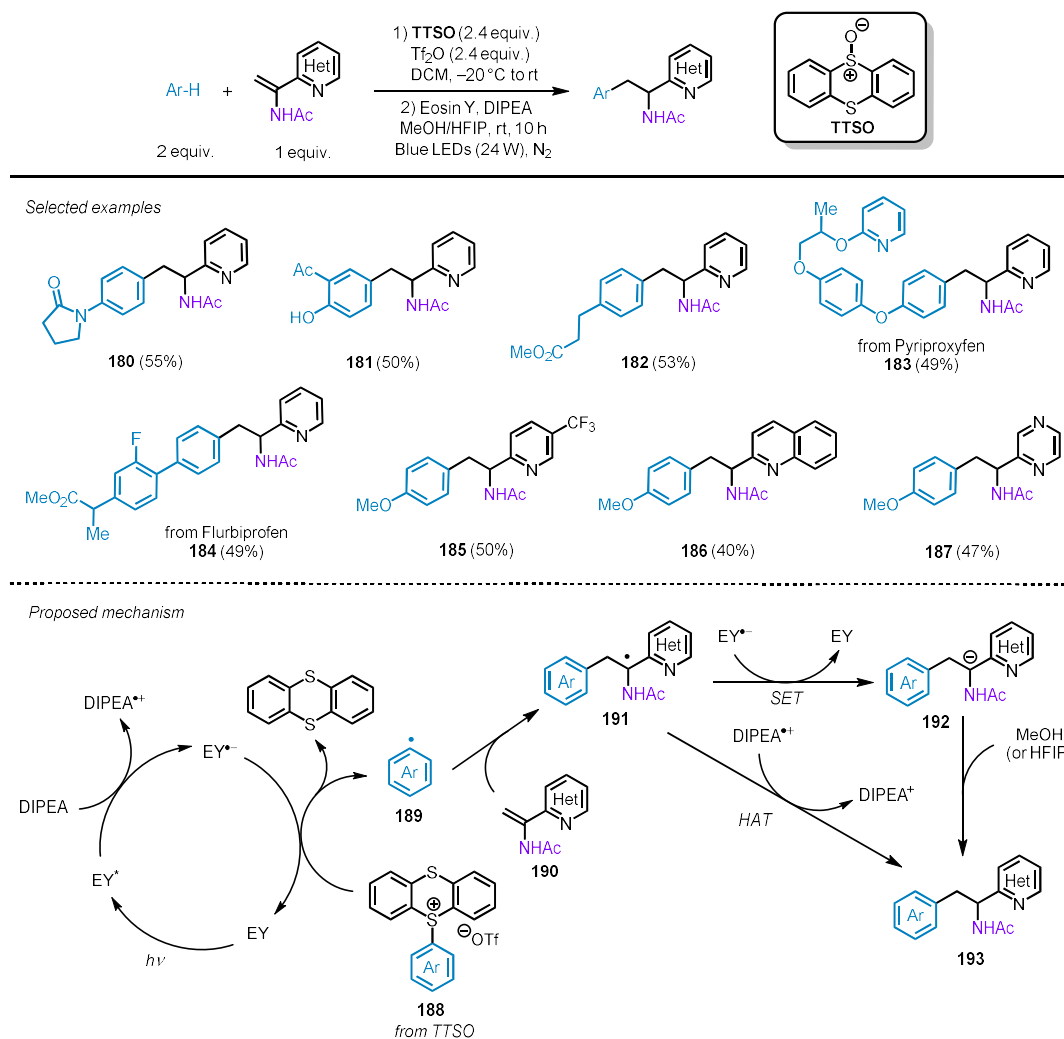
The proposed mechanism involving an electron-primed photocatalyst was supported by UV-vis experiments. However, the authors could not rule out that the carbon dioxide radical anion ($E_{1/2}(\text{CO}_2/\text{CO}_2^{\bullet-}) = -2.2$ V vs SCE) could also play a non-innocent role by allowing the reactivation of the photocatalyst through SET reduction and the direct reduction of aryl chlorides. However, this mechanistic pathway seems unlikely with electron-rich aryl chlorides such as chloroanisole. On the other hand, a potential halogen atom transfer mechanism was discarded by demonstrating that even non-halide derivatives such as anilinium and aryl phosphate salts could be reduced under the reaction conditions.



Scheme 17. Construction of arylethylamines via electron-primed photocatalysis using aryl chlorides.

In 2021, the group of Wang exploited the reactivity of aryl thianthrenium salts as radical precursors to develop a two-step one-pot photocatalytic hydroarylation of azine-substituted enamides (Scheme 18).^[44] This new protocol displays high tolerance to substitution on the azine ring and, besides pyridines, was compatible with other nitrogen heterocycles such as quinoline or pyrazine, offering a notable complement to previous methods making the β -arylethylamine framework. A wide array of electron-rich arenes were amenable to the transformation, including examples of late-stage functionalization of pyriproxyfen and flurbiprofen. Unfortunately, the heteroarene scope was not examined. The reaction mechanism is thought to involve the trifluoromethanesulfonylation of thianthrene S-oxide, followed by reaction with a given arene to generate the corresponding aryl thianthrenium salt **188** *in-situ*. In a second step, this species would react with an Eosin radical anion generated under photocatalytic conditions to form aryl radical **189**, which, in turn, would add to azine-substituted enamide **190** with anti-Markovnikov

selectivity to form α -amino radical **191**. Here, the regioselectivity of formation of the radical precursor depends on the electronic properties of the arene. Only electron-rich arenes were examined, which react at the *para* position with respect to the activating group. From there, two mechanisms are possible: a SET from the Eosin radical anion or a HAT from the *N,N*-diisopropylethylamine (DIPEA) radical cation. Finally, protonation with hexafluoroisopropanol (HFIP) or methanol would afford the final product. Despite the elegance of this approach, it is not atom economical since the reaction requires the use of excess thianthrene S-oxide and superstoichiometric quantities of base (DIPEA).

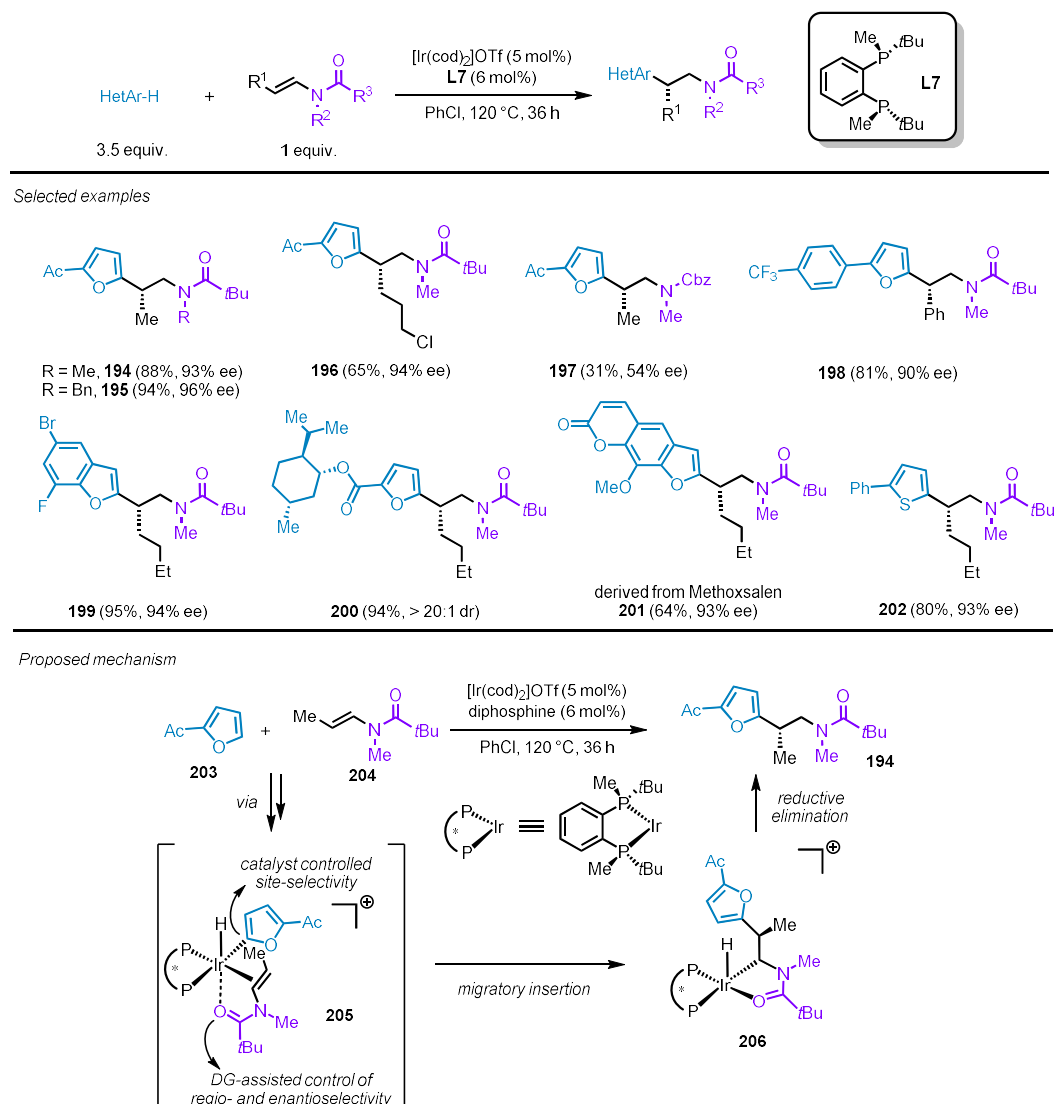


Scheme 18. Thianthrenation-enabled photocatalytic hydroarylation of azine-substituted enamides with arenes.

In parallel, several transition metal-catalyzed strategies have been developed. As an example, the group of Chatani described a Rh-catalyzed hydroarylation of *N*-vinylphthalimide following a

C–H activation process that involves the use of an 8-aminoquinoline unit as an *ortho* directing group.^[45] However, this approach is limited to terminal alkenes, which restricts the diversity of accessible β -(hetero)arylethylamine scaffolds.

The recent photocatalytic and transition metal-catalyzed hydroarylations of enamides described herein have laid the foundation for the development of more general and robust methods for the synthesis of β -(hetero)arylethylamine scaffolds. However, there is still room for improvement. Enantioselective hydroarylations of internal enamides remain scarce. The only example was reported by the group of Li, which changed tactics compared to Chatani by using the amide as a directing group. The major advantage of this approach is that no removal of the directing group is necessary since the amide provides a key functionality in the product, enabling access to a wide array of β -heteroarylethylamine scaffolds bearing furan, benzofuran, furanocoumarin, and thiophene moieties in moderate to high yields (31-96%) with excellent control of stereoselectivity (up to 97% ee) (Scheme 19).^[46] Naturally occurring Methoxsalen and furans derived from L-menthol underwent addition to enamides. Here, the combination of an iridium(I) complex and a bidentate phosphine ligand incorporating bulky *t*Bu substituents enforces the regioselective C–H oxidative addition of heteroaromatic substrate at the less congested side of the metal center (**205**). Meanwhile, the amide serves as a directing group, coordinating to the iridium complex to provide precise regio- and stereocontrol of the migratory insertion of the alkene into the Ir–C bond (**206**). The product is obtained following reductive elimination. The reaction was found to be highly dependent on the coordinating ability of the amide. Given the role of the amide in positioning the substrate, less coordinating amides, not surprisingly, led to lower yields and enantiomeric excesses (**197**). Although not rationalized in the study, the yields for β -heteroarylation did not exceed 21% (86% ee) when the amide methyl group was replaced with a H.



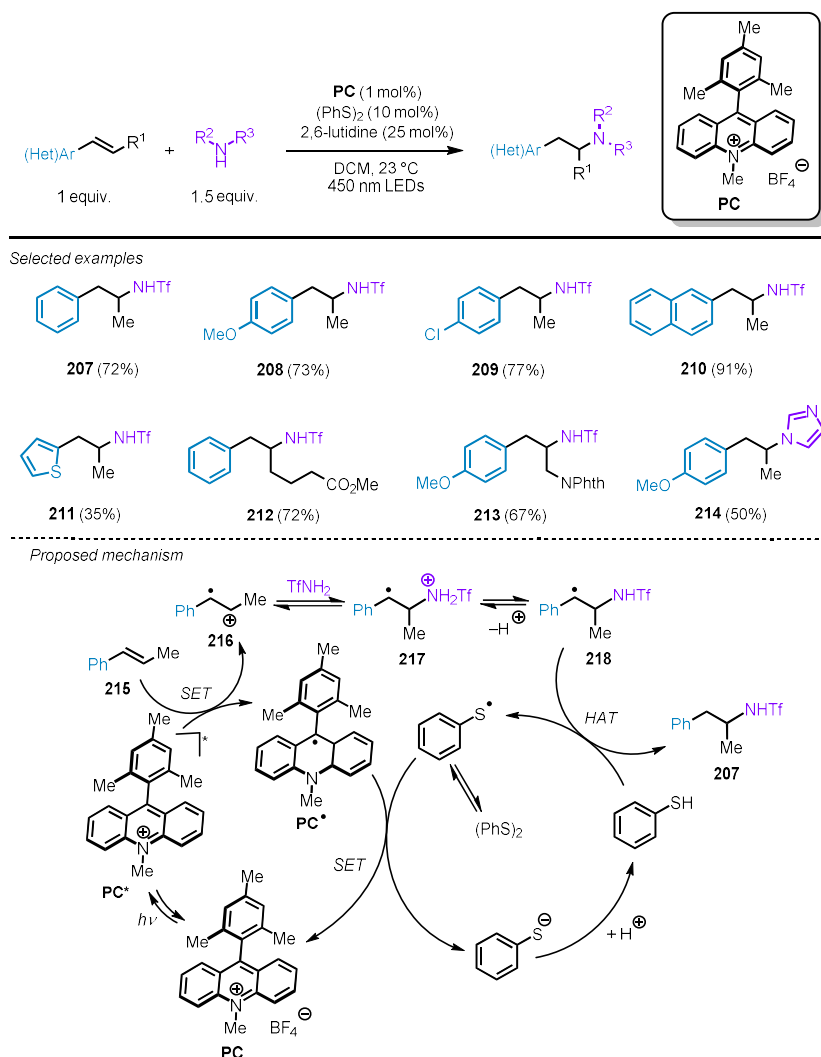
Scheme 19. Ir-catalyzed enantioselective functionalization of heteroaromatic C–H bonds with internal enamides.

Despite recent progress, the hydroarylation of enamides still requires further research, including enantioselective processes, which are currently limited to specific heterocycles, and the underexplored reactivity of internal enamides. Moreover, in all these examples, the β -(hetero)arylamines produced are always masked as an amide or carbamate, thereby necessitating an additional deprotection step for further functionalization, which renders access to *N*-alkylamines and the synthesis of the enamide substrate itself more laborious. In this regard, the hydroamination of styrene derivatives can provide streamlined and practical access to structurally diverse β -(hetero)arylamines.

Hydroamination and hydroamidation of vinyl (hetero)arenes

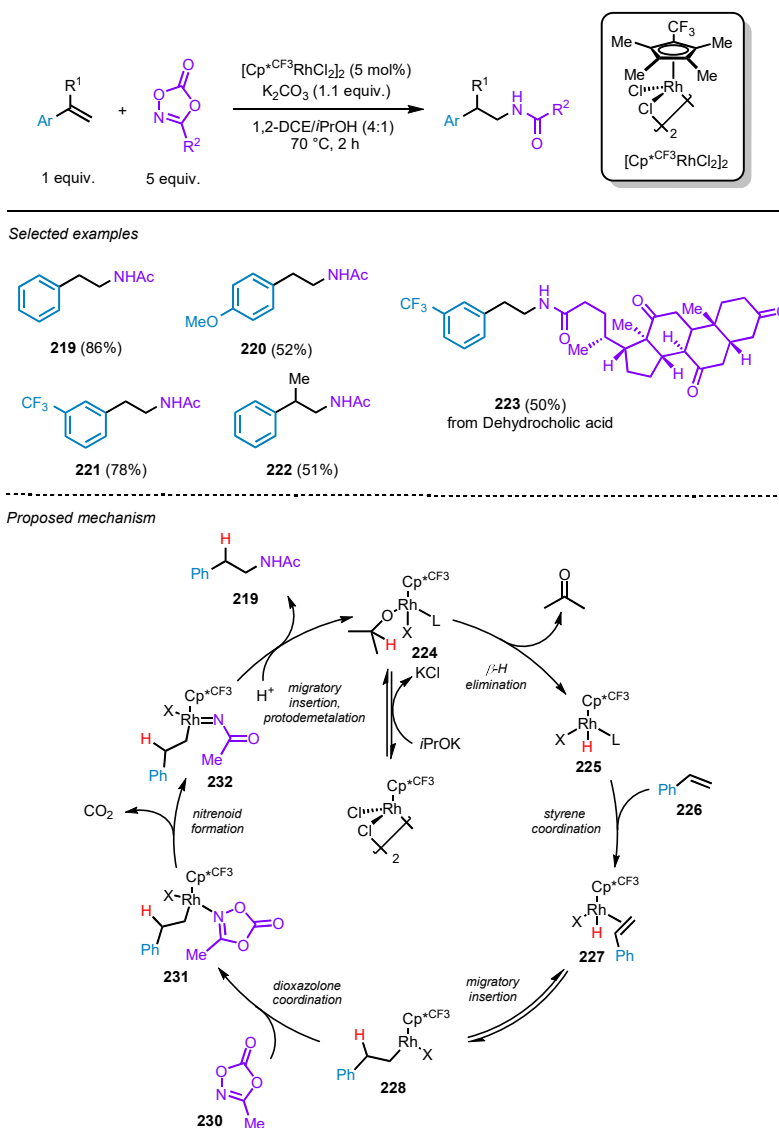
For the assembly of β -(hetero)arylamines, the anti-Markovnikov hydroamination and hydroamidation of vinyl (hetero)arenes brings several advantages compared to the hydroarylation of enamides.^[47] The disconnection of a single C–N bond breaks down the β -(hetero)arylethylamine scaffold into widely available feedstock materials such as vinyl (hetero)arenes and amines. Unlike the hydroarylation of enamides, the installation of electron-withdrawing protective groups onto the nitrogen functionality is not necessary to stabilize the alkene substrate, thereby enabling the use of a broader range of amine derivatives, such as aliphatic or aromatic amines and even ammonia. However, while manifold methods have been devised for the Markovnikov hydroamination of vinyl (hetero)arenes, anti-Markovnikov protocols are less common. Examples have appeared more frequently since the early 2000s but they often require the use of air- and moisture-sensitive basic amide complexes or precious transition metals under harsh conditions.^[48–53] Other indirect strategies involve two-step one-pot procedures such as the hydroboration/amination of styrenes or the Wacker oxidation/reductive amination of styrenes.^[54,55] Overall, these methods display a moderate substrate scope, with reactions mostly limited to simple styrenes, and to alkyl- and arylamines.

A breakthrough from the Nicewicz group devised the first photocatalytic system to execute anti-Markovnikov hydroamination of styrenes using trifluoromethanesulfonamide and nitrogen heterocycles as aminating agents (Scheme 20).^[56] The key is the use of a strongly oxidizing acridinium organophotocatalyst developed by Fukuzumi with phenyl disulfide as a co-catalyst under irradiation with blue light at room temperature. Although the explored scope remained largely dominated by 1,2-disubstituted styrenes incorporating electron-donating groups, the reaction also proceeded efficiently with less electron-rich styrenes, albeit at a slower rate, in line with the ease of styrene oxidation to the corresponding radical cation. Other amine sources such as TsNH₂, NsNH₂ and BocNH₂ were not tolerated under these reaction conditions. The postulated mechanism begins with the formation of radical cation **216** resulting from the oxidation of styrene **215** by the excited photocatalyst. This highly electrophilic species then undergoes a reversible nucleophilic addition by trifluoromethanesulfonamide at the less substituted position, furnishing the most stable distonic cationic radical **217**, which is subsequently deprotonated to give neutral carbon-based radical **218**. Meanwhile, thiophenol is eventually formed *in-situ* from (PhS)₂ after SET reactions with the reduced photocatalyst and protonation. It then transfers a hydrogen atom back to **218** to regenerate a thiyl radical and to yield the final hydroamination product.



Scheme 20. Anti-Markovnikov hydroamidation and -amination of styrene derivatives catalyzed by a two-component organic photoredox system.

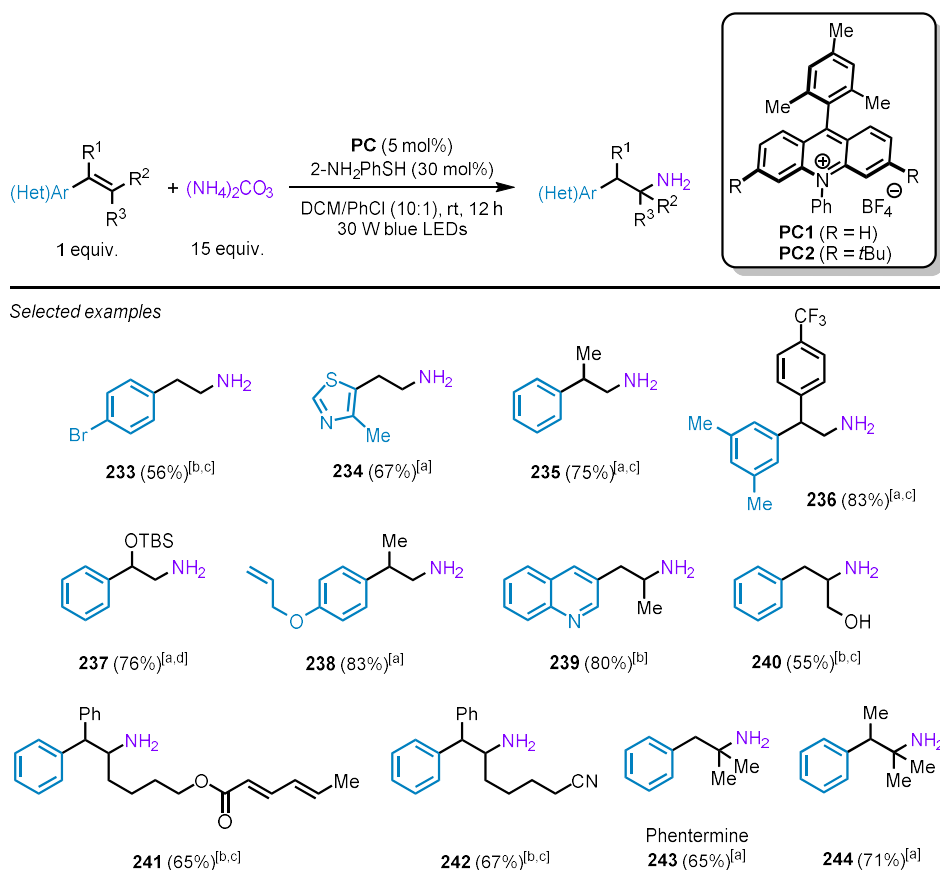
In contrast with aliphatic amines, anilines or even sulfonamides, the addition of amides across vinyl(hetero)arenes is still scarce, which can be attributed to the lower nucleophilicity of amides compounds compared to aliphatic amines. To circumvent this issue, the group of Rovis used readily available dioxazolones as electrophilic amidating agents and isopropanol as a hydride source in a rhodium-catalyzed hydroamidation process (Scheme 21).^[57] While mostly aliphatic alkenes were reported, mono- and 1,1-disubstituted styrenes were also compatible with their standard conditions to afford the corresponding β -(hetero)arylethylamides in yields ranging from 50 to 86%. The mechanistic studies conducted suggest the formation of key rhodium nitrenoid species **232** upon CO₂ extrusion from coordinated dioxazolone **231**. Subsequent alkyl migratory insertion into a [Rh]-nitrenoid and protodemetalation would deliver hydroamidation product **219**.



Scheme 21. Rh(III)-catalyzed anti-Markovnikov hydroamidation of styrenes using dioxazolones as amidating reagents.

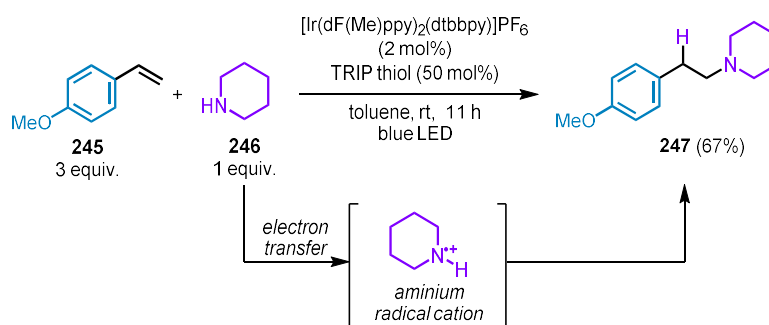
Despite several advances in the anti-Markovnikov hydroamination of vinyl (hetero)arenes, few reports tackled the production of unprotected primary aliphatic amines. However, nearly 20 years after the initial report by the group of Yamashita on the hydroamination of electron-rich styrenes with ammonia using stoichiometric amounts of dicyanobenzene (DCB) as photosensitizer,^[58] the group of Shu succeeded to solve this problem by devising an expedient strategy to access unprotected primary β -(hetero)arylethylamines (Scheme 22).^[59] This methodology represents a major step forward in terms of reactivity. Here, a tunable acridinium organophotocatalyst unlocked the SET oxidation of previously inaccessible vinyl (hetero)arenes. Moreover, the use of

ammonium carbonate as an ammonia surrogate avoids the manipulation of hazardous ammonia gas for saturation of the reaction medium. It is important to mention that this transformation was not restricted to terminal styrenes but could also be applied to di-, tri and tetrasubstituted olefins. From a synthetic point of view, this method proved compatible with a large set of functional groups on the aliphatic chain of the product, including halides, esters, nitriles, nitro groups, free alcohols, silyl ethers, and heteroaromatics, while being chemoselective in the presence of other alkenes. However, the reactivity of styrenes incorporating strong electron-withdrawing groups, such as cyano or nitro groups, directly on the aryl ring was not disclosed. Mechanistic investigations revealed a Hammett plot with a negative slope ($\rho = -0.82$), which is consistent with the build-up of a positive charge during a rate-determining SET oxidation to the radical cation. In addition, the authors demonstrated that the radical intermediate could be trapped by TEMPO. Thus, the reaction likely operates with a similar mechanism as the one described by the group of Nicewicz (see Scheme 20).



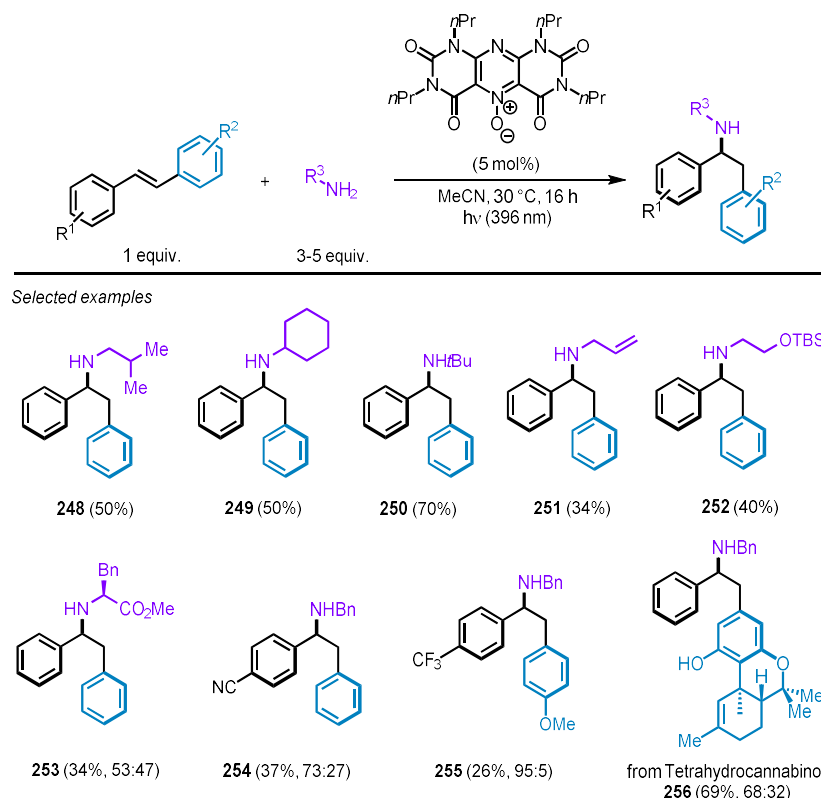
Scheme 22. Synthesis of primary aliphatic amines via photocatalytic hydroamination of styrene derivatives using ammonium carbonate as amine source. [a] PC1. [b] PC2 in DCM/MeCN (10:1). [c] Isolated yield of NHBoc.

Another important challenge in photocatalytic hydroamination is a more general use of unprotected alkyl amines. As illustrated by the group of Nicewicz in their studies, amines are often protected by electron-withdrawing groups, which confers them a higher oxidation potential and prevents their oxidation under photocatalytic conditions. Recently, several elegant reports involving alkyl amines have appeared from the Knowles group, which feature the generation of a key aminium radical cation from unprotected amines (Scheme 23); however, except for rare examples, their studies were mostly limited to aliphatic alkenes.^[60]



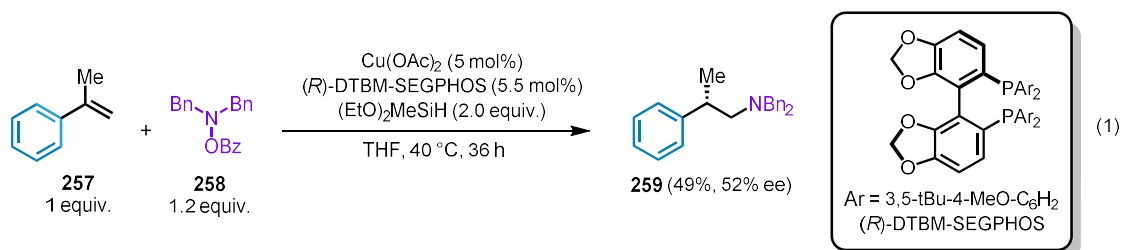
Scheme 23. Photocatalytic hydroamination of *p*-methoxystyrene with piperidine. TRIP thiol = 2,4,6-triisopropylbenzenethiol.

To tackle this issue, the group of Pospesch reported the use of a highly potent pyrimidopteridine-*N*-oxide photocatalyst, whose excited state has a high reduction potential ($E_{1/2}(\text{PC}^*/\text{PC}^-) = +2.29$ V vs SCE), allowing it to easily oxidize alkenes, including ones incorporating strong electron-withdrawing groups. They notably applied this system to the hydroamination of underexplored stilbenes using a broad range of aliphatic amines (Scheme 24).^[61] Atypically, the presence of an additional H-atom donor was not found to be required, which might indicate that the reduced catalyst can play the dual roles of proton acceptor and H atom transfer reagent. Of note, traditional photocatalysts such as the Fukuzumi acridinium or [Ru(dtbbpy)₃](PF₆)₂ were not capable of promoting this transformation. The regioselectivity of the amine addition was found to depend on the electronic properties of the aryl ring, with the more electron-deficient benzylic position being favored. Importantly, the stereochemistry of α -chiral amines was retained during the reaction. Kinetic studies revealed that *E*-stilbenes react faster than *Z*-stilbenes. In the case of *Z*-stilbenes, the steric repulsion between the *ortho*-C–H of the aryl rings precludes a planar arrangement of both rings and hampers an efficient conjugation of the radical cation formed upon oxidation. Consequently, these radical cations face competition with a back-electron transfer to the photocatalyst that inhibits addition by the amine.



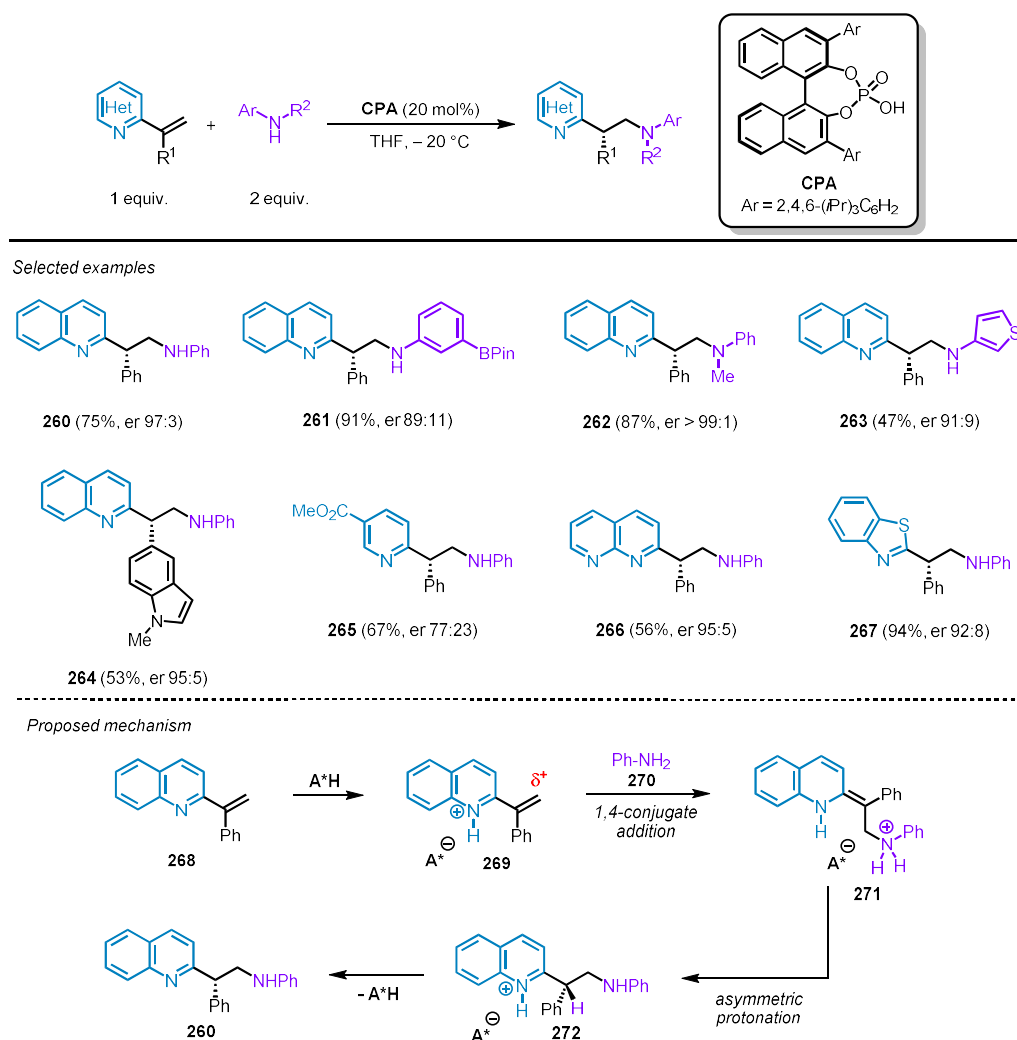
Scheme 24. Pyrimidopteridine-catalyzed hydroamination of stilbenes with primary aliphatic amines.

The asymmetric hydroamination of vinyl (hetero)arenes represents an open challenge. The Buchwald group reported an efficient copper-catalyzed enantioselective anti-Markovnikov hydroamination of aliphatic alkenes but obtained only moderate success with styrenes. For example, in the case of α -methylstyrene, the target product was obtained in 49% yield and 52% ee (Equation 1).^[62]



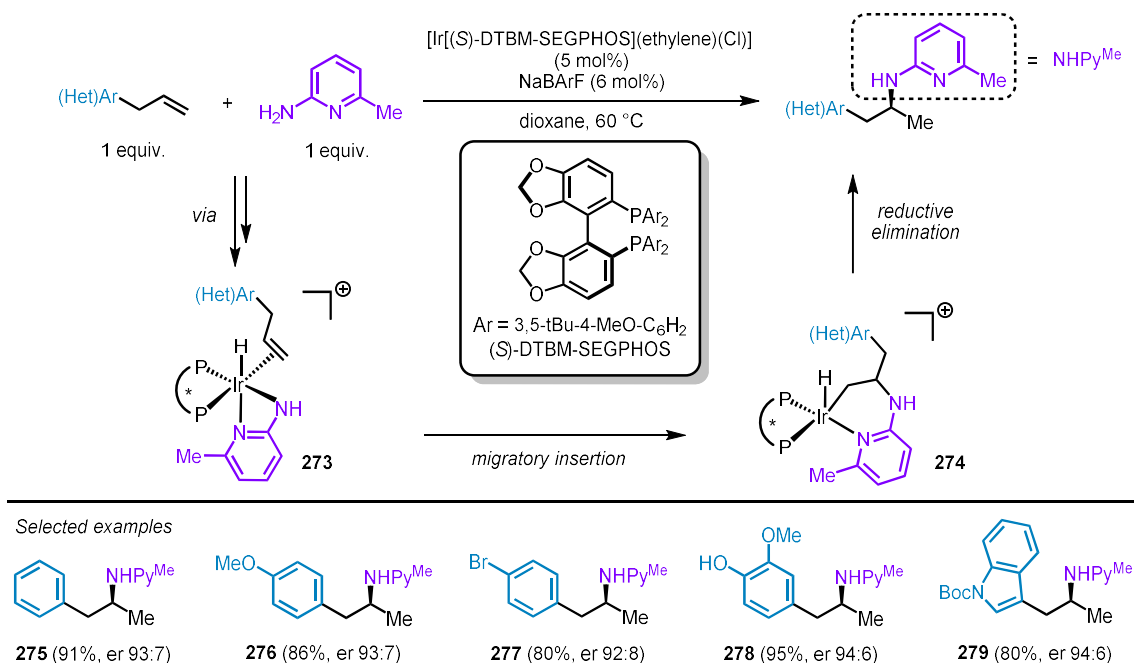
In 2018, the group of Watson reported an intriguing strategy to achieve enantioselective anti-Markovnikov hydroamination. Their idea revolves around the introduction of a nitrogen heterocycle on the alkene with the aim of triggering 1,4-conjugate additions in the presence of a Brønsted acid catalyst. They exploited a chiral phosphoric acid (CPA) for highly enantioselective conjugate addition of anilines to 1,1-vinyl aza-heterocycles (Scheme 25).^[63] The reaction protocol

accommodates a broad range of primary and secondary aza-heterocycles and anilines to give the corresponding products in yields ranging from 27 to 99% with excellent er (up to > 99:1). However, the reaction suffers from limitations. The procedure is not compatible with alkyl amines because of catalyst inhibition. For example, replacing the aryl group at the α -position by an alkyl group led to a significant decrease in efficiency and enantioinduction. Here, the initial protonation of the nitrogen atom of heterocycle **268** creates a positive charge and polarizes the double bond in favor of a 1,4-conjugate addition of the aniline to generate the corresponding enamine **271**. The bulky chiral anion controls the asymmetric protonation of the pro-chiral enamine intermediate by accepting H-bonds from the heterocyclic N-H and the anilinium (**272**) but is thought not to be directly involved in the proton transfer.



Scheme 25. Chiral phosphoric acid-catalyzed enantioselective synthesis of α -chiral azaheteroaryl ethylamines.

An alternative to the asymmetric synthesis of β -(hetero)arylamines is the use of common allyl arenes as substrates, which was recently described by the group of Hartwig through an iridium-catalyzed enantioselective Markovnikov hydroamination of unactivated alkenes with 6-methyl-2-aminopyridine (Scheme 26).^[60] Here, the additional presence of the pyridyl motif can ease oxidative addition into the N-H bond, while having the advantage of being easily cleaved. This protocol allows for simple access to chiral amines in high yields, breaking from traditional approaches, including enantioselective reductive amination, enzymatic amination, or hydrogenation of enamides and imines, which display limited substrate scope. During their investigations, the authors wished to prevent the isomerization of the alkene via retrohydroamination and the deactivation of the catalyst through the formation of off-cycle species. These challenges were overcome by developing an iridium complex bearing a monodentate volatile ethylene ligand, which enabled the reaction under milder reaction conditions with high stereoselectivity. The reaction is suggested to proceed via initial oxidative addition into the N-H bond of the amine (**273**), followed by Markovnikov insertion into the alkene (**274**) and subsequent reductive elimination to afford the hydroamination product. This order of events was supported by deuterium labeling experiments using *N*-deuterated aminopyridine, which resulted in significant incorporation of deuterium at the terminal carbon.

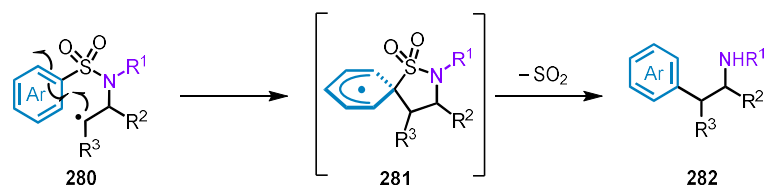


Scheme 26. Ir-catalyzed enantioselective hydroamination of unactivated alkenes.

In the past years, photocatalysis and transition metal catalysis have become prominent tools for the synthesis of β -(hetero)arylamines through anti-Markovnikov hydroamination and hydroamidation of vinyl (hetero)arenes. Advantageously, such transformations enable introducing of a large range of nitrogen-containing functionalities, including NH-heterocycles, ammonia, aliphatic, (hetero)aromatic, or *N*-protected amines, in contrast to other methods that feature alkenes as substrates. Although they allow for milder reaction conditions and can reach a broad structural diversity, they are fraught with the same limitations regarding asymmetric synthesis as the hydroarylation of enamides. The few methods described require the presence of highly specific scaffolds with an anchor for the chiral catalyst. Another issue is that the reactivity of highly electronically deactivated styrenes is never reported, which limits access to valuable products. Nonetheless, the fast-paced growth of this area is promising and will undoubtedly lead to significant improvements for the catalytic and enantioselective preparation of densely functionalized β -(hetero)arylamines.

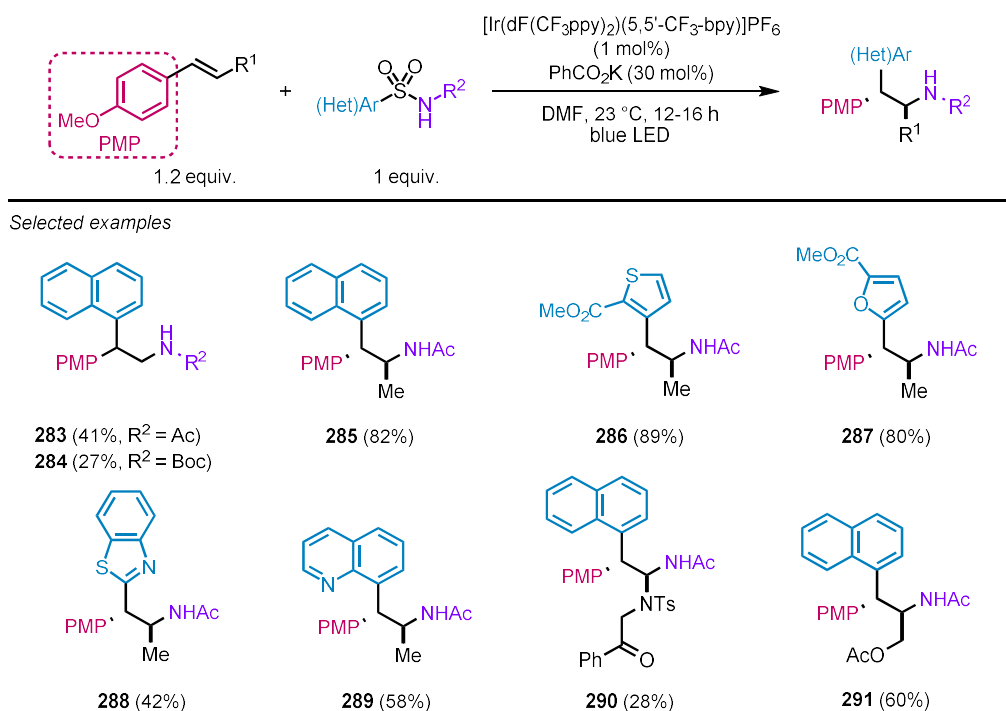
Truce-Smiles rearrangement

Another elegant way to forge β -(hetero)arylethylamine scaffolds is the Truce-Smiles rearrangement, which consists in the intramolecular migration of an aryl group via formal *ipso* substitution through typically radical or anionic pathways (Scheme 27).^[65] The driving force of this process is the release of SO₂ gas, which makes it irreversible. It represents a formal intermolecular aminoarylation of alkenes with the creation of a C–C and C–N bonds in a single step, which offers several advantages. As an intramolecular process, this transformation is typically achieved with a high level of efficacy and selectivity, while exhibiting a large functional group tolerance, either at the alkene or nitrogen moiety. The downside is however the necessity to pre-install all the key functionalities for the reaction. Nevertheless, the recent development of intermolecular protocols, relying notably on photocatalysis, and the development of creative ways to initiate the reaction marked the resurgence of this transformation to increase the molecular complexity of the compounds produced. In this part, multi-component reactions featuring a Truce-Smiles rearrangement to access β -(hetero)arylethylamine along with the introduction of a variety pharmacophores would not be commented as they were recently reviewed by the group of Greaney.^[6]



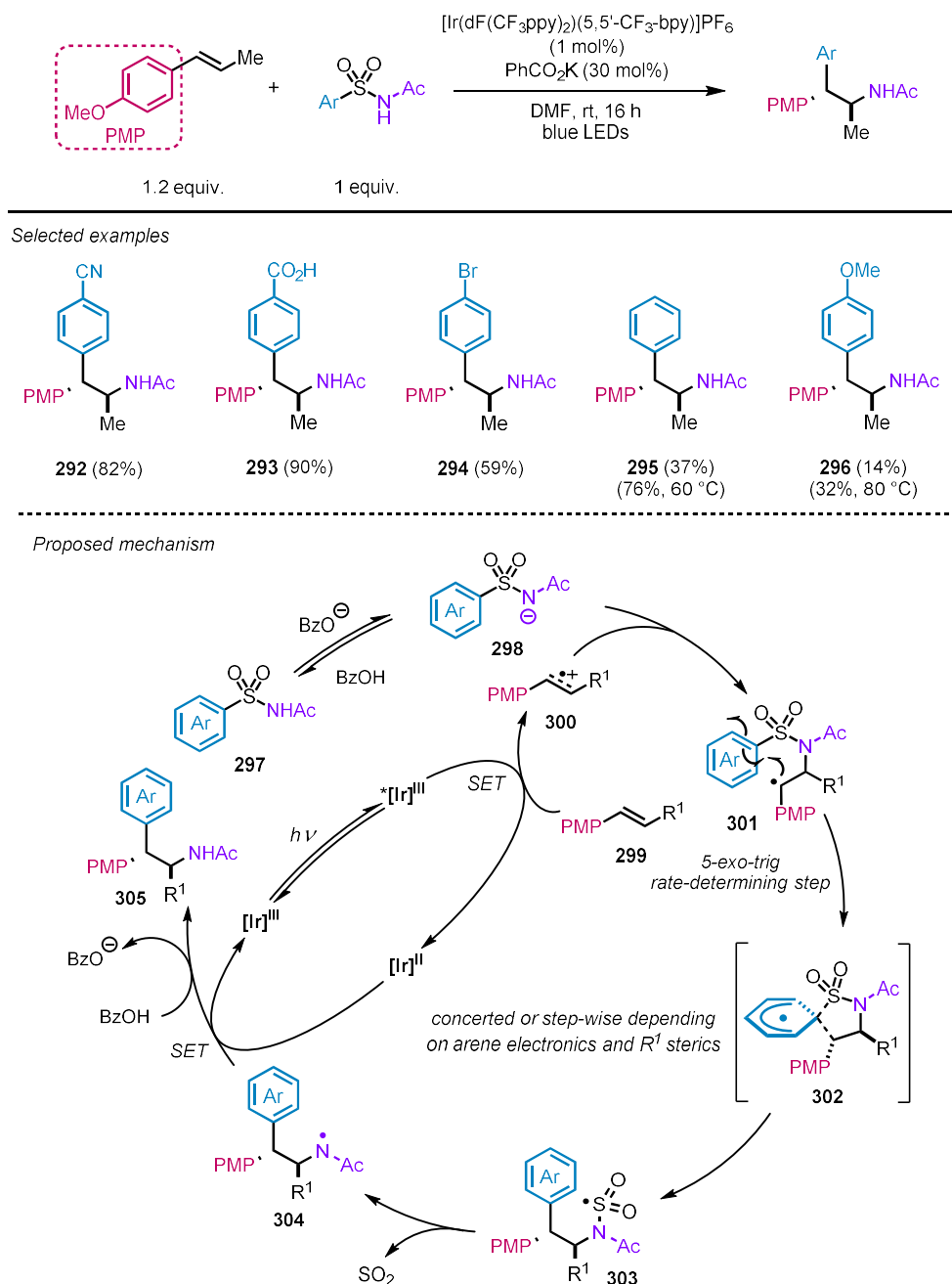
Scheme 27. Radical Truce-Smiles rearrangement.

In 2018, a major leap forward in the development of intermolecular Truce-Smiles rearrangement was made by the group of Stephenson. They described a sophisticated photocatalytic amino(hetero)arylation of alkenes using (hetero)arylsulfonylacetamides as the single source of both the heteroaryl and the amine functionalities (Scheme 28).^[66] The reaction tolerates a broad range of (hetero)aryl groups on the (hetero)arylsulfonylacetamides, affording the compounds in moderate to high yields with high levels of diastereoselectivity (drs > 20:1). However, the methodology was limited to *para*-methoxystyrenes, likely due to their lower oxidation potential, and consequent ease of forming the corresponding radical cation. Alternatively, intermolecular reactions of this type might simply be inherently challenging since *N*-acylsulfonamidyl radicals form phenols through rapid homolytic cleavage of the aryl-S bond, a process that is more competitive when less reactive alkenes are employed.



Scheme 28. Photocatalytic 1,2-aminoarylation of styrenes with arylsulfonylacetamides.

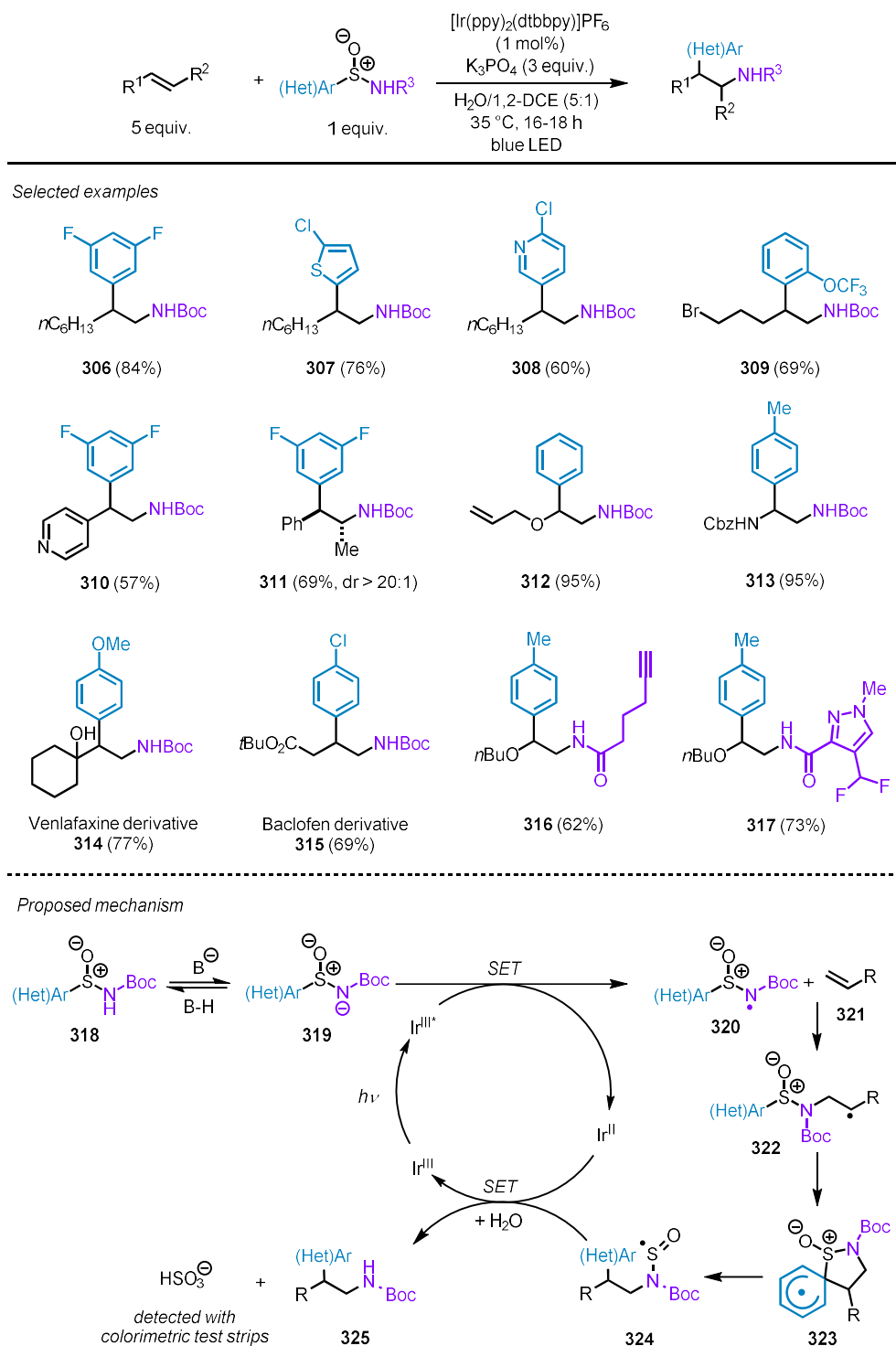
Later, in 2022, the same group reported in-depth mechanistic studies that shed light on the nature of the reactive intermediate, while significantly expanding the scope of arenes tolerated (Scheme 29).^[67] Combined computational studies and Stern-Volmer luminescence quenching experiments with various reaction components clearly indicated that electron-rich styrene **299** is preferably oxidized to radical cation **300** followed by addition of the deprotonated sulfonamide anion **298**. Theoretical modelling of transition states with various substituents on the migrating group suggests lower activation barriers for aryl groups bearing strongly deactivating substituents, which gives rise to short-lived Meisenheimer intermediates (**302**). In contrast, higher activation barriers were found for electron-rich aryl groups, which were found to proceed through a concerted Meisenheimer transition state. This result is corroborated by the Hammett plot constructed with various substituents on the arene moiety of the sulfonamide, which points to the buildup of negative charge on the benzene ring during the rate-determining Truce-Smiles rearrangement step. The observed diastereoselectivity is governed by sterics in the migrating group and in the substrate, which imposes an antiperiplanar arrangement of the *para*-methoxyphenyl and the methyl groups. The subsequent extrusion of SO₂ ensures the irreversibility of migration (**304**). Insights gained from the mechanistic studies are clearly reflected in the extended scope of the transformation. A series of substrates bearing strong electron-withdrawing groups successfully underwent the rearrangement to afford aminoarylation products in high yields. In the case of moderate electron-withdrawing and -donating groups, the aminoarylated products were obtained in yields around 50%. On the other hand, in agreement with the above mechanistic proposal, the presence of strong electron-donating substituents on the migrating aryl group resulted in low yields, even at elevated temperatures.



Scheme 29. Mechanistic understanding and resulting extended scope for photocatalytic 1,2-aminoarylation of styrenes with arylsulfonylacetamides.

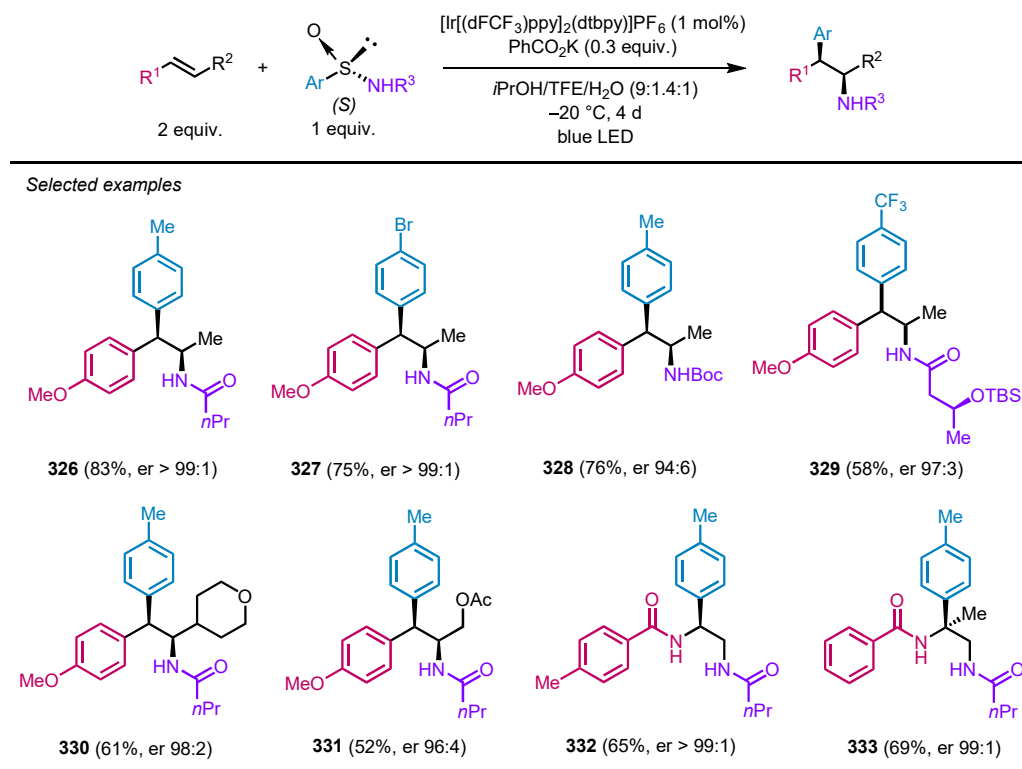
Despite this breakthrough, the starting alkenes that could be used lacked diversity, limiting the synthetic utility of this method to access β -(hetero)arylethylamines. To overcome this issue, the Stephenson group envisioned to replace the typical sulfonamide-based aminoarylating agent by one based on a sulfinamide. Their reasoning was that a lower sulfur oxidation state (IV vs VI) could provide numerous benefits for this transformation. Indeed, with respect to the intermolecular

Truce-Smiles rearrangements, one of the major limitations was a competitive pathway involving the direct homolysis of the *N*-acylsulfonamidyl radical intermediate's aryl-S bond to generate the corresponding phenol derivative. Since a sulfinamide is a worse leaving group than a sulfonamide, the authors hypothesized that the former should suppress the fragmentation pathway to phenols. Moreover, the contracted C(sp²)-S-N bond angle of ~96° in a sulfinamide, compared to the 109° angle in sulfonamides, brings the migrating aryl group closer to the carbon-centered radical and facilitates the rearrangement. This strategy proved highly successful and enabled the aminoarylation of a wide array of underexplored alkenes, including aliphatic alkenes, enols, enecarbamates, vinyl silanes and even simple styrene, with a large functional group tolerance and an excellent control of the diastereoselectivity (Scheme 30).^[68] Protected forms of marketed drugs such as Venlafaxine and Baclofen were obtained in synthetically useful yields. The proposed mechanistic scheme starts with deprotonation of sulfinamide **318** to generate sulfinamide anion **319**, which in turn would undergo SET by the photoexcited iridium catalyst to form a reactive N-centered radical **320**. This pathway was corroborated by a control experiment with deprotonated sulfinamide, in which the aminoarylation product was obtained in high yield without the presence of base. Stern-Volmer luminescence quenching studies with sulfinamide did not result in the quenching of the excited state of the photocatalyst, instead pointing to the oxidation of its conjugate base. Once the N-centered radical is generated, the mechanism is suggested to be identical to the Truce-Smiles rearrangement described in Scheme 29, leading to N-sulfinyl radical **324** before delivering final product and bisulfite, which was detected by colorimetric test strips.



Scheme 30. Photocatalytic aminoarylation of alkenes enabled by N-centered radical reactivity of sulfonamides.

In parallel with the studies of the group of Stephenson, the Nevado group recently devised a photocatalytic asymmetric aminoarylation via the Truce-Smiles rearrangement by employing chiral sulfinylamides (Scheme 31).^[69] The sulfinylamide group serves as a chiral auxiliary which can be easily cleaved through the concomitant extrusion of SO gas after the rearrangement (**370** to **371**). This new catalytic protocol efficiently delivered aminoarylation products in high yields with excellent stereo- and regioselectivities. Mechanistic investigations suggest a reaction pathway like the one described by the group of Stephenson (see Scheme 29). Stern-Volmer luminescence quenching experiments support the initial oxidation of styrene **335** to radical cation **336**. The subsequent addition of deprotonated sulfinylamide **334** to the radical cation is the enantiodetermining step as illustrated by DFT analysis of the reaction profile, which revealed a 1.32 kcal.mol⁻¹ difference between activation barriers leading to both stereoisomers. Analogous to the findings of Stephenson, the aryl migration occurs almost stereospecifically, with para-methoxyphenyl groups and alkyl substituents positioned in antiperiplanar fashion to minimize the steric clash (**338**). Despite the high stereoselectivity, the method suffers from the restriction to electron-rich alkenes for an easier initial oxidation to the radical cation.



Scheme 31. Visible light-mediated asymmetric aminoarylation of alkenes with chiral arylsulfinylamides.

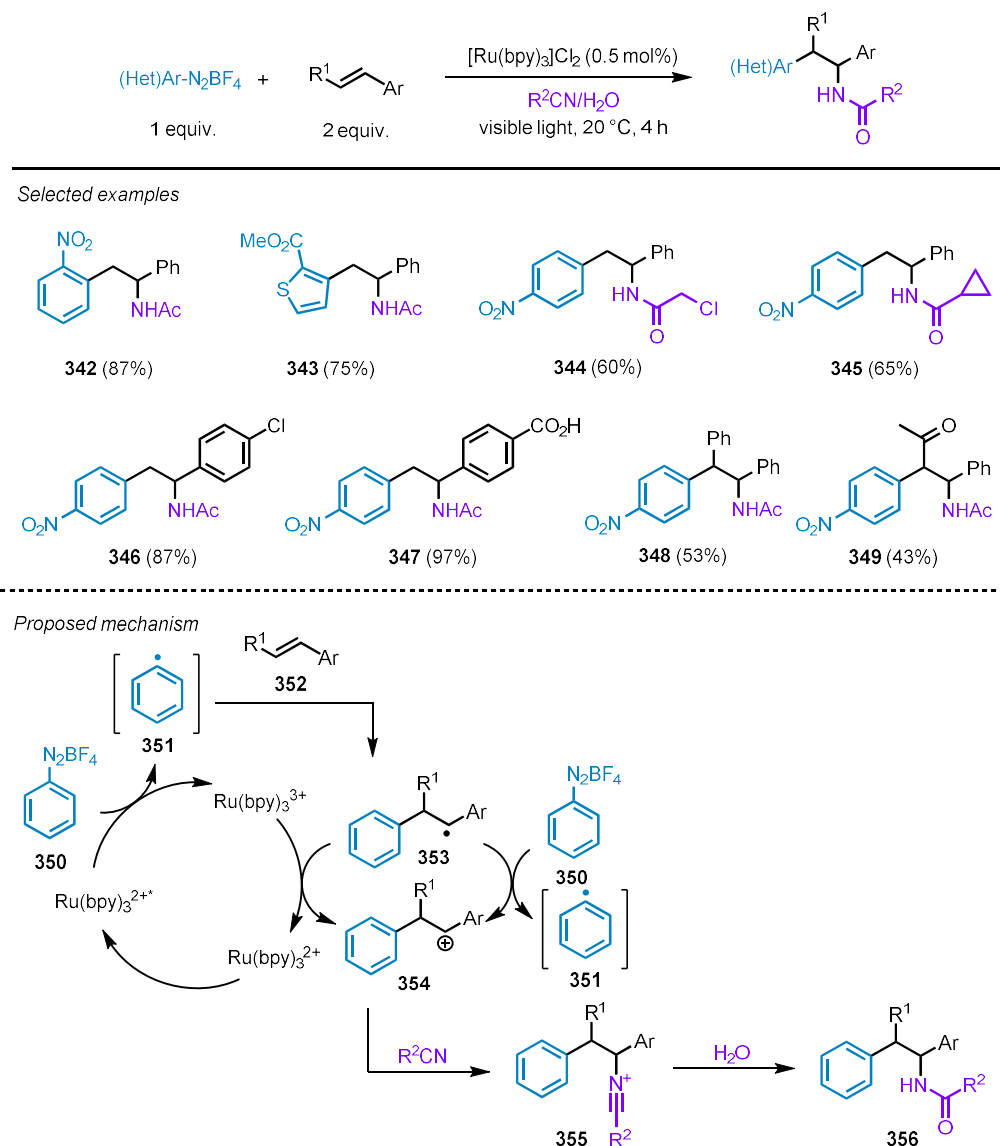
Until recently, the radical Truce-Smiles rearrangement was unlikely the first-choice method for the construction of β -(hetero)arylethylamine skeletons, as it often required complex tailored substrates. However, the development of more general intermolecular radical amination-rearrangement methodologies has enabled aminoarylation of not only inexpensive and readily available feedstocks such as aliphatic alkenes and electron-rich styrenes but also enamides under photocatalytic conditions. Seminal contributions by the group of Stephenson have paved the way towards future developments of this strategy. The positive aspects of this transformation include its high predictability and excellent diastereoselectivity, without needing any directing group. However, there is still room for improvement. In most cases, only secondary amines protected by electron-withdrawing groups were obtained. There are few or no examples that allow the introduction of aliphatic amines or the use of deactivated styrenes. In addition, catalytic enantioselective methods still need to be developed. To date, there is a single example of asymmetric synthesis with a chiral auxiliary reported by the group of Nevado. For these reasons, the classical amino(hetero)arylation of alkenes remains the best option to access β -(hetero)arylamines with broad versatility and functional group compatibility.

(Hetero)arylamination of alkenes

Of the various approaches for the preparation of β -(hetero)arylamines, the three-component intermolecular reaction of an alkene with an amine (or a surrogate) and an (hetero)aryl component is arguably the most straightforward method to build structural diversity and complexity from simple precursors. Unlike the methods previously described, it does not require the pre-installation of the nitrogen or (hetero)aryl functionalities. Evidently, the regioselectivity of this transformation is more arduous to control. However, remarkable systems relying on photocatalysis, directing group-assisted transition metal-catalyzed C–H activation, and SET were devised to achieve this endeavor. Thus, several alkenes aminoarylations along these lines have been reported over the past ten years.

In 2014, following seminal studies by the group of Greaney,^[70] the König group drove the growth of this area, unveiling the first example of a synergistic combination of a photo-Meerwein addition with a Ritter reaction to formally implement a 2,1-aminoarylation of styrenes (Scheme 32).^[71] In that study, diazonium salts bearing a wide range of substituents, including electron-donating and -withdrawing groups, were exploited as the aryl source while nitrile derivatives served as amide surrogates. Under visible light, a photoexcited ruthenium catalyst reacts with diazonium salt **350** to generate aryl radical **351** through SET, which readily adds to either a styrene or a stilbene. The resulting benzylic radical **353** is then oxidized to benzylic cation **354** by the photocatalyst or by

the diazonium salt, in the latter case generating a new aryl radical. The carbocation **354**, in turn, could be captured by various nitriles, with subsequent hydrolysis delivering amino-arylated products. Of note in this report is the low catalyst loading, the possibility to use poly-substituted alkenes, and the conversion of the aminoarylation products into 3-aryl-3,4-dihydroisoquinolines.

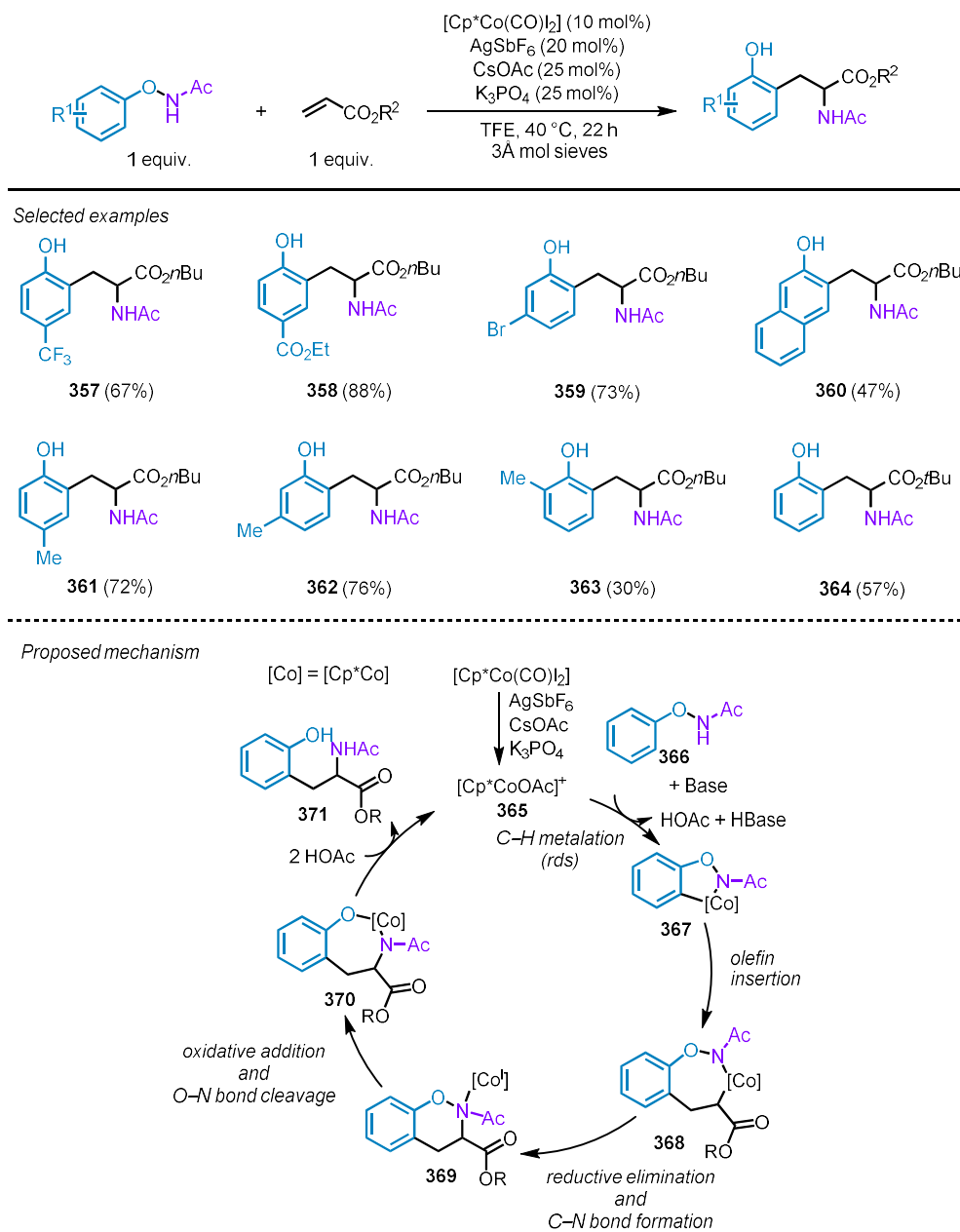


Scheme 32. Photocatalytic Meerwein addition/Ritter reaction for aminoarylation of styrenes.

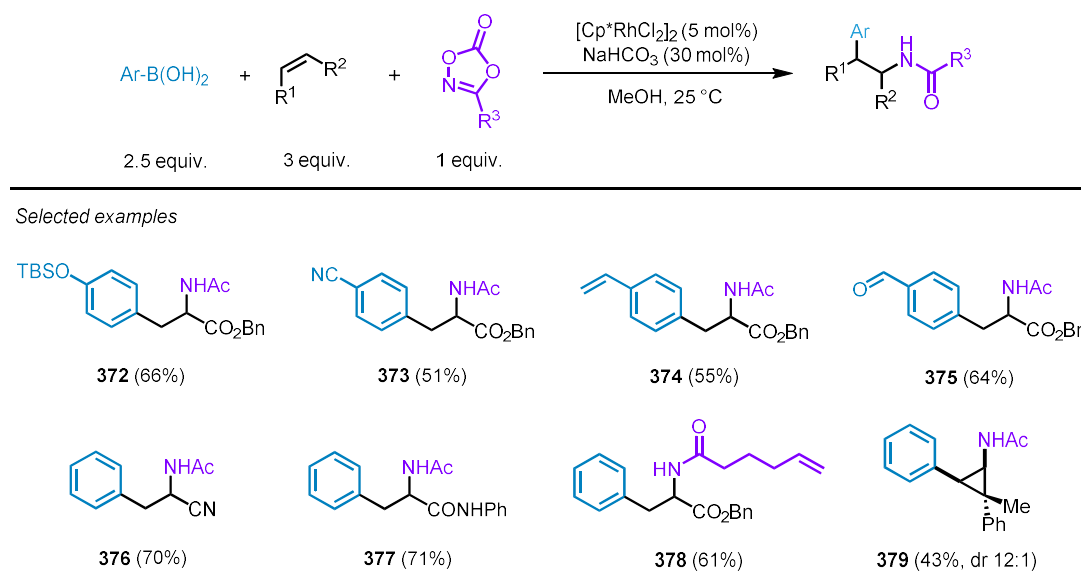
At the outset, aminoarylation protocols were essentially limited to styrenes. However, in 2016, the group of Glorius reported a pioneering regioselective and atom-economic method for the non-annulative carboamination of acrylates through C–H activation with an earth-abundant cobalt catalyst (Scheme 33).^[72–74] Unnatural amino acids, a particularly important family of compounds for drug design, were easily accessed in high yields. Based on the prior report of a Cp^{*}Rh(III)

catalyst for alkene carboamination by the group of Rovis,^[75] the authors explored an analogous Cp*Co(III) complex with the hope that it might overcome the β -H elimination side-reactions that plagued existing aminoarylation processes. Bifunctional phenoxyacetamides were used as a single source of the aryl and amino components. Electron-withdrawing groups such as trifluoromethyl or esters, and some electron-donating groups, were well-tolerated on the phenoxyacetamide ring. Moderate yields were reported in the case of *ortho*-substituted aryl rings, likely due to steric congestion in the transition state. Kinetic isotope experiments were performed and revealed that the C–H activation step was likely rate-determining, whereas labeling experiments showed that the reaction was indeed intermolecular. The authors proposed a mechanism where the rate-determining C–H metalation step (**365** to **367**) was followed by olefin insertion, yielding 7-membered-ring intermediate **368**. Subsequent reductive elimination and C–N bond formation formed Co(I) species **369**, which underwent oxidative addition and O–N bond cleavage to furnish 7-membered Co(III) intermediate **370**. Protodemetalation finally afforded potentially useful amino acid derivatives.

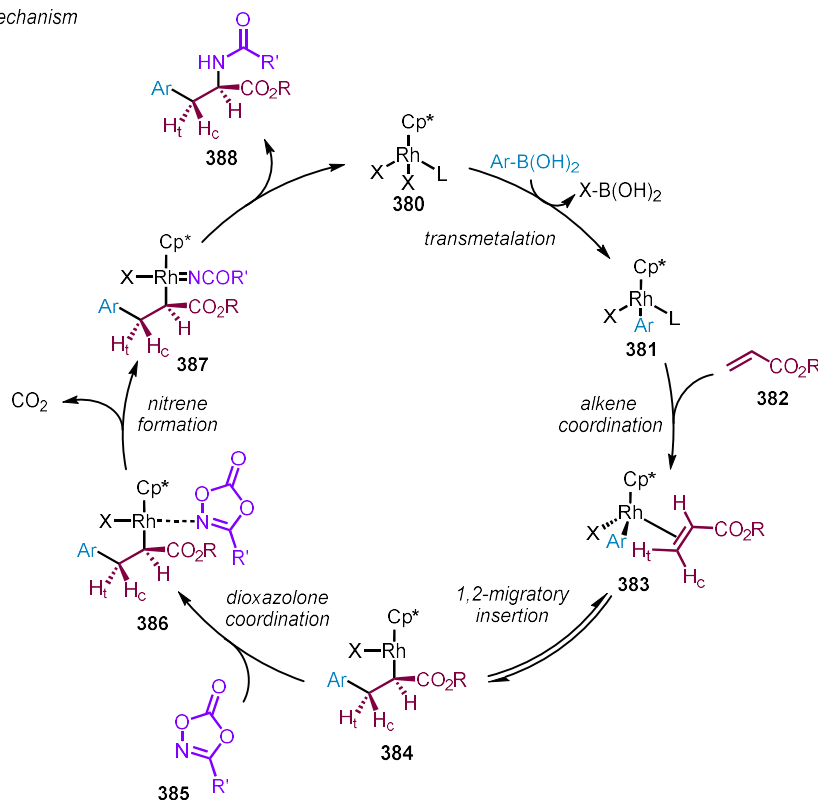
Due to their reliance on phenoxyacetamides, these methods are limited to the preparation of β -arylethylamines incorporating *ortho*-substituted phenol and acetamide functionalities. This issue was nevertheless overcome by the group of Rovis in 2021. Interested in developing a general approach to the aminoarylation of electron-deficient alkenes and cyclic alkenes, the authors looked into the possibility of assembling arylboronic acids, electron-deficient alkenes and dioxazolones as amidating agents through the use of a Rh(III) catalyst (Scheme 34).^[76] In doing so, they reported one of the widest scopes thus far with respect to the aryl component. For instance, various unprecedented substituents such as alkenyl, cyano, aldehyde and silyl ether groups could be installed starting from the corresponding arylboronic acids. These new functionalities were complemented by a good tolerance for electron-withdrawing groups within the alkene partner, including ester, amide and cyano groups. The authors also extended the reactivity to cyclopropenes with good dr.^[77] Based on their experiments, they proposed the following mechanism: rhodium complex **380** would first undergo transmetalation with arylboronic acid to form **381**, followed by the chelation of alkene **382** onto the metal center to give **383**. Then, turnover-limiting migratory insertion would occur to provide **384**, which, upon coordination of dioxazalone **385** onto the Rh center, would generate Rh(V)-nitrene **387** along with extrusion of CO₂. Finally, reductive elimination and proto-demetalation would yield the desired *syn*-carboamination product and regenerate the catalyst.



Scheme 33. Synthesis of unnatural amino acids via Co-catalyzed intermolecular arylamination of acrylates.



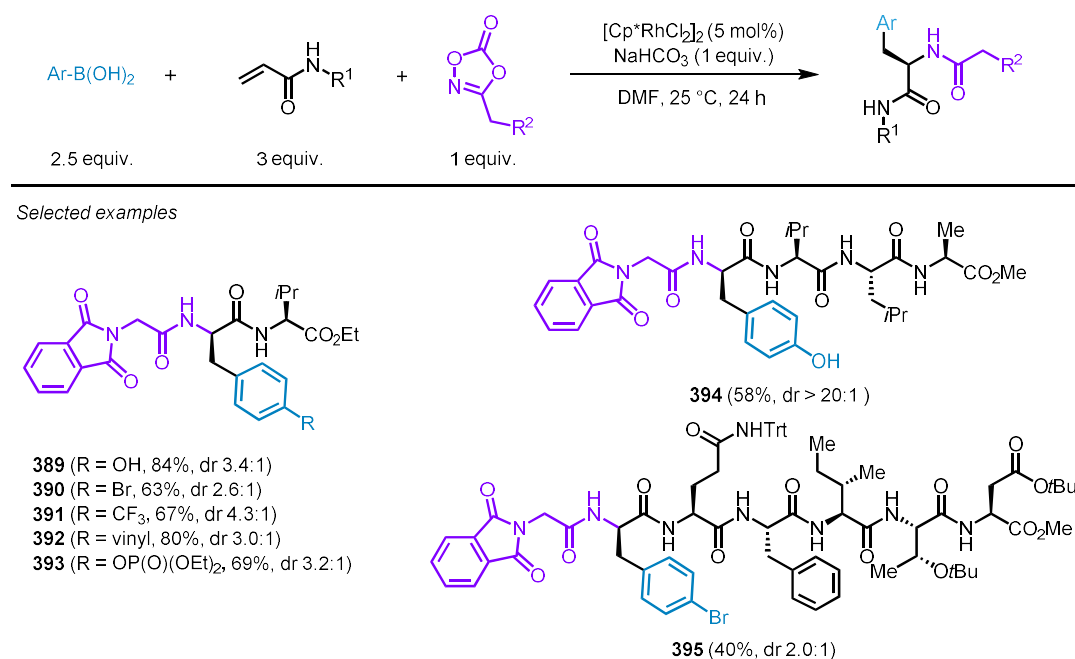
Proposed mechanism



Scheme 34. Rh-catalyzed three component *syn*-aminoarylation of alkenes.

Whereas most interest in aminoarylation reactions have come from chemists interested in the preparation of small molecules, the Rovis group has recently further extended their three-component arylamidation reaction to biomolecules (Scheme 35).^[78] For instance, they showed that by using peptides with a terminal acrylate residue, they could install various phenylalanine

analogues and an additional amide onto the alkene, thus extending the peptide chain. The methodology was compatible with strong electron-deficient as well as electron-rich arylboronic acids and gave satisfying yields and diastereoselectivities with peptides of different lengths. Interestingly, the authors demonstrated that they may ligate peptides when grafting a peptide onto the dioxazolone residue.

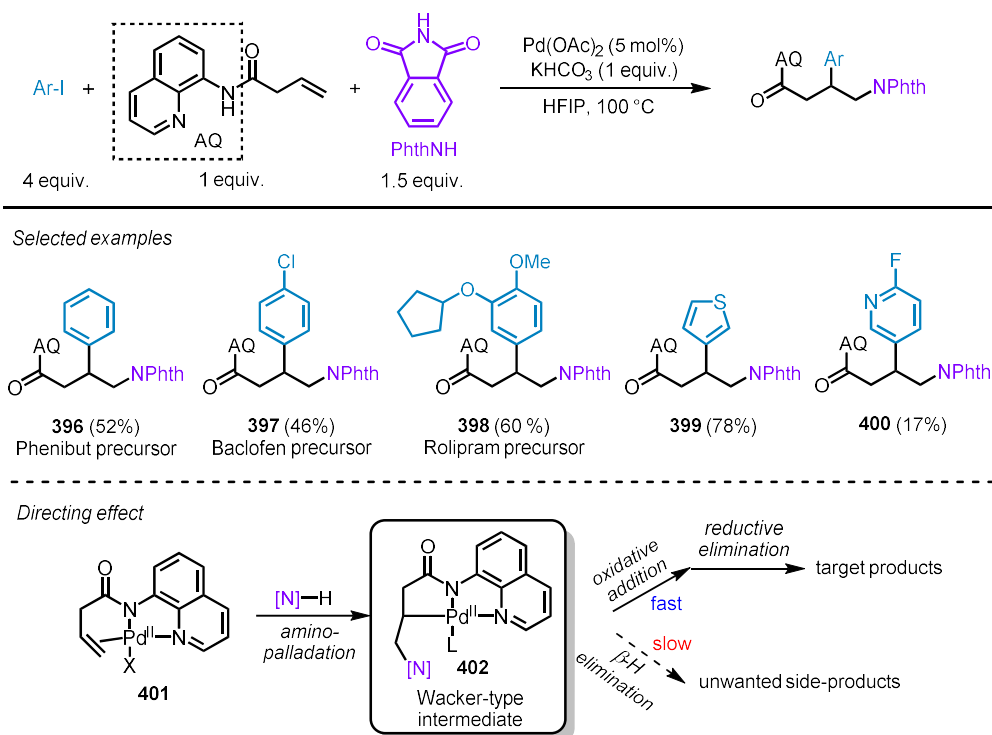


Scheme 35. Synthesis of unnatural peptides via diastereoselective aminoarylation of alkenes.

Almost all examples discussed so far yielded a regioselectivity such that the aryl is added to the terminal position of the alkene. Inverting the regioselectivity of aminoarylation processes has thus been an important challenge. In this regard, phenoxyacetamides are interesting reagents not only because they dually serve as the source of aryl and amine groups, but also because they may act as directing groups. They may orchestrate the C–H activation - not only powering the reaction, but also controlling it. Thus, the use of directing groups to tweak the regioselectivity of alkene aminoarylation processes has been investigated.

In this context, in 2017, the group of Engle reported the use of easily cleavable 8-aminoquinoline (AQ) substituted 3-butenic acid derivatives as alkenes of choice for aminoarylation (Scheme 36).^[79] The authors envisioned that the use of such a directing group could (i) exert control on the regioselectivity of the reaction and (ii) stabilize a Wacker-type aminopalladated intermediate, such that a subsequent oxidative addition to a carbon electrophile might outcompete β -hydride elimination. Such starting materials proved compatible for aminoarylation through the

complementary use of aryl iodides and phthalimide. Although few aromatics yielded the desired product, heteroaromatics including thiophene and pyridine (albeit in low yield) were also tolerated by this procedure. Importantly, this study displayed an inverted regioselectivity compared to previous methodologies, with the aryl group adding to the internal position of the alkene. This approach also met another challenge with respect to the aminoarylation of alkenes, namely the use of aliphatic alkenes, although this reactivity is limited by the presence of a directing group within the alkene structure. Notably, this strategy can serve as an entry point to several bioactive molecules such as Baclofen, Phenibut, and Rolipram.

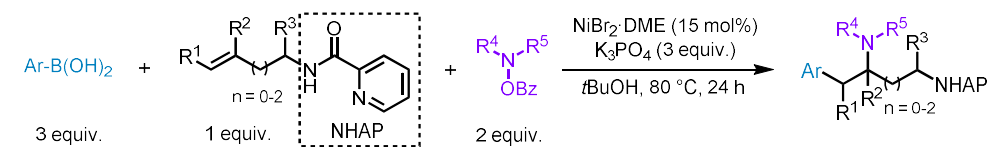


Scheme 36. Pd-catalyzed aminoarylation of aliphatic alkenes via directed aminopalladation.

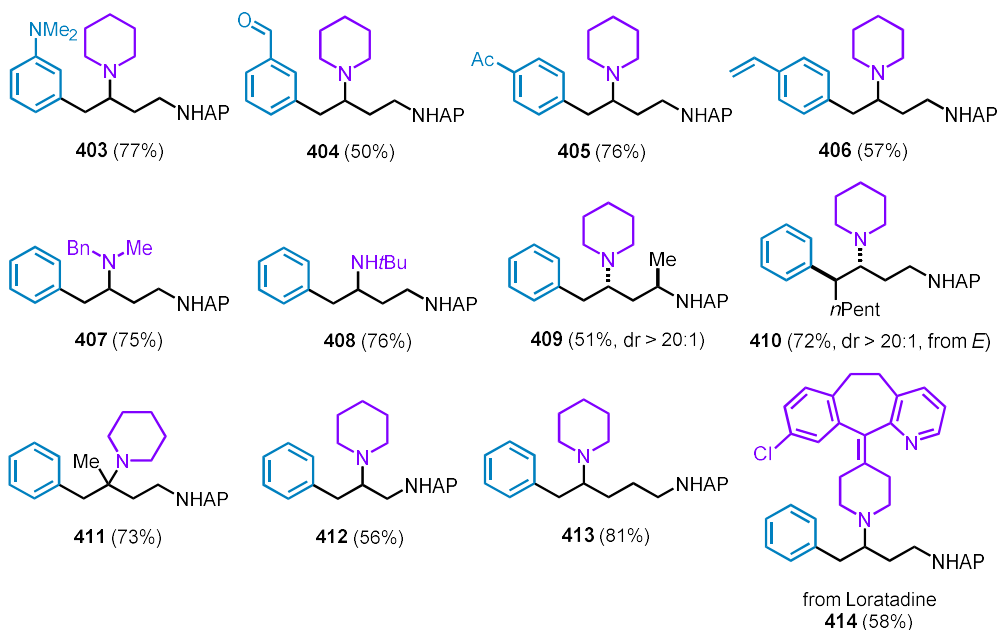
Although limited in terms of scope, the abovementioned method served as basis for further development of intermolecular arylamination processes, as it pioneered the use of alkenes bearing a tethered directing group for enabling and controlling the reactivity. Inspired by this methodology, in 2021 the group of Wang described a similar approach featuring the use of a nickel catalyst, arylboronic acids and *O*-benzoylhydroxylamines (Scheme 37).^[80] The authors anticipated that arylboronic acids could easily undergo transmetalation onto the nickel center, allowing them to act more effectively as an aryl source. Relying on a bidentate picolinamide directing group, this process displayed a large scope with respect to the alkene, aryl, and amine partners. A wide range of electron-rich and -deficient substituents was tolerated on the arene,

including protected alcohols, amines, halides, aldehydes, ketones, and alkenes. This approach allows the introduction of various secondary and tertiary aliphatic amines in the corresponding products. In addition, the reaction was not limited to homoallylamines, but could also be extended to different lengths of tether, notably allyl- and bishomoallylamines. Interestingly, α -substituted homoallylamines or internal alkenes also underwent the reaction to provide the arylation products with excellent control of the diastereoselectivity. Finally, this transformation proceeded smoothly with biologically relevant compounds such as Loratadine. Regarding the mechanism, it was proposed to operate through an initial transmetalation between nickel complex **415** and the arylboronic acid. Migratory insertion of the alkene into the metal-aryl bond would then yield alkyl nickel species **417**, into which the oxidative addition of *O*-benzoylhydroxylamine **418** would occur to form nickel amido complex **419**. Finally, reductive elimination would regenerate **415** and deliver the desired product. In support of this pathway, mechanistic experiments revealed the existence of intermediate **417** in DMF, which can catalyze the aminoarylation to afford the target product in 57% yield. It is noteworthy that the regioselectivity is reversed compared to the work of Engle, which might be attributed to the fact that the rate of arylboronic acids transmetalation is faster than the oxidative addition of *O*-benzoylhydroxylamines.

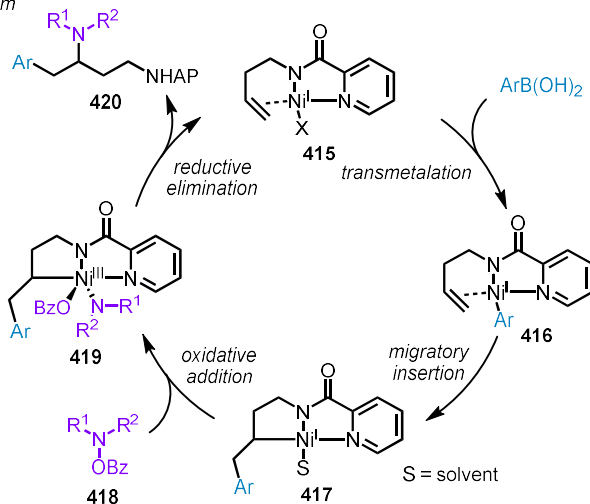
Remarkably, further studies by Engle group demonstrated that such type of directing group was not even necessary as simple alcohols or amines could be effectively used to control the regioselectivity of aminoarylation of aliphatic alkenes using arylboronate esters as arene components.^[81,82]



Selected examples



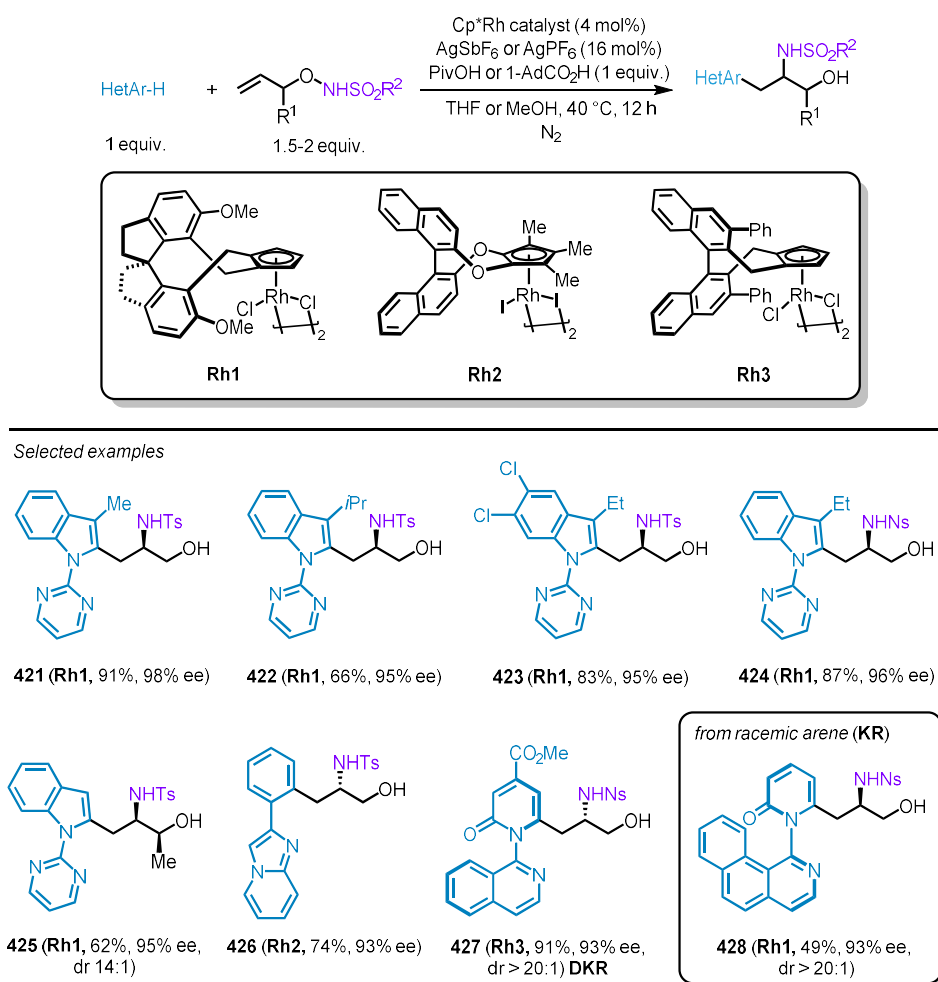
Proposed mechanism



Scheme 37. Ni-catalyzed directed aminoarylation of unactivated alkenes.

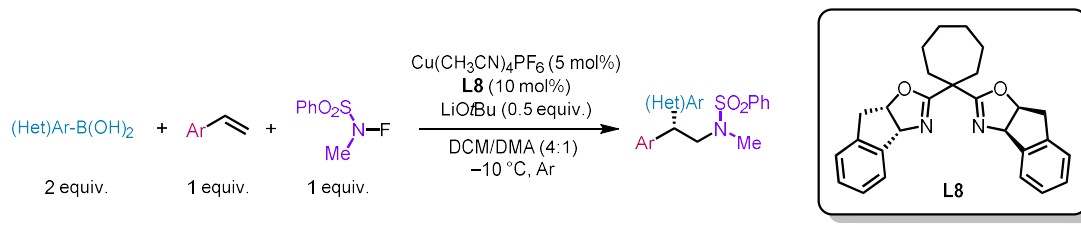
Very recently, Li and co-workers took advantage of a similar strategy, where a directing group located on the aryl component may coordinate to the metal center to orient the reaction. In their case, bifunctional O-allylhydroxyamines were dually used as substrate and amine source and the process proved highly stereoselective with various Cp^{*}Rh catalysts (Scheme 38).^[83] The use of a

bifunctional alkene favored specific chelation of the metal to induce stereocontrol. The reaction was compatible with a variety of bis-heterocyclic arene moieties bearing halide and alkyl groups. Various sulfonamides could be installed on the olefin to produce the desired aminoarylated products in excellent yields and enantiomeric excesses. Interestingly, when indoles were used, the selectivity was not impacted by the presence of bulky groups at the C3 position of indole. Having achieved a new synthesis of centrally chiral aminoarylated alcohols, the authors then looked at the synthesis of products displaying both central and axial chirality. The use of 2-pyridone motifs functionalized with bulky directing groups was investigated. Importantly, Dynamic Kinetic Resolution (DKR) could be achieved using prochiral arenes (**427**), whereas Kinetic Resolution (KR) could be realized when using racemic 2-pyridones (**428**). In both cases, twofold stereogenicity was observed with excellent yields and diastereomeric ratios.

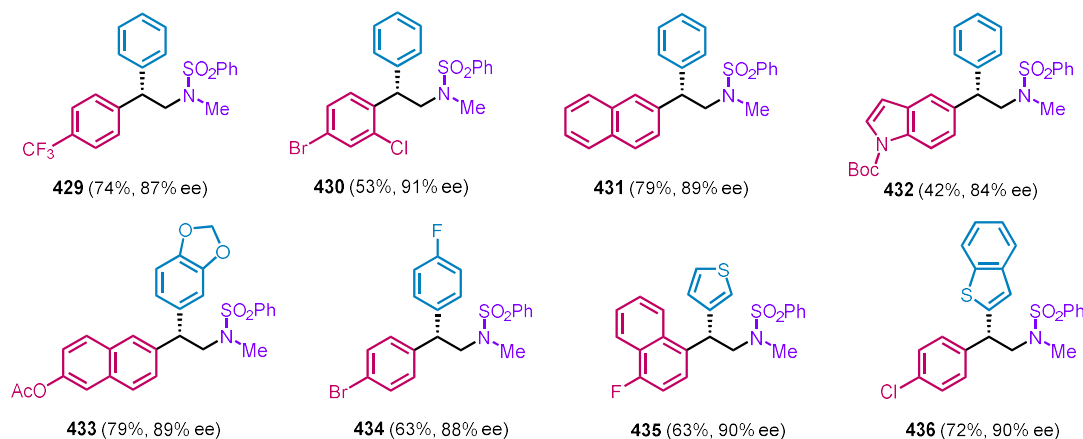


Scheme 38. Access to axially and centrally chiral compounds through bifunctional alkene (hetero)arylamidation.

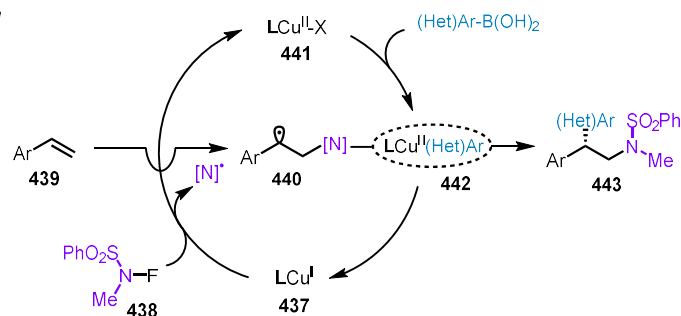
Although 2,1-aminoarylations of alkenes have been well-described, it has much less been the case for 1,2-aminoarylations, except for the use of biased substrates incorporating directing groups and for the Truce-Smiles rearrangement described previously. Gratifyingly, in recent years, new strategies have started to emerge. In 2017, the group of Liu killed two birds with one stone by reporting the first example of an enantioselective 1,2-aminoarylation process using a copper catalyst bearing a chiral bisoxazoline ligand to asymmetrically produce β,β -diarylethylamines from styrenes (electron-rich or poor, including trifluoromethyl substitution), arylboronic acids, and *N*-fluoro-*N*-alkylsulfonamide as the amine source (Scheme 39).^[84] Arylboronic acids presents numerous advantages due to their diversity, their general availability, and their ability to undergo transmetalation with relative ease. Although the scope of the aryl component in this study was still limited to electron-rich partners, this method allowed to overcome a longstanding limitation in the scope of aminoarylation reactions - the ability to easily install heteroarenes as part of the aryl component. Regarding the mechanism, the authors proposed that the reaction of *N*-fluoro-*N*-alkylsulfonamide **438** with the copper(I) catalyst **437** forms aminyl radicals, which readily react with styrene **439** at their terminal position to produce a β -amino benzylic radical **440**. In parallel, the (hetero)arylboronic acid undergoes transmetalation to form a $\text{LCu}^{\text{II}}\text{-(Het)Ar}$ species **442**, that could, thanks to the use of chiral bisoxazoline ligands, complete the aminoarylation process with good to excellent enantiomeric excesses. The proposed mechanism therefore explains why the regioselectivity is complementary to that observed in existing aminoarylation of styrenes that go through Meerwein pathways via a benzylic cation.



Selected examples



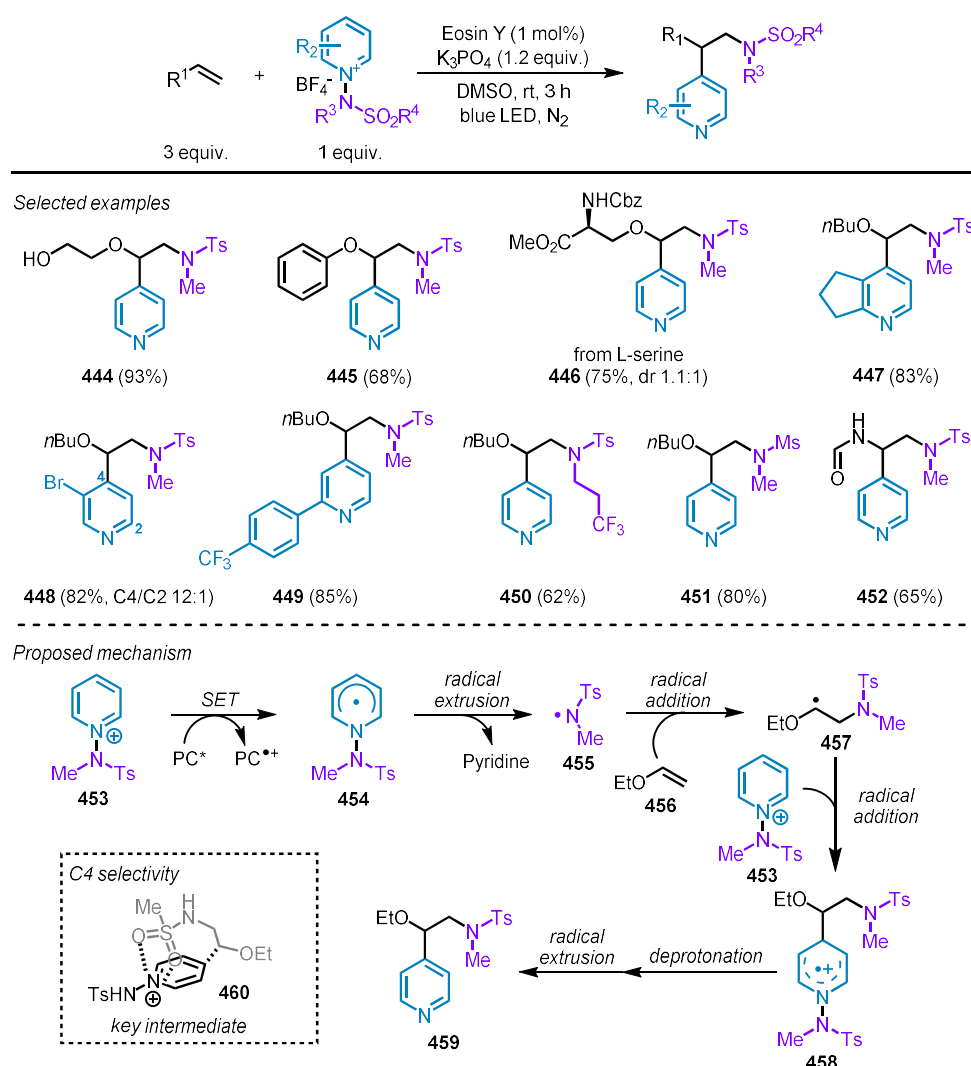
Proposed mechanism



Scheme 39. Cu-catalyzed enantioselective synthesis of β,β -diarylethylamines.

The difficulty of installing electron-poor heteroarenes has remained a key barrier to increase the utility and versatility of the aminoarylation of alkenes. This problem was partially tackled in 2019 by Hong and co-workers when they disclosed a clever use of *N*-aminopyridinium salts as bifunctional reagents to install *N*-alkyl sulfonamide and pyridyl moieties in a C4-selective fashion (Scheme 40).^[85] The authors showed that the N–N bond could be cleaved under photocatalytic conditions, resulting in the formation of a sulfonamidyl radical species **455** and pyridine. This generated radical could react at the terminal position of alkene **456** to give the corresponding alkyl radical **457**, which would then add to the C4 position of a second molecule of aminopyridinium salt **453**. Diverse substitution patterns on the pyridine ring proved compatible with the methodology. Regarding the alkene component, the reaction was largely applied to various

electron-rich vinyl ethers, which were previously rarely used in aminoarylation. As a mix of C2 and C4 products is classically observed in additions to pyridiniums, the authors performed mechanistic investigations to understand the origin of their unusually high C4 selectivity. DFT studies revealed that the *para* attack was slightly favored over the *ortho* attack, which was consistent with the observed results. Distortion-interaction analyses revealed a favorable electrostatic interaction between the oxygens of the Ts protecting group of the alkylamine with the nitrogen of the pyridine (**460**), resulting in closer proximity between the C4 position of the pyridinium and the alkene, rationalizing the observed selectivity.



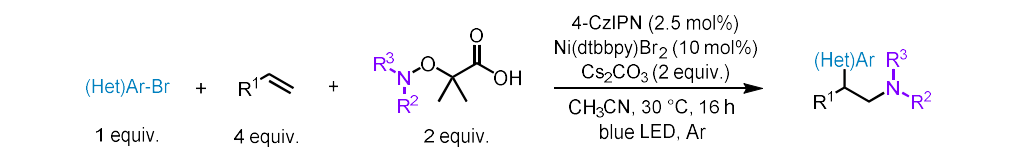
Scheme 40. Photocatalytic C4-aminopyridylation of alkenes using *N*-aminopyridinium salts.

Interestingly, subsequent studies by the same group showed that switching to *N*-aminopyridinium ylides had a dramatic effect on the selectivity, favoring a C2-selective process.^[86] Indeed,

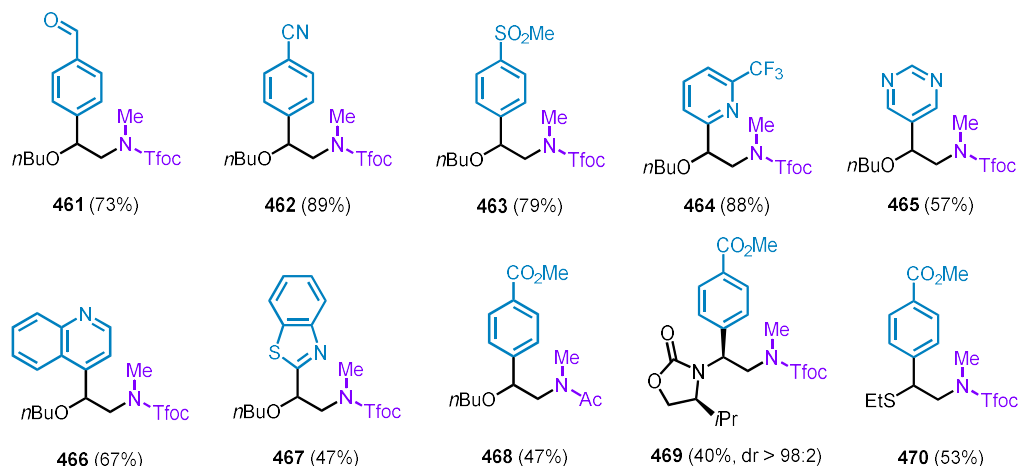
photocatalyst-mediated oxidation of the ylide would yield a radical cation, which would readily react with alkenes in a 1,3-cycloaddition, thereby providing the C2-selectivity in the thus-formed aminopyridylation products.

The group of Studer succeeded to expand the 1,2-amino(hetero)arylation processes to a broader range of electron-rich alkenes in 2021 (Scheme 41).^[87] They reported a three-component 1,2-amino(hetero)arylation acting on electron-rich vinyl ethers, enamides, enecarbamates and vinyl thioethers. Regarding the mechanism, the deprotonated form of protected hydroxamic acid derivative (**471**) could undergo SET with a photoexcited iridium catalyst to provide acyloxy radical **472**, which would in turn generate amidyl radical **473** upon fragmentation with release of carbon dioxide and acetone. This radical intermediate could then add onto alkene **474** at its terminal position to yield β -amino radical **475**. Nickel complex **476** resulting from the oxidative addition of (hetero)aryl bromide onto the nickel catalyst would capture the thus-generated radical species **475**, yielding aminoarylated product after reductive elimination. The authors described a large scope, with excellent tolerance to electron-withdrawing groups on heteroarenes, in good to excellent yields. Electron-rich arenes were found to be refractory reactants, likely because they disfavor oxidative addition.

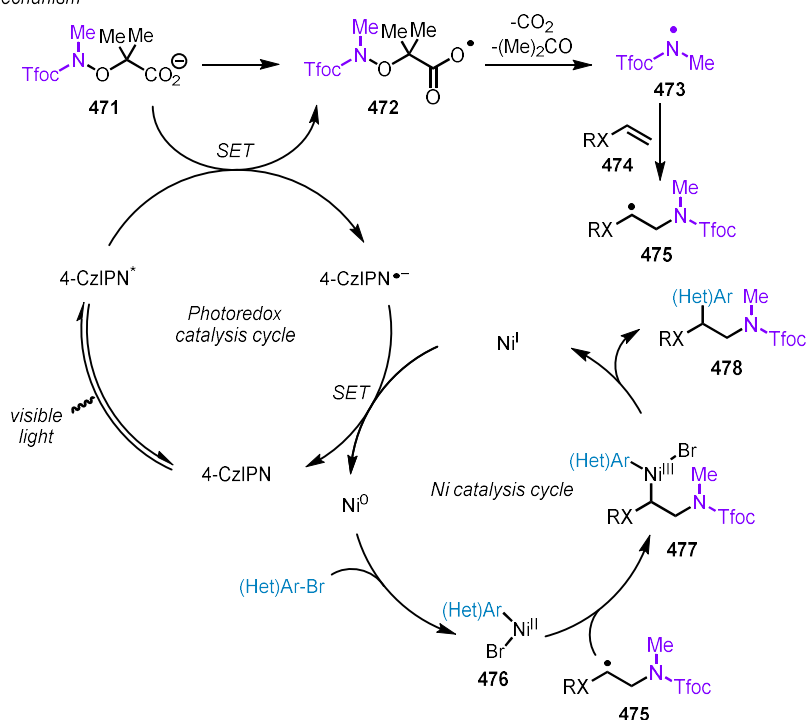
Within existing aminoarylation methodologies, two main limitations remain. From a synthetic point-of-view, the expansion to strongly electronically deactivated styrenes was long challenging to achieve. Perhaps more importantly, most aminoarylation processes reported thus far do not directly yield a primary amine, but rather a protected amine, which in many cases is not the direct compound of interest for the user, thus requiring additional (often challenging) deprotection steps.



Selected examples



Proposed mechanism



Scheme 41. Photoredox Ni-catalyzed three-component aminoarylation of electron-rich alkenes

Taken together, the various amino(hetero)arylations of alkenes described here have undoubtedly expanded the attainable chemical space, which is of crucial importance when considering the

biological relevance of β -(hetero)arylamine scaffolds. The large range of strategies proposed has allowed for a formidable control of the reactivity and the ability to access significantly more complex molecules than were previously possible. In particular, amino(hetero)arylation is one of the few available methods that is compatible with activated, aliphatic and heteroatom-substituted alkenes as well as electron-rich and highly electronically deactivated styrenes. However, the control over regioselectivity often comes at a cost: the common need for directing groups, especially in the case of aliphatic alkenes, requires the precise design of the starting materials, making the process non-economical and often creating limitations in terms of substrate availability. In addition, the enantiocontrol of aminoarylation processes remains a complicated task. Although the contribution of Liu and Lin is of high value for the rapid gain of molecular complexity, it is limited to specific styrenes and arylboronic acid sources. Rendering such procedures enantioselective is indeed challenging since most aminoarylation methodologies use highly reactive radicals. Yet, these works should pave the way for exciting new developments in the coming years, notably the development of enantioselective protocols.

Summary and Outlook

Over the past decade, the advances made in the design of new methods to access β -(hetero)arylamines have been substantial thanks to the emergence of photocatalysis and transition metal-catalyzed C–H activation. Each strategy has its benefits and disadvantages, allowing to access scaffolds of completely different types with complementary functional group tolerance. It is our hope that this review will inspire readers to work in this area and quickly guide them to a suitable method to access a desired framework.

Despite the progresses made, several gaps remain to be filled. As highlighted by this review, no matter the method chosen, asymmetric methods to rapidly access β -(hetero)arylamines are scarce and further development is required to uncover viable alternatives to enantioselective hydrogenation processes. Moreover, expanding the range of amine partners is essential to increase the synthetic utility of existing methods. Currently, they generally provide compounds whose nitrogen functionality is protected by electron-withdrawing groups such as sulfonyls, that are rarely present in the core of the corresponding bioactive molecules (see Figure 1). It means that additional deprotection steps -not always trivial – can be required, which might constitute a limiting factor for medicinal applications. As a result, designing new transformations that enable a more general introduction of aliphatic amines, notably primary ones, should be highly sought since these functionalities are ubiquitous in several known drugs. Among other challenges are the construction of quaternary centers, the introduction of heterocycles containing multiple nitrogens

or that of sterically hindered (hetero)aryl rings, as there are only scarce reports regarding these types of reactivity. Given the industrial relevance of β -(hetero)arylamine scaffolds, interest in the development of versatile and broadly applicable methodologies for their synthesis is not likely to wane.

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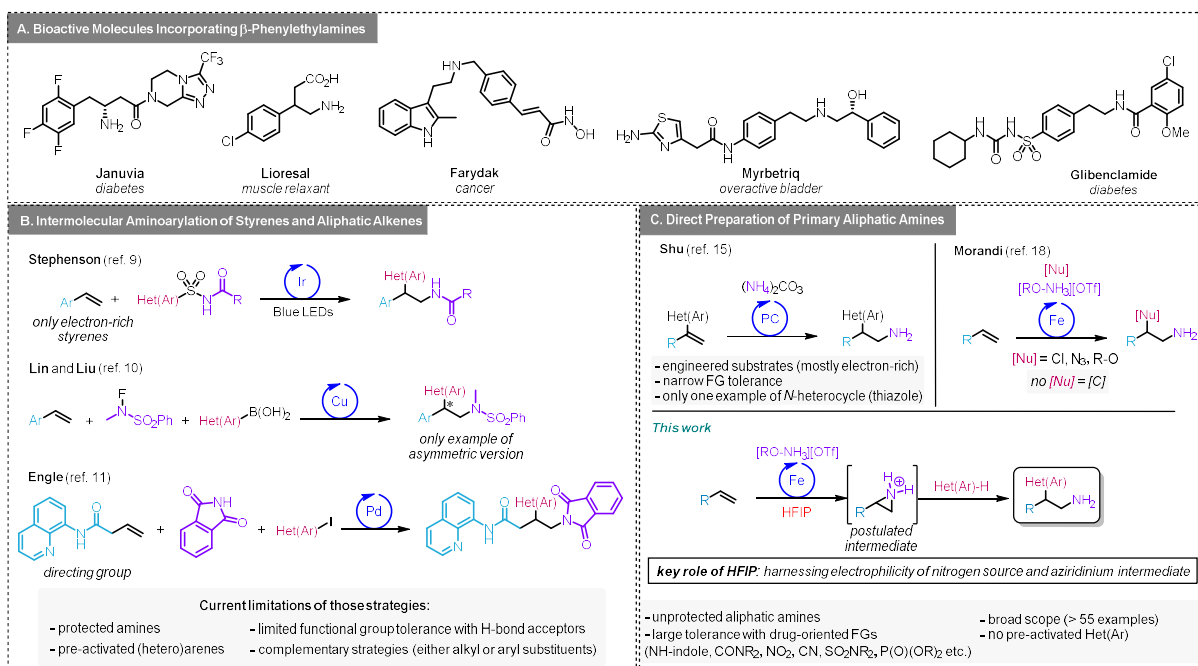
Main Text

Introduction

Aliphatic amines are at the core of fine chemical synthesis.^[1] They feature in more than 40% of drug molecules but are also versatile precursors for constructing more complex bioactive molecules, natural products, and polymers (Scheme 1A).^[2] Consequently, accessing densely functionalized primary aliphatic amines, notably β -arylethylamines, represents an important challenge in synthetic chemistry.^[3] Since the functional groups embedded in those molecules significantly influence its biological properties, synthetic methods that can provide structurally complex aliphatic amines are fundamental to expand into biologically relevant chemical space. Currently, common methods to forge β -aryl aliphatic primary amines include 1,4-addition to nitroalkenes,^[4] arylation of aziridines,^[5] and anti-Markovnikov hydroamination of alkenes.^[6] However, they often require engineered substrates, display limited functional group tolerance, or involve additional reduction or deprotection steps that further limit functional group compatibility.

Alkene difunctionalization^[7] is a straightforward way to assemble β -arylethylamines in a single step.^[8] In recent years, this challenge was taken up by several groups, notably Stephenson,^[9] Liu,^[10] and Engle^[11] (Scheme 1B).^[12,13] However, none of these strategies provide unprotected amines, and, in some cases, pre-activated (hetero)arenes or directing groups are required. Furthermore, they do not directly access several drug-relevant functional groups, including amides, sulfonamides, nitro groups, nitriles, phosphonates, and NH-indoles, among others. At least, one of these functional groups are found in most pharmaceuticals since they provide key interactions between drugs and their biologic targets.^[14] Given these existing limitations, the arylation of alkenes to the corresponding unprotected β -arylethylamines remains an open challenge in synthesis.

Shu accessed β -phenylethylamines through the hydroamination of 1,1-disubstituted alkenes using ammonium carbonate as an amine source (Scheme 1C).^[15] However, in this case, the aryl moiety must already be present in the alkene substrate. Furthermore, the alkene motif was unable to tolerate electron-withdrawing groups stronger than esters or a trifluoromethyl group and compatibility with *N*-heterocycles, notably with indole derivatives, was not explored. Alternatively, nitrogen-centered radicals are among the simplest ways to generate unprotected amines.^[16] Proven sources for the formation of those species are hydroxylamines,^[17] whose use has been exploited by the group of Morandi in iron(II)-catalyzed alkene aminochlorination, aminoazidation and aminohydroxylation (Scheme 1C).^[18] The use of (hetero)arene nucleophiles



Scheme 1. Importance of β -phenylethylamines and strategies to access them. FG = functional group.

remains unexplored, which can be attributed to the fact that arenes are easily aminated under those reaction conditions, as illustrated by Morandi,^[19] Jiao,^[20] Ritter,^[21] Phipps,^[22] and others.^[17b]

We envisaged a one-pot/two-step aminoarylation process featuring the amination of the alkene with hydroxylamines followed by the addition of a (hetero)arene nucleophile to trigger the ring-opening of a postulated aziridinium intermediate. The reaction would take place at the most substituted position of the aziridinium in analogy with our recent work on the arylation of phenoniums.^[23,24] We speculated that the use of hexafluoroisopropanol (HFIP) would allow us to overcome the problem of compatibility between (hetero)arenes and hydroxylamine radical chemistry and to widen the scope of compatible functional groups.^[25] Based on our previous studies on the reactivity of deactivated styrenes and epoxides,^[23,26] we suspected that HFIP could simultaneously stabilize radical and cationic intermediates while enhancing the electrophilicity of the key amine-centered radical and aziridinium components, allowing highly deactivated substrates to be used in the reaction.

Here, we disclose that HFIP enables 1,2-arylation of alkenes to directly access unprotected β -arylethylamines under conditions compatible with a broad range of functional groups. The user-friendly reaction offers a valuable alternative to well-established strategies for the aminoarylation of alkenes.

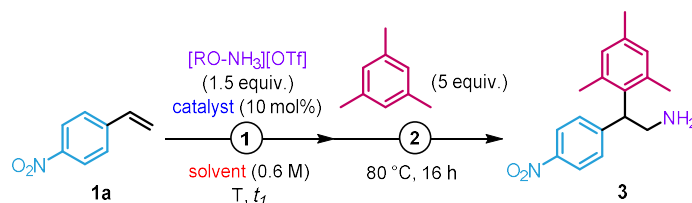
Results and Discussion

Optimization Studies

We began our optimization studies with 4-nitrostyrene **1a** as a model substrate and [MsO-NH₃][OTf] as an aminating agent (1.5 equiv), using FeSO₄·7H₂O as a catalyst (10 mol%) in HFIP (0.6 M) (Table 1).^[21] Initially, the first step was carried out at 60 °C for 6 h, before adding mesitylene as an arene nucleophile (5 equiv). After 16 h at 80 °C, the target product **3** was isolated in 48% yield (entry 1). Of note, no amination of the nitrobenzene ring was observed under those reaction conditions. Decreasing the temperature to 60 °C for the second step resulted in a significant drop in yield (16%) (entry 2). We then tested a series of common hydroxylammonium salts but none of them improved the yield of the reaction (entries 3-6). Either the amination did not occur in the first step (entries 3-5) or the amination of the nitrobenzene also took place as a side reaction (entry 6). By closely monitoring the first step, its reaction time could be reduced to 1 h, providing the aminoarylation product **3** in a slightly better yield (51%) (entry 7). Regarding the optimization, the screening of a series of Fe(II) salts revealed that FeSO₄·7H₂O and Fe(OTf)₂ are equally effective (entries 8-12). We opted for the former in our studies as it is cheap and air-insensitive. As anticipated, the reaction did not afford product **3** in conventional organic solvents (entries 13-17), highlighting the critical role of HFIP in the transformation. Other parameters such as the concentration, the temperature in the first step, and the number of equivalents of [MsO-NH₃][OTf] were evaluated but they did not improve degradation or side reactions (entries 18-21).^[27] The applicability of this protocol was demonstrated at a larger scale (5.46 mmol), which allowed the preparation of aminoarylated compound **3** in 54% yield (2.95 mmol, 840 mg) (entry 7).

From there, we tried to determine where the loss in yield occurred and to identify what side products and intermediates were generated. After the first step, a mixture of several products was obtained. However, conducting this step in the absence of iron(II) catalyst allowed us to monitor the reaction by ¹H NMR and to observe the formation of the dimer of 4-nitrostyrene (**2**), which likely undergoes subsequent reactions in the presence of iron. This compound was isolated in 15% yield (Equation 1), accounting for 30% of starting material. The formation of this product from a highly deactivated styrene might be explained by the acidic reaction conditions that favor its initial protonation prior to its dimerization.^[25b] In parallel, the aminated product obtained at the first step was protected with a Boc group to facilitate its characterization, delivering the corresponding aminoalcohol **3a** along with its regioisomer in 51% yield (ratio 88:12) (Equation 2). This result is in line with the yield obtained for the product **3**, demonstrating that the first step is the bottleneck of the reaction. Regarding the mechanism, interrupting the process after the first step allowed us

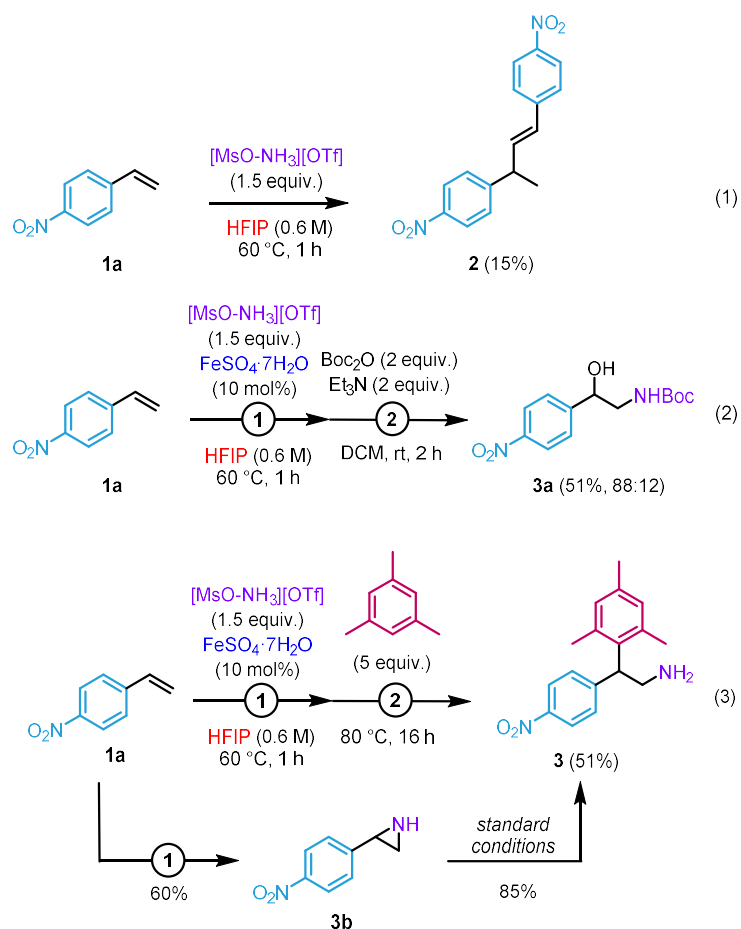
to isolate the corresponding aziridine **3b** in 60% yield. Re-engaging the aziridine in our standard conditions provided compound **3** in 85% yield, in line with its postulated intermediacy in the reaction (Equation 3).



Entry	Catalyst	[RO-NH ₃][OTf]	Solvent	T	t ₁	Yield ^[b] (%)
1	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	HFIP	60	6	48
2 ^[c]	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	HFIP	60	6	16
3	FeSO ₄ ·7H ₂ O	[PivO-NH ₃][OTf]	HFIP	60	6	-
4	FeSO ₄ ·7H ₂ O	[PNBO-NH ₃][OTf]	HFIP	60	6	-
5	FeSO ₄ ·7H ₂ O	[TsO-NH ₃][OTf]	HFIP	60	6	-
6	FeSO ₄ ·7H ₂ O	[NsO-NH ₃][OTf]	HFIP	60	6	27
7	FeSO₄·7H₂O	[MsO-NH₃][OTf]	HFIP	60	1	51 (54)^[d]
8	Fe(OTf) ₂	[MsO-NH ₃][OTf]	HFIP	60	1	52 ^[e]
9	Fe(OAc) ₂	[MsO-NH ₃][OTf]	HFIP	60	1	45 ^[e]
10	Fe(acac) ₂	[MsO-NH ₃][OTf]	HFIP	60	1	31 ^[e]
11	FeCl ₂	[MsO-NH ₃][OTf]	HFIP	60	1	44 ^[e]
12	FePc	[MsO-NH ₃][OTf]	HFIP	60	1	-
13	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	Toluene	60	1	-
14	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	MeNO ₂	60	1	-
15	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	1,2-DCE	60	1	-
16	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	<i>i</i> PrOH	60	1	-
17	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	TFE	60	1	25 ^[e]
18 ^[f]	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	HFIP	60	1	40
19	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	HFIP	40	1	-
20	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	HFIP	80	1	-
21 ^[g]	FeSO ₄ ·7H ₂ O	[MsO-NH ₃][OTf]	HFIP	60	1	13

[a] Standard reaction conditions: (1) **1a** (0.3 mmol), [RO-NH₃][OTf] (1.5 equiv.) and catalyst (10 mol%) in solvent (0.6 M), 60 °C, 1 h (in a sealed tube) then (2) mesitylene (5 equiv.), 80 °C, 16 h. [b] Isolated yield. [c] Second step at 60 °C. [d] 5.46 mmol scale. [e] NMR yield using triethylsilane as an external standard. [f] 0.2 M. [g] [MsO-NH₃][OTf] (2.5 equiv.). PNB = *para*-nitrobenzoyl. Pc = phthalocyanine.

Table 1. Optimization of the reaction conditions for the formation of aminoarylation compound **3**.



Reaction Scope

With the optimized conditions in hand (Table 1, entry 7), we explored the scope of the reaction, initially evaluating the reactivity of various electron-rich (hetero)arenes with 4-nitrostyrene **1a** (Scheme 2). Substrate **1a** underwent the reaction sequence smoothly with a diverse set of indoles to provide the corresponding products **4-13** in yields ranging from 40 to 64%.^[28] Here, two products - separable by flash column chromatography - were obtained in the case of 2-methylindole (**4**), resulting from the nucleophilic addition at C2 and C5. The reaction was tolerant to the presence of both electron-donating and -withdrawing groups at C5 (**9-12**) with no impact on the yield. The compound **12** obtained from the reaction between **1a** and 5-cyanoindole is an illustrative example of how our methodology enables the rapid synthesis of densely functionalized scaffolds, as four different nitrogen functionalities (nitro, cyano, NH-indole and primary NH_2) were all installed in one-pot. The reaction could be also applied to pyrrole derivatives to afford compounds **14** and **15** in 50 and 62% yield, respectively. Moreover, the reaction sequence is not limited to heteroarenes but could be also extended to electron-rich arenes, notably to methoxy-

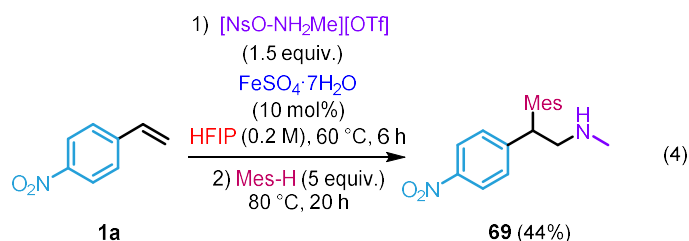
substituted arenes. In most cases, the products were obtained in good yields (**16-23**, 45-56%) and excellent regioselectivity (up to 90:10), except for anisole (**23**). Additional halide groups could be introduced together with methoxy groups without compromising the reactivity (**19-21**). The steric hindrance displayed by pentamethylbenzene did not hamper the reactivity, as the corresponding product **24** was obtained in 44% yield. While less electron-rich arenes such as *p*-xylene (**25**) or even benzene (**26**) could also be used in the transformation, we observed a decrease in yield (30 and 15%, respectively). As anticipated, naphthalene reacted unselectively to generate a 1:1 mixture of two regioisomers, albeit in high yield (**27**, 64%). In the case of phenol, only the *O*-alkylation occurred to form **29** in 40% yield. The same applied to diphenylamine (**30**, 50%). Increasing the steric hindrance around the OH functionality can reverse this trend, predominantly delivering 52% of *C*-alkylation vs. 20% *O*-alkylation in the case of 2,6-dimethylphenol (**28**). Indazole provided product **31** in 58% yield. It is noteworthy that thioanisole underwent demethylation under our reaction conditions to afford the product of aminosulfidation **32** (61%).

Mesitylene and 2-methylindole were then chosen as nucleophiles to examine the scope of this transformation with styrenes, focusing on substrates bearing functional groups that could be relevant to the synthesis of bioactive compounds. Remarkably, our protocol proved compatible with a broad range of deactivated styrenes, affording the corresponding products **33-55** in yields ranging from 35 to 81%. Gratifyingly, the products formed incorporate a broad range of functional groups of biological relevance that were hitherto never described, including nitro, cyano, amide, sulfonamide, sulfonate ester, pentafluorosulfanyl, phosphonate, and morpholine groups. Compounds such as **52**, arising from the reaction between 4-nitro-3-trifluoromethylstyrene and 5-methoxyindole, can bear up to five different functional groups often found in marketed pharmaceuticals. Furthermore, non-terminal styrene also underwent the reaction smoothly, producing compound **55** as a mixture of diastereoisomers in 60% yield.

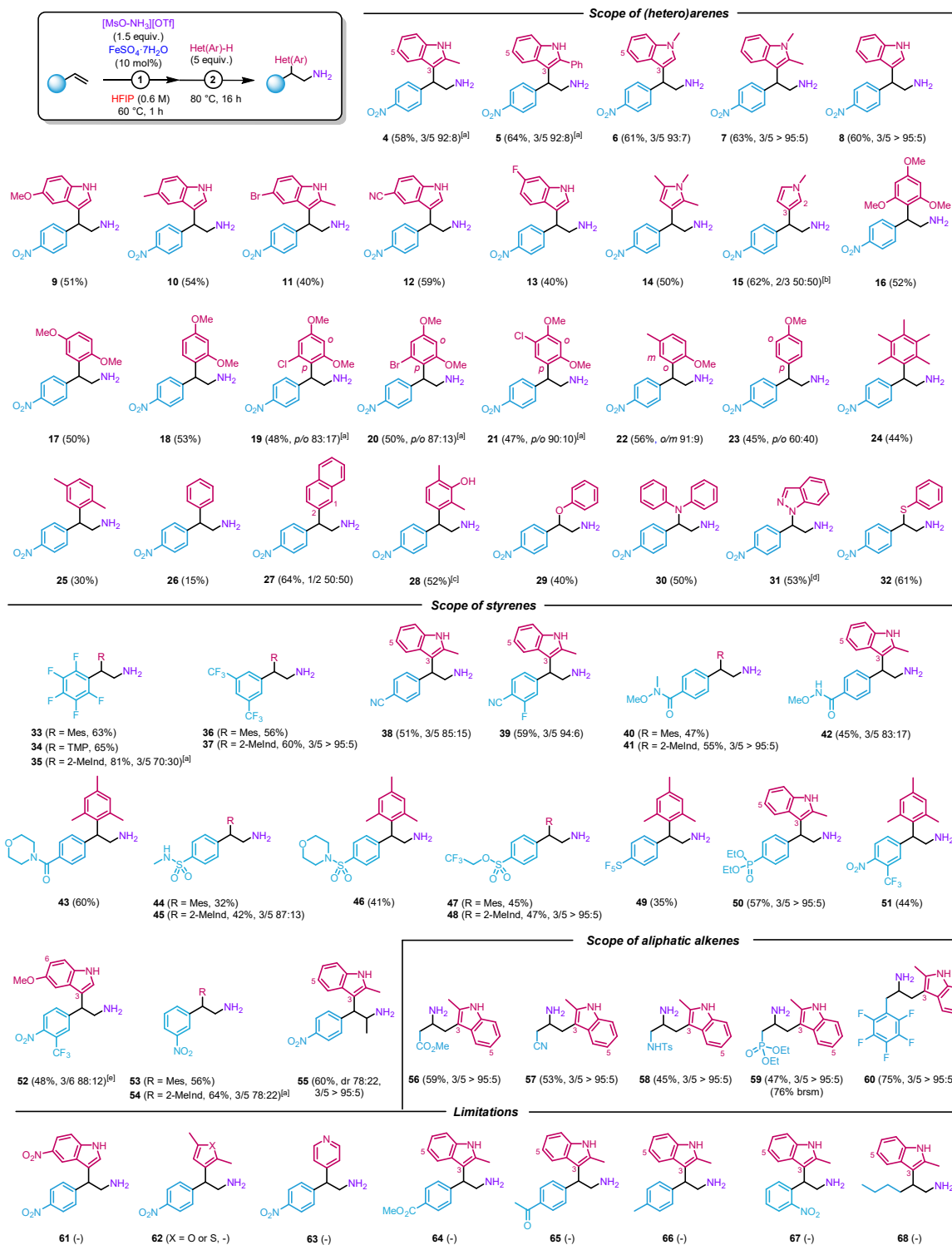
Importantly, the transformation is not restricted to styrene derivatives, as allyl substrates that are stable under highly acidic conditions readily react with 2-methylindole to yield aminoarylation compounds **56-60** in 45-75%. However, we noticed an inversion of regioselectivity as the reaction produced branched aliphatic amines. It might be explained by the presence of electron-withdrawing groups that reduce the electrophilicity of the internal position of the aziridinium intermediate, favoring the nucleophilic addition at the terminal position. The reaction is notably tolerant to ester, cyano, sulfonamide, phosphonate and pentafluorophenyl groups.

Regarding the limitations of this transformation, 5-nitroindole did not yield the target product **61**, reacting with itself following an oligomerization process.^[29] The reaction is also not compatible with furan and thiophene derivatives, which decomposed under the reaction conditions. In the case of pyridine (**63**), no reaction was observed, likely due to the trapping of the active species by pyridine. Additionally, styrenes containing an ester (**64**), a ketone (**65**), or, more generally, electron-rich olefins (**66**) did not provide the target products, as they rapidly oligomerized under our standard conditions in the first step. The same applied to 1-hexene (**68**). We also noticed that the presence of a nitro group at the *ortho* position was incompatible with the reaction (**57**), for reasons unclear.

It is important to point out that the reaction sequence is not limited to the preparation of primary amines but can also be employed to introduce secondary amines by using tailored hydroxylammonium salts. For instance, [NsO-NH₂Me][OTf]^[19b] delivered aminoarylation product **69** with a secondary aliphatic amine (44% yield) (Equation 4).

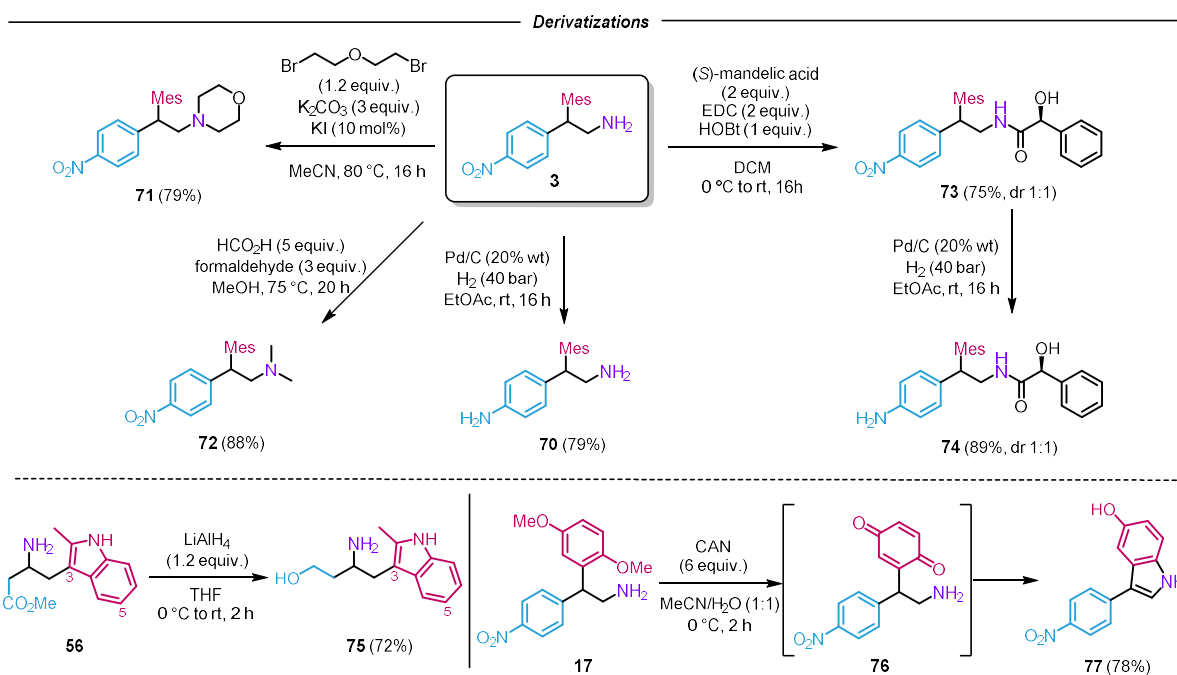


The synthetic utility of this transformation was also highlighted by a series of derivatizations to obtain compounds bearing pharmaceutically relevant moieties (Scheme 3). For instance, the nitro group of **3** was readily reduced with H₂ on Pd/C to furnish the corresponding aniline **70** in 79% yield. It also reacted with 2-bromoethyl ether to install a morpholine unit (**71**, 79%).^[30] Eschweiler-Clarke methylation afforded *N,N*-dimethylamine **72** in 88% yield. The amide coupling with (*S*)-mandelic acid, and the subsequent reduction of the nitro group furnished compound **74**, which can be used to synthesize analogs of Myrbetriq. In turn, ester **56** was also reduced to give the aminoalcohol **75** in 72% yield. Interestingly, the aminoarylation of product **17** incorporating a 1,4-dimethoxybenzene group led to indole **77** in the presence of cerium ammonium nitrate (CAN) (78%), which resulted from the *in-situ* cyclization of quinone intermediate **76**.



[a] Regioisomers were separated by flash column chromatography. [b] Second step at 40 °C. [c] O-alkylation product obtained in 20% yield. [d] Product of addition at the terminal position observed (around 10% yield). [e] Product unstable and thus protected by a Boc group for characterization. Mes = 1,3,5-trimethylphenyl. TMP = 1,3,5-trimethoxyphenyl. 2-MeInd = 2-methylindole. brsm = based on recovered starting material.

Scheme 2. Scope of 1,2-aminoarylation of alkenes.



Mes = 1,3,5-trimethylphenyl. EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. HOBT = 1-hydroxybenzotriazole. CAN = cerium ammonium nitrate.

Scheme 3. Applications of 1,2-aminoarylation of alkenes.

Conclusion

In summary, we have reported a practical method for the 1,2-aminoarylation of alkenes, allowing for a direct access to unprotected β -arylamines. This simple yet far from trivial sequential one-pot protocol relies on the combination of a cheap iron catalyst with HFIP. This reaction is operationally simple, scalable and exhibits broad functional group tolerance, notably with respect to drug-oriented functional groups. In addition, the compounds obtained can be rapidly functionalized to generate more complex molecules. Finally, this study represents yet another example of how HFIP can facilitate desirable reactivity when classical solvents fail.

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[18] a) L. Legnani, B. Morandi, *Angew. Chem. Int. Ed.* **2016**, *55*, 2248-2251; b) L. Legnani, G. Prina-Ceraï, T. Delcaillau, S. Willems, B. Morandi, *Science* **2018**, *362*, 434-439; c) E. Falk, S. Makai, T. Delcaillau, L. Gürtler, B. Morandi, *Angew. Chem. Int. Ed.* **2020**, *59*, 47, 21064-21071; d) S. Makai, E. Falk, B. Morandi, *J. Am. Chem. Soc.* **2020**, *142*, 21548-21555; e) S. Chatterjee, I. Harden, G. Bistoni, R. G. Castillo, S. Chhabra, M. van Gastel, A. Schnegg, E. Bill, J. A. Birrell, B. Morandi, F. Neese, S. DeBeer, *J. Am. Chem. Soc.* **2022**, *144*, 2637-2656.

[19] a) L. Legnani, G. Prina-Ceraï, B. Morandi, *ACS Catal.* **2016**, *6*, 8162-8165; b) E. Falk, V. C. M. Gasser, B. Morandi, *Org. Lett.* **2021**, *23*, 4, 1422-1426.

[20] J. Liu, K. Wu, T. Shen, Y. Liang, M. Zou, Y. Zhu, X. Li, X. Li, N. Jiao, *Chem. Eur. J.* **2017**, *23*, 563-567.

[21] E. M. D'Amato, J. Börgel, T. Ritter, *Chem. Sci.* **2019**, *10*, 2424-2428.

[22] J. E. Gillespie, C. Morrill, R. J. Phipps, *J. Am. Chem. Soc.* **2021**, *143*, 9355-9360.

[23] S. Zhang, M. Vayer, F. Noël, V. D. Vuković, A. Golushko, N. Rezajoei, C. N. Rowley, D. Leboeuf, J. Moran, *Chem* **2021**, *7*, 3425-3441.

[24] For a review on the reactivity of aziridinium ions, see: J. Ranjith, H.-J. Ha, *Molecules* **2021**, *26*, 1774.

[25] For selected reviews on HFIP, see: a) I. Colomer, A. E. R. Chamberlain, M. B. Haughey, T. J. Donohoe, *Nat. Rev. Chem.* **2017**, *1*, 0088; b) S. K. Sinha, T. Bhattacharya, D. Maiti, *React. Chem. Eng.* **2018**, *4*, 244-253; c) X.-D. An, J. Xiao, *Chem. Rec.* **2020**, *20*, 142-161; d) C. Yu, J. Sanjosé-Orduna, F. Patureau, M. Pérez-Temprano, *Chem. Soc. Rev.* **2020**, *49*, 1643-1652; e) V. Pozhydaiev, M. Power, V. Gandon, J. Moran, D. Leboeuf, *Chem. Commun.* **2020**, *56*, 11548-11564; f) T. Bhattacharya, A. Ghosh, D. Maiti, *Chem. Sci.* **2021**, *12*, 3857-3870; g) H. F. Motiwala, A. M. Armaly, J. G. Cacioppo, T. C. Coombs, K. R. K. Koehn, V. M. Norwood IV, J. Aubé, *Chem. Rev.* **2022**, *122*, 12544-12747.

[26] a) C. Qi, F. Hasenmaile, V. Gandon, D. Leboeuf, *ACS Catal.* **2018**, *8*, 1734-1739; b) C. Qi, V. Gandon, D. Leboeuf, *Angew. Chem. Int. Ed.* **2018**, *57*, 14245-14249; c) S. Wang, G. Force, R. Guillot, J.-F. Carpentier, Y. Sarazin, C. Bour, V. Gandon, D. Leboeuf, *ACS Catal.* **2020**, *10*, 10794-10802; d) C. Qi, G. Force, V. Gandon, D. Leboeuf, *Angew. Chem. Int. Ed.* **2021**, *60*, 946-953; e) M. Vayer, S. Zhang, J. Moran, D. Leboeuf, *ACS Catal.* **2022**, *12*, 3309-3316; f) M. Vayer, R. J. Mayer, J. Moran, D. Leboeuf, *ACS Catal.* **2022**, *12*, 10995-11001.

[27] As a control experiment, the first step was performed in the absence of an iron(II) source. However, the results were irreproducible with yields ranging from below 10% to 42%, which we attributed to a possible metal contamination.

[28] For selected examples of 1,2-difunctionalization of alkenes allowing the introduction of indoles, see: a) X.-H. Ouyang, R.-J. Song, M. Hu, Y. Yang, J.-H. Li, *Angew. Chem. Int. Ed.* **2016**, *55*, 3187-3191; b) Y. Yang, R.-J. Song, X.-H. Ouyang, C.-Y. Wang, J.-H. Li, S. Luo, *Angew. Chem. Int. Ed.* **2017**, *56*, 7916-7919; c) X.-H. Ouyang, M. Hu, R.-J. Song, J.-H. Li, *Chem. Commun.* **2018**, *54*, 12345-12348; d) F. J. R. Klauck, H. Yoon, M. J. James, M. Lautens, F. Glorius, *ACS Catal.* **2019**, *9*, 236-241; e) M. Lux, M. Klussmann, *Org. Lett.* **2020**, *22*, 3697-3701; f) J.-H. Qin, M.-J. Luo, D.-L. An, J.-H. Li, *Angew. Chem. Int. Ed.* **2021**, *60*, 1861-1868; g) C.-H. Xu, Z.-Q. Xiong, Y. Li, Y.-P. Zhu, J.-H. Li, *Org. Chem. Front.* **2022**, *9*, 476-480; h) L.-J. Zhong, Z.-Q. Xiong, X.-H. Ouyang, Y. Li, R.-J. Song, Q. Sun, X. Lu, J.-H. Li, *J. Am. Chem. Soc.* **2022**, *144*, 339-348.

[29] G. M. Shelke, A. Kumar, *Synthesis* **2017**, *49*, 4321-4326.

[30] An alternative to construct tertiary amines is to use hydroxylammonium salts as it was reported by Morandi group in reference 18c.

Supporting Information

It should be noted that only the characterization of the different products of the scope was kept inside of the thesis. All NMR spectra were not included but are available online.

1. General Remarks

Materials: All commercial materials were purchased from Sigma-Aldrich, TCI and FluoroChem, and were used as received, without further purification. HFIP (CAS: 920-66-1) was purchased from FluoroChem. The other starting materials were prepared according to known protocols.

Reactions were monitored by thin layer chromatography (TLC) performed on aluminum plates coated with silica gel F₂₅₄ with 0.2 mm thickness. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm and/or by staining using potassium permanganate. Flash column chromatography (FC) was performed using silica gel 60 (230-400 mesh, Merck and co.). Yields refer to chromatographically and spectroscopically pure compounds. When stated, NMR yields were calculated by using mesitylene as an external standard.

¹H NMR, ¹³C NMR, ¹⁹F NMR, ³¹P NMR spectra were recorded using a Bruker UltraShield 400 or 500 at 300K. ¹H NMR chemical shifts are reported in ppm using residual solvent peak as reference (CDCl₃: δ = 7.26 ppm; CD₂Cl₂: 5.32 ppm; MeOD: 3.31 ppm). Data for ¹H NMR are presented as follows: chemical shift δ (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constant *J* (Hz) and integration; ¹³C NMR spectra were recorded at 100, 126 MHz using broadband proton decoupling and chemical shifts are reported in ppm using residual solvent peaks as reference (CDCl₃: δ = 77.16 ppm; CD₂Cl₂: 53.84 ppm; MeOD: 49.00 ppm). Multiplicity was defined by recorded a ¹³C NMR spectra using the attached proton test (APT). ¹⁹F NMR spectra were recorded at 471 MHz at ambient temperature. ³¹P NMR spectra were recorded at 162 MHz at ambient temperature. High-resolution mass spectrometry (HRMS) analysis was performed on instruments GCT 1er Waters (EI and IC), MicroTOF-Q Bruker (ESI) and a GC Thermo Scientific Trace 1300 GC unit coupled to an APPI MasCom source mounted on a Thermo Scientific Exactive Plus EMR mass unit (Orbitrap FT-HRMS analyzer).

2. Preparation of Starting Materials

Substrates **1a**, **1b**, **1c**, **1d**, **1q**, **1r**, **1s**, **1t**, **1u**, **1v**, **1x** and **1z** were commercially available.

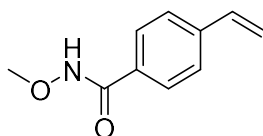
The following compounds were prepared according to known procedures:

1e: Scheidt, F.; Schäfer, M. Sarien J. C.; Daniliuc, C. G.; Molloy, J. J.; Gilmour, R. Enantioselective, Catalytic Vicinal Difluorination of Alkenes. *Angew. Chem. Int. Ed.* **2018**, 57, 16431-16435.

1f: Kawashima, S.; Aikawa, K.; Mikami, K. Rhodium-Catalyzed Hydrocarboxylation of Olefins with Carbon Dioxide. *Eur. J. Org. Chem.* **2016**, 3166-3170.

1g: Preparation was adapted from the protocol used for **1f**.

N*-Methoxy-4-vinylbenzamide **1g*



Chemical Formula: C₁₀H₁₁NO₂
Exact Mass: 177.0790

¹H NMR (400 MHz, CDCl₃): δ 9.01 (s, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 6.72 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.83 (d, *J* = 17.6 Hz, 1H), 5.36 (d, *J* = 10.9 Hz, 1H), 3.87 (s, 3H). **¹³C NMR (100 MHz, CDCl₃)**: δ 166.4, 141.4, 135.9, 130.9, 127.5, 126.5, 116.5, 64.8. **HRMS (ESI)**: *m/z* calcd. for C₁₀H₁₂NO₂ [M+H]⁺ 178.0863, found 178.0858.

1h: Lo, W. C.; Hunter, J. G.; Watson, G. B.; Pathy, A.; Iyer, P. S.; Boruwa. J. WO2014100163 A1, 2014.

1i: Kamogawa, H.; Kitamura, T. [Polymer Reagents Derived from Sodium *p*-Styrenesulfonate: *N*-Methyl-*N*-nitroso-*p*-styrenesulfonamide and *p*-Styrenesulfinic Acid Polymers](#). *Bull. Chem. Soc. Jpn.* **1989**, 62, 189-192

1j: Preparation was adapted from the protocol used for **1k**. The data are in agreement with those reported in the literature: Wang, X.; Yang, M. Ye, S.; Kuang, Y.; Wu. J. S(VI) in Three-Component Sulfonamide Synthesis: Use of Sulfuric Chloride as a Linchpin in Palladium-Catalyzed Suzuki-Miyaura Coupling. *Chem. Sci.* **2021**, 12, 6437-6441.

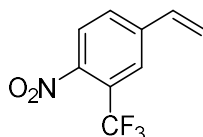
1k: Brendel, J. C.; Liu, F.; Lang, A. S.; Russell, T. P.; Thelakkat. M. Macroscopic Vertical Alignment of Nanodomains in Thin Films of Semiconductor Amphiphilic Block Polymers. *ACS Nano*, **2013**, 7, 6069-6078.

1l: Gibson, S. B.; Lauret, C. US20080200540 A1, 2008. The data are in agreement with those reported in the literature: Verschueren R. H.; Schmauck, J.; Perryman, M. S.; Yue, H.-L.; Riegger, J.; Schweitzer-Chaput, B.; Breugst, M.; Klusmann, M. Philicity of Acetonyl and Benzoyl Radicals: A Comparative Experimental and Computational Study. *Chem. Eur. J.* **2019**, *25*, 9088-9097.

1m: Zhang, R.; Xu, J.; Cai, Z.; Tang, G.; Fang, M.; Zhao, Y. Copper-Catalyzed C-P Bond via Direct Coupling of Phenylboronic Acids with H-Phosphonated Diesters. *Org. Lett.* **2011**, *13*, 8, 2110-2113.

1n: Preparation was adapted from the protocol in L. Joucla, G. Cusati, C. Pinel, L. Djakovitch, Efficient Heterogeneous Vinylation of Aryl Halides Using Potassium Vinyltrifluoroborate. *Tetrahedron Lett.* **2008**, *49*, 4738-4741.

1-Nitro-2-(trifluoromethyl)-4-vinylbenzene 1n



Chemical Formula: C₉H₆F₃NO₂

Exact Mass: 217.0351

¹H NMR (400 MHz, CDCl₃): δ 7.88 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 1.9 Hz, 1H), 7.70 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.77 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.96 (d, *J* = 17.6 Hz, 1H), 5.58 (d, *J* = 10.9 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 146.9, 142.5, 133.9, 130.1, 125.9, 125.6 (q, *J* = 5.4 Hz), 124.4 (q, *J* = 33.9 Hz), 122.1 (q, *J* = 273.4 Hz), 119.9.

¹⁹F NMR (471 MHz, CDCl₃): δ -60.1. **HRMS (ESI)**: *m/z* calcd. for C₉H₆F₃NO₂Na [M+Na]⁺ 240.0243, found 240.0241.

1o: Preparation was adapted from the protocol used for **1p** with BrPPh₃Me. The data are in agreement with those reported in the literature: Scheidt, F.; Neufeld, J.; Schäfer, M.; Thiehoff, C.; Gilmour, R. Catalytic Geminal Difluorination of Styrenes for the Construction of Fluorine-rich Bioisosteres. *Org. Lett.* **2018**, *20*, 8073-8076.

1p: Trost, B. M.; Schultz, J. E.; Chang, T.; Maduabum, M. R. Chemo-, Regio-, Diastereo-, and Enantioselective Palladium Allylic Alkylation of 1,3-Dioxaboroles as Synthetic Equivalents of α-Hydroxyketones. *J. Am. Chem. Soc.* **2019**, *141*, 9521-9526.

1w: Kawashima, S.; Aikawa, K.; Mikami, K. Rhodium-Catalyzed Hydrocarboxylation of Olefins with Carbon Dioxide. *Eur. J. Org. Chem.* **2016**, 3166-3170.

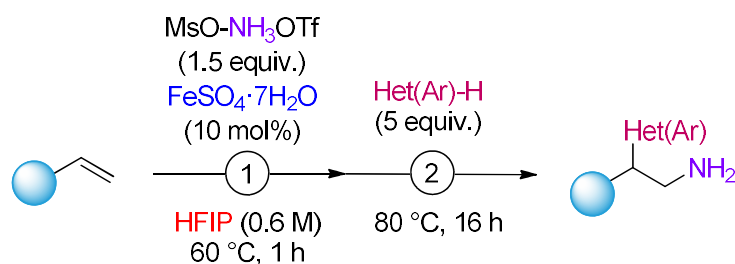
1y: Preparation was adapted from the protocol used for **1p** with BrPPh₃Me. The data are in agreement with those reported in the literature: Denmark, S. E.; Butler, C. R. Vinylation of Aryl Bromides Using Inexpensive Vinylpolysiloxane. *Org. Lett.* **2006**, *8*, 63-66.

[MsO-NH₃][OTf], [NsO-NH₃][OTf], [TsO-NH₃][OTf], [PivO-NH₃][OTf] and [PNPC(O)-NH₃][OTf] salts were prepared according to reported literature procedures:

(a) Legnani, L; Morandi, B. Direct Catalytic Synthesis of Unprotected 2-Amino-1-Phenylethanols from Alkenes by Using Iron(II) Phtalocyanine. *Angew. Chem. Int. Ed.* **2016**, *55*, 2248-2251. (b) Falk, E; Gasser, V. C. M.; Morandi, B. Synthesis of *N*-Alkyl Anilines from Arenes via Iron-Promoted Aromatic C–H Amination. *Org. Lett.* **2021**, *23*, 4, 1422-1426. (c) Gillespie, J. E.; Morrill, C.; Phipps, R. J. Regioselective Radical Arene Amination for the Concise Synthesis of *ortho*-Phenylenediamines. *J. Am. Chem. Soc.* **2021**, *143*, 25, 9355-9360.

3. Aminoarylation of Alkenes (Scheme 2)

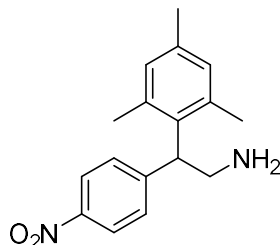
3.1 General Procedure (A) for the aminoarylation of electron poor styrenes



A 10 ml tube equipped with a Teflon-coated magnetic stir bar was charged with [MsO-NH₃][OTf] (1.5 equiv.). HFIP (0.6 M) was added followed by styrene **1** (1.0 equiv.) and FeSO₄·7H₂O (10 mol%) under air. The glass tube was sealed and heated at 60 °C for 1 h. The reaction was cooled down to room temperature and the arene nucleophile (5.0 equiv.) was added in one portion. Then, the mixture was heated at 80 °C for 16 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (10 mL) and then extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (FC) over silica gel to furnish the target products **3-65**.

3.2 Characterization Data of Aminoarylation Products 3-60

2-Mesityl-2-(4-nitrophenyl)ethan-1-amine **3**



Chemical Formula: C₁₇H₂₀N₂O₂
Exact Mass: 284.1525

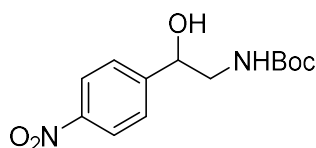
General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then mesitylene (208 μL, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 90/10) afforded **3** (44.0 mg, 0.153 mmol, 51% yield) as an orange oil.

¹H NMR (400 MHz, CDCl₃): δ 8.11 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 6.87 (s, 2H), 4.63 (dd, *J* = 8.7, 8.6 Hz, 1H), 3.66 (dd, *J* = 12.4, 8.7 Hz, 1H), 3.42 (dd, *J* = 12.4, 8.6 Hz, 1H), 2.27 (s, 3H), 2.15 (brs, 6H), 1.42 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 151.2 (C), 146.2 (C), 137.4 (2C), 136.9 (C), 134.8 (C), 130.6 (2CH), 128.1 (2CH), 123.6 (2CH), 47.6 (CH), 43.6 (CH₂), 21.6 (2CH₃), 20.9 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₇H₂₁N₂O₂ [M+H]⁺ 285.1598, found 285.1597.

Gram-scale experiment

Under argon, a 25 ml tube equipped with a Teflon-coated magnetic stir bar was charged with [MsO-NH₃][OTf] (2.18 g, 8.19 mmol, 1.5 equiv.). HFIP (9.0 mL, 0.6 M) was added followed by 4-nitrostyrene **1a** (700 μL, 5.46 mmol, 1.0 equiv.) and FeSO₄·7H₂O (152 mg, 0.546 mmol, 10 mol%) under air. The glass tube was sealed and heated at 60 °C for 1 h. The reaction was cooled down to room temperature and mesitylene (3.8 mL, 27.3 mmol, 5.0 equiv.) was added in one portion. Then, the mixture was heated at 80 °C for 16 h. Upon completion, the reaction mixture was quenched with a solution of sat. NaHCO₃ (80 mL) and then extracted with DCM (40 mL × 3). The combined organic layers were washed with brine (80 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude mixture was purified by FC over silica gel to furnish the target product **3** (840 mg, 2.95 mmol, 54%) as an orange oil. The obtained analytical data are in full agreement with those obtained from previous experiments.

Tert-butyl (2-hydroxy-2-(4-nitrophenyl)ethyl)carbamate 3a

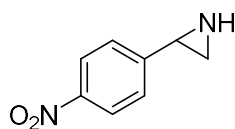


Chemical Formula: C₁₃H₁₈N₂O₅
Exact Mass: 282.1216

Upon completion of the first step, the reaction mixture was diluted by Et₂O and extracted with aqueous HCl 1 M (2 × 15 mL). The combined aqueous phases were concentrated *in vacuo* and re-dissolved in DCM (5 mL). The reaction mixture was cooled to 0 °C, triethylamine (2.0 equiv.) and Boc₂O (2.0 equiv.) were added, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched with water and then extracted with DCM (10 mL × 3). The combined organic layers were washed with a solution of sat. NaHCO₃ (15 mL), brine (15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Purification by FC over silica gel (*n*-pentane/EtOAc: 90/10 to 50/50, gradient) afforded **3a** (44.0 mg, 0.153 mmol, 51% yield, 1,2/2,1 88/12) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.22 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 5.15 – 5.08 (m, 1H), 5.04 (brs, 1H), 3.71 – 3.52 (m, 2H), 1.42 (brs, 1H), 1.39 (s, 9H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 155.8 (C=O), 148.3 (C), 146.3 (C), 128.8 (2CH), 124.2 (2CH), 80.2 (C), 61.1 (CH), 48.5 (CH₂), 28.4 (3CH₃).

2-(4-Nitrophenyl)aziridine 3b



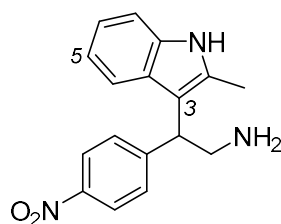
Chemical Formula: C₈H₈N₂O₂
Exact Mass: 164.0586

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then the temperature was decreased to 40 °C and the reaction mixture was stirred for 20 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 90/10) afforded **3b** (18.0 mg, 0.108 mmol, 36% yield) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 8.16 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 3.15 (dd, *J* = 6.3, 3.2 Hz, 1H), 2.37 (d, *J* = 6.3 Hz, 1H), 1.73 (d, *J* = 3.2 Hz, 1H), 1.29 (brs, 1H). **¹³C NMR (100 MHz, CDCl₃):** δ 148.7, 147.2, 126.7, 123.8, 31.4, 30.7. **HRMS (ESI):** *m/z* calcd. for C₈H₉N₂O₂ [M+H]⁺ 165.0659, found 165.0656.

The data are in agreement with those reported in the literature: Lebel, H.; Spitz, C.; Leogane, O.; Trudel, C.; Parmentier, M. *Org. Lett.* **2011**, *13*, 5460-5463.

2-(2-Methyl-1H-indol-3-yl)-2-(4-nitrophenyl)ethan-1-amine **4**

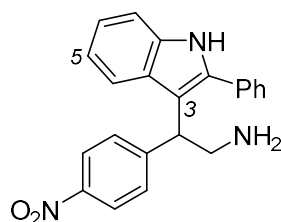


Chemical Formula: C₁₇H₁₇N₃O₂
Exact Mass: 295.1321

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-methylindole (197 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **4** (51.0 mg, 0.173 mmol, 58% yield, 3/5: 92/8) as a dark red oil. Regioisomers could be separated by flash column chromatography.

¹H NMR (400 MHz, CDCl₃): δ 8.28 (brs, 1H), 8.09 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 7.03 (t, *J* = 8.0 Hz, 1H), 4.35 (dd, *J* = 9.4, 6.2 Hz, 1H), 3.58 (dd, *J* = 12.3, 9.4 Hz, 1H), 3.50 (dd, *J* = 12.3, 6.2 Hz, 1H), 2.39 (s, 3H), 1.61 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 151.3 (C), 146.4 (C), 135.6 (C), 133.3 (C), 128.7 (2CH), 127.3 (C), 123.7 (2CH), 121.4 (CH), 119.8 (CH), 118.9 (CH), 110.8 (CH), 110.1 (C), 46.0 (CH), 45.5 (CH₂), 12.4 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₇H₁₈N₃O₂ [M+H]⁺ 296.1394, found 296.1413.

2-(4-Nitrophenyl)-2-(2-phenyl-1H-indol-3-yl)ethanamine 5

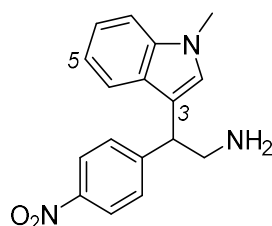


Chemical Formula: $C_{22}H_{19}N_3O_2$
Exact Mass: 357.1477

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-phenylindole (290 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **5** (69.0 mg, 0.19 mmol, 64% yield, 3/5: 92/8) as a yellow oil. Regioisomers could be separated by flash column chromatography.

¹H NMR (400 MHz, CD₂Cl₂): δ 9.32 (brs, 1H), 8.09 (d, J = 8.9 Hz, 2H), 7.56 – 7.47 (m, 5H), 7.48 – 7.38 (m, 4H), 7.22 – 7.14 (m, 1H), 7.03 (ddd, J = 8.1, 7.1, 1.0 Hz, 1H), 4.48 (dd, J = 9.5, 6.2 Hz, 1H), 3.59 (dd, J = 12.5, 9.5 Hz, 1H), 3.45 (dd, J = 12.5, 6.2 Hz, 1H), 1.49 (brs, 2H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 152.2 (C), 146.6 (C), 138.1 (C), 136.9 (C), 133.2 (C), 129.3 (2CH), 129.1 (2CH), 129.1 (2CH), 128.5 (CH), 127.4 (C), 123.8 (2CH), 122.5 (CH), 120.4 (CH), 120.1 (CH), 111.8 (CH), 111.1 (C), 46.6 (CH), 46.3 (CH₂). **HRMS (ESI):** m/z calcd. for $C_{22}H_{20}N_3O_2$ [M+H]⁺ 358.1550, found 358.1555.

2-(1-Methyl-1H-indol-3-yl)-2-(4-nitrophenyl)ethan-1-amine 6



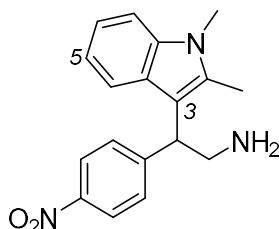
Chemical Formula: $C_{17}H_{17}N_3O_2$
Exact Mass: 295.1321

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 1-methylindole (187 μ L, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture

which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **6** (54.0 mg, 0.183 mmol, 61% yield, 3/5: 93/7) as a dark red oil.

¹H NMR (400 MHz, CDCl₃): δ 8.13 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.23 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.05 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.99 (s, 1H), 4.38 (dd, *J* = 7.3, 7.2 Hz, 1H), 3.79 (s, 3H), 3.47 (dd, *J* = 12.7, 7.2 Hz, 1H), 3.32 (dd, *J* = 12.7, 7.3 Hz, 1H), 1.70 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 151.3 (C), 146.6 (C), 137.3 (C), 129.0 (2CH), 127.1 (C), 126.3 (CH), 123.8 (2CH), 122.2 (CH), 119.3 (CH), 119.1 (CH), 114.4 (C), 109.5 (CH), 46.9 (CH₂), 46.6 (CH), 32.9 (CH₃). **HRMS (ESI):** *m/z* calcd. For C₁₇H₁₈N₃O₂ [M+H]⁺ 296.1394, found 296.1398.

2-(1,2-Dimethyl-1H-indol-3-yl)-2-(4-nitrophenyl)ethan-1-amine **7**

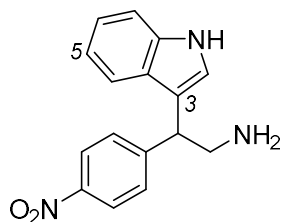


Chemical Formula: C₁₈H₁₉N₃O₂
Exact Mass: 309.1477

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 1,2-dimethylindole (218 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **7** (58.5 mg, 0.189 mmol, 63% yield, 3/5 >95/5) as a dark red oil.

¹H NMR (400 MHz, CDCl₃): δ 8.09 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.17 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.03 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 4.39 (dd, *J* = 9.4, 6.2 Hz, 1H), 3.70 (s, 3H), 3.59 (dd, *J* = 12.3, 9.4 Hz, 1H), 3.51 (dd, *J* = 12.3, 6.2 Hz, 1H), 2.41 (s, 3H), 1.61 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 151.5 (C), 146.3 (C), 137.1 (C), 135.1 (C), 128.7 (2CH), 126.4 (C), 123.6 (2CH), 121.0 (CH), 119.4 (CH), 118.9 (CH), 109.4 (C), 109.2 (CH), 46.3 (CH), 45.6 (CH₂), 29.8 (CH₃), 10.8 (CH₃). **HRMS (ESI):** *m/z* calcd. For C₁₈H₂₀N₃O₂ [M+H]⁺ 310.1550, found 310.1541.

2-(1H-Indol-3-yl)-2-(4-nitrophenyl)ethan-1-amine 8

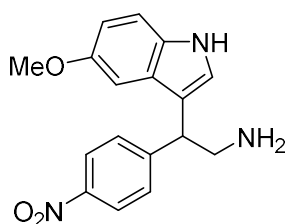


Chemical Formula: C₁₆H₁₅N₃O₂
Exact Mass: 281.1164

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then indole (176 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **8** (51.0 mg, 0.180 mmol, 60% yield, 3/5 >95/5) as a bright brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.44 (brs, 1H), 8.11 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.36 (dd, *J* = 8.1, 3.6 Hz, 2H), 7.20 – 7.11 (m, 2H), 7.01 (t, *J* = 7.6 Hz, 1H), 4.37 (dd, *J* = 7.2, 7.2 Hz, 1H), 3.46 (dd, *J* = 12.7, 7.2 Hz, 1H), 3.30 (dd, *J* = 12.7, 7.2 Hz, 1H), 1.54 (brs, 2H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 152.0 (C), 147.0 (C), 137.0 (C), 129.4 (2CH), 127.1 (C), 123.9 (2CH), 122.6 (CH), 122.1 (CH), 119.8 (CH), 119.2 (CH), 116.3 (C), 111.7 (CH), 47.2 (CH₂), 47.1 (CH). **HRMS (ESI):** *m/z* calcd. for C₁₆H₁₆N₃O₂ [M+H]⁺ 282.1237, found 282.1229.

2-(5-Methoxy-1H-indol-3-yl)-2-(4-nitrophenyl)ethan-1-amine 9

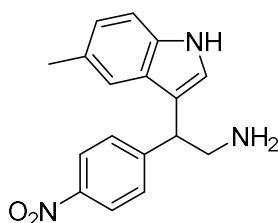


Chemical Formula: C₁₇H₁₇N₃O₃
Exact Mass: 311.1270

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 5-methoxyindole (221 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **9** (47.6 mg, 0.153 mmol, 51% yield) as a dark red oil.

¹H NMR (400 MHz, CDCl₃): δ 8.19 (brs, 1H), 8.14 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.79 (d, *J* = 2.4 Hz, 1H), 4.34 (dd, *J* = 7.3, 7.2 Hz, 1H), 3.76 (s, 3H), 3.47 (dd, *J* = 12.7, 7.3 Hz, 1H), 3.32 (dd, *J* = 12.7, 7.2 Hz, 1H), 1.63 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 154.2 (C), 151.2 (C), 146.8 (C), 131.8 (C), 129.1 (2CH), 127.3 (C), 123.9 (2CH), 122.4 (CH), 115.8 (C), 112.6 (CH), 112.2 (CH), 101.3 (CH), 56.0 (CH₃), 47.0 (CH₂), 46.8 (CH). **HRMS (ESI):** *m/z* calcd. For C₁₇H₁₈N₃O₃ [M+H]⁺ 312.1343, found 312.1333.

2-(5-Methyl-1H-indol-3-yl)-2-(4-nitrophenyl)ethan-1-amine 10

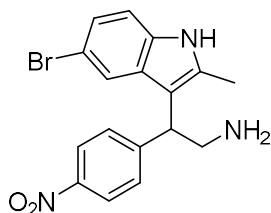


Chemical Formula: C₁₇H₁₇N₃O₂
Exact Mass: 295.1321

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 5-methylindole (197 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **10** (48.0 mg, 0.163 mmol, 54% yield) as a dark red oil.

¹H NMR (400 MHz, CDCl₃): δ 8.38 (brs, 1H), 8.13 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 1H), 7.16 (s, 1H), 7.06 (d, *J* = 1.6 Hz, 1H), 7.02 (dd, *J* = 8.3, 1.6 Hz, 1H), 4.35 (dd, *J* = 7.3, 7.2 Hz, 1H), 3.47 (dd, *J* = 12.7, 7.2 Hz, 1H), 3.31 (dd, *J* = 12.7, 7.3 Hz, 1H), 2.39 (s, 3H), 1.65 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 151.4 (C), 146.7 (C), 135.0 (C), 129.1 (C), 129.0 (2CH), 127.0 (C), 124.3 (CH), 123.9 (2CH), 121.8 (CH), 118.6 (CH), 115.4 (C), 111.2 (CH), 47.0 (CH₂), 46.8 (CH), 21.6 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₇H₁₈N₃O₂ [M+H]⁺ 296.1394, found 296.1386.

2-(5-Bromo-2-methyl-1H-indol-3-yl)-2-(4-nitrophenyl)ethan-1-amine **11**

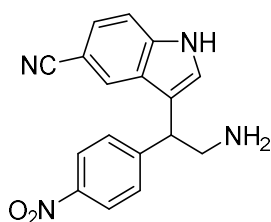


Chemical Formula: C₁₇H₁₆BrN₃O₂
Exact Mass: 373.0426

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 5-bromo-2-methylindole (315 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **11** (45.0 mg, 0.120 mmol, 40% yield) as a dark red oil.

¹H NMR (400 MHz, CDCl₃): δ 8.27 (brs, 1H), 8.11 (d, *J* = 8.8 Hz, 2H), 7.53 (s, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.21 – 7.14 (m, 2H), 4.31 (dd, *J* = 8.1, 5.7 Hz, 1H), 3.54 (dd, *J* = 11.5, 8.1 Hz, 1H), 3.49 (dd, *J* = 11.5, 5.7 Hz, 1H), 2.38 (s, 3H), 1.53 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 150.8 (C), 146.5 (C), 134.7 (C), 134.2 (C), 129.2 (C), 128.6 (2CH), 124.3 (CH), 123.8 (2CH), 121.3 (CH), 113.1 (C), 112.2 (CH), 110.1 (C), 45.9 (CH), 45.5 (CH₂), 12.5 (CH₃). **HRMS (ESI):** *m/z* calcd. For C₁₆H₁₇BrN₃O₂ [M+H]⁺ 374.0499, found 374.0493.

3-(2-amino-1-(4-nitrophenyl)ethyl)-1H-indole-5-carbonitrile **12**

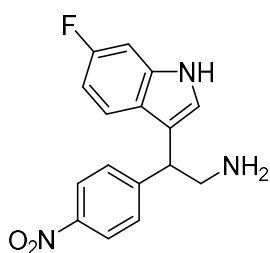


Chemical Formula: C₁₇H₁₄N₄O₂
Exact Mass: 306.1117

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 5-cyanoindole (213 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 85/15) afforded **12** (54.0 mg, 0.176 mmol, 59% yield) as a yellow oil.

¹H NMR (400 MHz, CD₃OD): δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.84 – 7.81 (m, 1H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.51 – 7.46 (m, 2H), 7.36 (dd, *J* = 8.5, 1.5 Hz, 1H), 4.48 (t, *J* = 7.5 Hz, 1H), 3.43 (dd, *J* = 12.8, 7.5 Hz, 1H), 3.28 (dd, *J* = 7.5 Hz, 1H). **¹³C NMR (100 MHz, CD₃OD):** δ 152.0 (C), 148.2 (C), 140.1 (C), 130.3 (CH), 128.0 (C), 125.8 (CH), 125.6 (CH), 125.3 (CH), 124.8 (CH), 121.7 (C), 117.5 (C), 113.7 (CH), 102.7 (C), 47.2 (CH₂), 46.6 (CH). **HRMS (ESI):** *m/z* calcd. For C₁₇H₁₅N₄O₂ [M+H]⁺ 307.1190, found 307.1180.

2-(6-Fluoro-1H-indol-3-yl)-2-(4-nitrophenyl)ethan-1-amine 13

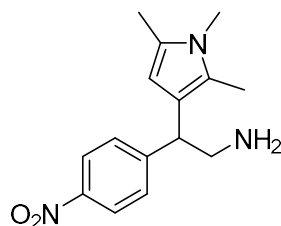


Chemical Formula: C₁₆H₁₄FN₃O₂
Exact Mass: 299.1070

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 6-fluoromethylindole (203 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **13** (36.0 mg, 0.120 mmol, 40% yield) as a dark purple oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.67 (brs, 1H), 8.12 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.26 (dd, *J* = 8.7, 5.3 Hz, 1H), 7.15 (s, 1H), 7.06 (dd, *J* = 9.7, 2.3 Hz, 1H), 6.78 (ddd, *J* = 9.7, 8.7, 2.3 Hz, 1H), 4.33 (dd, *J* = 7.3, 7.2 Hz, 1H), 3.44 (dd, *J* = 12.7, 7.3 Hz, 1H), 3.29 (dd, *J* = 12.7, 7.2 Hz, 1H), 1.60 (brs, 2H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 160.4 (d, *J* = 237.4 Hz, C), 151.7 (C), 147.1 (C), 136.9 (d, *J* = 12.5 Hz, C), 129.4 (2CH), 124.0 (2CH), 123.8 (C), 122.4 (d, *J* = 3.3 Hz, CH), 120.1 (d, *J* = 20.0 Hz, CH), 116.6 (C), 108.5 (d, *J* = 24.6 Hz, CH), 97.9 (d, *J* = 26.0 Hz, CH), 47.3 (CH), 47.1 (CH₂). **¹⁹F NMR (471 MHz, DMSO-*d*₆):** δ -122.1. **HRMS (ESI):** *m/z* calcd. For C₁₆H₁₅FN₃O₂ [M+H]⁺ 300.1143, found 300.1163.

2-(4-Nitrophenyl)-2-(1,2,5-trimethyl-1H-pyrrol-3-yl)ethan-1-amine 14

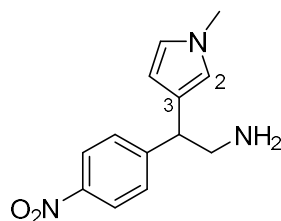


Chemical Formula: C₁₅H₁₉N₃O₂
Exact Mass: 273.1477

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 1,2,5-trimethylpyrrole (203 μL, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 20 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **14** (41.0 mg, 0.150 mmol, 50% yield) as an orange oil.

¹H NMR (400 MHz, CDCl₃): δ 8.12 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 5.78 (s, 1H), 3.95 (t, *J* = 7.6 Hz, 1H), 3.35 (s, 3H), 3.17 (d, *J* = 7.6 Hz, 2H), 2.20 (s, 3H), 2.08 (s, 3H), 1.78 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 152.8 (C), 146.4 (C), 128.7 (2CH), 127.9 (C), 125.1 (C), 123.9 (2CH), 117.4 (C), 103.3 (CH), 47.7 (CH), 47.0 (CH₂), 30.4 (CH₃), 12.6 (CH₃), 10.3 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₅H₂₀N₃O₂ [M+H]⁺ 274.1550, found 274.1565.

2-(1-Methyl-1H-pyrrol-2-yl)-2-(4-nitrophenyl)ethan-1-amine 15

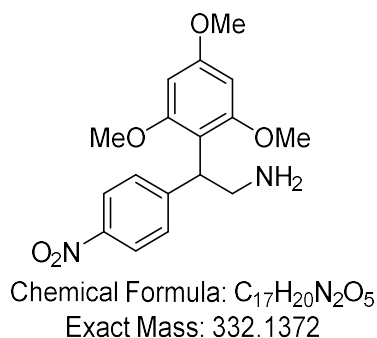


Chemical Formula: C₁₃H₁₅N₃O₂
Exact Mass: 245.1164

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 1-methylpyrrole (133 μL, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 40 °C for 20 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **15** (45.5 mg, 0.186 mmol, 62% yield, 2/3: 50/50) as an orange oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.15 – 8.12 (m, 4H), 7.44 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H), 6.58 (dd, J = 2.7, 1.8 Hz, 1H), 6.56 (dd, J = 2.5 Hz, 1H), 6.45 (t, J = 2.1 Hz, 1H), 6.16 – 6.13 (m, 1H), 6.13 – 6.10 (m, 1H), 5.96 (dd, J = 2.7, 1.8 Hz, 1H), 4.08 (t, J = 7.3 Hz, 1H), 3.97 (t, J = 7.4 Hz, 1H), 3.59 (s, 3H), 3.31 (s, 3H), 3.32 – 3.27 (m, 1H), 3.23 – 3.07 (m, 3H), 1.76 (br s, 4H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 153.0 (C), 150.5 (C), 147.2 (C), 146.83 (C), 132.1 (C), 129.4 (CH), 129.3 (CH), 124.2 (C), 124.1 (CH), 123.9 (CH), 122.8 (CH), 122.6 (CH), 120.0 (CH), 107.6 (CH), 107.2 (CH), 106.2 (CH), 48.4 (CH₃), 48.0 (CH₂), 47.79 (CH₃), 47.75 (CH₂), 36.4 (CH), 34.0 (CH). **HRMS (ESI):** m/z calcd. for C₁₃H₁₆N₃O₂ [M+H]⁺ 246.1237, found 246.1231.

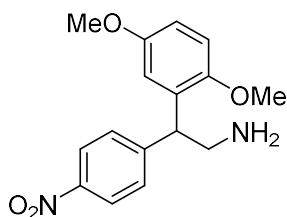
2-(4-Nitrophenyl)-2-(2,4,6-trimethoxyphenyl)ethan-1-amine 16



General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 1,3,5-trimethoxybenzene (252 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **16** (52.0 mg, 0.156 mmol, 52% yield) as a red oil.

¹H NMR (400 MHz, CDCl₃): δ 8.07 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 6.12 (s, 2H), 4.75 (t, J = 7.9 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 6H), 3.50 – 3.48 (m, 2H), 3.28 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 160.7 (C), 159.4 (2C), 151.3 (C), 146.1 (C), 128.8 (2CH), 123.3 (2CH), 109.1 (C), 91.2 (2CH), 55.7 (2CH₃), 55.4 (CH₃), 43.3 (CH₂), 42.9 (CH). **HRMS (ESI):** m/z calcd. for C₁₇H₂₁N₂O₅ [M+H]⁺ 333.1445, found 333.1455.

2-(2,5-Dimethoxyphenyl)-2-(4-nitrophenyl)ethan-1-amine 17

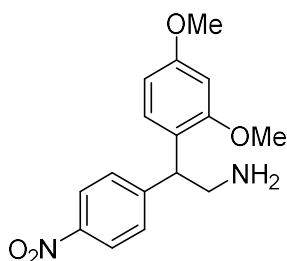


Chemical Formula: C₁₆H₁₈N₂O₄
Exact Mass: 302.1267

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 1,4-dimethoxybenzene (207 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **17** (45.0 mg, 0.150 mmol, 50% yield) as an orange oil.

¹H NMR (400 MHz, CDCl₃): δ 8.10 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 6.80 – 6.72 (m, 3H), 4.49 (dd, *J* = 7.7, 7.5 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.34 (dd, *J* = 12.8, 7.7 Hz, 1H), 3.27 (dd, *J* = 12.8, 7.5 Hz, 1H), 1.79 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 153.8 (C), 151.7 (C), 150.7 (C), 146.5 (C), 130.7 (C), 129.1 (2CH), 123.7 (2CH), 114.8 (CH), 111.9 (CH), 111.5 (CH), 56.0 (CH₃), 55.7 (CH₃), 47.6 (CH), 45.6 (CH₂). **HRMS (ESI):** *m/z* calcd. for NaC₁₆H₁₈N₂O₄ [M+Na]⁺ 325.1159, found 325.1151.

2-(2,4-Dimethoxyphenyl)-2-(4-nitrophenyl)ethan-1-amine 18



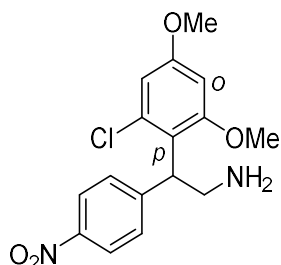
Chemical Formula: C₁₆H₁₈N₂O₄
Exact Mass: 302.1267

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 1,3-dimethoxybenzene (196 μL, 1.5 mmol, 5.0 equiv.) was added to the

reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **18** (48.0 mg, 0.159 mmol, 53% yield) as an orange oil.

¹H NMR (400 MHz, CDCl₃): δ 8.11 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.49 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.44 (d, *J* = 2.5 Hz, 1H), 4.42 (dd, *J* = 7.8, 7.5 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.33 (dd, *J* = 12.8, 7.8 Hz, 1H), 3.25 (dd, *J* = 12.8, 7.5 Hz, 1H), 1.41 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 160.0 (C), 158.5 (C), 151.6 (C), 146.5 (C), 129.1 (2CH), 128.1 (CH), 123.7 (2CH), 121.9 (C), 104.5 (CH), 99.1 (CH), 55.5 (CH₃), 55.4 (CH₃), 47.4 (CH), 45.9 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₆H₁₉N₂O₄ [M+H]⁺ 303.1339, found 303.1327.

2-(2-Chloro-4,6-dimethoxyphenyl)-2-(4-nitrophenyl)ethan-1-amine **19**

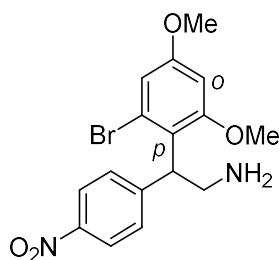


Chemical Formula: C₁₆H₁₇ClN₂O₄
Exact Mass: 336.0877

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 1-chloro-3,5-dimethoxybenzene (258 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **19** (49.0 mg, 0.144 mmol, 48% yield, *p/o*: 83/17) as a bright orange oil. Regioisomers could be separated by flash column chromatography.

¹H NMR (400 MHz, CDCl₃): δ 8.09 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 6.58 (d, *J* = 2.4 Hz, 1H), 6.34 (d, *J* = 2.4 Hz, 1H), 4.78 (t, *J* = 7.7 Hz, 1H), 3.78 (s, 3H), 3.64 (s, 3H), 3.54 – 3.49 (m, 2H), 1.49 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 159.9 (C), 159.7 (C), 150.5 (C), 146.2 (C), 136.3 (C), 128.7 (2CH), 123.3 (2CH), 120.0 (C), 106.6 (CH), 98.7 (CH), 55.7 (CH₃), 55.6 (CH₃), 48.1 (CH), 43.4 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₆H₁₈ClN₂O₄ [M+H]⁺ 337.0950, found 337.0967.

2-(2-Bromo-4,6-dimethoxyphenyl)-2-(4-nitrophenyl)ethan-1-amine 20

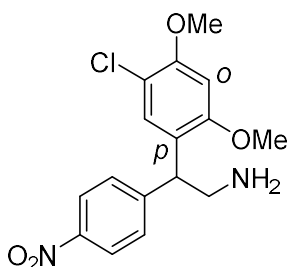


Chemical Formula: $C_{16}H_{17}BrN_2O_4$
Exact Mass: 380.0372

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 1-bromo-3,5-dimethoxybenzene (324 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **20** (57.0 mg, 0.150 mmol, 50% yield, *p*/*o*: 87/13) as a red oil. Regioisomers could be separated by flash column chromatography.

¹H NMR (400 MHz, CDCl₃): δ 8.09 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 2.4 Hz, 1H), 6.37 (d, *J* = 2.4 Hz, 1H), 4.78 (t, *J* = 7.6 Hz, 1H), 3.78 (s, 3H), 3.60 (s, 3H), 3.52 (d, *J* = 7.6 Hz, 2H), 1.53 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 160.1 (C), 159.3 (C), 150.5 (C), 146.2 (C), 128.6 (2CH), 127.1 (C), 123.2 (2CH), 121.7 (C), 109.8 (CH), 99.5 (CH), 55.7 (CH₃), 55.5 (CH₃), 51.2 (CH), 43.4 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₆H₁₈BrN₂O₄ [M+H]⁺ 381.0445, found 381.0428.

2-(5-Chloro-2,4-dimethoxyphenyl)-2-(4-nitrophenyl)ethan-1-amine 21



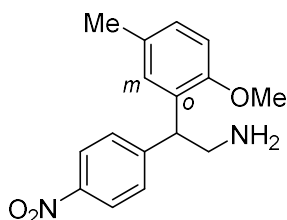
Chemical Formula: $C_{16}H_{17}ClN_2O_4$
Exact Mass: 336.0877

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at

60 °C for 1 h, then 1-chloro-2,4-dimethoxybenzene (258 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **21** (46.0 mg, 0.137 mmol, 47% yield, *p/o*: 90/10) as a green oil. Regioisomers could be separated by flash column chromatography.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.11 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.18 (s, 1H), 6.51 (s, 1H), 4.39 (t, *J* = 7.6 Hz, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.26 (m, 2H), 1.53 (brs, 2H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 157.5 (C), 155.0 (C), 151.4 (C), 146.9 (C), 129.4 (2CH), 128.9 (CH), 123.8 (2CH), 123.2 (C), 113.7 (C), 97.4 (CH), 56.6 (CH₃), 56.2 (CH₃), 47.3 (CH), 45.9 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₆H₁₈ClN₂O₄ [M+H]⁺ 337.0950, found 337.0956.

2-(2-Methoxy-5-methylphenyl)-2-(4-nitrophenyl)ethanamine **22**

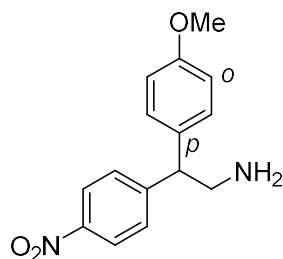


Chemical Formula: C₁₆H₁₈N₂O₃
Exact Mass: 286.1317

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.7 mg, 0.30 mmol) [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 4-methylanisole (189 μL, 0.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 97/3) afforded **22** (48.0 mg, 0.17 mmol, 56% yield, *o/m*: 91/9) as a brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.11 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.07 – 6.90 (m, 2H), 6.78 (d, *J* = 8.0 Hz, 1H), 4.47 (dd, *J* = 7.7, 7.5 Hz, 1H), 3.72 (s, 3H), 3.33 (dd, *J* = 12.8, 7.7 Hz, 1H), 3.26 (dd, *J* = 12.8, 7.5 Hz, 1H), 2.28 (s, 3H), 1.77 (brs, 2H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 155.7 (C), 151.8 (C), 146.7 (C), 130.3 (C), 129.7 (C), 129.5 (2CH), 128.7 (CH), 128.6 (CH), 123.7 (2CH), 111.3 (CH), 55.8 (CH₃), 48.0 (CH), 45.9 (CH₂), 20.7 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₆H₁₉N₂O₃ [M+H]⁺ 287.1390, found 285.1386.

2-(4-Methoxyphenyl)-2-(4-nitrophenyl)ethan-1-amine 23

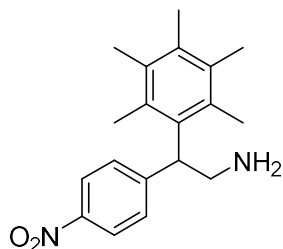


Chemical Formula: C₁₅H₁₆N₂O₃
Exact Mass: 272.1161

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then anisole (163 μL, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **23** (32.7 mg, 0.120 mmol, 45% yield, *p/o*: 60/40) as an orange oil.

¹H NMR (400 MHz, CDCl₃): δ 8.14 – 8.09 (m, 4H, **o** + **p**), 7.41 – 7.37 (m, 4H, **o** + **p**), 7.25 – 7.18 (m, 2H, **o**), 7.13 (d, *J* = 8.6 Hz, 2H, **p**), 6.95 (t, *J* = 7.5 Hz, 1H, **o**), 6.88 – 6.85 (m, 3H, **o** + **p**), 4.52 (t, *J* = 7.6 Hz, 1H, **o**), 4.06 (t, *J* = 7.5 Hz, 1H, **p**), 3.77 (s, 3H, **o**), 3.75 (s, 2H, **p**), 3.39 – 3.26 (m, 4H, **o** + **p**), 1.78 (brs, 4H, **o** + **p**). **¹³C NMR (100 MHz, CDCl₃):** δ 158.8 (C, **p**), 157.4 (C, **o**), 151.1 (C, **p**), 151.0 (C, **o**), 146.6 (C, **p**), 146.5 (C, **o**), 133.0 (C, **p**), 129.3 (C, **o**), 129.2 (2CH, **p**), 129.1 (2CH, **p**), 128.9 (2CH, **o**), 128.3 (CH, **o**), 127.5 (CH, **o**), 123.9 (2CH, **p**), 123.6 (2CH, **o**), 120.9 (CH, **o**), 114.5 (2CH, **p**), 111.1 (CH, **o**), 55.4 (CH₃, **o**), 55.3 (CH₃, **p**), 53.8 (CH, **p**), 47.5 (CH, **o**), 46.6 (CH₂, **p**), 45.6 (CH₂, **o**). **HRMS (ESI):** *m/z* calcd. for C₁₅H₁₇N₂O₃ [M+H]⁺ 273.1234, found 273.1222.

2-(4-Nitrophenyl)-2-(2,3,4,5,6-pentamethylphenyl)ethan-1-amine 24

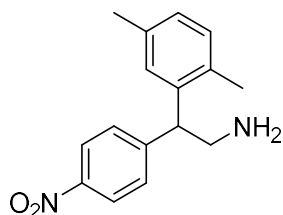


Chemical Formula: C₁₉H₂₄N₂O₂
Exact Mass: 312.1838

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then pentamethylbenzene (222 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **24** (42.0 mg, 0.132 mmol, 44% yield) as an orange oil.

¹H NMR (400 MHz, CDCl₃): δ 8.11 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 4.78 (dd, *J* = 8.3, 8.2 Hz, 1H), 3.72 (dd, *J* = 12.3, 8.3 Hz, 1H), 3.40 (dd, *J* = 12.3, 8.2 Hz, 1H), 2.27 (s, 3H), 2.22 (s, 6H), 2.10 (brs, 6H), 1.35 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 152.4 (C), 146.0 (C), 135.3 (C), 134.4 (C), 133.7 (2C), 133.1 (2C), 127.8 (2CH), 123.7 (2CH), 48.6 (CH), 44.7 (CH₂), 18.4 (2CH₃), 17.3 (CH₃), 17.2 (2CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₉H₂₄N₂O₂ [M+H]⁺ 313.1911, found 313.1899.

2-(2,5-Dimethylphenyl)-2-(4-nitrophenyl)ethan-1-amine **25**

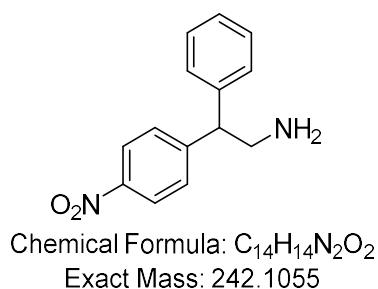


Chemical Formula: C₁₆H₁₈N₂O₂
Exact Mass: 270.1368

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then *p*-xylene (185 μL, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **25** (25.0 mg, 0.100 mmol, 30% yield) as an orange oil.

¹H NMR (400 MHz, CDCl₃): δ 8.13 (d, J = 8.7 Hz, 2H), 7.36 (d, J = 8.7 Hz, 2H), 7.07 – 7.05 (m, 2H), 6.99 (dd, J = 7.6, 1.8 Hz, 1H), 4.29 (t, J = 7.4, 7.3 Hz, 1H), 3.38 (dd, J = 12.8, 7.4 Hz, 1H), 3.29 (dd, J = 12.8, 7.3 Hz, 1H), 2.35 (s, 3H), 2.19 (s, 3H), 1.90 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 150.6 (C), 146.7 (C), 138.6 (C), 136.1 (C), 134.0 (C), 131.2 (CH), 129.3 (2CH), 127.9 (CH), 127.1 (CH), 123.9 (2CH), 50.5 (CH), 46.7 (CH₂), 21.4 (CH₃), 19.5 (CH₃). **HRMS (ESI):** m/z calcd. for C₁₆H₁₉N₂O₂ [M+H]⁺ 271.1441, found 271.1433.

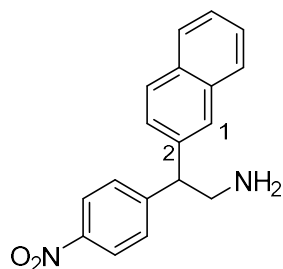
2-(4-Nitrophenyl)-2-phenylethan-1-amine 26



General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzene (134 μ L, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **26** (11.0 mg, 0.045 mmol, 15% yield) as an orange oil.

¹H NMR (400 MHz, CDCl₃): δ 8.16 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 7.34 (dd, J = 8.4, 6.9 Hz, 2H), 7.28 – 7.21 (m, 3H), 4.11 (t, J = 7.5 Hz, 1H), 3.43 – 3.32 (m, 2H), 1.43 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 150.8 (C), 146.8 (C), 141.2 (C), 129.2 (2CH), 129.1 (2CH), 128.2 (2CH), 127.4 (CH), 124.0 (2CH), 54.9 (CH), 46.8 (CH₂). **HRMS (ESI):** m/z calcd. for C₁₄H₁₄N₂O₂ [M+H]⁺ 243.1128, found 243.1127.

2-(Naphthalen-2-yl)-2-(4-nitrophenyl)ethan-1-amine 27



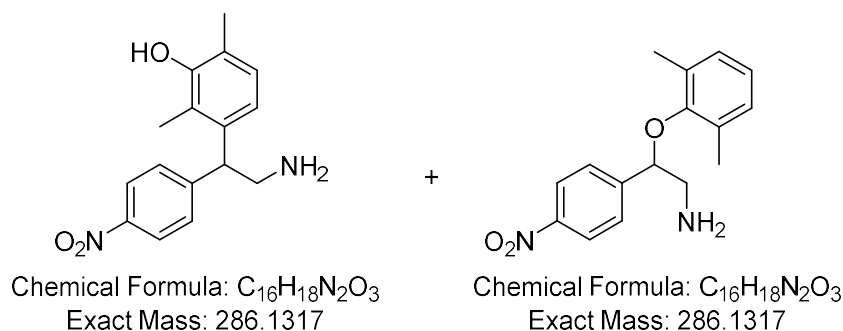
Chemical Formula: $C_{18}H_{16}N_2O_2$
Exact Mass: 292.1212

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then naphthalene (192 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **28** (56.0 mg, 0.192 mmol, 64% yield, 1/2: 50/50) as a red oil.

1H NMR (400 MHz, $CDCl_3$): δ 8.19 – 8.10 (m, 4H), 8.01 – 7.96 (m, 1H), 7.84 (m, 5H), 7.72 (m, 1H), 7.52 – 7.42 (m, 10H), 7.30 (m, 1H), 4.92 (t, J = 7.3 Hz, 1H), 4.28 (t, J = 7.5 Hz, 1H), 3.59 – 3.40 (m, 4H), 1.41 (brs, 4H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 150.9, 150.7, 146.8, 138.6, 136.6, 134.4, 133.6, 132.6, 132.1, 129.2, 129.2, 129.0, 128.2, 127.9, 127.8, 126.8, 126.6, 126.4, 126.2, 126.0, 125.5, 124.5, 124.0, 123.3, 54.9, 50.1, 47.0, 46.6. **HRMS (ESI):** m/z calcd. for $C_{18}H_{17}N_2O_2$ $[M+H]^+$ 293.1285, found 293.1278.

3-(2-Amino-1-(4-nitrophenyl)ethyl)-2,6-dimethylphenol **28**

2-(2,6-Dimethylphenoxy)-2-(4-nitrophenyl)ethanamine **28'**



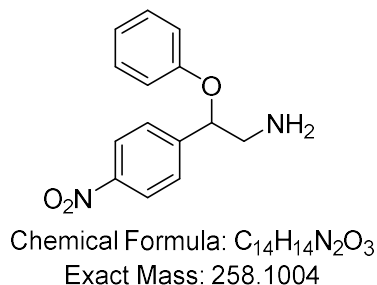
General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2,6-dimethylphenol (183 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction

mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 90/10) afforded **26** (44.5 mg, 0.156 mmol, 52% yield) as an orange oil and **26'** (17.1 mg, 0.06 mmol, 20% yield) as an orange oil.

26: ¹H NMR (400 MHz, CD₂Cl₂): δ 8.13 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 6.61 (s, 1H), 6.50 (s, 1H), 5.25 – 4.00 (brs, 3H), 4.64 (dd, *J* = 5.3, 2.0 Hz, 1H), 3.71 (dd, *J* = 12.9, 5.3 Hz, 1H), 3.27 (dd, *J* = 12.9, 2.0 Hz, 1H), 2.23 (s, 3H), 2.11 (s, 3H). ¹³C NMR (100 MHz, CD₂Cl₂): δ 157.2 (C), 148.2 (C), 146.8 (C), 138.2 (C), 137.7 (C), 129.2 (2CH), 123.8 (2CH), 122.4 (CH), 122.0 (C), 117.2 (CH), 45.4 (CH), 43.9 (CH₂), 20.7 (CH₃), 20.6 (CH₃). HRMS (ESI): *m/z* calcd. for C₁₆H₁₉N₂O₃ [M+H]⁺ 287.1390, found 287.1395.

26': ¹H NMR (400 MHz, CD₂Cl₂): δ 8.19 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 6.57 (s, 1H), 6.46 (s, 2H), 5.21 (t, *J* = 5.6 Hz, 1H), 3.09 (d, *J* = 5.6 Hz, 2H), 2.21 (s, 6H), 2.00 (brs, 2H). ¹³C NMR (100 MHz, CD₂Cl₂): δ 157.6 (C), 147.7 (C), 147.5 (C), 139.5 (CH), 127.1 (2CH), 124.1 (2CH), 123.5 (2C), 113.6 (2CH), 80.8 (CH), 49.1 (CH₂), 21.5 (2CH₃). HRMS (ESI): *m/z* calcd. for C₁₆H₁₉N₂O₃ [M+H]⁺ 287.1390, found 287.1378.

2-(4-Nitrophenyl)-2-phenoxyethan-1-amine **29**

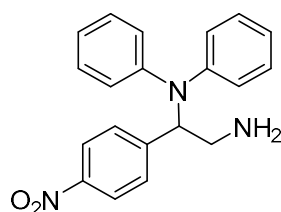


General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then phenol (141 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **29** (31.0 mg, 0.120 mmol, 40% yield) as an orange oil.

¹H NMR (400 MHz, CDCl₃): δ 8.19 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.22 – 7.17 (m, 2H), 6.91 (td, *J* = 7.4, 1.0 Hz, 1H), 6.84 – 6.79 (m, 2H), 5.23 (dd, *J* = 6.5, 4.7 Hz, 1H), 3.17 – 3.07 (m, 2H), 1.86 (brs, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 157.5 (C), 147.7 (C), 147.2 (C), 129.7

(2CH), 127.1 (2CH), 124.1 (2CH), 121.7 (CH), 115.8 (2CH), 81.1 (CH), 49.1 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₄H₁₅N₂O₃ [M+H]⁺ 259.1007, found 259.1083.

1-(4-Nitrophenyl)-N',N'-diphenylethane-1,2-diamine 30

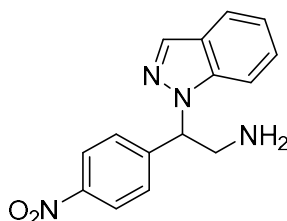


Chemical Formula: C₂₀H₁₉N₃O₂
Exact Mass: 333.1477

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then diphenylamine (254 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **30** (50.0 mg, 0.150 mmol, 50% yield) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 8.15 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.27 – 7.21 (m, 4H), 7.00 (t, *J* = 7.4 Hz, 2H), 6.92 (d, *J* = 7.7 Hz, 4H), 5.30 (dd, *J* = 7.2, 7.1 Hz, 1H), 3.34 (dd, *J* = 13.1, 7.1 Hz, 1H), 3.23 (dd, *J* = 13.1, 7.2 Hz, 1H), 1.28 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 148.6 (C), 147.2 (C), 146.6 (2C), 129.5 (4CH), 128.6 (2CH), 123.8 (2CH), 123.1 (4CH), 122.7 (2CH), 65.1 (CH), 43.8 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₂₀H₂₀N₃O₂ [M+H]⁺ 334.1550, found 334.1554.

2-(1H-Indazol-1-yl)-2-(4-nitrophenyl)ethan-1-amine 31

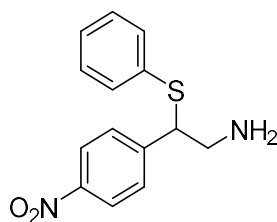


Chemical Formula: C₁₅H₁₄N₄O₂
Exact Mass: 282.1117

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then indazole (177 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 90/10) afforded **31** (45.0 mg, 0.159 mmol, 53% yield) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.16 (d, *J* = 8.8 Hz, 2H), 8.09 (d, *J* = 0.7 Hz, 1H), 7.73 – 7.66 (m, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.30 (ddd, *J* = 8.7, 6.6, 1.1 Hz, 1H), 7.09 (ddd, *J* = 8.3, 6.6, 0.7 Hz, 1H), 5.65 (dd, *J* = 9.1, 4.7 Hz, 1H), 3.85 (dd, *J* = 13.6, 9.1 Hz, 1H), 3.45 (dd, *J* = 13.6, 4.7 Hz, 1H), 1.50 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 149.4 (C), 147.9 (C), 145.8 (C), 127.9 (2CH), 126.6 (CH), 124.1 (2CH), 124.0 (CH), 122.4 (CH), 121.9 (C), 120.4 (CH), 117.9 (CH), 69.7 (CH), 46.8 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₅H₁₅N₄O₂ [M+H]⁺ 283.1190, found 283.1171.

2-(4-Nitrophenyl)-2-(phenylthio)ethan-1-amine **32**



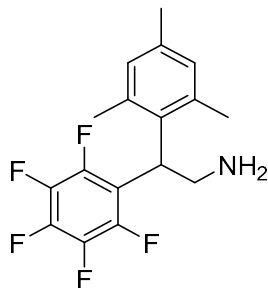
Chemical Formula: C₁₄H₁₄N₂O₂S

Exact Mass: 274.0776

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then thioanisole (177 μL, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **32** (51.0 mg, 0.183 mmol, 61% yield) as an orange oil.

¹H NMR (400 MHz, CDCl₃): δ 8.12 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.26 – 7.19 (m, 5H), 4.22 (t, *J* = 6.9 Hz, 1H), 3.22 – 3.10 (m, 2H), 1.48 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 148.4 (C), 147.2 (C), 133.1 (2CH), 133.0 (C), 129.2 (2CH), 129.0 (2CH), 128.1 (CH), 123.9 (2CH), 57.0 (CH), 46.8 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₄H₁₅N₂O₂S [M+H]⁺ 275.0849, found 275.0858.

2-Mesityl-2-(perfluorophenyl)ethanamine **33**

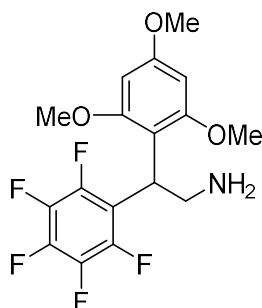


Chemical Formula: C₁₇H₁₆F₅N
Exact Mass: 329.1203

General Procedure **A** was followed with 1,2,3,4,5-pentafluoro-6-vinylbenzene **1b** (58.2 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then mesitylene (209 μ L, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 85/15) afforded **33** (62.2 mg, 0.19 mmol, 63% yield) as a brown oil.

¹H NMR (400 MHz, CDCl₃): δ 6.84 (s, 2H), 4.68 (dd, *J* = 8.9, 7.3 Hz, 1H), 3.61 (dd, *J* = 13.0, 8.9 Hz, 1H), 3.23 (dd, *J* = 13.0, 7.3 Hz, 1H), 2.28 (s, 6H), 2.25 (s, 3H), 1.44 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 146.0 (dm, *J* = 246.4 Hz, 2C), 139.8 (dm, *J* = 250.1 Hz, C), 137.8 (dm, *J* = 250.0 Hz, 2C), 136.9 (C), 136.8 (2C), 133.6 (C), 130.6 (2CH), 115.6 (m, C), 43.7 (CH₂), 43.2 (t, *J* = 4.3 Hz, CH), 20.8 (CH₃), 20.6 (2CH₃). **¹⁹F NMR (377 MHz, CDCl₃):** -138.4 (m), -156.4 (t, *J* = 21.5 Hz), -161.8 (m). **HRMS (ESI):** *m/z* calcd. for C₁₇H₁₇NF₅ [M+H]⁺ 330.1276, found 330.1275.

2-(Perfluorophenyl)-2-(2,4,6-trimethoxyphenyl)ethanamine **34**

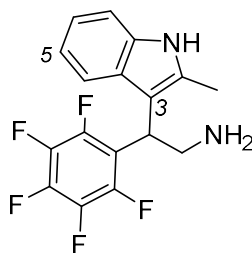


Chemical Formula: C₁₇H₁₆F₅NO₃
Exact Mass: 377.1050

General Procedure **A** was followed with 1,2,3,4,5-pentafluoro-6-vinylbenzene **1b** (58.2 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then trimethoxybenzene (252 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **34** (74.0 mg, 0.20 mmol, 65% yield) as a brown oil.

¹H NMR (400 MHz, CDCl₃): δ 6.10 (s, 2H), 4.80 (dd, *J* = 8.6, 7.5 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 6H), 3.39 (dd, *J* = 12.9, 7.5 Hz, 1H), 3.33 (dd, *J* = 12.9, 8.6 Hz, 1H), 1.69 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 160.7 (C), 159.3 (2C), 146.0 (dm, *J* = 247.4 Hz, 2C), 139.3 (dm, *J* = 250.5 Hz, C), 137.3 (dm, *J* = 250.0 Hz, 2C), 116.5 (m, C), 108.4 (C), 91.0 (2CH), 55.7 (2CH₃), 55.4 (CH₃), 43.4 (t, *J* = 4.2 Hz, CH), 37.1 (CH₂). **¹⁹F NMR (100 MHz, CDCl₃):** -142.7 (m), -161.0 (t, *J* = 21.5 Hz), -166.4 (dt, *J* = 21.5, 6.6 Hz). **HRMS (ESI):** *m/z* calcd. for C₁₇H₁₇O₃NF₅ [M+H]⁺ 378.1123, found 378.1119.

2-(2-Methyl-1*H*-indol-3-yl)-2-(perfluorophenyl)ethanamine **35**



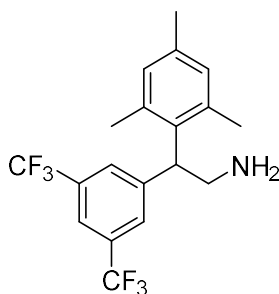
Chemical Formula: C₁₇H₁₃F₅N₂
Exact Mass: 340.0999

General Procedure **A** was followed with 1,2,3,4,5-pentafluoro-6-vinylbenzene **1b** (58.2 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-methyl-1*H*-indole (197 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 85/15) afforded **35** (82.5 mg, 0.24 mmol, 81% yield, 3/5: 70/30) as a dark purple oil. Regioisomers could be separated by flash column chromatography.

¹H NMR (400 MHz, CDCl₃): δ 8.30 (s, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.11 – 7.06 (m, 1H), 7.06 – 7.01 (m, 1H), 4.59 (dd, *J* = 8.4, 7.7 Hz, 1H), 3.66 (ddt, *J* = 12.2, 8.4, 1.8 Hz, 1H), 3.51 (dd, *J* = 12.2, 7.7 Hz, 1H), 2.44 (s, 3H), 1.48 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 145.7 (dm, *J* = 245.0 Hz, 2C), 139.9 (dm, *J* = 250.9 Hz, C), 138.0 (dm, *J* = 251.3 Hz, 2C), 135.6 (C), 133.6 (C), 127.6 (C), 121.4 (CH), 119.9 (CH), 118.7 (t, *J* = 3.0 Hz, CH), 117.2 (m, C), 110.8

(CH), 109.0 (C), 44.1 (t, $J = 3.4$ Hz, CH), 38.6 (CH₂), 12.5 (t, $J = 1.9$ Hz, CH₃). **¹⁹F NMR (471 MHz, CDCl₃)**: -141.6 (m), -158.8 (m), -163.4 (m). **HRMS (ESI)**: m/z calcd. for C₁₇H₁₄N₂F₅ [M+H]⁺ 341.1072, found 341.1059.

2-(3,5-Bis(trifluoromethyl)phenyl)-2-mesitylethan-1-amine 36

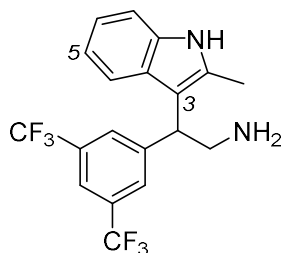


Chemical Formula: C₁₉H₁₉F₆N
Exact Mass: 375.1422

General Procedure **A** was followed with 3,5-bis(trifluoromethyl)styrene **1c** (72.0 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then mesitylene (208 μ L, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **36** (63.0 mg, 0.168 mmol, 56% yield) as bright brown oil.

¹H NMR (400 MHz, CDCl₃): δ 7.70 (s, 1H), 7.60 (s, 2H), 6.88 (s, 2H), 4.65 (t, $J = 7.7, 7.6$ Hz, 1H), 3.66 (dd, $J = 12.4, 7.6$ Hz, 1H), 3.44 (dd, $J = 12.4, 7.7$ Hz, 1H), 2.28 (s, 3H), 2.15 (brs, 6H), 1.52 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃)**: δ 146.0 (C), 137.3 (2C), 137.0 (C), 134.0 (C), 131.6 (q, $J = 32.9$ Hz, 2C), 130.8 (2CH), 127.6 (m, 2CH), 123.6 (q, $J = 272.7$ Hz, 2C), 120.0 (m, CH), 47.1 (CH), 43.8 (CH₂), 21.6 (2CH₃), 20.9 (CH₃). **¹⁹F NMR (471 MHz, CDCl₃)**: δ -62.7. **HRMS (ESI)**: m/z calcd. for C₁₉H₂₀F₆N [M+H]⁺ 376.1495, found 375.1510.

2-(3,5-Bis(trifluoromethyl)phenyl)-2-(2-methyl-1H-indol-3-yl)ethan-1-amine 37

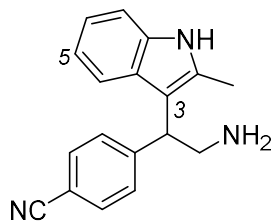


Chemical Formula: $C_{19}H_{16}F_6N_2$
Exact Mass: 386.1218

General Procedure **A** was followed with 3,5-bis(trifluoromethyl)styrene **1c** (72.0 mg, 0.30 mmol) and $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, 2-methylindole (197 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **37** (69.5 mg, 0.180 mmol, 60% yield, 3/5 >95/5) as dark purple oil.

1H NMR (400 MHz, $CDCl_3$): δ 8.18 (brs, 1H), 7.78 (s, 2H), 7.71 (s, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.14 (ddd, J = 8.0, 7.1, 1.1 Hz, 1H), 7.05 (ddd, J = 8.0, 7.1, 1.1 Hz, 1H), 4.38 (dd, J = 9.5, 6.0 Hz, 1H), 3.59 (dd, J = 12.3, 9.5 Hz, 1H), 3.50 (dd, J = 12.3, 6.0 Hz, 1H), 2.39 (s, 3H), 1.79 (brs, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 146.0 (C), 135.7 (C), 133.3 (C), 132.7 (q, J = 32.7 Hz, 2C), 128.1 (m, 2CH), 127.1 (C), 123.7 (q, J = 272.7 Hz, 2C), 121.6 (CH), 120.4 (m, CH), 120.0 (CH), 118.7 (CH), 110.9 (CH), 109.6 (C), 45.5 (CH_2), 45.4 (CH), 12.5 (CH_3). **^{19}F NMR (471 MHz, $CDCl_3$):** δ -62.7. **HRMS (ESI):** m/z calcd. for $C_{19}H_{17}F_6N_2$ $[M+H]^+$ 387.1290, found 387.1310.

4-(2Amino-1-(2-methyl-1H-indol-3-yl)ethyl)benzonitrile **38**



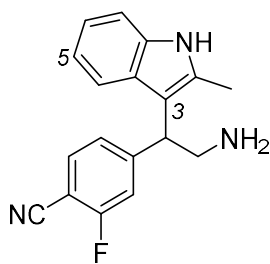
Chemical Formula: $C_{18}H_{17}N_3$
Exact Mass: 275.1422

General Procedure **A** was followed with 4-vinylbenzonitrile **1d** (38.7 mg, 0.30 mmol) and $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-methyl-1H-indole (197 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction

mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel previously neutralized by 5% Et₃N (DCM/MeOH: 100/0 to 85/15) afforded **38** (42.0 mg, 0.15 mmol, 51% yield, 3/5: 85/15) as a dark purple oil

¹H NMR (400 MHz, CD₂Cl₂): δ 8.26 (brs, 1H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.10 – 7.04 (m, 1H), 7.00 – 6.94 (m, 1H), 4.31 (t, *J* = 7.8 Hz, 1H), 3.53 – 3.40 (m, 2H), 2.38 (s, 3H), 2.05 (brs, 2H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 149.5 (C), 136.0 (C), 133.8 (C), 132.5 (2CH), 129.0 (2CH), 127.7 (C), 121.4 (CH), 119.8 (CH), 119.3 (C), 119.1 (CH), 111.0 (CH), 110.5 (C), 110.2 (C), 46.1 (CH), 45.5 (CH₂), 12.5 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₈H₁₈N₃ [M+H]⁺ 276.1495, found 276.1491.

4-(2-Amino-1-(2-methyl-1H-indol-3-yl)ethyl)-2-fluorobenzonitrile **39**

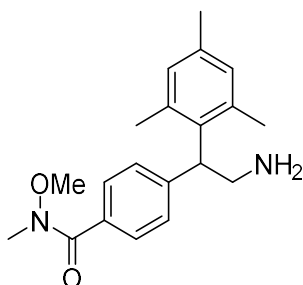


Chemical Formula: C₁₈H₁₆FN₃
Exact Mass: 293.1328

General Procedure **A** was followed with 2-fluoro-4-vinylbenzonitrile **1e** (44.1 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-methyl-1H-indole (197 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/ *i*-PrOH: 100/0 to 80/20) afforded **39** (52.0 mg, 0.18 mmol, 59% yield, 3/5: 94/6) as a dark purple oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.26 (brs, 1H), 7.55 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.10 – 7.04 (m, 1H), 7.00 – 6.94 (m, 1H), 4.31 (t, J = 7.8 Hz, 1H), 3.53 – 3.40 (m, 2H), 2.38 (s, 3H), 2.05 (brs, 2H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 163.6 (d, J = 257.1 Hz, C), 153.31 (d, J = 7.2 Hz, C), 136.0 (C), 133.8 (C), 133.5 (CH), 127.6 (C), 124.9 (d, J = 3.1 Hz, CH), 121.6 (CH), 119.9 (CH), 119.0 (CH), 116.1 (d, J = 19.8 Hz, CH), 114.5 (C), 111.0 (CH), 110.1 (C), 99.0 (d, J = 15.6 Hz, C), 46.3 (d, J = 1.3 Hz, CH), 45.5 (CH₂), 12.4 (CH₃). **¹⁹F NMR (471 MHz, CD₂Cl₂):** -108.0. **HRMS (ESI):** m/z calcd. for C₁₈H₁₈N₃ [M+H]⁺ 276.1495, found 276.1491.

4-(2-Amino-1-mesitylethyl)-N-methoxy-N-methylbenzamide 40

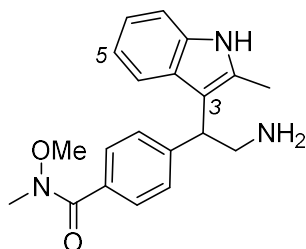


Chemical Formula: C₂₀H₂₆N₂O₂
Exact Mass: 326.1994

General Procedure **A** was followed with *N*-methoxy-*N*-methyl-4-vinylbenzamide **1f** (57.3 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then mesitylene (209 μ L, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel previously neutralized by 5% Et₃N (DCM/MeOH: 100/0 to 90/10) afforded **40** (46.0 mg, 0.14 mmol, 47% yield) as a brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.55 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.85 (s, 2H), 4.60 (dd, J = 8.7, 6.6 Hz, 1H), 3.64 (dd, J = 12.3, 6.6 Hz, 1H), 3.53 (s, 3H), 3.35 (dd, J = 12.3, 8.7 Hz, 1H), 3.29 (s, 3H), 2.25 (s, 3H), 2.16 (s, 6H), 1.85 (brs, 3H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 170.0 (C=O), 146.2 (C), 137.8 (2C), 136.6 (C), 136.1 (C), 132.1 (C), 130.5 (2CH), 128.5 (2CH), 127.2 (2CH), 61.2 (CH₃), 47.6 (CH), 43.6 (CH₂), 34.0 (CH₃), 21.6 (2CH₃), 20.8 (CH₃). **HRMS (ESI):** m/z calcd. for C₂₀H₂₇N₂O₂ [M+H]⁺ 327.2067, found 327.2057.

4-(2-Amino-1-(2-methyl-1H-indol-3-yl)ethyl)-N-methoxy-N-methylbenzamide 41

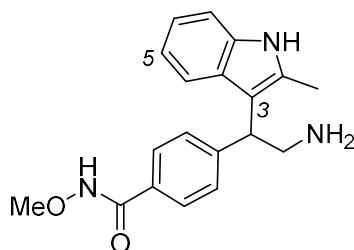


Chemical Formula: $C_{20}H_{23}N_3O_2$
Exact Mass: 337.1790

General Procedure **A** was followed with *N*-methoxy-*N*-methyl-4-vinylbenzamide **1f** (57.3 mg, 0.30 mmol) and $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-methyl-1*H*-indole (197 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel previously neutralized by 5% Et_3N (DCM/MeOH: 100/0 to 80/20) afforded **41** (54.0 mg, 0.17 mmol, 55% yield, 3/5 >95/5) as a dark purple oil.

1H NMR (400 MHz, CD_2Cl_2): δ 8.76 (brs, 1H), 7.54 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 7.9 Hz, 1H), 7.04 (dd, J = 7.5, 0.9 Hz, 1H), 6.95 (dd, J = 7.5, 0.9 Hz, 1H), 4.30 (t, J = 7.8 Hz, 1H), 3.52 (s, 3H), 3.47 (d, J = 7.8 Hz, 2H), 3.29 (s, 3H), 2.47 (brs, 2H), 2.33 (s, 3H). **^{13}C NMR (100 MHz, CD_2Cl_2):** δ 170.1 (C=O), 146.5 (C), 136.0 (C), 133.8 (C), 132.4 (C), 128.6 (2CH), 127.8 (C), 127.8 (2CH), 121.2 (CH), 119.5 (CH), 119.2 (CH), 111.0 (CH), 110.8 (C), 61.3 (CH_3), 45.6 (CH), 45.4 (CH_2), 34.1 (CH_3), 12.4 (CH_3). **HRMS (ESI):** m/z calcd. for $C_{20}H_{24}N_3O_2$ $[M+H]^+$ 338.1863, found 338.1854.

4-(2-Amino-1-(2-methyl-1*H*-indol-3-yl)ethyl)-*N*-methoxybenzamide **42**



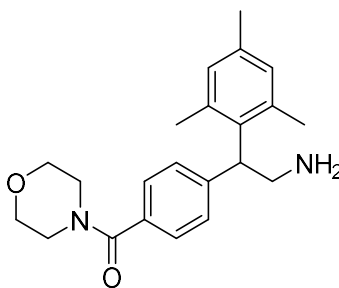
Chemical Formula: $C_{19}H_{21}N_3O_2$
Exact Mass: 323.1634

General Procedure **A** was followed with *N*-methoxy-4-vinylbenzamide **1g** (53.0 mg, 0.30 mmol) and $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-methyl-1*H*-indole (197 mg, 1.5 mmol, 5.0 equiv.) was added to the

reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel previously neutralized by 5% Et₃N (DCM/MeOH: 100/0 to 70/30) afforded **42** (43.2 mg, 0.14 mmol, 45% yield, 3/5: 83/17) as a dark purple oil.

¹H NMR (400 MHz, MeOD): δ 7.65 (d, J = 8.4 Hz, 2H), 7.43 – 7.38 (m, 3H), 7.27 (dt, J = 8.1, 0.8 Hz, 1H), 7.04 – 6.98 (m, 1H), 6.92 – 6.87 (m, 1H), 4.36 (dd, J = 9.8, 6.3 Hz, 1H), 3.77 (s, 3H), 3.49 (dd, J = 12.4, 9.8 Hz, 1H), 3.42 (dd, J = 12.4, 6.3 Hz, 1H), 2.40 (s, 3H), 2H unobserved. **¹³C NMR (100 MHz, MeOD):** δ 167.7 (C=O), 149.2 (C), 137.4 (C), 134.8 (C), 131.0 (C), 129.1 (2CH), 128.5 (C), 128.2 (2CH), 121.6 (CH), 119.8 (CH), 119.5 (CH), 111.8 (CH), 110.4 (C), 64.2 (CH₃), 46.2 (CH), 45.7 (CH₂), 12.0 (CH₃). **HRMS (ESI):** m/z calcd. for C₁₉H₂₂N₃O₂ [M+H]⁺ 324.1701, found 324.1697.

(4-(2-Amino-1-mesitylethyl)phenyl)(morpholino)methanone 43

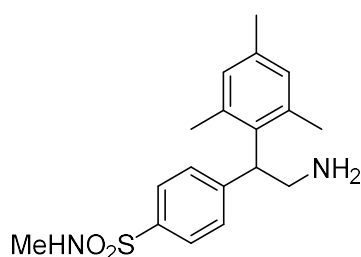


Chemical Formula: C₂₂H₂₈N₂O₂
Exact Mass: 352.2151

General Procedure **A** was followed with morpholino(4-vinylphenyl)methanone **1h** (65.1 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then mesitylene (209 μ L, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 75/25) afforded **43** (63.1 mg, 0.18 mmol, 60% yield) as a brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.28 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.84 (s, 2H), 4.61 (dd, *J* = 8.7, 7.6 Hz, 1H), 3.78 – 3.44 (m, 9H), 3.35 (dd, *J* = 12.4, 8.7 Hz, 1H), 2.24 (s, 3H), 2.16 (brs, 6H), 2.01 (brs, 2H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 170.5 (C=O), 145.2 (C), 137.8 (2C), 136.6 (C), 135.9 (C), 133.4 (C), 130.6 (2CH), 127.7 (2CH), 127.5 (2CH), 67.2 (4CH₂), 47.4 (CH), 43.6 (CH₂), 21.7 (2CH₃), 20.8 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₂₂H₂₉N₂O₂ [M+H]⁺ 353.2224, found 353.2220.

4-(2-Amino-1-mesitylethyl)-N-methylbenzenesulfonamide 44

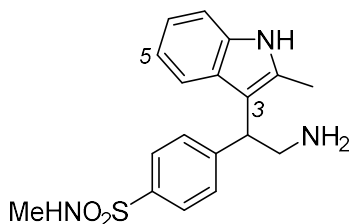


Chemical Formula: C₁₈H₂₄N₂O₂S
Exact Mass: 332.1558

General Procedure **A** was followed with *N*-methyl-4-vinylbenzenesulfonamide **1i** (65.1 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then mesitylene (209 μL, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **44** (32.2 mg, 0.10 mmol, 32% yield) as a brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 6.85 (s, 2H), 4.78 (brs, 1H), 4.61 (dd, *J* = 8.5, 7.4 Hz, 1H), 3.65 (dd, *J* = 12.4, 7.4 Hz, 1H), 3.37 (dd, *J* = 12.4, 8.5 Hz, 1H), 2.57 (s, 3H), 2.25 (s, 3H), 2.13 (brs, 6H), 1.66 (brs, 2H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 149.0 (C), 137.8 (2C), 136.8 (C), 136.5 (C), 135.6 (C), 130.6 (2CH), 128.4 (2CH), 127.4 (2CH), 47.7 (CH), 43.7 (CH₂), 29.6 (CH₃), 21.6 (2CH₃), 20.8 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₈H₂₅N₂O₂S [M+H]⁺ 333.1631, found 333.1627.

4-(2-Amino-1-(2-methyl-1H-indol-3-yl)ethyl)-N-methylbenzenesulfonamide 45

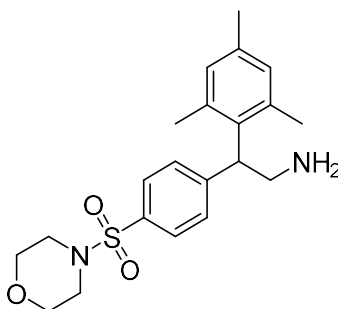


Chemical Formula: $C_{18}H_{21}N_3O_2S$
Exact Mass: 343.1354

General Procedure **A** was followed with *N*-methyl-4-vinylbenzenesulfonamide **1i** (65.1 mg, 0.30 mmol) and $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-methyl-1*H*-indole (197 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 80/20) afforded **45** (42.9 mg, 0.13 mmol, 42% yield, 3/5: 87/13) as a dark purple oil.

1H NMR (400 MHz, CD_3OD): δ 7.71 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 7.9 Hz, 1H), 7.28 (d, J = 7.9 Hz, 1H), 7.01 (dd, J = 7.9, 0.7 Hz, 1H), 6.91 (dd, J = 7.9, 0.7 Hz, 1H), 4.40 (dd, J = 9.7, 6.3 Hz, 1H), 3.51 (dd, J = 12.4, 9.7 Hz, 1H), 3.45 (dd, J = 12.4, 6.3 Hz, 1H), 2.47 (s, 3H), 2.41 (s, 3H), 4H unobserved. **^{13}C NMR (100 MHz, CD_3OD):** δ 150.0 (C), 138.1 (C), 137.4 (C), 135.0 (C), 129.6 (2CH), 128.4 (C), 128.2 (2CH), 121.6 (CH), 119.9 (CH), 119.4 (CH), 111.8 (CH), 110.0 (C), 46.0 (CH), 45.6 (CH_2), 29.2 (CH_3), 12.0 (CH_3). **HRMS (ESI):** m/z calcd. for $C_{18}H_{22}N_3O_2S$ $[M+H]^+$ 344.1427, found 344.1424.

2-Mesityl-2-(4-(morpholinosulfonyl)phenyl)ethanamine **46**



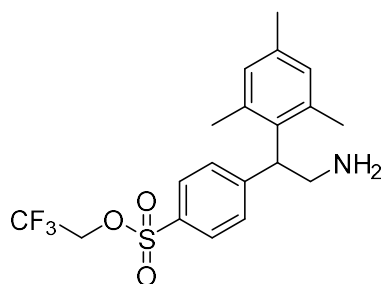
Chemical Formula: $C_{21}H_{28}N_2O_3S$
Exact Mass: 388.1821

General Procedure **A** was followed with 4-((4-vinylphenyl)sulfonyl)morpholine **1j** (75.9 mg, 0.30 mmol) and $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction

mixture was stirred at 60 °C for 1 h, then mesitylene (209 μ L, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. NaOH 1M was used instead of NaHCO₃ sat. to quench the reaction. Purification by FC over silica gel previously neutralized by 5% Et₃N (DCM/MeOH: 100/0 to 95/5) afforded **46** (48.0 mg, 0.12 mmol, 41% yield) as a brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.61 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 7.8 Hz, 2H), 6.86 (s, 2H), 4.62 (dd, J = 8.5, 6.7 Hz, 1H), 3.72 – 3.68 (m, 4H), 3.65 (dd, J = 12.5, 6.7 Hz, 1H), 3.37 (dd, J = 12.5, 8.5 Hz, 1H), 2.95 – 2.87 (m, 4H), 2.25 (s, 3H), 2.14 (brs, 6H), 1.59 (brs, 2H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 149.7 (C), 137.7 (2C), 136.8 (C), 135.7 (C), 132.5 (C), 130.5 (2CH), 128.5 (2CH), 128.1 (2CH), 66.4 (2CH₂), 47.7 (CH), 46.5 (2CH₂), 43.7 (CH₂), 21.6 (2CH₃), 20.8 (CH₃). **HRMS (ESI):** m/z calcd. for C₂₁H₂₉N₂O₃S [M+H]⁺ 389.1893, found 389.1893.

2,2,2-Trifluoroethyl 4-(2-amino-1-mesitylethyl)benzenesulfonate **47**

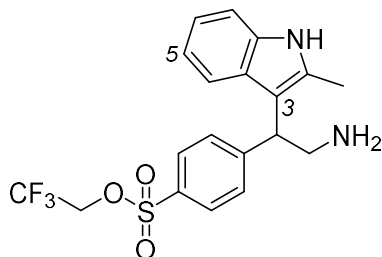


Chemical Formula: C₁₉H₂₂F₃NO₃S
Exact Mass: 401.1272

General Procedure **A** was followed with 2,2,2-trifluoroethyl 4-vinylbenzenesulfonate **1k** (79.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then mesitylene (209 μ L, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 90/10) afforded **47** (54.1 mg, 0.13 mmol, 45% yield) as a brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.80 (d, J = 8.6 Hz, 2H), 7.41 (d, J = 8.6 Hz, 2H), 6.87 (s, 2H), 4.63 (dd, J = 8.3, 6.8 Hz, 1H), 4.37 (q, J = 8.0 Hz, 2H), 3.64 (dd, J = 12.4, 6.8 Hz, 1H), 3.38 (dd, J = 12.4, 8.3 Hz, 1H), 2.26 (s, 3H), 2.14 (brs, 6H), 1.36 (brs, 2H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 152.0 (C), 137.7 (2C), 137.0 (C), 135.5 (C), 132.1 (C), 130.6 (2CH), 129.0 (2CH), 128.3 (2CH), 122.5 (q, J = 277.7 Hz, C), 65.1 (q, J = 37.9 Hz, CH₂), 48.0 (CH), 43.8 (CH₂), 21.6 (2CH₃), 20.8 (CH₃). **¹⁹F NMR (471 MHz, CD₂Cl₂):** -74.3. **HRMS (ESI):** m/z calcd. for C₁₉H₂₃F₃NO₃S [M+H]⁺ 402.1345, found 402.1335.

2,2,2-Trifluoroethyl 4-(2-amino-1-(2-methyl-1H-indol-3-yl)ethyl)benzenesulfonate 48

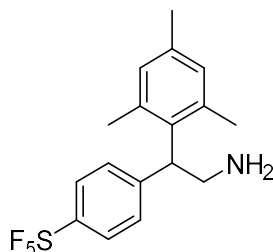


Chemical Formula: C₁₉H₁₉F₃N₂O₃S
Exact Mass: 412.1068

General Procedure **A** was followed with 2,2,2-trifluoroethyl 4-vinylbenzenesulfonate **1k** (79.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-methyl-1H-indole (197 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **48** (58.5 mg, 0.14 mmol, 47% yield, 3/5 >95/5) as a dark purple oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.40 (brs, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.12 – 7.05 (m, 2H), 7.01 – 6.94 (m, 1H), 4.39 – 4.32 (m, 3H), 3.57 – 3.44 (m, 2H), 2.39 (s, 3H), 1.84 (brs, 2H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 151.9 (C), 136.0 (C), 133.8 (C), 132.5 (C), 129.4 (2CH), 128.4 (2CH), 127.7 (C), 122.4 (q, *J* = 277.6 Hz, C), 121.5 (CH), 119.8 (CH), 119.0 (CH), 111.0 (CH), 110.4 (C), 65.1 (q, *J* = 37.9 Hz, CH₂), 46.3 (CH), 45.6 (CH₂), 12.4 (CH₃). **¹⁹F NMR (471 MHz, CD₂Cl₂):** -74.3. **HRMS (ESI):** *m/z* calcd. for C₁₉H₂₀N₂O₃S [M+H]⁺ 413.1141, found 413.1128.

2-Mesityl-2-(4-(pentafluoro-λ⁶-sulfaneyl)phenyl)ethan-1-amine 49

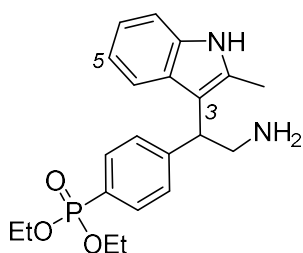


Chemical Formula: C₁₇H₂₀F₅NS
Exact Mass: 365.1237

General Procedure **A** was followed with pentafluoro(4-vinylphenyl)- λ^6 -sulfane **1l** (69.0 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then mesitylene (209 μ L, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. NaOH 1M was used instead of NaHCO₃ sat. to quench the reaction. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 90/10) afforded **49** (38.6 mg, 0.11 mmol, 35% yield) as a brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.63 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 6.86 (s, 2H), 4.58 (dd, *J* = 8.8, 5.4 Hz, 1H), 3.61 (dd, *J* = 12.0, 5.4 Hz, 1H), 3.36 (dd, *J* = 12.0, 8.8 Hz, 1H), 2.25 (s, 3H), 2.14 (brs, 6H), 1.45 (brs, 2H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 151.7 (m, C), 148.1 (C), 137.7 (2C), 136.8 (C), 135.5 (C), 130.6 (2CH), 128.0 (2CH), 126.0 (m, 2CH), 47.6 (CH), 43.8 (CH₂), 21.6 (2CH₃), 20.8 (CH₃). **¹⁹F NMR (471 MHz, CD₂Cl₂):** -71.9, -73.5 (d, *J* = 5.7 Hz). **HRMS (ESI):** *m/z* calcd. for C₂₇H₂₀F₅NS [M+H]⁺ 366.1309, found 366.1300.

Diethyl (4-(2-amino-1-(2-methyl-1H-indol-3-yl)ethyl)phenyl)phosphonate 50



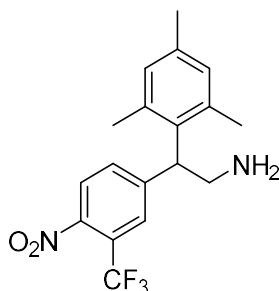
Chemical Formula: C₂₁H₂₇N₂O₃P
Exact Mass: 386.1759

General Procedure **A** was followed with diethyl (4-vinylphenyl)phosphonate **1m** (36.0 mg, 0.15 mmol) and [MsO-NH₃][OTf] (60 mg, 0.23 mmol, 1.5 equiv.) in HFIP (0.25 mL). The reaction mixture was stirred at 60 °C for 2 h, then 2-methyl-1*H*-indole (98.5 mg, 0.75 mmol, 5.0 equiv.)

was added to the reaction mixture which was stirred at 80 °C for 16 h. NaOH 1M was used instead of NaHCO₃ sat. to quench the reaction. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 70/30) afforded **52** (32.8 mg, 0.09 mmol, 57% yield, 3/5 >95/5) as a dark purple oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.38 (brs, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.45 – 7.39 (m, 3H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.08 – 7.03 (m, 1H), 6.98 – 6.94 (m, 1H), 4.29 (t, *J* = 7.8 Hz, 1H), 4.09 – 3.98 (m, 4H), 3.54 – 3.43 (m, 2H), 2.40 (s, 3H), 1.81 (brs, 2H), 1.27 (t, *J* = 7.1 Hz, 6H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 148.7 (d, *J* = 3.1 Hz, C), 136.1 (C), 133.7 (C), 132.1 (d, *J* = 10.3 Hz, 2CH), 128.4 (d, *J* = 15.2 Hz, 2CH), 127.8 (C), 126.3 (d, *J* = 189.6 Hz, C), 121.2 (CH), 119.6 (CH), 119.2 (CH), 111.0 (CH), 110.7 (C), 62.4 (d, *J* = 5.5 Hz, 2CH₂), 46.1 (CH), 45.5 (CH₂), 16.5 (d, *J* = 6.5 Hz, 2CH₃), 12.5 (CH₃). **³¹P NMR (162 MHz, CD₂Cl₂):** 18.6. **HRMS (ESI):** *m/z* calcd. for C₂₁H₂₈N₂O₃P [M+H]⁺ 387.1832, found 387.1821.

2-Mesityl-2-(4-nitro-3-(trifluoromethyl)phenyl)ethanamine **51**



Chemical Formula: C₁₈H₁₉F₃N₂O₂

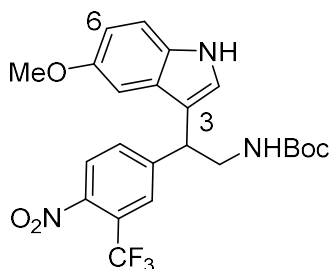
Exact Mass: 352.1399

General Procedure **A** was followed with 1-nitro-2-(trifluoromethyl)-4-vinylbenzene **1n** (67.0 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then mesitylene (209 μL, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 90/10) afforded **51** (48.0 mg, 0.14 mmol, 44% yield) as a red oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.82 (d, *J* = 8.5 Hz, 1H), 7.69 (s, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 6.88 (s, 2H), 4.61 (dd, *J* = 7.9, 7.1 Hz, 1H), 3.63 (dd, *J* = 12.4, 7.1 Hz, 1H), 3.40 (dd, *J* = 12.4, 7.9 Hz, 1H), 2.26 (s, 3H), 2.13 (brs, 6H), 1.40 (brs, 2H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 150.5 (C), 146.1 (C), 137.6 (2C), 137.3 (C), 134.6 (C), 132.4 (CH), 130.8 (2CH), 127.2 (q, *J* = 5.4 Hz, CH), 125.5 (CH), 123.5 (q, *J* = 33.4 Hz, C), 122.7 (q, *J* = 273.2 Hz, C), 47.7 (CH), 44.1 (CH₂), 21.6 (2CH₃),

20.9 (CH₃). **¹⁹F NMR (471 MHz, CD₂Cl₂):** -60.2. **HRMS (ESI):** *m/z* calcd. for C₁₈H₂₀F₃N₂O₂ [M+H]⁺ 353.1471, found 353.1460.

Tert-butyl (2-(5-methoxy-1H-indol-3-yl)-2-(4-nitro-3-(trifluoromethyl)phenyl)ethyl)carbamate 52'

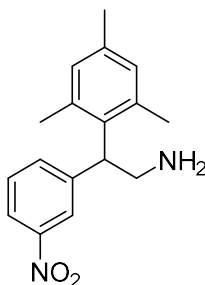


Chemical Formula: C₂₃H₂₄F₃N₃O₅
Exact Mass: 479.1668

General Procedure **A** was followed with 1-nitro-2-(trifluoromethyl)-4-vinylbenzene **1n** (67.0 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 5-methoxyindole (221 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **52** (54.5 mg, 0.144 mmol, 48% yield, 3/6: 88/12) as an orange oil. Due to the rapid protonation of **52** under air, the amine was protected with a Boc group for its characterization (**52'**).

¹H NMR (400 MHz, CD₂Cl₂): δ 8.09 (d, *J* = 8.9 Hz, 2H), 7.35 (dd, *J* = 8.9, 0.9 Hz, 2H), 6.85 (s, 2H), 4.73 (dd, *J* = 7.6, 7.2 Hz, 1H), 3.53 (dd, *J* = 11.6, 7.2 Hz, 1H), 3.21 (dd, *J* = 11.6, 7.6 Hz, 1H), 2.47 (s, 3H), 2.25 (s, 3H), 2.12 (brs, 6H), 1.69 (brs, 1H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 156.0 (C=O), 154.6 (C), 149.3 (C), 146.9 (C), 133.2 (CH), 132.0 (C), 128.2 (q, *J* = 10.3 Hz, CH), 127.2 (C), 125.8 (CH), 123.0 (CH), 122.6 (q, *J* = 273.2 Hz, C), 114.6 (C), 112.9 (CH), 112.5 (CH), 101.0 (CH), 79.8 (C), 56.0 (CH₃), 45.1 (CH₂), 43.5 (CH), 28.4 (3CH₃), one C hidden. **¹⁹F NMR (471 MHz, CD₂Cl₂):** -60.2. **HRMS (ESI):** *m/z* calcd. for C₂₃H₂₄F₃N₃O₅Na [M+Na]⁺ 502.1560, found 502.1550.

2-Mesityl-2-(3-nitrophenyl)ethanamine 53

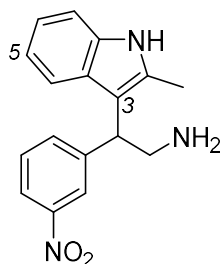


Chemical Formula: C₁₇H₂₀N₂O₂
Exact Mass: 284.1525

General Procedure **A** was followed with 3-nitrostyrene **1o** (14.9 mg, 0.10 mmol) and [MsO-NH₃][OTf] (40 mg, 0.15 mmol, 1.5 equiv.) in HFIP (0.17 mL). The reaction mixture was stirred at 60 °C for 1 h, then mesitylene (70 µL, 0.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 90/10) afforded **53** (15.9 mg, 0.06 mmol, 56% yield) as a brown oil.

¹H NMR (400 MHz, CDCl₃): δ 8.06 (s, 1H), 8.03 (dd, *J* = 5.3, 3.7 Hz, 1H), 7.46 – 7.37 (m, 2H), 6.86 (s, 2H), 4.64 (dd, *J* = 8.8, 7.3 Hz, 1H), 3.68 (dd, *J* = 12.2, 7.3 Hz, 1H), 3.44 (dd, *J* = 12.2, 8.8 Hz, 1H), 2.27 (s, 3H), 2.16 (brs, 6H), 1.55 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 148.5 (C), 145.4 (C), 137.4 (2C), 136.9 (C), 134.6 (C), 133.9 (CH), 130.7 (2CH), 129.2 (CH), 122.1 (CH), 121.1 (CH), 47.1 (CH), 43.6 (CH₂), 21.6 (2CH₃), 20.9 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₇H₂₁N₂O₂ [M+H]⁺ 285.1598, found 285.1594.

2-(2-Methyl-1H-indol-3-yl)-2-(3-nitrophenyl)ethan-1-amine 54

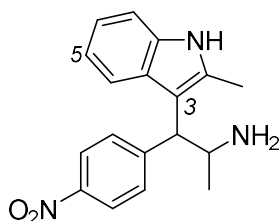


Chemical Formula: $C_{17}H_{17}N_3O_2$
Exact Mass: 295.1321

General Procedure **A** was followed with 3-nitrostyrene **1o** (44.8 mg, 0.30 mmol) and $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, 2-methylindole (197 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **54** (56.7 mg, 0.192 mmol, 64% yield, 3/5: 78/22) as a bright yellow oil. Regioisomers could be separated by flash column chromatography.

1H NMR (400 MHz, CD_2Cl_2): δ 8.19 – 8.17 (m, 1H), 8.14 (brs, 1H), 8.02 (ddd, J = 8.1, 2.4, 1.0 Hz, 1H), 7.68 (ddt, J = 7.7, 1.8, 0.9 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.08 (td, J = 8.2, 7.6, 1.2 Hz, 1H), 6.97 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H), 4.35 (dd, J = 7.8, 7.7 Hz, 1H), 3.54 – 3.49 (m, 2H), 2.43 (s, 3H), 1.64 (brs, 2H). **^{13}C NMR (100 MHz, CD_2Cl_2):** δ 148.8 (C), 146.3 (C), 136.0 (C), 134.7 (CH), 133.7 (C), 129.6 (CH), 127.7 (C), 123.0 (CH), 121.6 (CH), 121.5 (CH), 119.8 (CH), 119.1 (CH), 111.0 (CH), 110.8 (C), 45.9 (CH), 45.8 (CH₂), 12.5 (CH₃). **HRMS (ESI):** m/z calcd. for $C_{17}H_{18}N_3O_2$ $[M+H]^+$ 296.1394, found 296.1392.

1-(2-Methyl-1H-indol-3-yl)-1-(4-nitrophenyl)propan-2-amine **55**



Chemical Formula: $C_{18}H_{19}N_3O_2$
Exact Mass: 309.1477

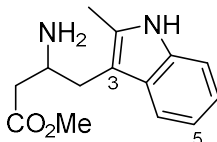
General Procedure **A** was followed with 1-nitro-4-(prop-1-en-1-yl)benzene **1p** (48.9 mg, 0.30 mmol) and $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-methylindole (197 mg, 1.5 mmol, 5.0 equiv.) was added

to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **55** (55.4 mg, 0.18 mmol, 60% yield, *dr*: 78/22, 3/5: >95/5) as a brown oil. Diastereoisomers could be separated by flash column chromatography.

¹H NMR (400 MHz, CD₂Cl₂, major diastereoisomer): δ 8.10 (d, *J* = 8.8 Hz, 2H), 8.02 (brs, 1H), 7.66 – 7.59 (m, 3H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.09 – 7.00 (m, 2H), 4.17 (dq, *J* = 10.2, 6.2 Hz, 1H), 3.97 (d, *J* = 10.2 Hz, 1H), 2.44 (s, 3H), 1.50 (brs, 2H), 1.08 (d, *J* = 6.2 Hz, 3H). **¹³C NMR (100 MHz, CD₂Cl₂, major diastereoisomer):** δ 152.5 (C), 146.6 (C), 135.8 (C), 132.4 (C), 129.5 (2CH), 127.4 (C), 123.9 (2CH), 121.4 (CH), 119.9 (CH), 119.4 (CH), 112.8 (C), 110.9 (CH), 53.3 (CH), 49.0 (CH), 22.9 (CH₃), 12.6 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₈H₂₀N₃O₂ [M+H]⁺ 310.1550, found 310.1544.

¹H NMR (400 MHz, CD₂Cl₂, minor diastereoisomer): δ 8.13 (s, 1H), 8.08 (d, *J* = 8.8 Hz, 2H), 7.77 – 7.67 (m, 1H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.51 – 7.28 (m, 1H), 7.19 – 6.95 (m, 2H), 4.13 (dt, *J* = 9.7, 6.1 Hz, 1H), 3.97 (d, *J* = 9.7 Hz, 1H), 2.41 (s, 3H), 1.83 (brs, 2H), 1.13 (d, *J* = 6.1 Hz, 3H). **¹³C NMR (100 MHz, CD₂Cl₂, minor diastereoisomer):** δ 151.9 (C), 146.1 (C), 135.4 (C), 133.2 (C), 128.8 (2CH), 126.9 (C), 123.4 (2CH), 121.0 (CH), 119.6 (CH), 118.7 (CH), 110.9 (C), 110.6 (CH), 52.9 (CH), 48.7 (CH), 22.1 (CH₃), 12.1 (CH₃).

Methyl 4-amino-3-(2-methyl-1H-indol-3-yl)butanoate **56**



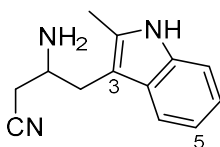
Chemical Formula: C₁₄H₁₈N₂O₂
Exact Mass: 246.1368

General Procedure **A** was followed with methyl but-3-enoate **1q** (33.0 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, 2-methylindole (197 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) afforded **56** (43.6 mg, 0.177 mmol, 59% yield, 3/5 >95/5) as a dark purple oil.

¹H NMR (400 MHz, CDCl₃): δ 8.22 (brs, 1H), 7.56 – 7.51 (m, 1H), 7.29 – 7.26 (m, 1H), 7.15 – 7.07 (m, 2H), 3.68 (s, 3H), 3.64 – 3.58 (m, 1H), 2.87 (dd, *J* = 14.2, 6.1 Hz, 1H), 2.77 (dd, *J* = 14.2, 7.9 Hz, 1H), 2.59 (dd, *J* = 16.1, 4.3 Hz, 1H), 2.42 (dd, *J* = 16.1, 8.7 Hz, 1H), 2.38 (s, 3H), 2.21 (brs, 2H). **¹³C NMR (100 MHz, CDCl₃):** δ 173.2 (C=O), 135.4 (C), 132.5 (C), 128.8 (C), 121.2

(CH), 119.4 (CH), 118.2 (CH), 110.4 (CH), 108.1 (C), 51.6 (CH₃), 49.2 (CH), 41.6 (CH₂), 32.3 (CH₂), 11.9 (CH₃). **HRMS (ESI):** m/z calcd. for C₁₄H₁₈N₂O₂ [M+H]⁺ 247.1441, found 247.1435.

4-Amino-3-(2-methyl-1H-indol-3-yl)butanenitrile **57**

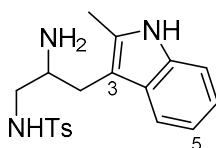


Chemical Formula: C₁₃H₁₅N₃
Exact Mass: 213.1266

General Procedure **A** was followed with but-3-enenitrile **1r** (20.1 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-methyl-1H-indole (197 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/ *i*-PrOH: 100/0 to 80/20) afforded **57** (33.7 mg, 0.16 mmol, 53% yield, 3/5 >95/5) as a dark purple oil.

¹H NMR (400 MHz, MeOD): δ 7.48 – 7.43 (m, 1H), 7.26 – 7.22 (m, 1H), 7.05 – 6.99 (m, 1H), 6.99 – 6.95 (m, 1H), 3.41 – 3.32 (m, 1H), 2.87 (dd, J = 7.0, 0.8 Hz, 2H), 2.53 (dd, J = 16.8, 5.3 Hz, 1H), 2.43 (dd, J = 16.8, 6.1 Hz, 1H), 2.40 (s, 3H), 3H unobserved. **¹³C NMR (100 MHz, MeOD):** δ 137.2 (C), 134.1 (C), 129.8 (C), 121.7 (CH), 119.8 (CH), 119.6 (C), 118.4 (CH), 111.5 (CH), 107.3 (C), 50.5 (CH), 32.2 (CH₂), 25.1 (CH₂), 11.6 (CH₃). **HRMS (ESI):** m/z calcd. for C₁₃H₁₆N₃ [M+H]⁺ 214.1339, found 214.1332.

N-(3-Amino-2-(2-methyl-1H-indol-3-yl)propyl)-4-methylbenzenesulfonamide **58**



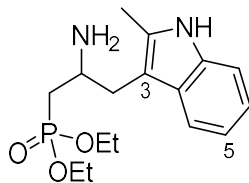
Chemical Formula: C₁₉H₂₃N₃O₂S
Exact Mass: 357.1511

General Procedure **A** was followed with *N*-allyl-4-methylbenzenesulfonamide **1s** (64.0 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, 2-methylindole (197 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-

PrOH: 100/0 to 80/20) afforded **58** (48.3 mg, 0.135 mmol, 45% yield, 3/5 >95/5) as a bright brown oil.

¹H NMR (400 MHz, CDCl₃): δ 8.04 (brs, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.33 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.25 – 7.21 (m, 3H), 7.09 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.02 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 3.46 – 2.43 (brs, 3H), 3.11 (ddt, *J* = 8.0, 5.4, 4.0 Hz, 1H), 3.06 – 3.01 (m, 1H), 2.80 – 2.70 (m, 2H), 2.59 (dd, *J* = 14.4, 8.2 Hz, 1H), 2.39 (s, 3H), 2.28 (s, 3H). **¹³C NMR (100 MHz, CDCl₃):** δ 143.4 (C), 136.8 (C), 135.4 (C), 132.6 (C), 129.8 (2CH), 128.7 (C), 127.1 (2CH), 121.2 (CH), 119.4 (CH), 117.9 (CH), 110.5 (CH), 107.4 (C), 51.4 (CH), 48.7 (CH₂), 30.5 (CH₂), 21.6 (CH₃), 11.9 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₉H₂₄N₃O₂S [M+H]⁺ 358.1584, found 358.1572.

Diethyl (3-amino-2-(2-methyl-1H-indol-3-yl)propyl)phosphonate 59

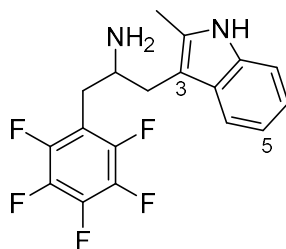


Chemical Formula: C₁₆H₂₅N₂O₃P
Exact Mass: 324.1603

General Procedure **A** was followed with diethyl allylphosphonate **1t** (53.5 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-methyl-1H-indole (197 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel previously neutralized by 5% Et₃N (DCM/*i*-PrOH: 100/0 to 80/20) afforded **59** (46.1 mg, 0.14 mmol, 47% yield, 76% yield brsm, 3/5: 95/5) as a dark purple oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.47 (brs, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.11 – 7.05 (m, 1H), 7.04 – 7.00 (m, 1H), 4.10 – 3.92 (m, 4H), 3.57 – 3.43 (m, 1H), 2.87 (dd, *J* = 14.2, 6.1 Hz, 1H), 2.78 (ddd, *J* = 14.2, 7.7, 2.2 Hz, 1H), 2.37 (s, 3H), 2.34 (brs, 2H), 2.02 – 1.93 (m, 1H), 1.88 – 1.77 (m, 1H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 135.8 (C), 133.2 (C), 129.2 (C), 121.2 (CH), 119.4 (CH), 118.3 (CH), 110.6 (CH), 108.2 (C), 62.1 (d, *J* = 6.5 Hz, CH₂), 62.0 (d, *J* = 6.4 Hz, CH₂), 48.3 (d, *J* = 4.3 Hz, CH), 34.0 (d, *J* = 10.4 Hz, CH₂), 33.2 (d, *J* = 131.8 Hz, CH₂), 16.6 (CH₃), 16.5 (CH₃), 12.0 (CH₃). **³¹P NMR (162 MHz, CD₂Cl₂):** 30.3. **HRMS (ESI):** *m/z* calcd. for C₁₆H₂₆N₂O₃P [M+H]⁺ 325.1676, found 325.1675.

2-(2-Methyl-1H-indol-3-yl)-3-(perfluorophenyl)propan-1-amine 60



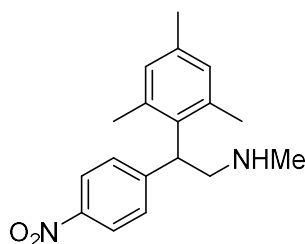
Chemical Formula: C₁₈H₁₅F₅N₂

Exact Mass: 354.1155

General Procedure **A** was followed with but-3-enenitrile **1u** (62.4 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-methyl-1H-indole (197 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/ *i*-PrOH: 100/0 to 85/15) afforded **60** (79.4 mg, 0.22 mmol, 75% yield, 3/5: 95/5) as a dark purple oil.

¹H NMR (500 MHz, CD₂Cl₂): δ 8.02 (brs, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.08 (m, 1H), 7.03 (m, 1H), 3.39 – 3.32 (m, 1H), 2.94 – 2.85 (m, 2H), 2.79 – 2.63 (m, 2H), 2.38 (s, 3H), 1.51 (brs, 2H). **¹³C NMR (126 MHz, CD₂Cl₂):** δ 145.7 (dm, *J* = 242.8 Hz, 2C), 139.9 (dm, *J* = 250.2 Hz, C), 137.7 (dm, *J* = 246.6 Hz, 2C), 135.7 (C), 132.9 (C), 129.1 (C), 121.3 (CH), 119.5 (CH), 118.2 (CH), 113.9 (td, *J* = 19.0, 4.2 Hz, C), 110.5 (CH), 108.5 (C), 52.6 (CH), 33.6 (CH₂), 31.0 (CH₂), 12.0 (CH₃). **¹⁹F NMR (471 MHz, CD₂Cl₂):** -143.2 (m), -158.7 (m), -164.0 (m). **HRMS (ESI):** *m/z* calcd. for C₁₈H₁₆N₂F₅ [M+H]⁺ 355.1228, found 355.1223.

2-Mesityl-N-methyl-2-(4-nitrophenyl)ethanamine 69



Chemical Formula: C₁₈H₂₂N₂O₂

Exact Mass: 298.1681

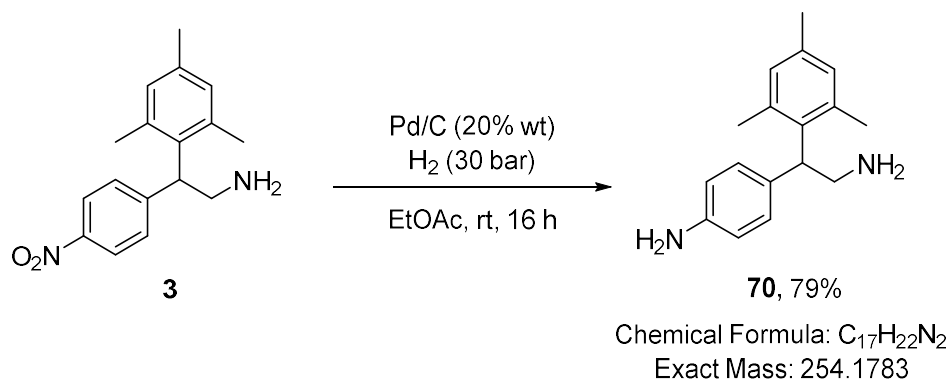
General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol) and [NsO-NH₂Me][OTf] (170 mg, 0.45 mmol, 1.5 equiv.) in HFIP (1.5 mL). The reaction mixture was stirred

at 60 °C for 6 h, then mesitylene (209 μ L, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/ *i*-PrOH: 100/0 to 90/10) afforded **69** (39.5 mg, 0.13 mmol, 44% yield) as a brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.09 (d, *J* = 8.9 Hz, 2H), 7.35 (dd, *J* = 8.9, 0.9 Hz, 2H), 6.85 (s, 2H), 4.73 (dd, *J* = 7.6, 7.2 Hz, 1H), 3.53 (dd, *J* = 11.6, 7.2 Hz, 1H), 3.21 (dd, *J* = 11.6, 7.6 Hz, 1H), 2.47 (s, 3H), 2.25 (s, 3H), 2.12 (brs, 6H), 1.69 (brs, 1H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 152.0 (C), 146.4 (C), 137.6 (2C), 137.0 (C), 135.8 (C), 130.7 (2CH), 128.6 (2CH), 123.6 (2CH), 54.0 (CH₂), 44.7 (CH), 36.9 (CH₃), 21.5 (2CH₃), 20.8 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₈H₂₃N₂O₂ [M+H]⁺ 299.1754, found 299.1744.

4. Derivatizations of aminoarylation compounds (Scheme 3)

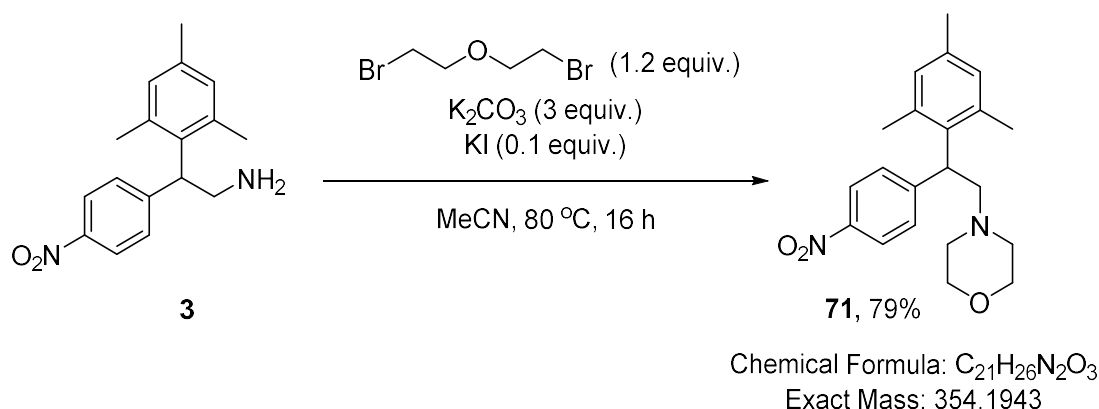
Reduction of **3** to aniline **70**



A glass vial (8 mL) with a Teflon-coated magnetic stir bar was charged with amine **3** (60 mg, 0.21 mmol), Pd/C (12 mg, 20% wt) and EtOAc (4 mL). The reaction mixture was placed under H₂ gas at 30 bar for 16 h. Then, the reaction mixture was filtered over a pad of celite (rinsed with DCM). The crude product purified by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20, gradient) to afford **70** (42.2 mg, 0.166 mmol, 79% yield) as a brown oil.

¹H NMR (400 MHz, CDCl₃): δ 6.89 (d, *J* = 8.6 Hz, 2H), 6.83 (s, 2H), 6.58 (d, *J* = 8.6 Hz, 2H), 4.47 (dd, *J* = 9.1, 6.7 Hz, 1H), 3.53 (dd, *J* = 12.5, 6.7 Hz, 1H), 3.27 (dd, *J* = 12.5, 9.1 Hz, 1H), 2.25 (s, 3H), 2.22 (brs, 4H), 2.18 (brs, 6H). **¹³C NMR (100 MHz, CDCl₃):** δ 144.9 (C), 137.8 (2C), 136.9 (C), 136.0 (C), 132.6 (C), 130.4 (2CH), 128.3 (2CH), 115.2 (2CH), 47.1 (CH), 43.8 (CH₂), 21.6 (2CH₃), 20.8 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₇H₂₃N₂ [M+H]⁺ 255.1856, found 255.1862.

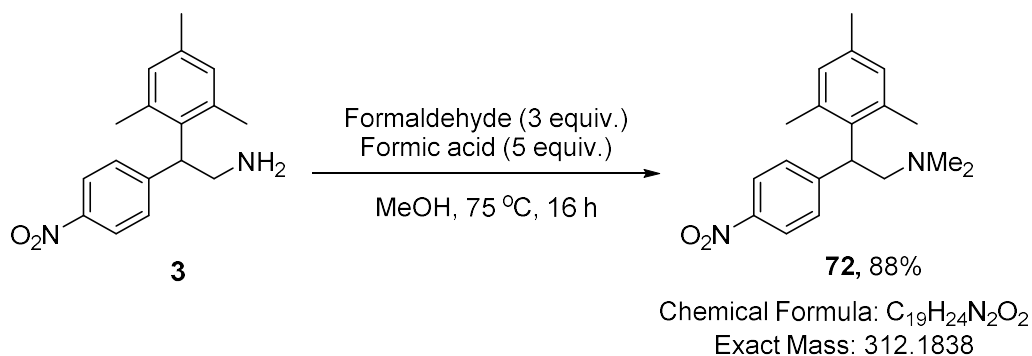
Cyclization of **3** to piperidine **71**



A 10 mL tube equipped with a Teflon-coated magnetic stir bar was charged with amine **3** (71 mg, 0.25 mmol, 1.0 equiv.), 2-bromoethyl ether (38 μ L, 0.30 mmol, 1.2 equiv.), potassium carbonate (104 mg, 0.75 mmol, 3 equiv.), potassium iodide (4.2 mg, 25 μ mol, 0.10 equiv.) and MeCN (0.85 mL). The reaction mixture was heated at 80 $^\circ$ C for 16 h. Upon completion, the reaction mixture was quenched with a solution of sat. NaHCO₃ (10 mL) and then extracted with DCM (10 mL $\times$ 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude mixture was purified by FC over silica gel (DCM/*i*-PrOH, 100/0 to 90/10, gradient) to furnish **71** (70.0 mg, 0.198 mmol, 79% yield) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.09 (d, *J* = 8.9 Hz, 2H), 7.50 (d, *J* = 8.9 Hz, 2H), 6.86 (s, 2H), 4.75 (dd, *J* = 9.7, 3.8 Hz, 1H), 3.70 (qdd, *J* = 11.2, 6.0, 3.2 Hz, 4H), 3.44 (dd, *J* = 13.0, 9.7 Hz, 1H), 2.68 – 1.73 (m, 14H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 152.8 (C), 146.3 (2C), 137.0 (C), 136.8 (C), 130.6 (2CH), 129.2 (2CH), 123.4 (2CH), 67.4 (2CH₂), 54.4 (CH₂), 41.6 (CH), 21.5 (2CH₃), 20.8 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₂₁H₂₇N₂O₃ [M+H]⁺ 355.2016, found 355.2003.

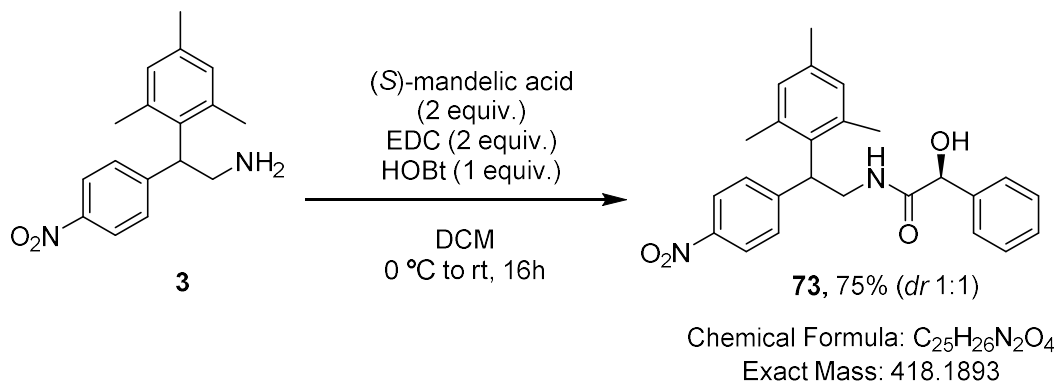
Eschweiler-Clarke methylation of **3**



A 10 mL tube equipped with a Teflon-coated magnetic stir bar was charged with amine **3** (71 mg, 0.25 mmol, 1.0 equiv.), formic acid (48 μ L, 1.25 mmol, 5.0 equiv.), formaldehyde 37% w/w in H₂O (60 μ L, 0.75 mmol, 3.0 equiv.) and MeOH (0.60 mL). The reaction mixture was heated at 75 °C for 16 h. Upon completion, the reaction mixture was quenched with a solution of sat. NaHCO₃ (10 mL) and then extracted with DCM (10 mL $\times$ 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude mixture was purified by FC over silica gel (DCM/*i*-PrOH, 100/0 to 90/10, gradient) to furnish **72** (70.0 mg, 0.22 mmol, 88% yield) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.08 (d, J = 8.9 Hz, 2H), 7.47 (d, J = 8.9 Hz, 2H), 6.86 (s, 2H), 4.68 (dd, J = 9.8, 4.1 Hz, 1H), 3.42 (dd, J = 12.9, 9.8 Hz, 1H), 2.49 (dd, J = 12.9, 4.1 Hz, 1H), 2.34 (s, 6H), 2.26 (s, 3H), 2.05 (brs, 6H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 152.8 (C), 146.3 (2C), 137.1 (C), 137.0 (C), 136.7 (C), 130.7 (2CH), 129.2 (2CH), 123.4 (2CH), 63.1 (CH₂), 45.9 (2CH₃), 42.8 (CH), 21.5 (2CH₃), 20.8 (CH₃). **HRMS (ESI):** m/z calcd. for C₁₉H₂₅N₂O₂ [M+H]⁺ 313.1911, found 313.1901.

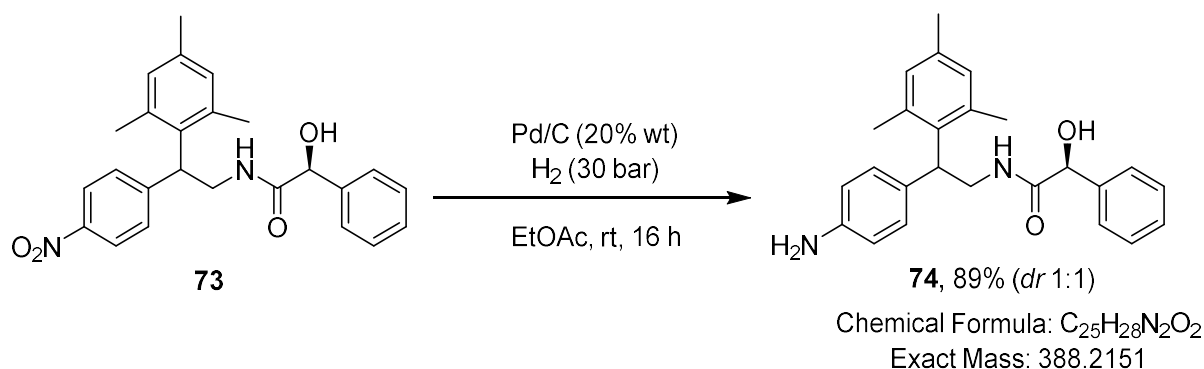
Amide coupling of **3** with (S)-mandelic acid



To a solution of amine **3** (71 mg, 0.25 mmol, 1.0 equiv.) and (S)-mandelic acid (50 mg, 0.50 mmol, 2.0 equiv.) in DCM (4 mL) was added Et₃N (70 μ L, 0.50 mmol, 2.0 equiv.) followed by EDC (120 mg, 0.50 mmol, 2.0 equiv.) and HOBT (45 mg, 0.25 mmol, 1.0 equiv.) at 0 $^{\circ}$ C. The reaction mixture was stirred for 1 h at 0 $^{\circ}$ C and then, overnight at room temperature. The solvent was evaporated under reduced pressure and EtOAc (20 mL) was added. The organic layer was washed consecutively with a solution of HCl (1 N), a solution of sat. NaHCO₃ (20 mL), and brine (20 mL), dried over Na₂SO₄ and evaporated under reduced pressure. The crude mixture was purified by FC over silica gel (pentane/EtOAc, 100/0 to 60/40, gradient) to furnish **73** (78.5 mg, 0.188 mmol, 75% yield, *dr* 1:1) as a yellow solid.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.99 (d, *J* = 8.9 Hz, 2H), 7.96 (d, *J* = 8.9 Hz, 2H), 7.21 – 7.15 (m, 14H), 6.75 (s, 2H), 6.71 (s, 2H), 6.26 – 6.25 (m, 1H), 6.07 – 6.04 (m, 1H), 4.81 (s, 1H), 4.78 (s, 1H), 4.68 – 4.61 (m, 2H), 4.36 – 4.27 (m, 2H), 3.69 – 3.49 (m, 4H), 2.18 (s, 3H), 2.17 (s, 3H), 1.91 (brs, 12H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 172.4, 172.3, 150.2, 146.6, 146.5, 139.8 (2C), 137.6, 137.4, 137.3, 134.1, 133.8, 130.8, 129.1, 129.0, 128.9, 128.8, 128.2, 127.0, 126.9, 123.9, 123.8, 74.5, 74.4, 44.0, 43.8, 40.6, 40.5, 21.3, 20.9. **HRMS (ESI):** *m/z* calcd. for C₂₅H₂₆N₂O₄Na [M+Na]⁺ 441.1785, found 441.1770.

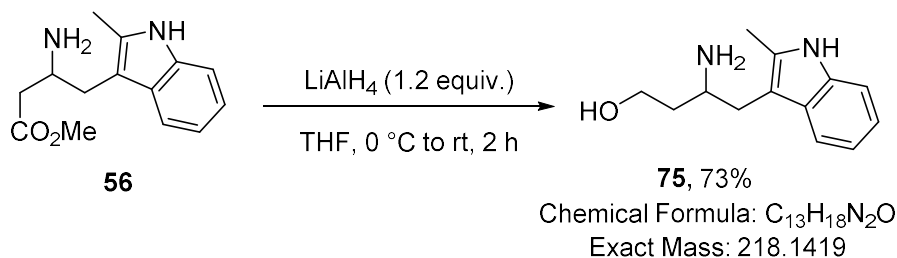
Reduction of **73** to **74**



A glass vial with a Teflon-coated magnetic stir bar was charged with amide **73** (78.5 mg, 0.188 mmol), Pd/C (15.7 mg, 20% wt) and EtOAc (4 mL). The reaction mixture was placed under H_2 gas at 30 bar for 16 h. Then, the reaction mixture was filtered over a pad of celite (rinsed with DCM). Then, the crude product was purified by FC over silica gel (DCM/*i*-PrOH: 100/0 to 80/20) to afford **74** (64.8 mg, 0.167 mmol, 89% yield, *dr* 1:1) as a brown oil.

^1H NMR (400 MHz, CD_2Cl_2): δ 7.30 – 7.25 (m, 6H), 7.20 – 7.17 (m, 2H), 7.13 – 7.11 (m, 2H), 6.84 – 6.78 (m, 8H), 6.57 – 6.53 (m, 4H), 6.28 – 6.25 (m, 1H), 6.12– 6.09 (m, 1H), 4.83 (s, 1H), 4.81 (s, 1H), 4.59 – 4.51 (m, 2H), 4.37 – 4.14 (m, 2H), 3.90 – 3.55 (m, 8H), 2.27 (s, 3H), 2.26 (s, 3H), 2.05 (brs, 6H), 2.02 (brs, 6H). **^{13}C NMR (100 MHz, CD_2Cl_2):** δ 172.3, 172.2, 145.0 (2C), 140.1, 140.0, 137.7, 137.6, 136.4, 135.6, 135.4, 131.5, 131.4, 130.6 (br), 129.0, 128.9, 128.7, 128.6, 128.1, 128.0, 127.0, 126.9, 115.3, 74.4, 74.3, 42.9, 42.8, 41.0, 40.8, 21.3, 21.2, 20.9. **HRMS (ESI):** m/z calcd. for $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 389.2224, found 389.2210.

Reduction of ester **56**

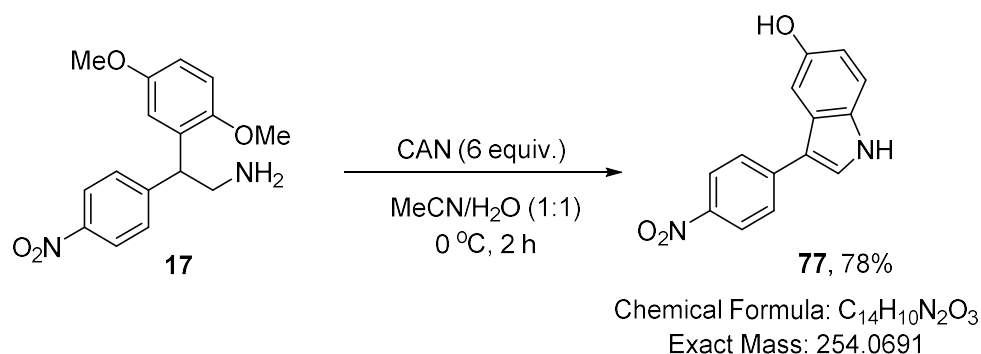


To a solution of ester **56** (39 mg, 0.158 mmol, 1.0 equiv.) in dry THF (1.0 mL) was added in one portion LiAlH_4 (8.0 mg, 0.19 mmol, 1.2 equiv.) at 0 °C under Ar atmosphere. The reaction mixture was stirred for 30 min at 0 °C, and then for 2 hours at rt. The mixture was carefully quenched with

H₂O (10 mL). The aqueous layer was extracted with DCM (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, and concentrated under reduced pressure. Purification by FC over silica gel (DCM/MeOH: 100/0 to 30/70) afforded **75** (25.0 mg, 0.12 mmol, 72% yield) as a colorless oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.05 (brs, 1H), 7.48 – 7.42 (m, 1H), 7.30 – 7.26 (m, 1H), 7.11 – 7.06 (m, 1H), 7.05 – 7.01 (m, 1H), 3.83 – 3.70 (m, 2H), 3.30 – 3.14 (m, 1H), 2.83 (dd, *J* = 14.2, 5.6 Hz, 1H), 2.68 (dd, *J* = 14.2, 8.0 Hz, 1H), 2.39 (s, 3H), 1.78 – 1.71 (m, 1H), 1.61 (brs, 3H), 1.59 – 1.49 (m, 1H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 135.8 (C), 132.7 (C), 129.3 (C), 121.3 (CH), 119.5 (CH), 118.3 (CH), 110.6 (CH), 108.8 (C), 63.2 (CH₂), 54.4 (CH), 37.9 (CH₂), 35.2 (CH₂), 12.1 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₃H₁₉N₂O [M+H]⁺ 219.1492, found 219.1485.

Oxidation of dimethoxybenzene **17** to **77**



Under air, a 10 mL tube equipped with a Teflon-coated magnetic stir bar was charged with amine **17** (35.0 mg, 0.12 mmol, 1.0 equiv.), MeCN (2.0 mL) and H₂O (2.0 mL). The mixture was cooled down to 0 °C in an ice bath. Then, ceric ammonium nitrate (350 mg, 0.72 mmol, 6.0 equiv.) was added and the reaction was stirred at 0 °C for 2 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (3 × 10 mL), dried over Na₂SO₄, and concentrated under reduced pressure to furnish **77** (24 mg, 94 μmol, 78% yield) as an orange solid.

¹H NMR (400 MHz, acetone-*d*₆): δ 10.65 (brs, 1H), 8.28 (d, *J* = 9.0 Hz, 2H), 7.94 (d, *J* = 9.0 Hz, 2H), 7.93 (s, 1H), 7.87 (d, *J* = 2.5 Hz, 1H), 7.44 – 7.34 (m, 2H), 6.83 (dd, *J* = 8.7, 2.5 Hz, 1H). **¹³C NMR (100 MHz, acetone-*d*₆):** δ 153.3 (C), 145.6 (C), 144.8 (C), 133.1 (C), 127.0 (2CH), 126.9 (CH), 126.8 (C), 124.9 (2CH), 115.0 (C), 113.6 (CH), 113.3 (CH), 104.3 (CH). **HRMS (ESI):** *m/z* calcd. for C₁₄H₁₀N₂O₃Na [M+Na]⁺ 277.0584, found 277.0579.

Chapter 2: Iron(II)-Catalyzed 1,2-Diamination of Styrenes Installing a Terminal -NH₂ Group Alongside Unprotected Amines

Introduction

Recent Advances in the Synthesis of 1,2-Vicinal Diamines

The vicinal diamine motif is present in several marketed pharmaceuticals and popular catalysts (Figure 1). To date, the most common methods to access this scaffold rely on classical ionic reactions, including radical coupling of aldimines and ketimines, hydroamination of allyl amines and enamines, ring-opening of aziridines, C–H amination among others. In most cases, the first nitrogen must already be present in the starting material, which requires additional synthetic steps for the construction of 1,2-diamine scaffolds. The rich arsenal of modern radical organic chemistry, and particularly recent developments in the field of N-centered radicals, has paved the way for the construction of 1,2-diamines in one step starting from simple feedstocks such as alkenes, which are byproducts of the petrochemical industry. The direct diamination of olefins is more atom-economic and environmentally friendlier due to the reduced use of solvents and reactants. This introduction will cover recent advances in the synthesis of 1,2-vicinal diamines via the intermolecular diamination of alkenes, in which the two installed nitrogen moieties are not covalently linked to each other. Here, the aim of this part is not to give an exhaustive account but rather an overview of strategies, while discussing the key features of these reaction designs with their strengths and limitations.

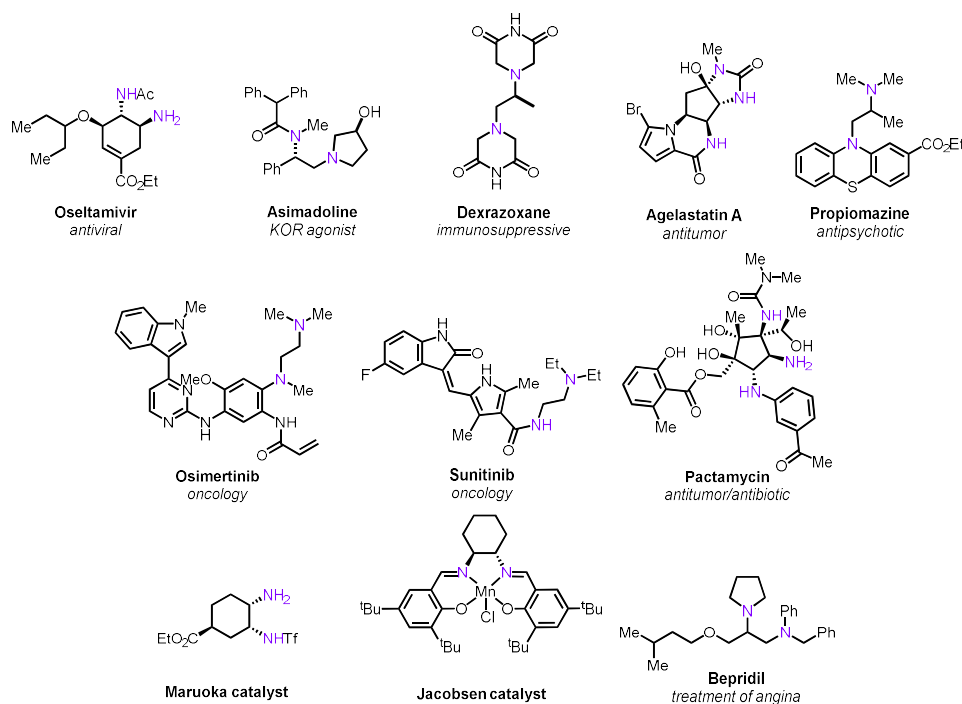


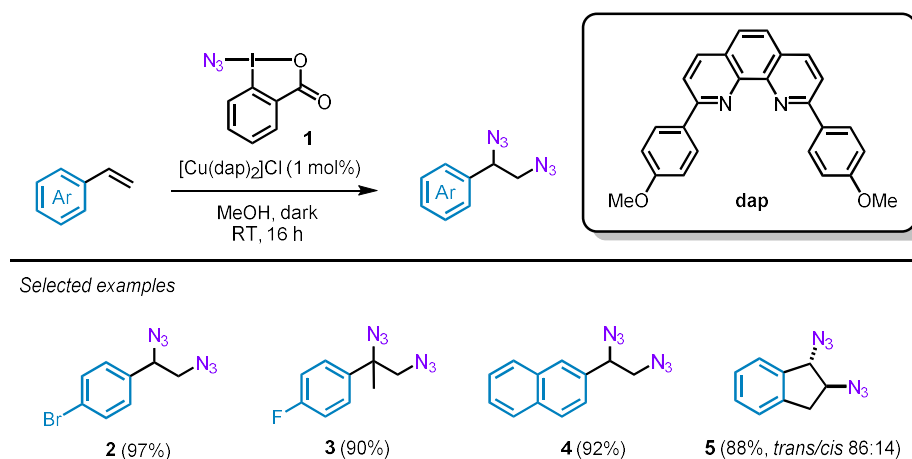
Figure 1. Selected examples of bioactive molecules and catalysts incorporating 1,2-vicinal diamines

Diazidation of alkenes

Diazidation of alkenes is a convenient way of constructing 1,2-vicinal diamines by masking the amine functionality. It presents the advantage of preventing the poisoning of many metal-based catalytic systems since unprotected aliphatic amines are strong coordinating ligands. The installed azido groups can be used to connect the molecule with a different molecular fragment bearing an alkynyl group via copper (I)-catalyzed azide-alkyne cycloaddition or to be directly reduced to NH₂ groups via hydrogenation or Staudinger reaction. On the other hand, incorporating two identical functions may represent a challenge for further functionalizations, because of the difficult control of chemoselectivity. Moreover, the use of hazardous azide sources in combination with transition metals raises serious safety issues for a potential scale-up, which, in turn, drastically reduces the attractiveness of this route towards 1,2-vicinal diamines.

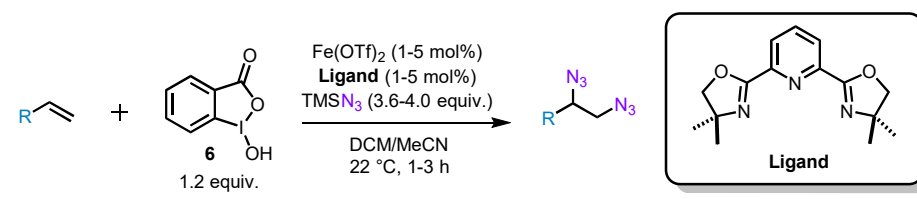
Due to the recent growing interest in radical chemistry coupled with transition metal catalysis, manifold mild and general methodologies have been recently reported. Most of these reactions proceed via the formation of azidyl radicals followed by their addition across the double bond – a general reactivity pattern discussed in Chapter 1. First-row transition metals were identified as effective catalysts since they readily engage in one-electron processes. The role of transition metals often consists in the initial coordination of azides to the metal followed by one-electron inner sphere oxidation which generates the reactive species.

In 2015, the group of Greaney reported a mild diazidation method relying on Zhdankin reagent **1** as a source of azide in the presence of copper complex [Cu(dap)₂]Cl (dap = 2,9- bis(*p*-anisyl)-1,10-phenanthroline) as a catalyst (Scheme 1).^[1] The copper complex is thought to reduce the hypervalent iodine reagent by forming the azidyl radical which would then undergo addition to the double bond. In the presence of light, the resulting benzyl radical is thought to be oxidized into benzyl cation, which immediately combines with the solvent molecule to afford the corresponding 1,2-azido methoxide product. When the reaction is carried out in the dark, the benzyl radical is long-lived enough to react with a second azidyl radical to form the 1,2-diazide. The reaction is inhibited in the presence of TEMPO or oxygen which hints at the involvement of a radical pathway. Although the scope of the diazidation was not extensively explored, halide-substituted styrenes, 2-vinylnaphtalene and indene reacted smoothly to deliver diazidation products **2-5** in high yields.

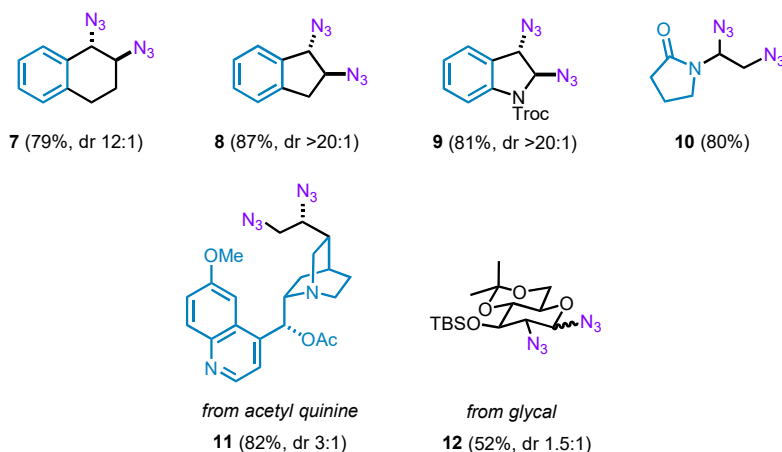


Scheme 1. Cu-catalyzed diazidation of styrenes with Zhdankin reagent.

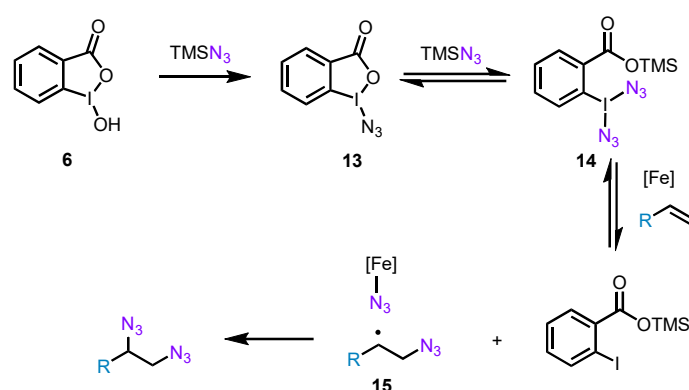
A conceptually similar system based on Fe catalysis was developed by the group of Xu (Scheme 2).^[2] Compared to the prior art, the new catalytic system enables diazidation of a broad range of alkenes in a diastereoselective fashion that go beyond styrenyl derivatives. The reaction design was based on a combination of $\text{Fe}(\text{OTf})_2$ with azidoiodinane **13** as an azido group transfer reagent, bis(oxazonilyl)pyridine ligand serving to control the diastereoselectivity of the process. During the initial screening studies, the authors noticed that **13** could be replaced by a safer bench-stable benziodoxole **6**, suggesting that **13** can be transiently formed during the reaction. A series of control mechanistic experiments revealed that azidation does not take place in the absence of TMSN_3 , ruling out the intermediacy of **13** during the azidation step. Carrying out the reaction in the presence of TEMPO allowed the trapping of **15**, thereby supporting the radical pathway. Based on the gathered data, the authors proposed a mechanism involving the conversion of benziodoxole **6** into azidoiodinane **13** by TMSN_3 followed by its transformation into intermediate **14**. **14** is suggested to serve as a source of azidyl radicals similarly to the Zhdankin reagent. The iron-azido complex is supposed to be involved in the second azidation to induce diastereoselectivity.



Selected examples



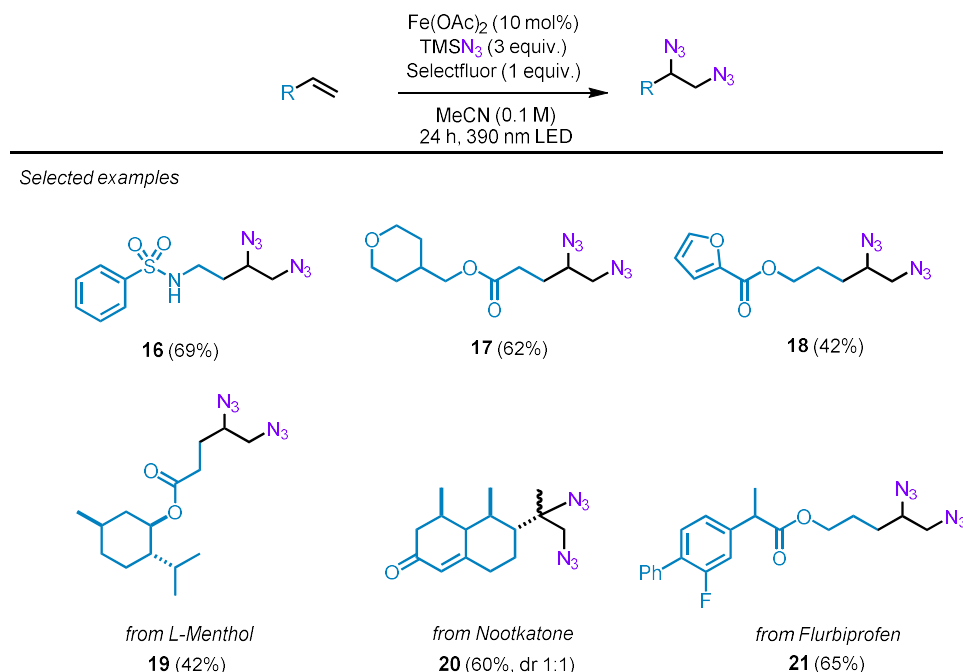
Proposed mechanism



Scheme 2. Fe-catalyzed diazidation of olefins.

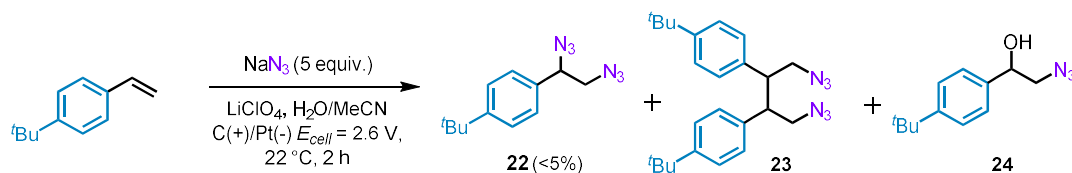
A photocatalytic modification of Fe-catalyzed diazidation was recently reported by West and co-workers (Scheme 3).^[3] The new reaction protocol enabled diazidation of a wide array of drug or natural product derivatives. Upon irradiation with light, the ligand to metal charge transfer in the $[\text{Fe}^{\text{III}}]\text{-N}_3$ complex affords a free azidyl radical and reduces Fe^{III} . Control experiments with radical clocks along with the absence of reactivity in the dark corroborate the radical pathway. Selectfluor is suggested to serve as a terminal oxidant to regenerate $[\text{Fe}^{\text{III}}]\text{-N}_3$ species from $[\text{Fe}^{\text{II}}]$. The major strength of the catalytic system lies in its three-facet reactivity depending on the nature of the added nucleophile. By replacing TMSN_3 with NaCl , dichlorination of alkenes was achieved, while

increasing the amount of Selectfluor to 1.7 equivalents afforded fluorochlorination products. The fluorination presumably occurred through the halogen atom transfer step between the C-centered radical intermediate and Selectfluor.



Scheme 3. Photocatalytic Fe-catalyzed diazidation of olefins.

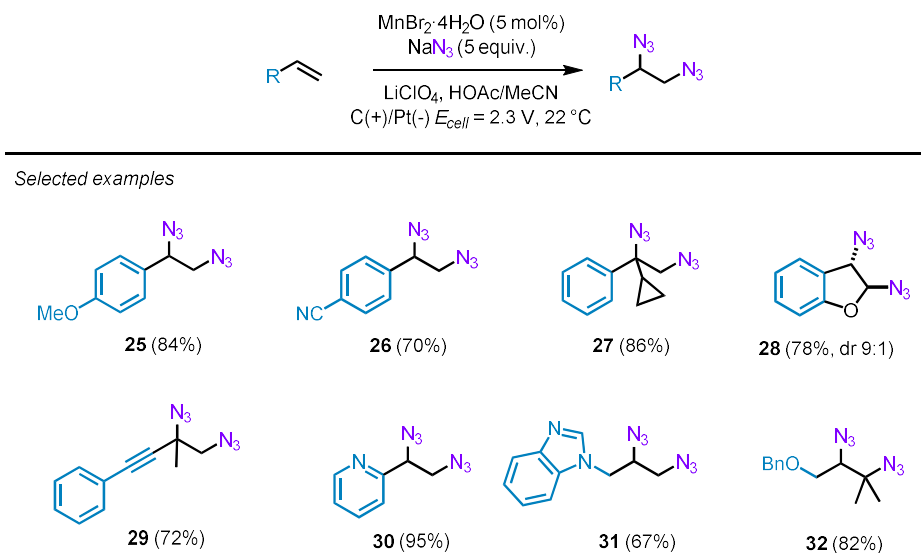
Another remarkable method for the direct diazidation of alkenes employing Mn catalysis coupled with electrochemistry was recently disclosed by the group of Lin (Scheme 4).^[4] At the outset, they sought to achieve diazidation via the direct oxidation of an azide anion to form an azidyl radical (Equation 1). However, only a few percent of diazidation product **22** were obtained, the remaining products coming from side reactions such as radical recombination (**23**) or addition of water (**24**).



Equation 1. Proof-of-concept for the electrochemical diazidation of alkenes.

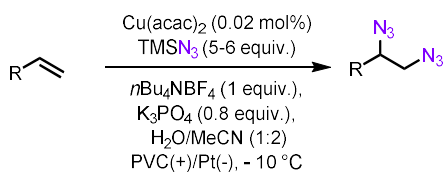
The subsequent screening of metal salts revealed the high catalytic activity of MnBr₂ and the significant improvement of yields with respect to diazidation products. The reaction protocol displayed remarkable compatibility with various substitution patterns, including coordinating N-heterocycles (**30** and **31**) as well as alkynes (**29**). Functional groups such as thioether or aldehyde

that are sensitive to oxidation were tolerated as well. Control experiments with radical clocks and carbocation traps clearly support the radical pathway with the participation of a putative $[\text{Mn}^{\text{III}}]\text{-N}_3$ complex as an azide transfer agent.

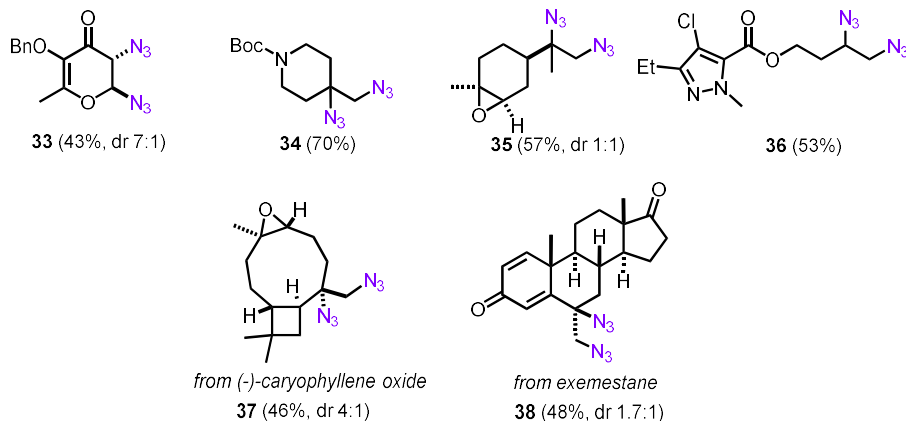


Scheme 4. Mn-catalyzed electrochemical diazidation of alkenes.

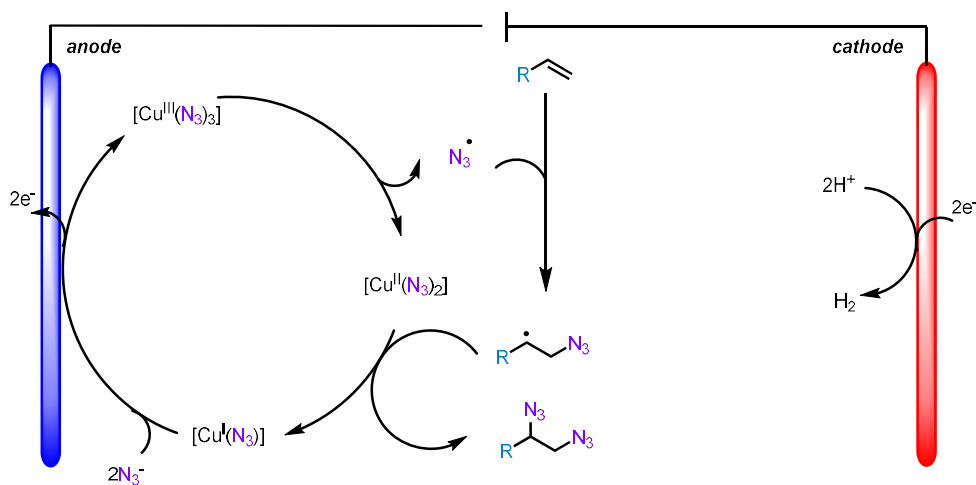
An alternative Cu-catalyzed electrochemical protocol for the diazidation of alkenes was later developed by the group of Xu (Scheme 5).^[5] The major improvement of the new protocol when compared to the previous work from the Lin group is a far lower catalyst loading (200 ppm). The protocol displayed excellent compatibility with biologically relevant frameworks and enabled diazidation of natural products (**37** and **38**) in moderate yields. Cyclic voltammetry experiments revealed that $[\text{Cu}]\text{-N}_3$ species - formed upon mixing $\text{Cu}(\text{acac})_2$ and TMSN_3 - are oxidized at lower potentials than N_3^- or TMSN_3 , which points to their potential involvement in the azidation process. Interestingly, the intensity of the irreversible wave of the $[\text{Cu}^{\text{II}}]\text{-N}_3/[\text{Cu}^{\text{III}}]\text{-N}_3$ redox couple does not change in the presence of the alkene. This result renders the direct addition of the azide ligand from the $[\text{Cu}^{\text{III}}]\text{-N}_3$ complex to the alkene unlikely. Additionally, the reaction did not take place in the absence of electricity, which argues against the participation of $[\text{Cu}^{\text{II}}]\text{-N}_3$ in the azide transfer. Considering the abovementioned results, the reaction mechanism likely involves the release of free azidyl radicals from the $[\text{Cu}^{\text{III}}]\text{-N}_3$ complex, which then adds to the alkene. However, the authors highlighted that the direct generation of a small quantity of azidyl radicals through electrochemical oxidation of the azide anions cannot be completely ruled out.



Selected examples



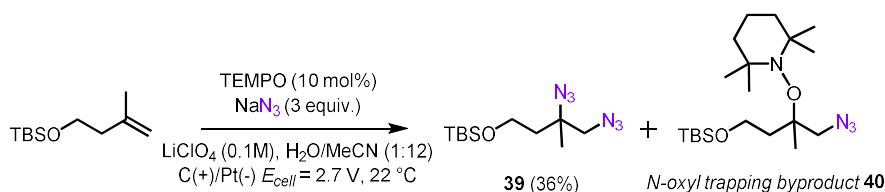
Proposed mechanism



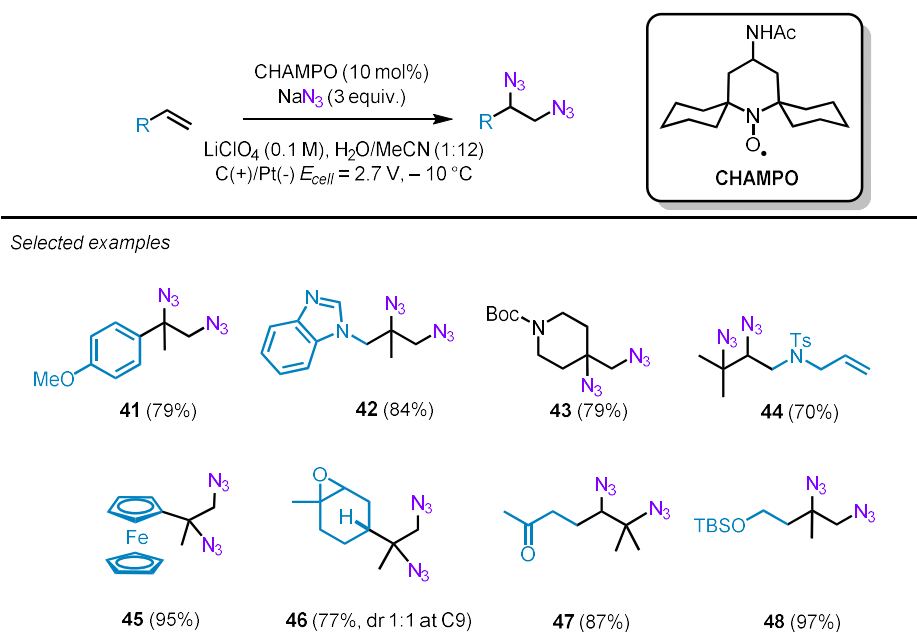
Scheme 5. Cu-catalyzed electrochemical diazidation of alkenes.

When searching for ways to reduce safety hazards of metal-catalyzed diazidations, the Lin group hypothesized that *N*-oxyls such as TEMPO could form a TEMPO- N_3 species serving as an azide transfer agent akin to metal-azide complexes (Scheme 6).^[6] Initial tests were promising, yielding the corresponding diazidation product **39** along with the *N*-oxyl trapping product **40** (Equation 2). This irreversible *N*-oxyl trapping consumes TEMPO and halts the catalytic turnover. To overcome this issue, a new *N*-oxyl CHAMPO was synthesized. Sterically demanding groups around nitrogen prevented the trapping by CHAMPO and enabled the efficient catalytic turnover to deliver **39** in

97% yield. Mechanistic investigations corroborate the radical mechanism. Similarly to the Cu-catalyzed example discussed above, the first azidation is suggested to take place between a free azidyl radical that was slowly released by CHAMPO- N_3 and an alkene, followed by the fast second azidation mediated by CHAMPO- N_3 via direct ligand transfer akin to $[\text{Cu}^{\text{II}}]\text{-N}_3$. Nevertheless, the major strength of the method- avoiding the use of transition metal salts - is counterbalanced by the cost associated with the synthesis of a custom catalyst, CHAMPO, which may limit the usefulness of the protocol for industrial applications.



Equation 2. Proof-of-concept for the TEMPO-catalyzed electrochemical diazidation of alkenes.



Scheme 6. Aminoxyl-catalyzed electrochemical diazidation of alkenes.

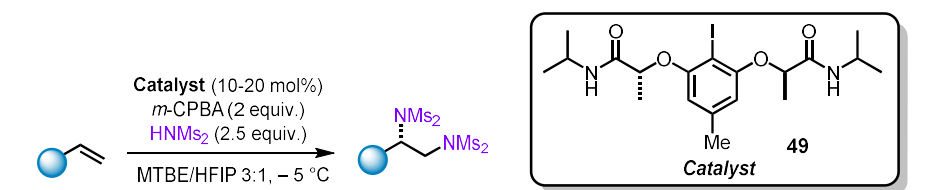
Although diazidation is a convenient route towards 1,2-vicinal diamines, several shortcomings hinder the application of these methodologies beyond the small laboratory scale. Almost all the above-presented methodologies employ transition metals, which bears the risk of formation of explosive metal azides, a serious risk to keep in mind when considering a potential scale-up. Moreover, superstoichiometric quantities of azide sources are required in all cases which brings risks and hazards related to their handling. Among positive aspects worth highlighting are mild

reaction conditions and the efficiency of these processes in “green” solvents such as methanol and acetonitrile. The development of cheaper organocatalyst alternatives and safer azide sources would reinforce the strengths of this synthetic route and increase its attractiveness for accessing 1,2-vicinal diamines outside the academic community.

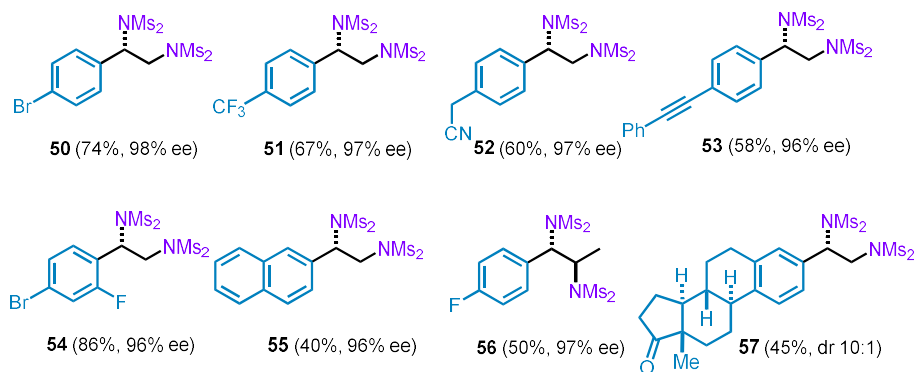
Diamination of alkenes to protected 1,2-vicinal diamines

A plethora of modern diaminations of alkenes do not unequivocally fall into a specific category. Selected examples that highlight recent advances will be briefly discussed in this section. The common feature of these transformations is the use of less conventional catalysts or reagents and the introduction of protected amino groups, notably sulfonamides that can be challenging to remove chemoselectively. These drawbacks might decrease their synthetic utility in real-life applications, yet the employed strategies can still serve as a source of inspiration for the conceptual development of new diamination methods.

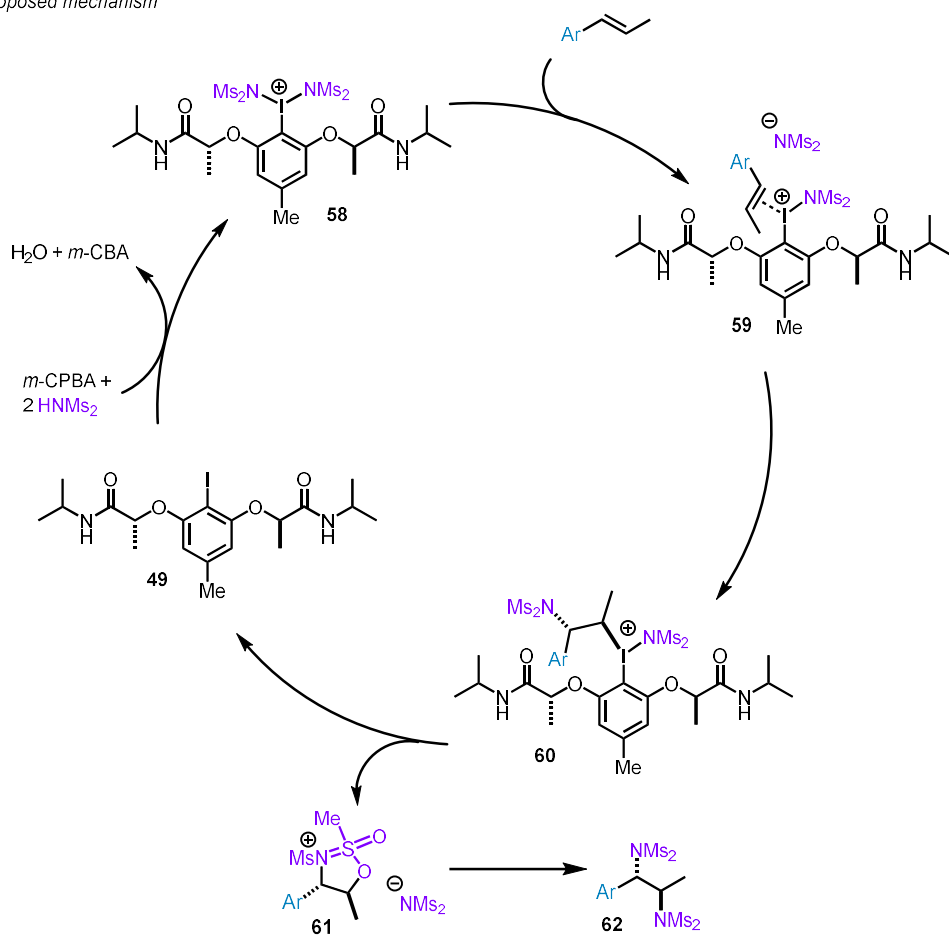
In 2017, the group of Muñiz reported a stereoselective diamination of styrenes catalyzed by a chiral aryl iodide catalyst (Scheme 7).^[7] The new protocol afforded diamination products with excellent enantiomeric ratios and introduced amino groups as bissulfonimides. An interesting observation was made in the case of an internal styrene, as final product **56** contained amino groups in an *anti* configuration. Regarding the mechanism, catalyst **49** is suggested to undergo oxidation with *m*-CPBA and to react with two equivalents of bismesyylimide to form **58**. The incoming alkene is then coordinated to **59** and activated towards 1,4-conjugate addition of bismesyylimide anion. The chiral environment around the iodide enables the differentiation of two sides of the alkene and favors the addition of bismesyylimide anion from one face. The observed *anti* relationship with internal styrenes might be explained by the formation of cyclic product **61**, which is then stereospecifically opened by another molecule of bismesyylimide anion to afford the final product. The overall catalytic activity is achieved through the cycle of the I(I)/I(III) redox couple.



Selected examples

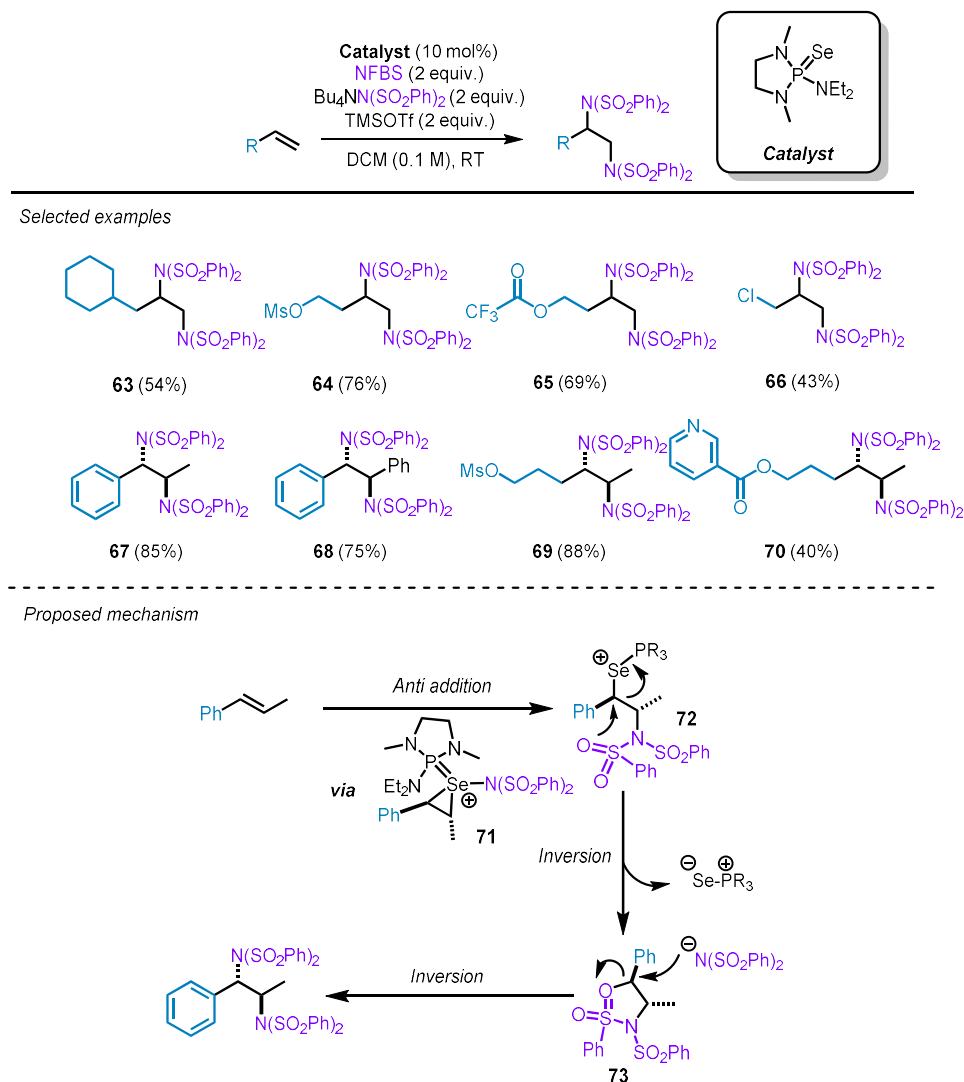


Proposed mechanism



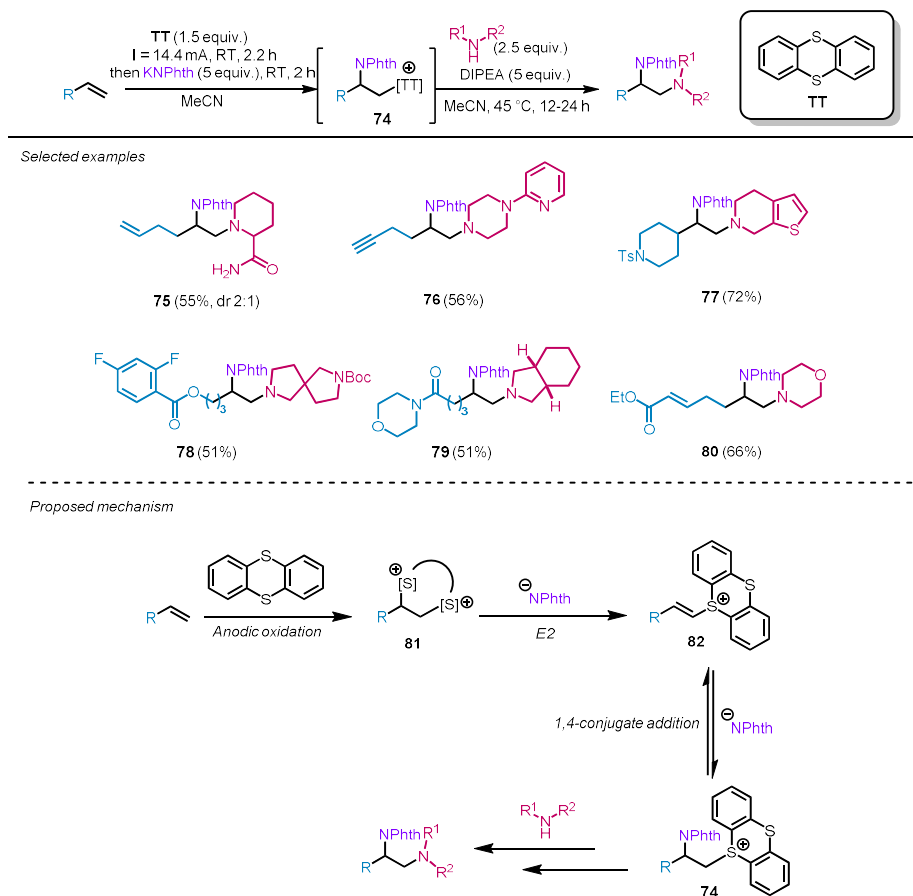
Scheme 7. Asymmetric diamination of styrenes catalyzed by chiral aryliodide **49**.

A different approach to tackling diamination was recently reported by the group of Michael which relies on a new selenophosphoramidate catalyst to introduce sequentially two bisulfonimide groups across the double bond (Scheme 8).^[8] A wide array of aliphatic alkenes was converted into corresponding 1,2-diamines in yields ranging from 40 to 93%. Unexpectedly, internal (*E*)-alkenes delivered exclusively diamines in *anti* configuration **67-70**. Although the reaction mechanism was not studied in detail, the initial addition of the first bisulfonimide moiety is suggested to proceed via seleniranium intermediate **71**. The origin of the *anti* configuration might be explained by the double inversion of stereochemistry upon the expulsion of the selenium organocatalyst by the bisulfonimide group in intermediate **72** followed by a stereospecific ring-opening by another bisulfonimide anion in **73**.



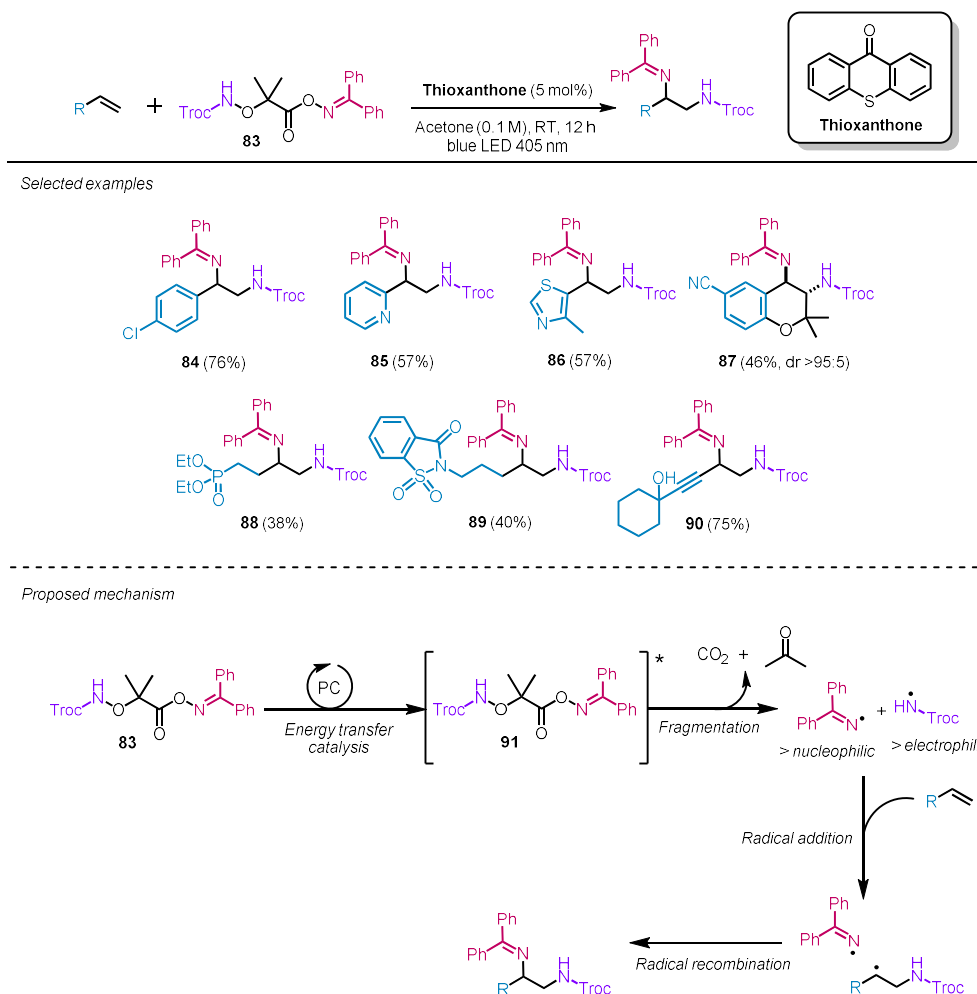
Scheme 8. Selenophosphoramidate-catalyzed diamination of alkenes.

An unusual strategy based on the synthesis of a dielectrophilic intermediate was reported by the group of Wickens in 2023 (Scheme 9).^[9] This new protocol displayed remarkable efficiency and enabled 1,2-diamination of a broad range of aliphatic alkenes, while introducing various medicinally relevant amines with complete control of the regioselectivity. The overall concept relies on the initial electrochemical oxidation of thianthrene followed by its addition to the alkene to form a bridged dicationic strongly electrophilic intermediate **81**. Upon the addition of potassium phthalimide, intermediate **81** undergoes an E2 reaction to afford **82**, which is an excellent Michael acceptor. The second phthalimide anion adds to **82** via 1,4-conjugate addition to afford **74**, which is a bench-stable crystalline solid. If an amine nucleophile is added to the reaction mixture, thianthrenium is substituted by the amine via S_N2 pathway to deliver the corresponding 1,2-vicinal diamine. Due to the formation of a transient Michael acceptor, this approach offers complete control over the regioselectivity of diamination and is advantageous over methods going through aziridinium intermediate. However, one of the amino groups is still incorporated under its protected form, albeit easier to remove compared to sulfonamides.



Scheme 9. Regiospecific diamination of alkenes via an electrogenerated dielectrophile **81**.

The group of Glorius has recently disclosed an elegant approach for 1,2-diamination of alkenes enabled by energy transfer to activate radical precursor **83** (Scheme 10).^[10] Combined electrochemical, spectroscopic, and computational investigations showed that the direct SET event between the excited state of the photocatalyst and reagent **83** cannot take place. Triplet-to-triplet energy transfer is suggested to occur, which leads to the fragmentation of the precursor from an excited state (**91**) to generate amidyl and iminyl radicals. If two different N-centered radicals are simultaneously generated, one may wonder which of them is more reactive. The control over the regioselectivity of radical addition is achieved due to different “philicities” of those radicals. Being more electrophilic, the amidyl radical first reacts with the alkene with the expected anti-Markovnikov selectivity. The more nucleophilic iminyl radical recombines with the C-centered radical to afford the diamination product. Both protecting groups on amines are orthogonal, which is useful for further functionalizations.

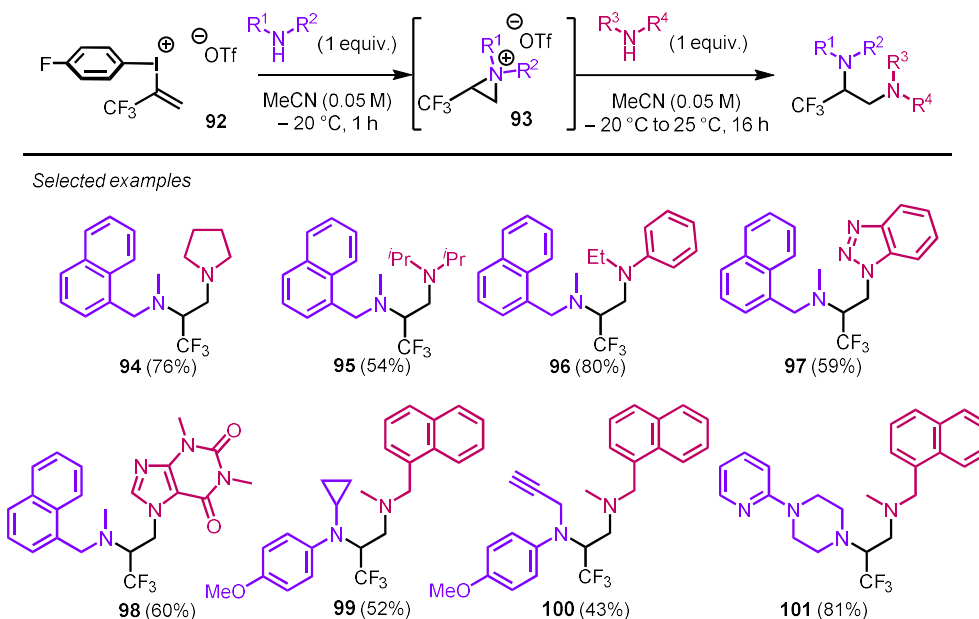


Scheme 10. Energy transfer-enabled unsymmetrical diamination using bifunctional N-radical precursors.

Diamination via the aziridine intermediate

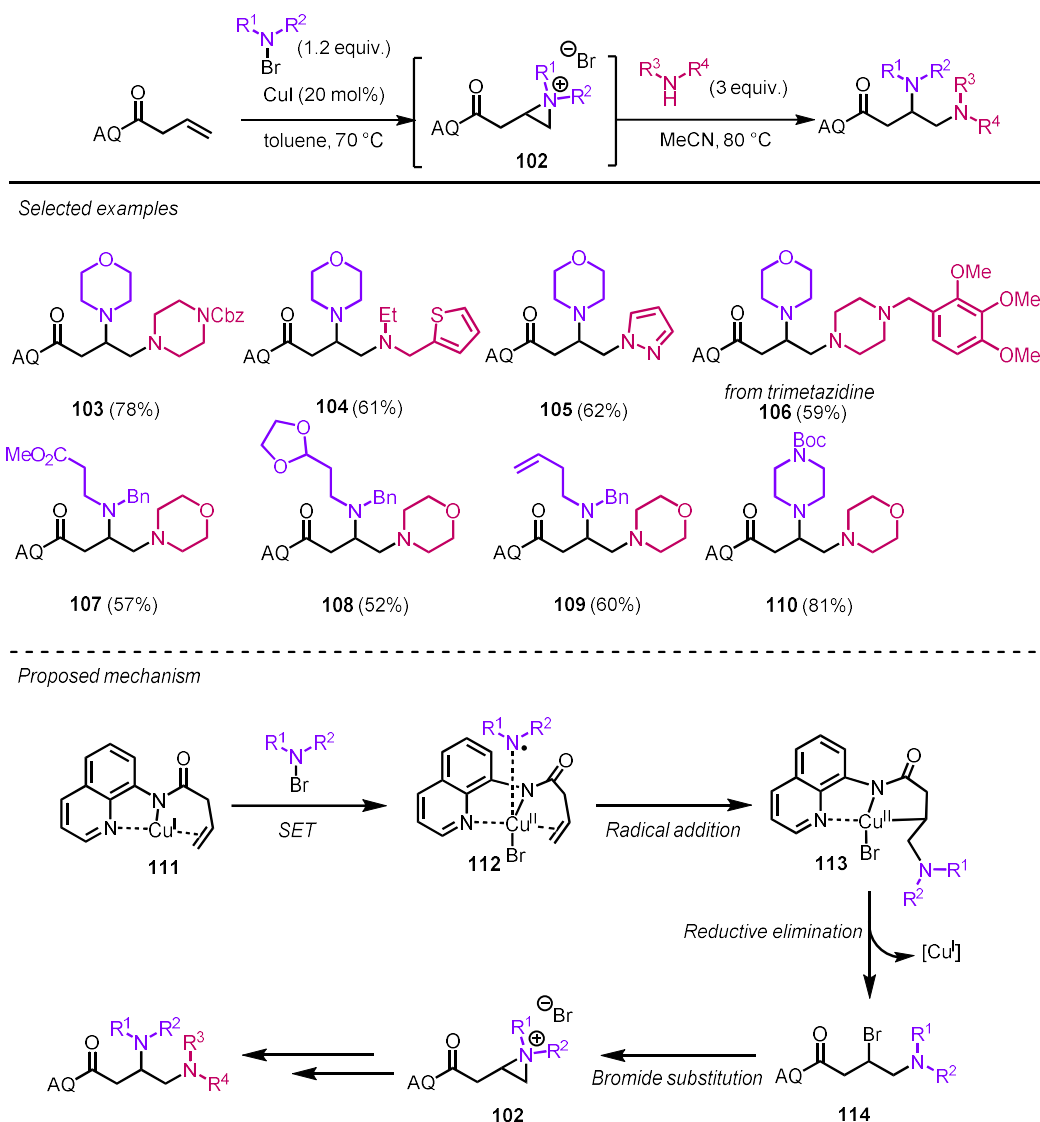
The direct diamination of alkenes which installs two different unprotected alkylamines is a more atom-economic approach and is advantageous over other methods since it can build complex scaffolds in one pot. Not surprisingly, there is a scarcity of reports describing such transformations, which highlights challenges associated with achieving this reactivity due to the propensity of amines to sequester metal catalysts. The most common strategy involves the initial aziridination of the double bond - often achieved via a radical pathway - followed by the S_N2-type ring opening with a different amine nucleophile. The aziridination step is often the bottleneck and the source of substrate limitations, while the ring-opening is usually compatible with a large range of N-nucleophiles.

Following this concept, the group of Novák has recently disclosed a two-step diamination protocol starting from hypervalent trifluoropropenylidonium triflate salt **92** (Scheme 11).^[11] Owing to its strongly electrophilic character, reagent **92** undergoes 1,4-conjugate addition of an amine nucleophile, followed by a ring-closing to form aziridinium intermediate **93**. The addition of a different amine nucleophile leads to the ring-opening of the aziridinium at the less substituted side due to the deactivating effect of the CF₃ group. A broad range of secondary amines bearing medicinally relevant moieties efficiently reacted to afford the corresponding 1,2-vicinal diamines in moderate to high yields. Additionally, nearly any type of nucleophilic N-heterocycle (**97** and **98**) could be employed for the opening of aziridinium. However, the scope of alkenes was not evaluated, and reagent **92** was essentially the only substrate tested for compatibility with the reaction conditions. The need to synthesize a specific alkenyliodonium salt reduces the practicality of the method. Moreover, the scope of amine nucleophiles essentially focused on secondary anilines or alkylamines, while the reactivity of their primary congeners (except for one example with *n*-hexylamine) was not mentioned.



Scheme 11. Vicinal diamination of the trifluoropropenyliodonium salt **92**.

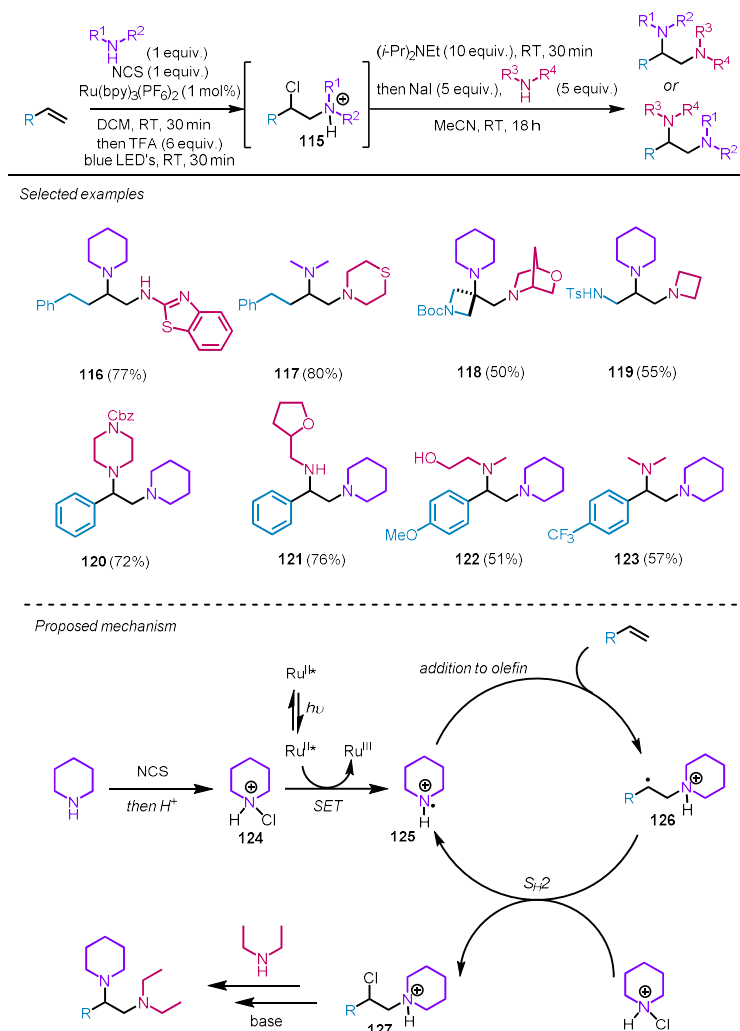
Another interesting example of Cu-catalyzed directing group-assisted alkene diamination was described by the group of Fu (Scheme 12).^[12] This new protocol builds on their previous findings on the aminoazidation of alkenes - a formal 1,2-diamination – to introduce two different alkylamines across the double bond via a sequential aziridination-ring opening sequence.^[13] The reaction is proposed to proceed via reductive SET to induce the homolysis of the N–Br bond to form the aminyl radical along with the bromide anion. The role of the directing group is to keep the aminyl radical within the coordination sphere of copper long enough to enable its reaction with the alkene also bound to copper. Reductive elimination followed by the displacement of bromide with the amine would form aziridinium intermediate **102**. The presence of the directing 8-aminoquinoline group decreases the synthetic utility of the transformation but shows again that the aziridination-ring opening sequence is a robust way to construct the 1,2-vicinal diamine scaffold. Another inconvenience is the necessity to swap toluene for acetonitrile after the first step. If both the bromoamine reagent and the second amine are mixed at the beginning, a mixture of symmetrical and unsymmetrical diamines was obtained. The direct use of amine nucleophiles instead of tailored N–Br reagents would probably make this method more attractive. Of note, the amine scope was almost exclusively focused on secondary aliphatic amines, and its generality towards primary aliphatic amines and anilines was not detailed, although aniline and benzylamine were successfully tested.



Scheme 12. Directing group-assisted Cu-catalyzed diamination of alkenes.

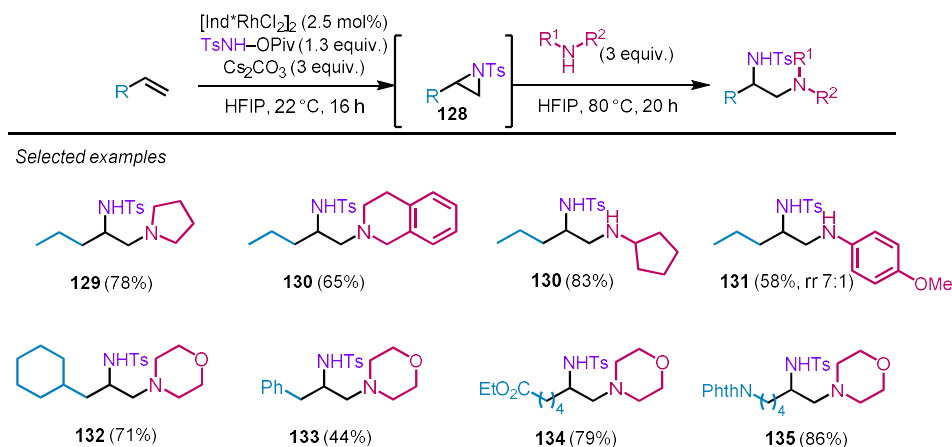
A similar strategy relying on aminohalide radical precursors to achieve 1,2-diamination of alkenes was employed by the group of Leonori in 2020 (Scheme 13).^[14] This multi-component protocol is a combination of five separate reactions performed one after another. In the first step, a chloroamine radical precursor is obtained *in situ* upon the reaction of amine with *N*-chlorosuccinimide. Afterward, a Brønsted acid is added, and the reaction mixture is irradiated with light to induce Ru-photocatalyzed SET reduction of chloroamine **124**, followed by the homolysis of the N–Cl bond and the subsequent formation of electrophilic aminium radical **125**. The resulting C-centered radical **126** can either be oxidized and recombine with the chloride anion or react with

another molecule of chloroamine in a homolytic substitution of chloride. The subsequent addition of the base deprotonates ammonium **127**, while the added iodide anion substitutes the chloride and facilitates the formation of aziridinium due to its much better nucleofugality. Finally, the second amine nucleophile preferably opens the aziridinium from the less substituted site in the case of aliphatic alkenes (**116-119**) or at the benzylic position in the case of styrenes (**120-123**). The new methodology displayed excellent compatibility with various drug-relevant moieties, although the choice of N-nucleophiles was still strongly biased towards secondary amines, which resonates with previous studies. Given the electrophilic nature of the aminium radical, electron-rich substrates would perform best under the given reaction conditions. Although two examples with *p*- and *o*-trifluoromethylstyrenes were reported, the limits of this methodology towards even more strongly deactivated styrenes were not explored.



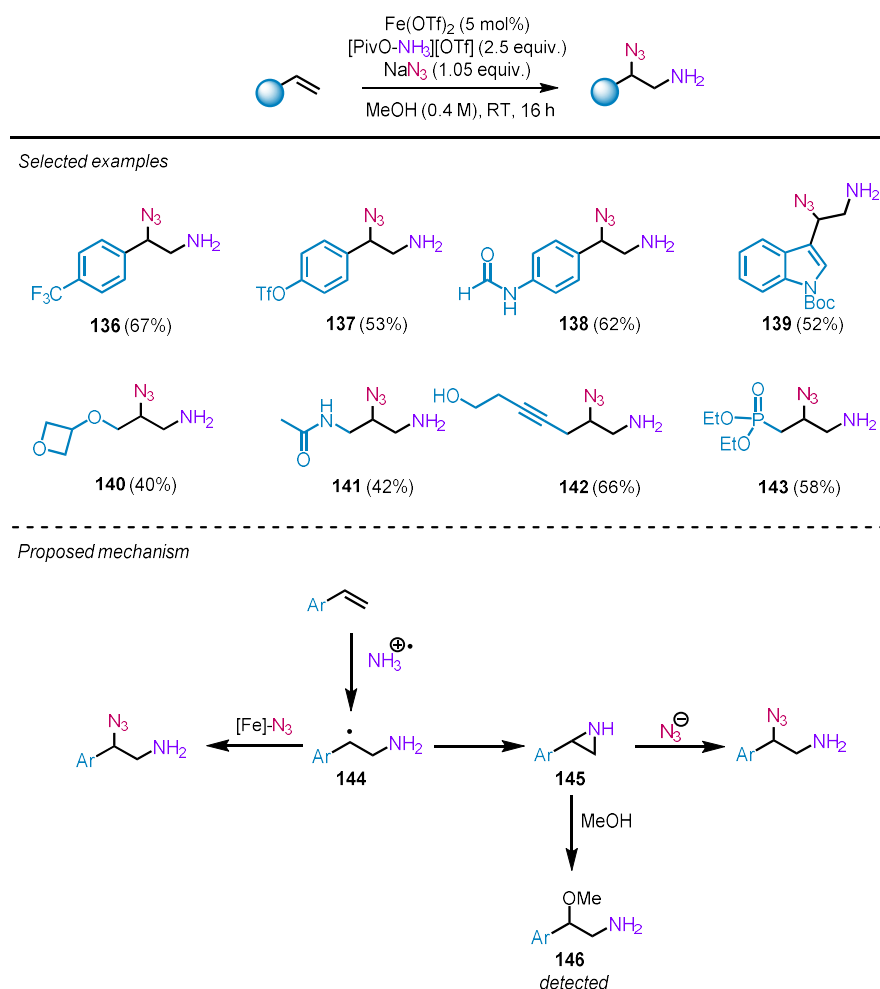
Scheme 13. Ru-photocatalyzed diamination of alkenes with alkylamines.

The group of Rovis has recently disclosed a Rh(III)-catalyzed sequential 1,2-diamination of alkenes in HFIP (Scheme 14).^[15] The key feature of the reaction design is the use of a Rh-nitrene complex to access a non-isolated aziridine intermediate, followed by its ring opening in the second step. Metal nitrene complexes are congeners of carbene complexes and readily insert into double bonds, offering an alternative to the radical and ionic approaches discussed before. The nitrene complex is formed from the protected hydroxylamine precursor TsNH–OPiv, which then reacts to afford the aziridine intermediate **128**. This protocol was successfully employed for the diamination of various aliphatic alkenes, yet the reactivity of electron-deficient amine nucleophiles and alkenes was not explored. The group of Blakey has recently modified the rhodium ligand and the protocol to enable enantioselective aziridination, which increases the usefulness of the method.^[16]



Scheme 14. Rh(III)-catalyzed 1,2-diamination of unactivated alkenes in HFIP. Ind* = heptamethylindenyl.

In 2020, the group of Morandi disclosed a powerful method for the synthesis of differentiated 1,2-vicinal aminoazides, which accommodated a broad range of styrenyl and aliphatic alkenes **136–143** (Scheme 15).^[17] The new protocol harnessed the reactivity of hydroxylammonium triflate salt [PivO–NH₃][OTf] as a source of NH₃⁺ radicals to introduce the primary unprotected amine that is immediately available for further N-functionalizations along with the azide group. Mechanistic studies on styrenes suggest the initial radical amination of the double bond, followed by the reaction of the C-centered radical **144** with the putative [Fe]–N₃ complex as an azide transfer agent. However, the oxidation of **144** to the benzylic carbocation followed by the formation of the aziridine **145** and its subsequent ring-opening by an azide anion cannot be completely ruled out. The plausibility of the ionic pathway was supported by the formation of a solvent adduct **146** suggesting the formation of a benzylic carbocation at some point. The interplay between radical and ionic pathways likely operates in styrenes, since the methanol adduct was never observed for aliphatic alkenes.



Scheme 15. Fe(II)-catalyzed 1,2-aminoazidation of alkenes.

The two-step sequential strategy relying on aziridination of the double bond in the first step followed by its ring opening by another amine nucleophile proved advantageous over other methods since it directly constructs a 1,2-vicinal diamine scaffold ready for further functionalizations without additional reduction/deprotection steps. However, several limitations, notably concerning the stereochemistry of final products, hamper its widespread use. Although electronic and steric effects are good predictors of the regioselectivity of the ring-opening, these are not absolute rules. Mixtures of both regioisomers were sometimes obtained in the above-discussed protocols, especially with anilines. Another important point to address by the research community is the enantioselective addition of N-centered radicals. Since the S_N2 -type ring opening conserves the stereochemistry, the first amination step is the bottleneck. The development of a general robust method for aziridination of alkenes akin to the synthesis of

epoxides via oxidation with *m*-CPBA will make this route towards 1,2-vicinal diamines particularly attractive.

Summary and Outlook

The overview of recent literature on direct diaminations of alkenes shows that we are still far from having a general and practical protocol to rapidly assemble 1,2-vicinal diamine scaffolds. All highly desirable reaction traits are already present in the above transformations on a case-by-case basis, but we have not so far succeeded in combining them in a single protocol. To become attractive for a more widespread use outside the academic research context, the ideal 1,2-diamination method should be compatible with a wide range of N-nucleophiles such as ammonia, primary/secondary aliphatic amines, anilines, NH-heterocycles, (sulfox)imines and (sulfon)amides irrespective of their electronic properties. In the case of differentiated 1,2-vicinal diamines, methods that could simultaneously control enantio- and regioselectivity are yet to be reported, while the reactivity of alkenes bearing strongly electron-withdrawing groups has not been explored in detail so far. Addressing these issues with the ever-evolving field of chemistry of N-centered radicals will open new avenues for the rapid assembly of high-value-added molecules incorporating a 1,2-vicinal diamine scaffold.

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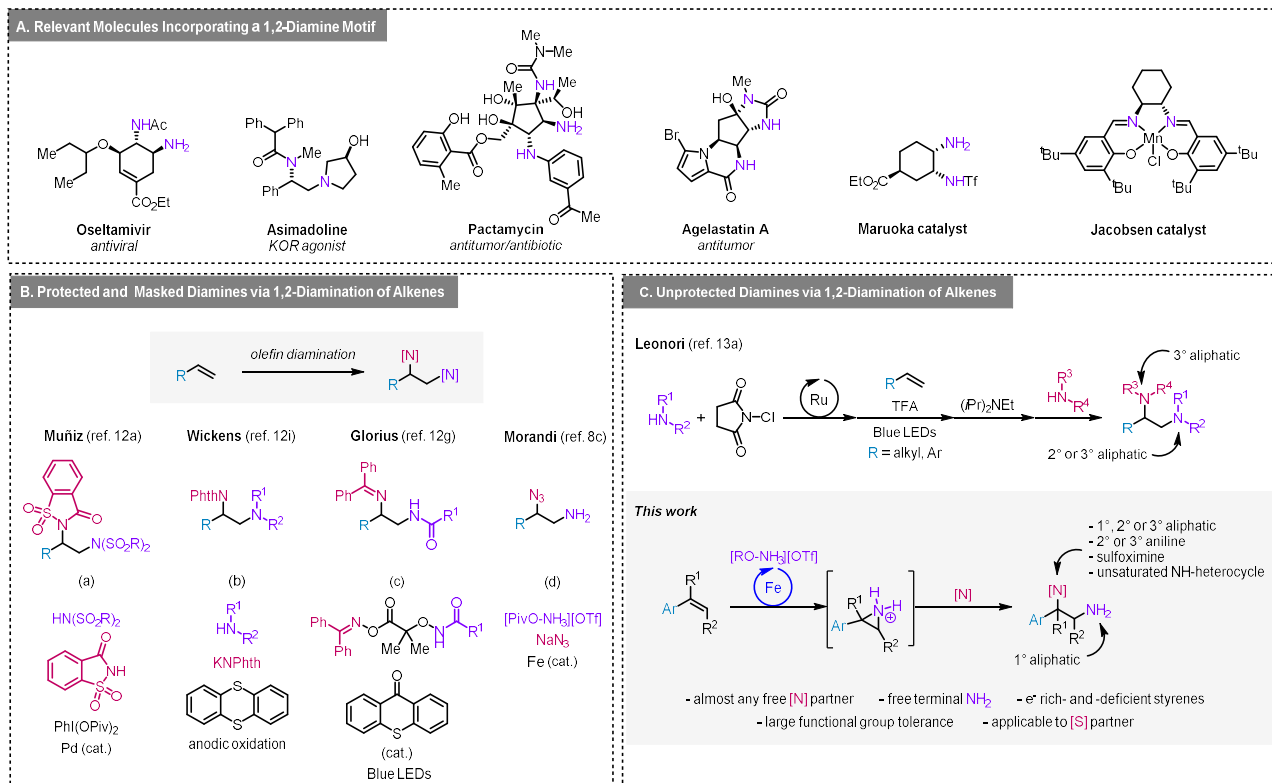
Main Text

Introduction

Vicinal diamines are privileged structural motifs in biologically active compounds and have also found extensive use in transition metal catalysis and organocatalysis (Scheme 1A).^[1] As a result, a plethora of synthetic methods featuring various disconnections have been devised to prepare vicinal diamines,^[2] including reactions with aldimines and ketimines,^[3] hydroamination of allylamines and enamines,^[4] aminolysis of aziridines,^[5] C–H amination,^[6] and amination of diols via hydrogen borrowing strategy.^[7] Most of these methods require starting materials where one of the nitrogen functionalities is pre-installed. More importantly, they are rarely compatible with a wide range of amino groups, notably alkylamines. Furthermore, they typically result in N-protected products, requiring additional protection/deprotection steps, lengthening the overall synthesis.

The intermolecular diamination of alkenes, and related transformations such as aminoazidation^[8] and diazidation,^[9] represent attractive strategies to prepare vicinal diamines from feedstock alkenes. However, accessing differentiated vicinal diamines proved difficult, especially when both nitrogen functionalities are not covalently linked within the reactant.^[10,11] Several groups have designed methods for the direct formation of differentially protected diamines from alkenes via 1,2-diamination (Scheme 1B).^[12] However, they typically install only one class of protected/masked amino groups at the internal position and they do not provide access to terminal primary aliphatic amines, except for the aminoazidation of alkenes reported by the group of Morandi.^[8c] Yet, additional synthetic steps are required to convert the azide into amino functionalities.

Methods that enable diamination of alkenes that directly access unprotected differentiated vicinal diamines would be particularly attractive from a synthetic standpoint but remain rare.^[13] The group of Leonori described a one-pot sequence that incorporates unprotected secondary and tertiary alkylamines at the terminal position, whereas mainly unprotected secondary alkylamines could be installed at the internal position (Scheme 1C).^[13a] However, the use of less nucleophilic amines such as aniline or trifluoroethylamine led to a mixture of regioisomers, while the reactivity of amines bearing alkenyl or alkynyl moieties was not reported.



Scheme 1. Vicinal diamines and their synthesis by 1,2-diamination of alkenes.

Despite the above-described important advances for alkene 1,2-diamination, a method that would directly embed a free NH_2 group at the terminal position and a broad array of nitrogen-containing motifs at the internal position is still missing. Moreover, this NH_2 represent a convenient synthetic handle for divergent synthesis as opposed to previous reports that usually led to products incorporating either terminal EWG-protected amines or alkylamines at the terminal position. Another critical problem to address is the reactivity of highly electronically deactivated styrenes, which remain underrepresented even among methods that deliver protected unsymmetrical vicinal diamines.^[8c,8d,12b,12h]

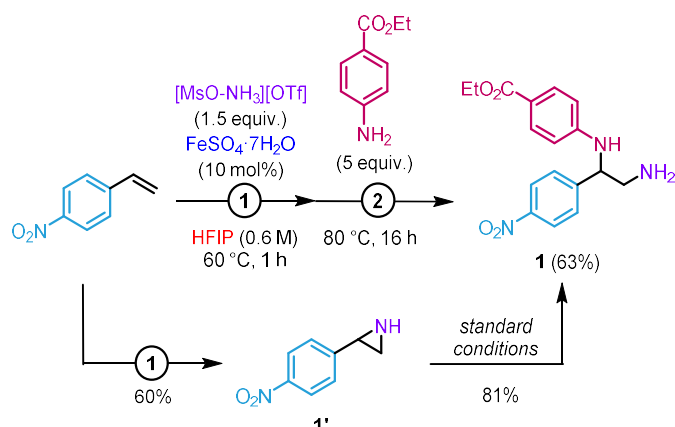
Here, we report streamlined protocols for 1,2-diamination of sterically and electronically varied styrenes, which introduce an unprotected primary amine at the terminal position and a wide variety of nitrogen nucleophiles at the internal position such as unprotected primary or secondary alkyl or aromatic amines, sulfoximines, *N*-heterocycles, sulfoximines, and an ammonia surrogate.

Results and Discussion

Reaction Conceptualization and Development

At the outset of this study, we envisioned that the diamination of styrenes to give unprotected amines could be achieved in a one-pot/two-step sequence involving the initial formation of an aziridinium intermediate that will react with a second amine (Scheme 1C). This strategy is inspired by the work of the Morandi group on the aminofunctionalization of alkenes that allows the incorporation of primary aliphatic amines with hydroxylammonium salts.^[8c,14,15] In their studies, simple nucleophilic partners, which did not interfere with the amine source, such as water, alcohols, sodium chloride and sodium azide were used. However, in the case of 1,2-diamination, the formation of the aziridinium and its opening needed to be separated in time due to the propensity of amines to react with hydroxylammonium salts.^[15] Our previous studies on iron(II)-catalyzed (hetero)arylation of highly deactivated styrenes showed that such temporal separation is feasible when hexafluoroisopropanol (HFIP) is used as a solvent.^[16] We attributed this result to the inherent ability of HFIP to prevent any trapping of the catalyst, to extend the lifetime of cationic and radical species, and to increase the electrophilicity of reactive intermediates.^[17] Nevertheless, the (hetero)arylation protocol was far from general; the transformation was not compatible with deactivated styrenes bearing, for instance, ester, CF₃, or halide substituents, nor with electron-rich styrenes. Importantly, during our investigations on (hetero)arylation, we observed that weakly basic diphenylamine substrates delivered products of diamination rather than aminoarylation. We posited that this observation could be exploited to develop a general 1,2-diamination of styrenes that was independent of the basicity and nucleophilicity of the amine.

Using *p*-nitrostyrene and benzocaine (anesthetic) as a representative aniline, we found that the devised reaction sequence led to the densely functionalized product **1** in 63% yield, incorporating three different nitrogen units and an ester (Scheme 2).^[18] Decreasing the excess of benzocaine led to reduced yields (21% with 1 equivalent and 53% with 3 equivalents). Interrupting the process after the first step allowed us to isolate the corresponding aziridine **1'** in 60% yield. Re-engaging the aziridine in our standard conditions provided compound **1** in 81% yield, in line with its intermediacy in the reaction. As anticipated, when benzocaine was present from the start, the desired reaction did not proceed and *p*-nitrostyrene was fully recovered, suggesting a competitive reaction with the hydroxylammonium salt.



Scheme 2. Benchmark 1,2-diamination of *p*-nitrostyrene with benzocaine.

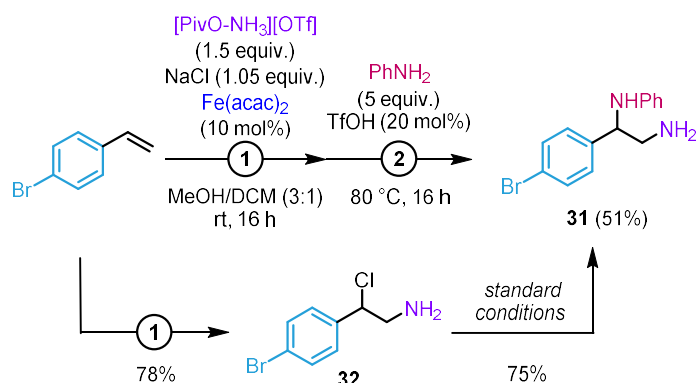
Reaction Scope

Having demonstrated the efficiency of our protocol with a primary aniline, we examined its compatibility with diverse *para*-substituted anilines (Conditions A) (Scheme 3). All smoothly reacted to afford the corresponding diamination products **2-9** in yields ranging from 33 to 71%. We notably introduced several relevant functional groups such as nitro, cyano, trifluoromethyl, ester, primary amide, halide, ether, and alkyl. A chloride substituent could be positioned at the *para*, *meta* or *ortho* position without a significant impact on the reactivity (**10-12**). Even a sterically hindered aniline could be used to afford the target product **13** in 47% yield. The transformation was extended to primary naphthylamines, delivering compounds **14** and **15** in 65 and 54% yield, respectively. Next, we examined the reactivity of secondary anilines (**16-19**), which proved to be equally efficient as nucleophiles. Remarkably, the alkene and alkyne moieties in products derived from *N*-allylaniline **18** and *N*-propargyl aniline **19** remained intact and no cyclization product arising from hydroamination was observed.

We then explored the scope with respect to electron-deficient styrenes, using benzocaine as a model nucleophile. Our protocol allowed a rapid assembly of vicinal diamines (**20-28**) from a broad range of deactivated styrenes incorporating medicinally relevant and derivatizable substituents in yields ranging from 40 to 90%, including a perfluoro motif, a trifluoromethyl group, secondary and tertiary sulfonamides, a sulfonyl ester, a secondary amide, a Weinreb amide and a pentafluorosulfonyl group. Using **20** as an example, we confirmed the scalability of the protocol on 5 mmol (80%, 1.68 g).

We developed a second set of reaction conditions for electron-rich and mildly deactivated styrenes, which are prone to oligomerization under the original conditions in HFIP. Building on a previous study by the group of Morandi on aminochlorination,^[14b] we achieved the desired

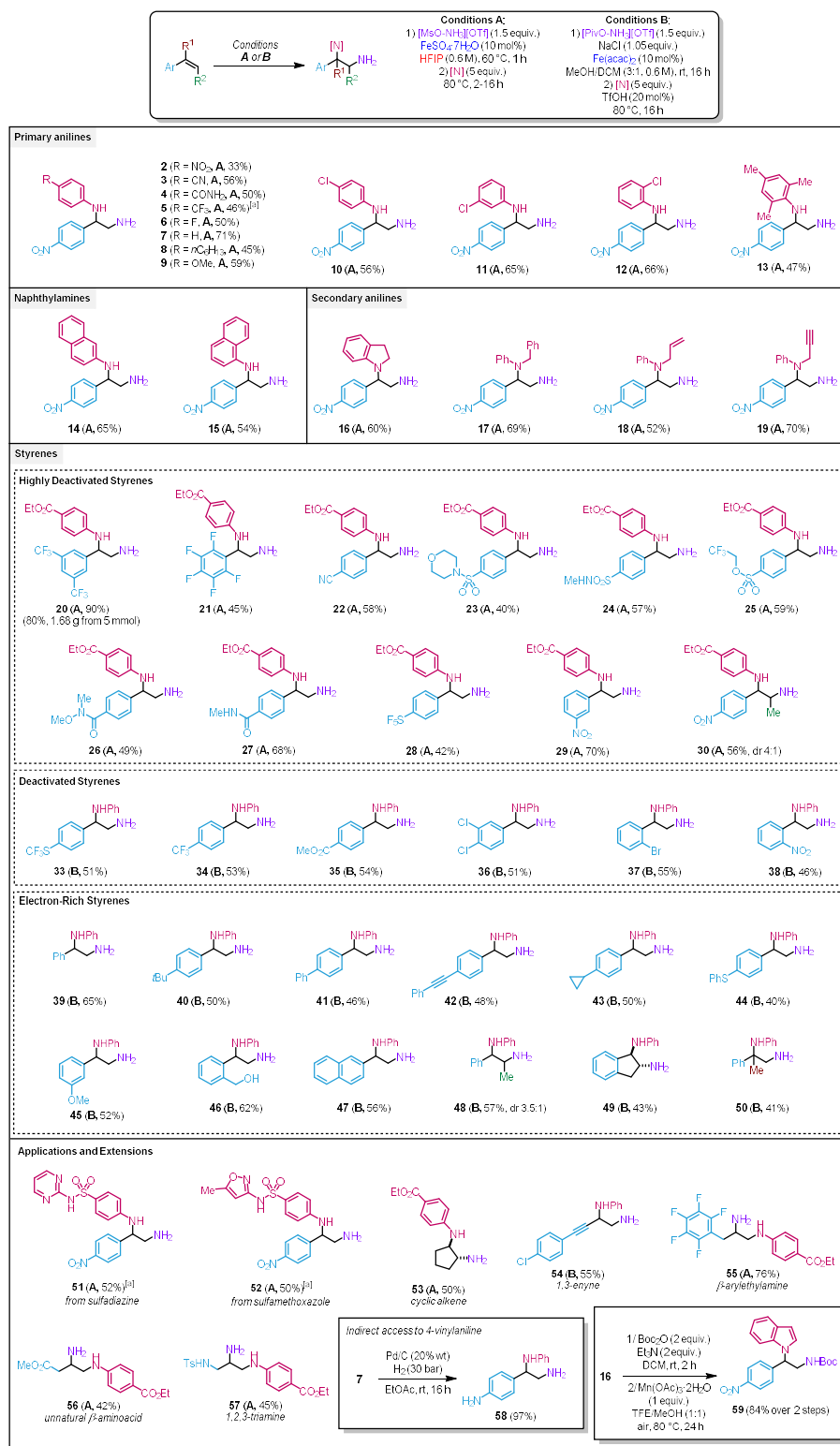
reactivity through a two-step one-pot protocol, first involving the formation of aminochlorinated product **32**, which could be isolated in 78% yield, followed by an in situ nucleophilic substitution of the chloride by aniline in the presence of triflic acid (TfOH) (Conditions B) (Scheme 4).



Scheme 4. Benchmark 1,2-diamination of *p*-bromostyrene with aniline.

Conditions B enabled diamination of a series of deactivated styrenes containing SCF_3 , trifluoromethyl, ester, and halide groups (**33-37**, 51-55%) as well as electron-rich styrenes (**39-47**, 40-65% yields), which were previously incompatible with the reaction sequence in HFIP. Alkyl, aryl, alkynyl, cyclopropyl, ether and thioether substituents were well-tolerated. Remarkably, even the presence of an internal nucleophile on the arene did not disrupt the reaction (**46**, 62%). Of note, those conditions do not work with highly deactivated substrates such as *p*-nitrostyrene. In turn, *m*- and *o*-nitrostyrene reacted smoothly to provide the corresponding products **29** and **38** in 70 and 46% yields, using conditions A and B, respectively. The protocol is not limited to mono-substituted styrenes but is also applicable to electron-rich and -deficient internal styrenes (**30**, **48** and **49**, 43-57%) and α -methylstyrenes such as **50** (41%). Unfortunately, electron-rich vinyl heteroarenes such as 2-vinylthiophene or 3-vinylindole are too reactive; during the aminochlorination step, the intermediate reacts with the solvent (methanol) to give an aminoetherification product which is unreactive in the presence of triflic acid and aniline.

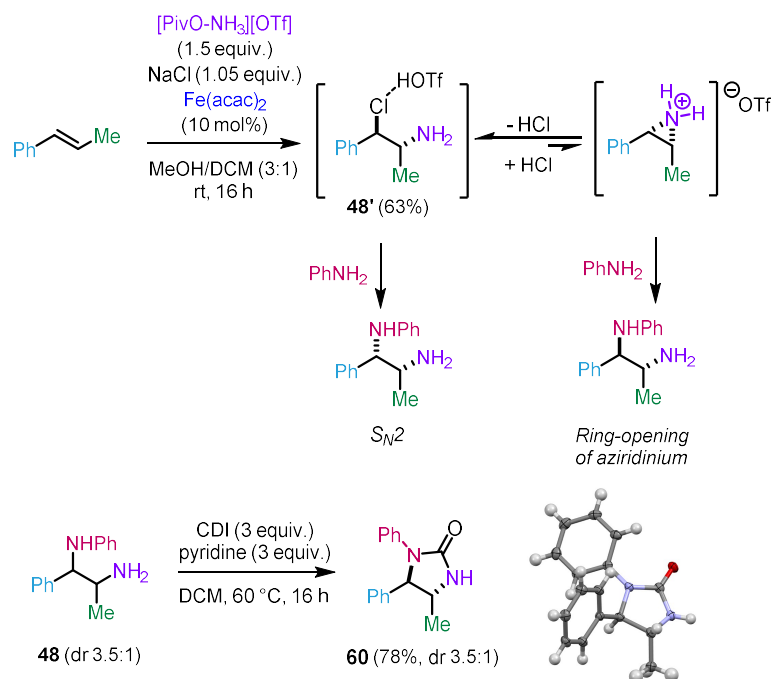
When bioactive molecules such as sulfadiazine (antibiotic) and sulfamethoxazole (antibiotic) were used in the reaction sequence, diamination products **51** and **52** were obtained in 52% and 50% yields, respectively. Our strategies were also applied to cyclic alkenes such as cyclopentene, producing compound **53** in 50% yield,^[19] and to a 1,3-enyne to furnish product **54** in 55% yield. In the case of allylic substrates, the regioselectivity was, however, reversed in favor of the addition at the terminal position, in line with the observation of the Leonori group for related starting materials.^[13a] Attractively, the protocol offers a rapid access to β -arylethyamines (**55**), which are key scaffolds in drug discovery,^[20] unnatural β -amino acids (**56**), and 1,2,3-triamines (**57**).



Scheme 3. Scope of 1,2-diamination of styrenes with anilines. [a] Isolated yield of Boc-protected compound.

Although 4-vinylaniline cannot be used directly for this reaction sequence, the corresponding product **58** was formally obtained via reduction of the nitro group of diamine **7** in nearly quantitative yield (97%). Oxidation of the indoline moiety of Boc-protected diamine **16** by $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ delivered indole **59** in 84% yield over 2 steps, representing an indirect way to add indoles to an alkene at NH rather than at C3.^[16]

To gain insight into the role of TfOH in the second set of conditions, we studied the reactivity of *trans* β -methylstyrene. From the known aminochlorinated intermediate **48'**,^[14b] here isolated in 63% yield as a single diastereoisomer, two mechanistic pathways were envisioned for the activation of benzyl chloride by TfOH: (1) a direct $\text{S}_{\text{N}}2$ pathway would lead to the *cis* product, whereas (2) a pathway involving the formation of an aziridinium and a subsequent ring-opening would lead to the *trans* product. To differentiate between these scenarios, **48** was engaged in a reaction with carbonyldiimidazole (CDI) to form cyclic product **60** as a mixture of diastereoisomers (78% yield, dr 3.5:1). The structure of the major diastereoisomer was ascertained by X-ray crystallography, showing a *trans* configuration, which is consistent with the second proposed mechanism. Additional observations further clarify the mechanism. During the second step, the use of a catalytic amount of TfOH proved essential to obtain the product **48** in a satisfying yield (57%). In its absence, **48** was obtained only in 15% yield. Furthermore, the formation of the aziridine was not observed in the absence of aniline. Thus, we assume that, in solution, there is an equilibrium between the aminochlorinated and aziridinium intermediates that favors the former, and that aniline reacts irreversibly with the aziridinium to form diamination product **48**. Given that both diastereoisomers were obtained, both mechanisms are likely at play, with the second one being the major path.



Scheme 5. Studies regarding the role of triflic acid in the reaction sequence.

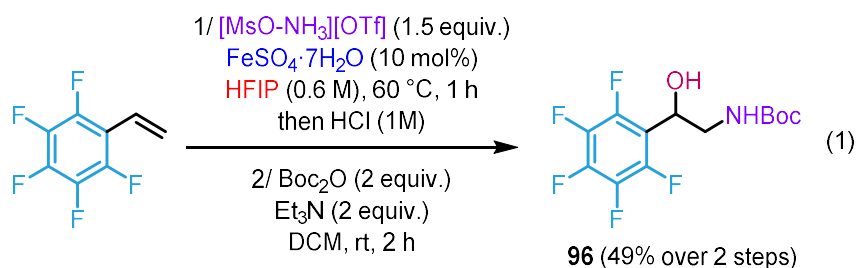
Next, we expanded the protocol to aliphatic amines. Primary aliphatic amines bearing functions of interest such as alkenyl (**61**), alkynyl (**62** and **63**), cyclopropyl (**64**), trifluoromethyl (**65**), (hetero)aryl (**66-68**) and protected amino acid (**69**) groups were successfully introduced into the product (Scheme 6). In turn, a complex mixture was obtained with *tert*-butylamine. In some cases, the product was isolated as a mixture of the free base and its ammonium salt, in which case it was Boc-protected to simplify characterization. Here, cyclopropylamine unexpectedly acted as a surrogate of ammonia, affording vicinal primary diamine **72**, whose formation likely results from the protonation of the cyclopropyl group (**70**) followed by hydrolysis of resulting iminium **71** to the primary amine.^[21] To the best of our knowledge, it constitutes the first example of a direct 1,2-diamination of styrenes to afford unprotected vicinal primary amines in one-pot. Additionally, our protocol enabled the incorporation of medically relevant cyclic amines, including morpholine (**73**), piperazine (**74** and **75**) such as amoxapine (antidepressant, **75**), piperidine (**76**), pyrrolidine (**77**) and tetrahydroisoquinoline (**78**) moieties as well as diallylamine (**79**) and rasagiline (treatment of Parkinson's disease, **80**) in yields ranging from 40 to 52%.

We then wondered if related nitrogen nucleophiles such as sulfoximines, which have emerged as relevant functional groups in drug discovery,^[22] would be compatible with this reaction sequence. Since they display similar pKa as anilines, we considered that they should, in principle, display similar reactivity,^[23] which was confirmed with compounds **81-83**. NH-heterocycles such as

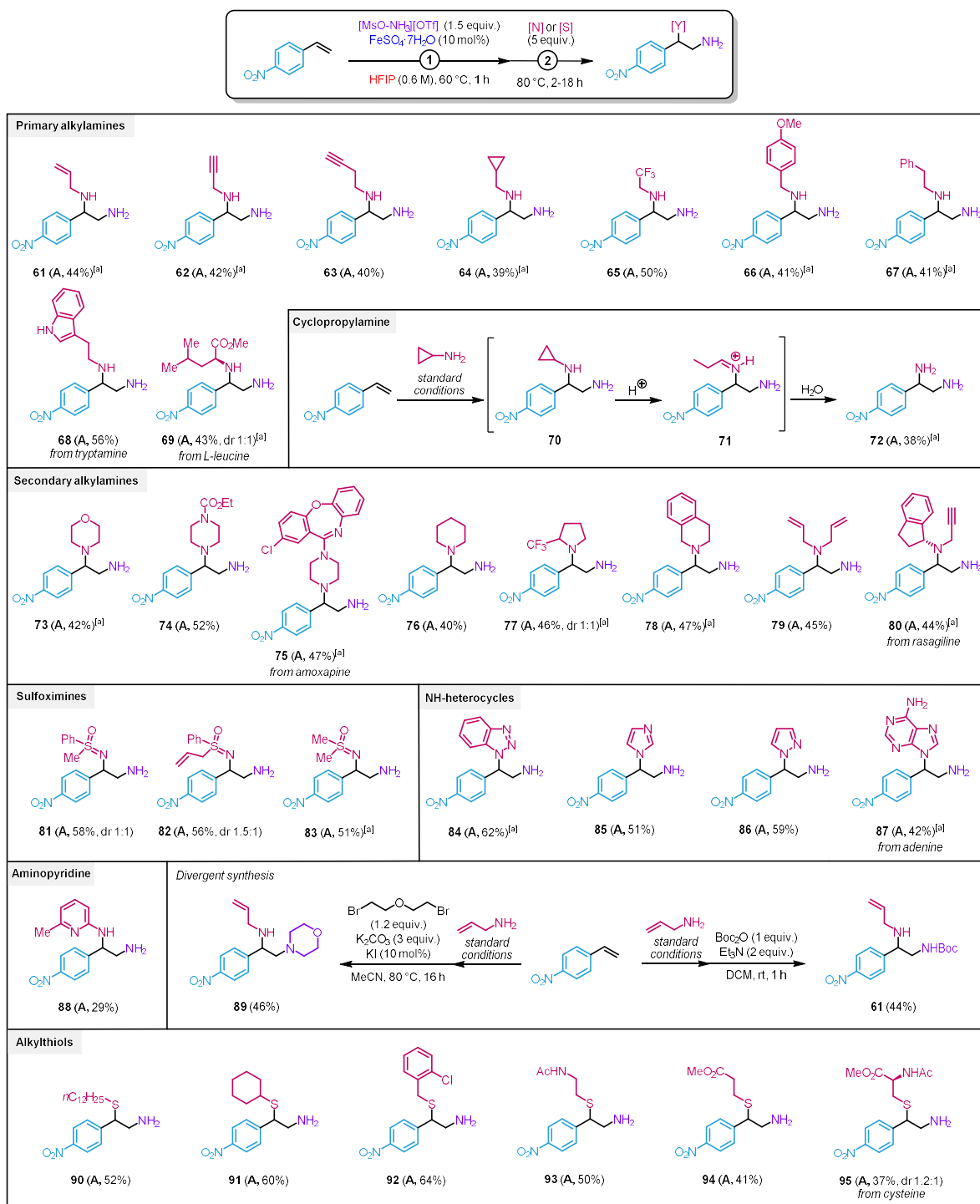
benzotriazole (**84**), imidazole (**85**), pyrazole (**86**) and adenine (**87**) also proved to be competent nucleophiles for the devised 1,2-diamination transformation. This protocol can also be used to install a pyridine motif, albeit in a lower yield (**88**, 29%). As discussed in the introduction, the primary aliphatic amine formed can serve as a platform for divergent synthesis, to either introduce an EWG-group such as Boc (**61**) or a cyclic amine such as morpholine (**89**).

Moreover, this reaction sequence was successfully expanded to embody the aminothiolation of styrenes, adding an NH₂ group and S-nucleophiles, including underexplored alkylthiols.^[24] The corresponding aminosulfidation products **90-95** were synthesized from diversely functionalized alkylthiols, notably protected cysteine, in 37-64% yields.

Lastly, we demonstrated that our protocol is also applicable to the hydroxylation of highly deactivated styrenes. Morandi's pioneering report of styrene hydroxylation notably did not include substrates bearing electron-withdrawing groups stronger than a trifluoromethyl group.^[14a] In our case, using pentafluorostyrene as substrate led to product **96** in 49% yield (over 2 steps) following Boc protection (Equation 1).



To obtain a better insight into the role of HFIP in the first amination step, additional kinetic and electrochemical studies were carried out, and the more extended discussion of these results is provided in the supporting information of this chapter (section 6 on p. 264 and section 7 on p. 269).



Scheme 6. Scope of 1,2-diamination of styrenes with various amino groups. [a] Isolated yield of Boc-protected compound.

Conclusions

In conclusion, we developed a general and versatile method for rapid access to 1,2-diamines in moderate to high yields, starting from readily available styrenes, hydroxylammonium salts, and amine nucleophiles. Compared to previous approaches, our operationally simple one-pot/two-step protocol enables a modular construction of densely functionalized vicinal diamines where one of the nitrogen functionalities is a primary aliphatic amine. A hallmark of this transformation is its capacity to accommodate many classes of amine and sulfur nucleophiles, including bioactive molecules. Depending on the electronic nature of the substrate studied, two different sets of conditions were developed which collectively cover a large variety of drug-relevant functional groups. The numerous functional groups incorporated into the target products could enable manifold derivatizations, creating high value-added building blocks for diversity-oriented synthesis, notably the design and preparation of analogs in drug discovery.

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[24] For rare examples of aminothiolation of styrenes with alkylthiols, see: a) M. Iwasaki, K. Nonaka, S. Zou, Y. Sawanaka, T. Shinozaki, T. Fujii, K. Nakajima, Y. Nishihara, *J. Org. Chem.* **2019**, *84*, 15373-15379; b) W. Wang, L. Zhao, H. Wu, Y. He, G. Wu, *Org. Lett.* **2023**, *25*, 7078-7082.

Supporting Information

It should be noted that only the characterization of the different products of the scope was kept inside of the thesis. All NMR spectra were not included but are available online.

1. General Remarks

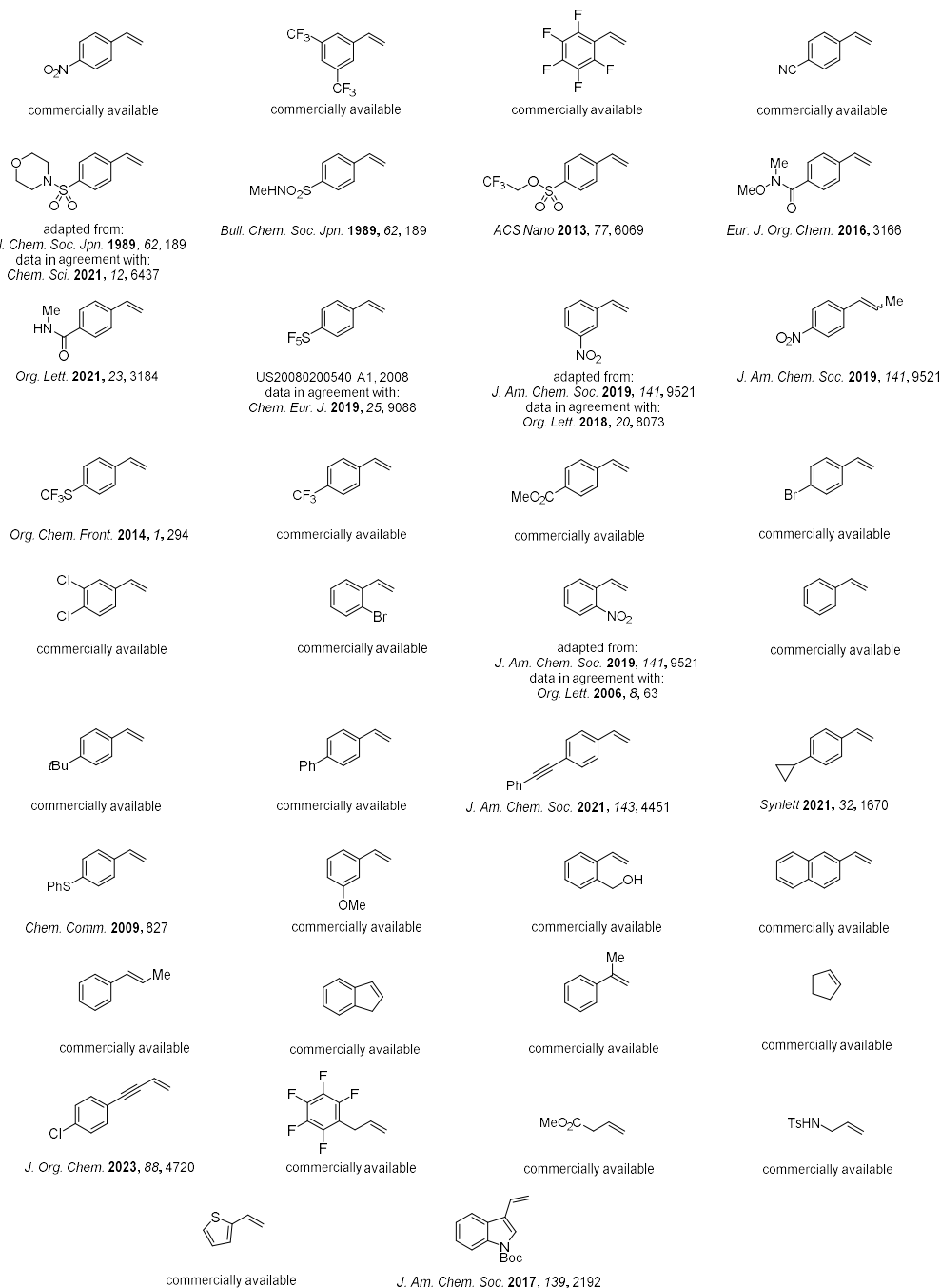
Materials: All commercial materials were purchased from Sigma-Aldrich, TCI and FluoroChem, and were used as received, without further purification. HFIP (CAS: 920-66-1) was purchased from FluoroChem. The other starting materials were prepared according to known protocols.

Reactions were monitored by thin layer chromatography (TLC) performed on aluminum plates coated with silica gel F₂₅₄ with 0.2 mm thickness. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm and/or by staining using potassium permanganate. Flash column chromatography (FC) was performed using silica gel 60 (230-400 mesh, Merck and co.). Yields refer to chromatographically and spectroscopically pure compounds. When stated, NMR yields were calculated by using mesitylene as an external standard.

¹H NMR, ¹³C NMR, ¹⁹F NMR, ³¹P NMR spectra were recorded using a Bruker UltraShield 400 or 500 at 300K. ¹H NMR chemical shifts are reported in ppm using residual solvent peak as reference (CDCl₃: δ = 7.26 ppm; CD₂Cl₂: 5.32 ppm; CD₃OD: 3.31 ppm). Data for ¹H NMR are presented as follows: chemical shift δ (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constant *J* (Hz) and integration; ¹³C NMR spectra were recorded at 100, 126 MHz using broadband proton decoupling and chemical shifts are reported in ppm using residual solvent peaks as reference (CDCl₃: δ = 77.16 ppm; CD₂Cl₂: 53.84 ppm; CD₃OD: 49.00 ppm). Multiplicity was defined by recorded a ¹³C NMR spectra using the attached proton test (APT). ¹⁹F NMR spectra were recorded at 471 MHz at ambient temperature. ³¹P NMR spectra were recorded at 162 MHz at ambient temperature. High-resolution mass spectrometry (HRMS) analysis was performed on instruments GCT 1er Waters (EI and IC), MicroTOF-Q Bruker (ESI) and a GC Thermo Scientific Trace 1300 GC unit coupled to an APPI MasCom source mounted on a Thermo Scientific Exactive Plus EMR mass unit (Orbitrap FT-HRMS analyzer).

2. Preparation of Starting Materials

The following substrates were either commercially available or prepared according to known procedures:

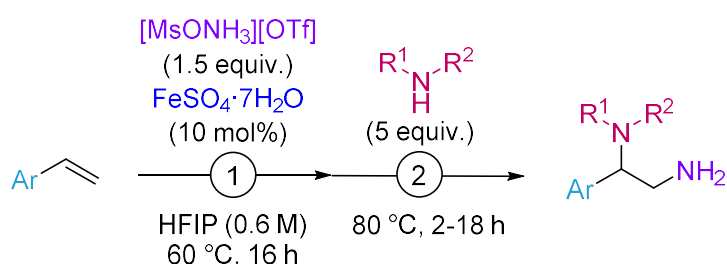


[MsO-NH₃][OTf] and [PivO-NH₃][OTf] salts were prepared according to reported literature procedures:

(a) Legnani, L.; Morandi, B. Direct Catalytic Synthesis of Unprotected 2-Amino-1-Phenylethanols from Alkenes by Using Iron(II) Phtalocyanine. *Angew. Chem. Int. Ed.* **2016**, *55*, 2248-2251. (b) Falk, E; Gasser, V. C. M.; Morandi, B. Synthesis of *N*-Alkyl Anilines from Arenes via Iron-Promoted Aromatic C–H Amination. *Org. Lett.* **2021**, *23*, 4, 1422-1426. (c) Gillespie, J. E.; Morrill, C.; Phipps, R. J. Regioselective Radical Arene Amination for the Concise Synthesis of *ortho*-Phenylenediamines. *J. Am. Chem. Soc.* **2021**, *143*, 25, 9355-9360.

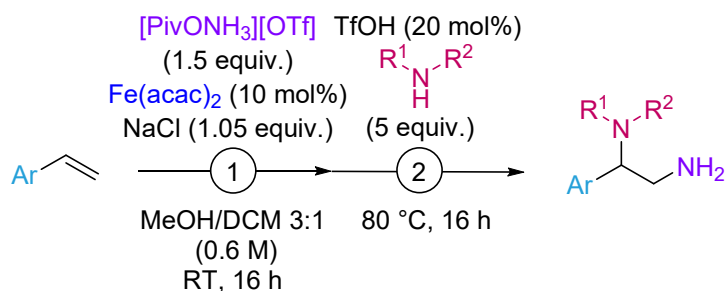
3. Diamination of Styrenes

3.1 General Procedure (A) for the Diamination



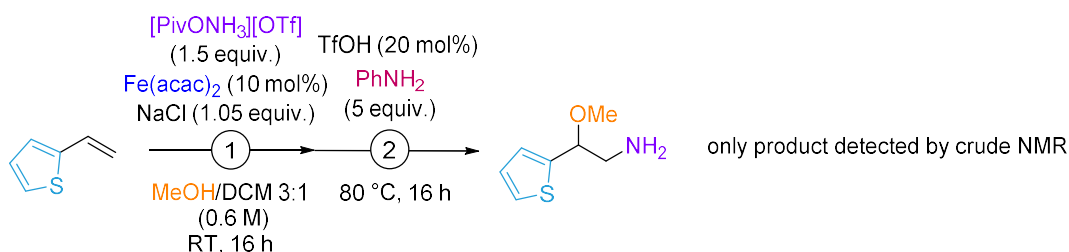
A 10 ml tube equipped with a Teflon-coated magnetic stir bar was charged with [MsO-NH₃][OTf] (1.5 equiv.). HFIP (0.6 M) was added followed by styrene (1.0 equiv.) and FeSO₄·7H₂O (10 mol%) under air. The glass tube was sealed, and the reaction mixture was stirred at 60 °C for 1 h. After cooling down to room temperature, the amine (5.0 equiv.) was added. Then, the reaction mixture was stirred at 80 °C for 2-18 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (anilines and alkyl thiols) or NaOH 1M (alkyl amines, sulfoximines and NH-heterocycles) (10 mL) and then extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (FC) over silica gel to furnish the target products.

3.2 General Procedure (B) for the Diamination

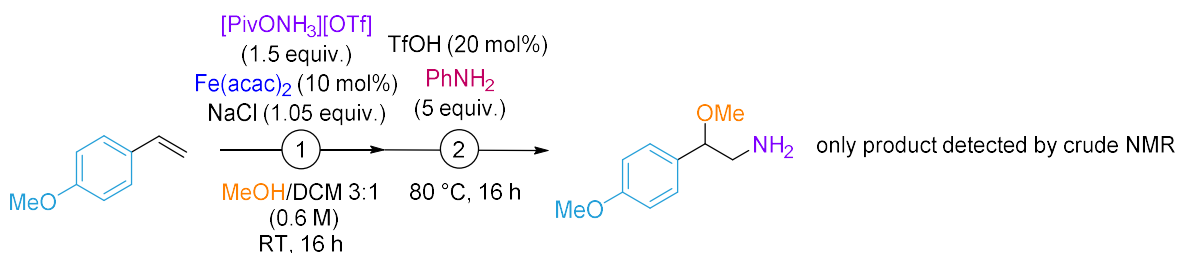
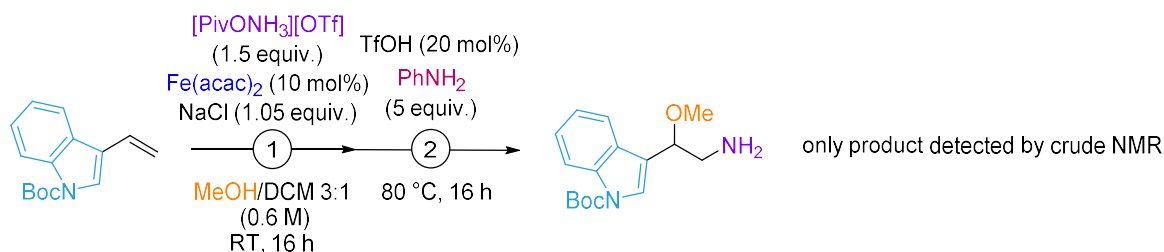


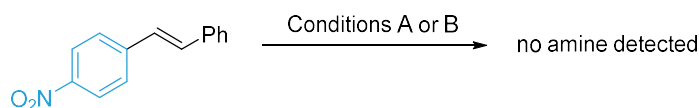
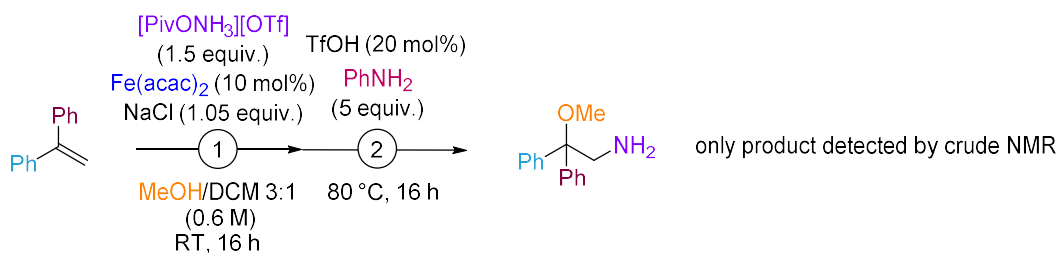
A 10 ml tube equipped with a Teflon-coated magnetic stir bar was charged with [PivO-NH₃][OTf] (1.5 equiv.). A solution of MeOH/DCM 3:1 (0.6 M) was added followed by styrene (1.0 equiv.), Fe(acac)₂ (10 mol%) and NaCl (1.05 equiv.) under air. The glass tube was sealed, and the reaction mixture was stirred at RT for 16 h. Afterwards, the amine (5.0 equiv.) and trifluoromethanesulfonic acid (20 mol%) were added. Then, the reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (10 mL) and then extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (FC) over silica gel to furnish the target products.

3.3 Unsuccessful Substrates



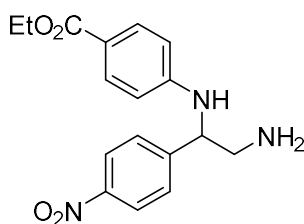
In the case of 2-vinyl thiophene, the product was in fact already obtained after 1 h during the first step. Thus, the reaction time is not the issue.





3.4 Characterization Data of Diamination Products

Ethyl 4-((2-amino-1-(4-nitrophenyl)ethyl)amino)benzoate 1

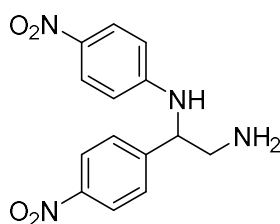


Chemical Formula: C₁₇H₁₉N₃O₄
Exact Mass: 329.1376

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzocaine (248 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **1** (63.0 mg, 0.189 mmol, 63% yield) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 6.49 (d, *J* = 8.6 Hz, 2H), 5.62 (d, *J* = 5.4 Hz, 1H), 4.52 (dd, *J* = 6.4, 4.6 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.19 (dd, *J* = 12.7, 4.6 Hz, 1H), 3.02 (dd, *J* = 12.7, 6.4 Hz, 1H), 1.43 (brs, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 166.8 (C), 151.2 (C), 149.8 (C), 147.8 (C), 131.5 (CH), 127.9 (CH), 124.2 (CH), 119.7 (C), 112.8 (CH), 60.5 (CH₂), 58.7 (CH), 48.2 (CH₂), 14.6 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₇H₂₀N₃O₄ [M+H]⁺ 330.1448, found 330.1439.

***N'*,1-bis(4-nitrophenyl)ethane-1,2-diamine 2**

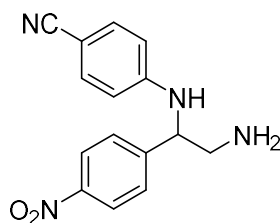


Chemical Formula: C₁₄H₁₄N₄O₄
Exact Mass: 302.1015

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 4-nitroaniline (207 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 85/15) afforded **2** (30.0 mg, 0.100 mmol, 33% yield) as a yellow oil.

¹H NMR (400 MHz, CD₃OD): δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 9.4 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 6.59 (d, *J* = 9.4 Hz, 2H), 4.69 (dd, *J* = 8.0, 5.1 Hz, 1H), 3.08–2.94 (m, 2H), NH and NH₂ unobserved. **¹³C NMR (101 MHz, CD₃OD):** δ 154.8 (C), 150.1 (C), 148.8 (C), 139.0 (C), 128.9 (CH), 127.0 (CH), 124.9 (CH), 112.9 (CH), 60.8 (CH), 48.7 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₄H₁₅N₄O₄ [M+H]⁺ 303.1088, found 303.1083.

4-((2-amino-1-(4-nitrophenyl)ethyl)amino)benzonitrile 3

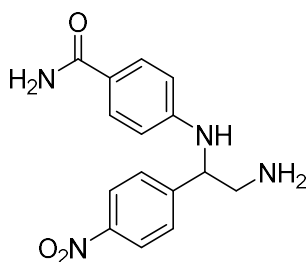


Chemical Formula: C₁₅H₁₄N₄O₂
Exact Mass: 282.1117

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 4-cyanoaniline (177 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **3** (47.0 mg, 0.168 mmol, 56% yield) as an orange oil.

¹H NMR (400 MHz, CD₃OD): δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 6.61 (d, *J* = 8.6 Hz, 2H), 4.62 (dd, *J* = 8.1, 5.0 Hz, 1H), 3.05–2.90 (m, 2H), NH and NH₂ unobserved. **¹³C NMR (101 MHz, CD₃OD):** δ 152.8 (C), 150.6 (C), 148.8 (C), 134.5 (CH), 128.9 (CH), 124.9 (CH), 121.2 (C), 114.1 (CH), 99.1 (C), 60.7 (CH), 48.9 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₅H₁₅N₄O₂ [M+H]⁺ 283.1190, found 283.1189.

4-((2-amino-1-(4-nitrophenyl)ethyl)amino)benzamide 4

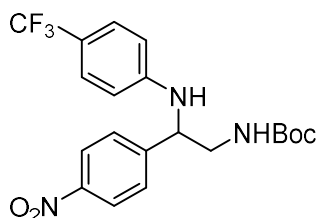


Chemical Formula: C₁₅H₁₆N₄O₃
Exact Mass: 300.1222

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 4-aminobenzamide (204 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 80/20) afforded **4** (45.0 mg, 0.150 mmol, 50% yield) as a yellow solid.

¹H NMR (400 MHz, CD₃OD): δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 2H), 6.57 (d, *J* = 8.9 Hz, 2H), 4.64 (dd, *J* = 8.3, 4.8 Hz, 1H), 3.04–2.91 (m, 2H), NH and NH₂ unobserved. **¹³C NMR (101 MHz, CD₃OD):** δ 172.5 (C), 152.4 (C), 151.1 (C), 148.7 (C), 130.3 (CH), 128.9 (CH), 124.8 (CH), 122.4 (C), 113.3 (CH), 60.8 (CH), 49.8 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₅H₁₇N₄O₃ [M+H]⁺ 301.1295, found 301.1289.

Tert-butyl (2-(4-nitrophenyl)-2-((4-(trifluoromethyl)phenyl)amino)ethyl)carbamate 5



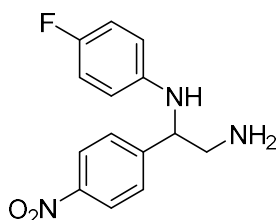
Chemical Formula: C₂₀H₂₂F₃N₃O₄
Exact Mass: 425.1562

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 4-(trifluoromethyl)aniline (242 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded target product, which was contaminated by a by-product.

The mixture was re-dissolved in DCM (5 mL) and cooled to 0 °C. Triethylamine (84 µL, 0.60 mmol, 2.0 equiv.) and Boc₂O (66 mg, 0.30 mmol, 1.0 equiv.) were then added, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (15 mL) and then extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FC over silica gel (DCM/MeOH: 100/0 to 99/1) afforded **5** (58.0 mg, 0.137 mmol, 46% yield over 2 steps) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 8.22 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 6.42 (d, *J* = 8.4 Hz, 2H), 4.91 (t, *J* = 6.6 Hz, 1H), 4.55 (dd, *J* = 8.1, 3.8 Hz, 1H), 3.66–3.40 (m, 2H), 1.47 (s, 9H). **¹³C NMR (101 MHz, CDCl₃):** δ 157.9 (C), 149.5 (C), 148.2 (C), 147.8 (C), 127.6 (CH), 126.7 (q, *J* = 3.8 Hz, CH), 124.9 (d, *J* = 270.4 Hz, CF₃), 124.4 (CH), 119.5 (q, *J* = 33.0 Hz, CH), 112.5 (CH), 80.9 (C), 60.6 (CH), 47.0 (CH₂), 28.4 (CH₃). **¹⁹F NMR (471 MHz, CDCl₃):** δ -61.1. **HRMS (ESI):** *m/z* calcd. for C₂₀H₂₂N₃O₄SF₃ [M+H]⁺ 426.1635, found 426.1621.

N*'-(4-fluorophenyl)-1-(4-nitrophenyl)ethane-1,2-diamine **6*

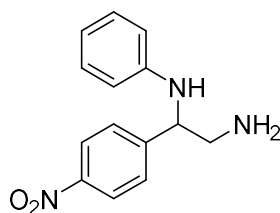


Chemical Formula: C₁₄H₁₄FN₃O₂
Exact Mass: 275.1070

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 4-fluoroaniline (167 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **6** (42.0 mg, 0.150 mmol, 50% yield) as a dark violet oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 6.81–6.77 (m, 2H), 6.47–6.39 (m, 2H), 4.97 (brs, 1H), 4.34 (dd, *J* = 7.3, 4.5 Hz, 1H), 3.15 (dd, *J* = 12.6, 4.5 Hz, 1H), 2.91 (dd, *J* = 12.6, 7.3 Hz, 1H), 1.35 (brs, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 156.2 (d, *J* = 234.6 Hz, C), 150.6 (C), 147.7 (C), 144.1 (C), 128.0 (CH), 124.2 (CH), 115.8 (d, *J* = 22.4 Hz, CH), 114.8 (d, *J* = 7.4 Hz, CH), 60.2 (CH), 48.7 (CH₂). **¹⁹F NMR (471 MHz, CD₂Cl₂):** δ -128.5 (m). **HRMS (ESI):** *m/z* calcd. for C₁₄H₁₅FN₃O₂ [M+H]⁺ 276.1143, found 276.1152.

1-(4-nitrophenyl)-N¹-phenylethane-1,2-diamine 7

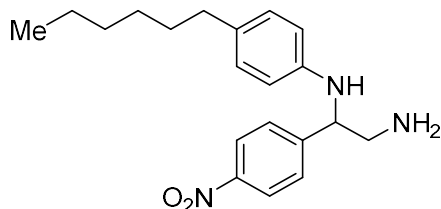


Chemical Formula: C₁₄H₁₅N₃O₂
Exact Mass: 257.1164

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **7** (55.0 mg, 0.213 mmol, 71% yield) as a brown oil.

¹H NMR (400 MHz, CD₃OD): δ 8.15 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.04–6.98 (m, 2H), 6.57–6.51 (m, 3H), 4.54 (dd, *J* = 8.3, 4.7 Hz, 1H), 3.01–2.84 (m, 2H), NH and NH₂ unobserved. **¹³C NMR (101 MHz, CD₃OD):** δ 152.0 (C), 148.9 (C), 148.5 (C), 130.0 (CH), 129.0 (CH), 124.7 (CH), 118.3 (C), 114.5 (CH), 61.2 (CH), 49.1 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₄H₁₆N₃O₂ [M+H]⁺ 258.1237, found 258.1245.

N¹-(4-hexylphenyl)-1-(4-nitrophenyl)ethane-1,2-diamine 8

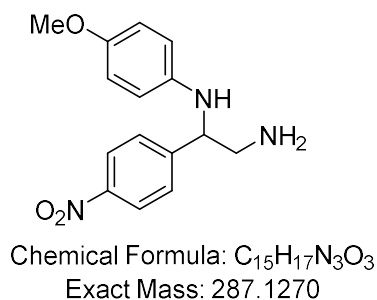


Chemical Formula: C₂₀H₂₇N₃O₂
Exact Mass: 341.2103

General Procedure **A** was followed with 4-nitrostyrene **1a** (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 4-hexylaniline (267 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **8** (46.0 mg, 0.135 mmol, 45% yield) as a brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 6.42 (d, *J* = 8.3 Hz, 2H), 4.89 (s, 1H), 4.38 (dd, *J* = 7.3, 4.4 Hz, 1H), 3.14 (dd, *J* = 12.7, 4.4 Hz, 1H), 2.91 (dd, *J* = 12.7, 7.3 Hz, 1H), 2.45–2.39 (m, 2H), 1.48 (m, 4H), 1.33–1.19 (m, 6 H), 0.88–0.84 (m, 3H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 151.1 (C), 147.6 (C), 145.4 (C), 132.7 (C), 129.3 (CH), 128.0 (CH), 124.1 (CH), 114.0 (CH), 60.0 (CH), 48.7 (CH₂), 35.3 (CH₂), 32.2 (CH₂), 32.1 (CH₂), 29.4 (CH₂), 23.0 (CH₂), 14.2 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₂₀H₂₈N₃O₂ [M+H]⁺ 342.2176, found 342.2169.

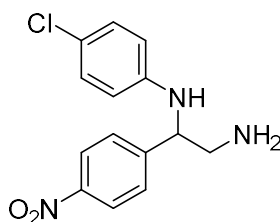
N*'-(4-methoxyphenyl)-1-(4-nitrophenyl)ethane-1,2-diamine **9*



General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then *p*-anisidine (185 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **9** (51.0 mg, 0.177 mmol, 59% yield) as a dark brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.16 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 8.9 Hz, 2H), 6.45 (d, *J* = 8.9 Hz, 2H), 4.78 (brs, 1H), 4.35 (dd, *J* = 7.6, 4.3 Hz, 1H), 3.65 (s, 3H), 3.13 (dd, *J* = 12.7, 4.3 Hz, 1H), 2.90 (dd, *J* = 12.7, 7.6 Hz, 1H), 1.61 (brs, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 152.7 (C), 151.1 (C), 147.6 (C), 141.7 (C), 128.0 (CH), 124.1 (CH), 115.2 (CH), 115.0 (CH), 60.4 (CH), 55.9 (CH₃), 48.7 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₅H₁₈N₃O₃ [M+H]⁺ 288.1343, found 288.1352.

***N'*-(4-chlorophenyl)-1-(4-nitrophenyl)ethane-1,2-diamine 10**

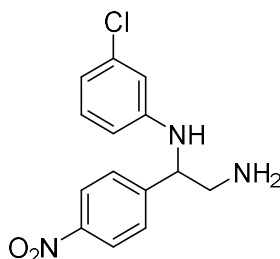


Chemical Formula: C₁₄H₁₄ClN₃O₂
Exact Mass: 291.0775

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 4-chloroaniline (192 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **10** (49.0 mg, 0.168 mmol, 56% yield) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.17 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 8.9 Hz, 2H), 6.43 (d, *J* = 8.9 Hz, 2H), 5.13 (s, 1H), 4.37 (dd, *J* = 7.0, 4.6 Hz, 1H), 3.16 (dd, *J* = 12.7, 4.6 Hz, 1H), 2.94 (dd, *J* = 12.7, 7.0 Hz, 1H), 1.25 (brs, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 150.3 (C), 147.7 (C), 146.2 (C), 129.2 (CH), 128.0 (CH), 124.2 (CH), 122.4 (C), 115.1 (CH), 59.5 (CH), 48.5 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₄H₁₅ClN₃O₂ [M+H]⁺ 292.0847, found 292.0854.

***N'*-(3-chlorophenyl)-1-(4-nitrophenyl)ethane-1,2-diamine 11**



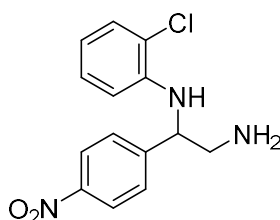
Chemical Formula: C₁₄H₁₄ClN₃O₂
Exact Mass: 291.0775

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 3-chloroaniline (192 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by

FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **11** (57.0 mg, 0.195 mmol, 65% yield) as an orange oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.18 (d, *J* = 8.6 Hz, 2H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.00 (t, *J* = 8.1 Hz, 1H), 6.61 (ddd, *J* = 8.1, 2.1, 0.9 Hz, 1H), 6.47 (t, *J* = 2.1 Hz, 1H), 6.39 (ddd, *J* = 8.1, 2.1, 0.9 Hz, 1H), 5.21 (d, *J* = 4.2 Hz, 1H), 4.40 (dd, *J* = 6.7, 4.7 Hz, 1H), 3.16 (dd, *J* = 12.7, 4.7 Hz, 1H), 2.95 (dd, *J* = 12.7, 6.7 Hz, 1H), 1.28 (brs, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 150.1 (C), 148.8 (C), 147.7 (C), 135.0 (C), 130.5 (CH), 127.9 (CH), 124.2 (CH), 117.8 (CH), 113.5 (CH), 112.3 (CH), 59.1 (CH), 48.4 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₄H₁₅ClN₃O₂ [M+H]⁺ 292.0847, found 292.0840.

N*¹-(2-chlorophenyl)-1-(4-nitrophenyl)ethane-1,2-diamine **12*

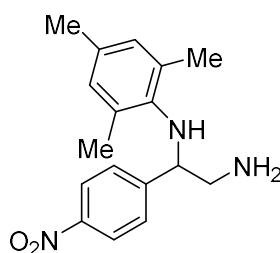


Chemical Formula: C₁₄H₁₄ClN₃O₂
Exact Mass: 291.0775

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-chloroaniline (192 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **12** (58.0 mg, 0.198 mmol, 66% yield) as an orange oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.27 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.94 (ddd, *J* = 8.1, 7.6, 1.5 Hz, 1H), 6.60 (td, *J* = 7.6, 1.5 Hz, 1H), 6.28 (dd, *J* = 8.1, 1.5 Hz, 1H), 5.66 (d, *J* = 5.3 Hz, 1H), 4.49 (dd, *J* = 6.6, 4.7 Hz, 1H), 3.22 (dd, *J* = 12.8, 4.7 Hz, 1H), 3.04 (dd, *J* = 12.8, 6.6 Hz, 1H), 1.31 (brs, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 150.0 (C), 147.8 (C), 143.3 (C), 129.5 (CH), 128.0 (CH), 127.9 (CH), 124.2 (CH), 120.0 (C), 118.2 (CH), 113.0 (CH), 59.3 (CH), 48.5 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₄H₁₅ClN₃O₂ [M+H]⁺ 292.0847, found 292.0840.

***N'*-mesityl-1-(4-nitrophenyl)ethane-1,2-diamine 13**



Chemical Formula: C₁₇H₂₁N₃O₂

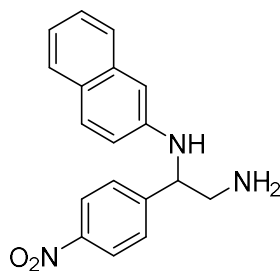
Exact Mass: 299.1634

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2,4,6-trimethylaniline (203 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **13** (43.0 mg, 0.141 mmol, 47% yield) as a dark red oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.14 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 6.74 (s, 2H), 4.27 (t, *J* = 5.0 Hz, 1H), 3.20 (dd, *J* = 12.7, 4.6 Hz, 1H), 3.05 (dd, *J* = 12.7, 5.3 Hz, 1H), 2.17 (s, 3H), 2.16 (brs, 2H), 2.13 (s, 6H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 151.3 (C), 147.4 (C), 142.8 (C), 131.0 (C), 129.9 (CH), 129.0 (C), 128.3 (CH), 123.8 (CH), 63.2 (CH), 47.3 (CH₂), 20.5 (CH₃), 19.2 (CH₃).

HRMS (ESI): *m/z* calcd. for C₁₇H₂₂N₃O₂ [M+H]⁺ 300.1707, found 300.1700.

***N'*-(naphthalen-2-yl)-1-(4-nitrophenyl)ethane-1,2-diamine 14**



Chemical Formula: C₁₈H₁₇N₃O₂

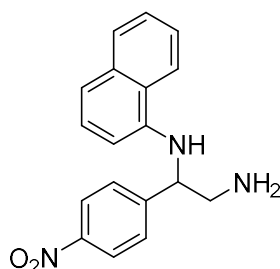
Exact Mass: 307.1321

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-naphtylamine (215 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by

FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **14** (60.0 mg, 0.195 mmol, 65% yield) as a brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.17 (d, J = 8.8 Hz, 2H), 7.66–7.57 (m, 4H), 7.42 (d, J = 8.8 Hz, 1H), 7.28 (ddd, J = 8.2, 6.8, 1.3 Hz, 1H), 7.16 (ddd, J = 8.2, 6.8, 1.3 Hz, 1H), 7.00 (dd, J = 8.8, 2.4 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 5.26 (brs, 1H), 4.54 (dd, J = 6.9, 4.6 Hz, 1H), 3.21 (dd, J = 12.7, 4.6 Hz, 1H), 3.00 (dd, J = 12.7, 6.9 Hz, 1H), 1.45 (brs, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 150.5 (C), 147.7 (C), 145.2 (C), 135.3 (C), 129.3 (CH), 128.0 (CH), 127.9 (C), 127.8 (CH), 126.6 (CH), 126.1 (CH), 124.2 (CH), 122.5 (CH), 118.6 (CH), 106.0 (CH), 59.4 (CH), 48.5 (CH₂). **HRMS (ESI):** m/z calcd. for C₁₈H₁₈N₃O₂ [M+H]⁺ 308.1394, found 308.1385.

N*¹-(naphthalen-1-yl)-1-(4-nitrophenyl)ethane-1,2-diamine **15*

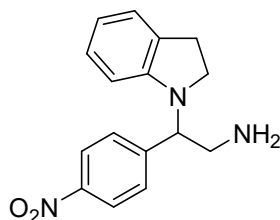


Chemical Formula: C₁₈H₁₇N₃O₂
Exact Mass: 307.1321

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 1-naphtylamine (215 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **15** (50.0 mg, 0.162 mmol, 54% yield) as a dark red oil.

¹H NMR (400 MHz, CD₃OD): δ 8.32–8.26 (m, 1H), 8.10 (d, J = 8.8 Hz, 2H), 7.72–7.68 (m, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.48–7.38 (m, 2H), 7.12–7.03 (m, 2H), 6.26 (dd, J = 7.2, 1.5 Hz, 1H), 4.70 (t, J = 6.5 Hz, 1H), 3.07 (d, J = 6.5 Hz, 2H), NH and NH₂ unobserved. **¹³C NMR (101 MHz, CD₃OD):** δ 151.7 (C), 148.5 (C), 143.7 (C), 135.9 (C), 129.4 (CH), 128.8 (CH), 127.2 (CH), 126.7 (CH), 125.6 (CH), 125.3 (C), 124.7 (CH), 122.1 (CH), 118.5 (CH), 107.0 (CH), 61.4 (CH), 49.1 (CH₂). **HRMS (ESI):** m/z calcd. for C₁₈H₁₈N₃O₂ [M+H]⁺ 308.1394, found 308.1386.

2-(Indolin-1-yl)-2-(4-nitrophenyl)ethan-1-amine 16

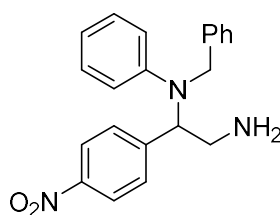


Chemical Formula: C₁₆H₁₇N₃O₂
Exact Mass: 283.1321

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then indoline (180 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **16** (51.0 mg, 0.180 mmol, 60% yield) as a dark red oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.16 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.04 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.95 (td, *J* = 7.7, 1.3 Hz, 1H), 6.59 (td, *J* = 7.4, 0.9 Hz, 1H), 6.38 (d, *J* = 7.7 Hz, 1H), 4.63 (dd, *J* = 7.9, 6.0 Hz, 1H), 3.54 (td, *J* = 8.8, 7.5 Hz, 1H), 3.41–3.18 (m, 3H), 3.06–2.91 (m, 2H), 1.50 (brs, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 151.6 (C), 147.8 (C), 147.6 (C), 130.2 (C), 129.0 (CH), 127.5 (CH), 125.0 (CH), 123.9 (CH), 117.9 (CH), 107.2 (CH), 62.4 (CH), 48.1 (CH₂), 43.8 (CH₂), 28.6 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₆H₁₈N₃O₂ [M+H]⁺ 284.1394, found 284.1387.

***N*'-benzyl-1-(4-nitrophenyl)-*N*'-phenylethane-1,2-diamine 17**



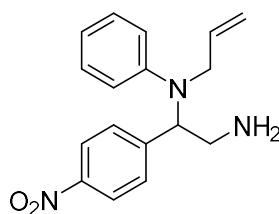
Chemical Formula: C₂₁H₂₁N₃O₂
Exact Mass: 347.1634

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then *N*-benzylaniline (275 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by

FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **17** (72.0 mg, 0.207 mmol, 69% yield) as a dark red oil.

¹H NMR (400 MHz, CD₃OD): δ 8.14 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 7.22–7.19 (m, 4H), 7.16–7.11 (m, 3H), 6.93–6.89 (m, 2H), 6.74 (t, J = 7.3 Hz, 1H), 5.16 (dd, J = 8.2, 6.1 Hz, 1H), 4.47 (d, J = 16.8 Hz, 1H), 4.33 (d, J = 16.8 Hz, 1H), 3.30–3.17 (m, 2H), NH₂ unobserved. **¹³C NMR (101 MHz, CD₃OD):** δ 150.5 (C), 148.53 (C), 148.52 (C), 140.6 (C), 130.1 (CH), 130.0 (CH), 129.4 (CH), 128.0 (CH), 127.8 (CH), 124.5 (CH), 120.2 (CH), 117.8 (CH), 67.0 (CH), 51.3 (CH₂), 44.0 (CH₂). **HRMS (ESI):** m/z calcd. for C₂₁H₂₂N₃O₂ [M+H]⁺ 348.1707, found 348.1698.

N*¹-allyl-1-(4-nitrophenyl)-*N*¹-phenylethane-1,2-diamine **18*

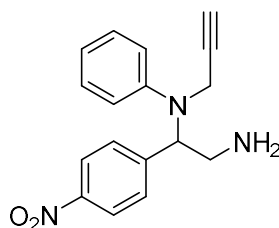


Chemical Formula: C₁₇H₁₉N₃O₂
Exact Mass: 297.1477

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then *N*-allylaniline (200 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **18** (47.0 mg, 0.156 mmol, 52% yield) as a dark red oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.15 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 7.23–7.17 (m, 2H), 6.86 (d, J = 8.0 Hz, 2H), 6.76 (t, J = 7.3 Hz, 1H), 5.86 (ddt, J = 17.2, 10.3, 5.1 Hz, 1H), 5.21–5.12 (m, 2H), 4.98 (t, J = 6.9 Hz, 1H), 3.86 (ddt, J = 11.1, 5.1, 1.8 Hz, 2H), 3.37–3.25 (m, 2H), 1.38 (brs, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 149.4 (C), 148.6 (C), 147.5 (C), 135.9 (CH), 129.4 (CH), 128.8 (CH), 123.9 (CH), 118.5 (CH), 116.7 (CH₂), 115.4 (CH), 65.4 (CH), 49.7 (CH₂), 44.1 (CH₂). **HRMS (ESI):** m/z calcd. for C₁₇H₂₀N₃O₂ [M+H]⁺ 298.1550, found 298.1544.

1-(4-Nitrophenyl)-N¹-phenyl-N¹-(prop-2-yn-1-yl)ethane-1,2-diamine 19



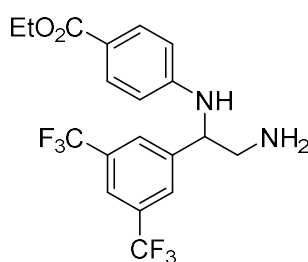
Chemical Formula: C₁₇H₁₇N₃O₂

Exact Mass: 295.1321

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then *N*-propargylaniline (197 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **19** (62.0 mg, 0.210 mmol, 70% yield) as an orange oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.16 (d, *J* = 8.9 Hz, 2H), 7.49 (d, *J* = 8.9 Hz, 2H), 7.25 (dd, *J* = 8.8, 7.3 Hz, 2H), 6.98 (dt, *J* = 7.8, 1.0 Hz, 2H), 6.86–6.82 (m, 1H), 4.96 (t, *J* = 6.7 Hz, 1H), 4.01 (d, *J* = 2.4 Hz, 2H), 3.36–3.32 (m, 2H), 2.33 (t, *J* = 2.4 Hz, 1H), 1.47 (brs, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 148.8 (C), 148.3 (C), 147.7 (C), 129.6 (CH), 128.9 (CH), 124.1 (CH), 119.7 (CH), 116.0 (CH), 80.9 (C), 72.7 (CH), 65.0 (CH), 44.5 (CH₂), 37.6 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₇H₁₈N₃O₂ [M+H]⁺ 296.1394, found 296.1388.

Ethyl 4-((2-amino-1-(3,5-bis(trifluoromethyl)phenyl)ethyl)amino)benzoate 20



Chemical Formula: C₁₉H₁₈F₆N₂O₂

Exact Mass: 420.1272

General Procedure **A** was followed with 3,5-bis(trifluoromethyl)styrene (72.0 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzocaine (248 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h. Purification

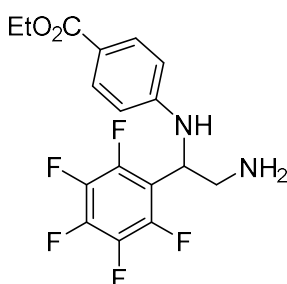
by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **20** (113.0 mg, 0.270 mmol, 90% yield) as a purple oil.

¹H NMR (400 MHz, DMSO-*d*₆): δ 8.06 (s, 2H), 7.94 (s, 1H), 7.64 (d, *J* = 8.9 Hz, 2H), 7.10 (d, *J* = 7.4 Hz, 1H), 6.60 (d, *J* = 8.9 Hz, 2H), 4.68 (q, *J* = 6.4 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.90 (m, 2H), 1.69 (brs, 2H), 1.23 (t, *J* = 7.1 Hz, 3H). **¹³C NMR (101 MHz, DMSO-*d*₆):** δ 165.7 (C), 151.8 (C), 146.3 (C), 130.9 (CH), 130.1 (q, *J* = 32.6 Hz, C), 127.6 (m, CH), 123.2 (q, *J* = 273.5 Hz, C), 120.8 (m, CH), 117.1 (C), 111.9 (CH), 59.6 (CH₂), 58.8 (CH), 48.2 (CH₂), 14.3 (CH₃). **¹⁹F NMR (471 MHz, DMSO-*d*₆):** δ -61.2. **HRMS (ESI):** *m/z* calcd. for C₁₉H₁₉F₆N₂O₂ [M+H]⁺ 421.1345, found 421.1335.

Gram-scale experiment

Under argon, a 25 ml tube equipped with a Teflon-coated magnetic stir bar was charged with [MsO-NH₃][OTf] (2.0 g, 7.5 mmol, 1.5 equiv.). HFIP (8.4 mL, 0.6 M) was added followed by 3,5-bis(trifluoromethyl)styrene (1.2 g, 5.0 mmol, 1.0 equiv.) and FeSO₄·7H₂O (140 mg, 0.5 mmol, 10 mol%) under air. The glass tube was sealed, and the reaction mixture was stirred at 60 °C for 1 h. After cooling down to room temperature, benzocaine (4.12 g, 25.0 mmol, 5.0 equiv.) was added. Then, the reaction mixture was stirred at 80 °C for 4 h. Upon completion, the reaction mixture was quenched with a solution of sat. NaHCO₃ (80 mL) and then extracted with DCM (40 mL × 3). The combined organic layers were washed with brine (80 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude mixture was purified by FC over silica gel to furnish the target product **20** (1.68 g, 4.0 mmol, 80%) as a purple oil.

Ethyl 4-((2-amino-1-(perfluorophenyl)ethyl)amino)benzoate **21**



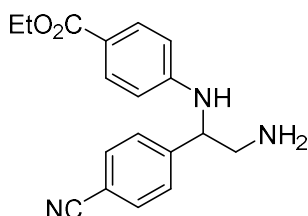
Chemical Formula: C₁₇H₁₅F₅N₂O₂
Exact Mass: 374.1054

General Procedure **A** was followed with 2,3,4,5,6-pentafluorostyrene (58.2 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzocaine (248 mg, 1.5

mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **21** (51.0 mg, 0.135 mmol, 45% yield) as a purple oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.80 (d, *J* = 8.8 Hz, 2H), 6.61 (d, *J* = 8.8 Hz, 2H), 4.96–4.83 (m, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.27 (dd, *J* = 13.0, 6.6 Hz, 1H), 3.13 (dd, *J* = 13.0, 5.8 Hz, 1H), 1.44 (brs, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 166.6 (C), 150.7 (C), 145.4 (dm, *J* = 244.3 Hz, C), 140.5 (dm, *J* = 261.1 Hz, C), 138.2 (dm, *J* = 255.0 Hz, C), 131.8 (CH), 120.6 (C), 115.1 (m, C), 112.5 (CH), 60.7 (CH₂), 52.2 (CH), 46.2 (CH₂), 14.6 (CH₃). **¹⁹F NMR (471 MHz, CD₂Cl₂):** δ -144.4 (m), -155.9 (m), -162.4 (m). **HRMS (ESI):** *m/z* calcd. for C₁₇H₁₆F₅N₂O₂ [M+H]⁺ 375.1126, found 375.116.

Ethyl 4-((2-amino-1-(4-cyanophenyl)ethyl)amino)benzoate 22

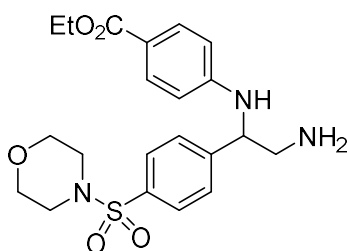


Chemical Formula: C₁₈H₁₉N₃O₂
Exact Mass: 309.1477

General Procedure **A** was followed with 4-cyanostyrene (38.7 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzocaine (248 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **22** (54.0 mg, 0.174 mmol, 58% yield) as a brown oil.

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 8.9 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 6.8 Hz, 1H), 6.52 (d, *J* = 8.9 Hz, 2H), 4.49 (q, *J* = 6.8 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.90–2.79 (m, 2H), 1.84 (brs, 2H), 1.23 (t, *J* = 7.1 Hz, 3H). **¹³C NMR (101 MHz, DMSO-*d*₆):** δ 165.7 (C), 152.0 (C), 148.5 (C), 132.3 (CH), 130.8 (CH), 127.7 (CH), 118.9 (C), 116.7 (C), 111.8 (CH), 109.7 (C), 59.6 (CH), 59.5 (CH₂), 48.3 (CH₂), 14.3 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₈H₂₀N₃O₂ [M+H]⁺ 310.1550, found 310.1542.

Ethyl 4-((2-amino-1-(4-(morpholinosulfonyl)phenyl)ethyl)amino)benzoate 23



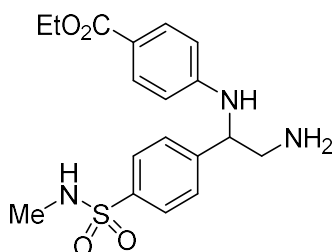
Chemical Formula: C₂₁H₂₇N₃O₅S

Exact Mass: 433.1671

General Procedure **A** was followed with 4-((4-vinylphenyl)sulfonyl)morpholine (76.0 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzocaine (248 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **23** (52.0 mg, 0.120 mmol, 40% yield) as a dark red oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.75 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 6.49 (d, *J* = 8.8 Hz, 2H), 5.61 (d, *J* = 5.5 Hz, 1H), 4.51 (dd, *J* = 6.4, 4.6 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.70 (dd, *J* = 5.7, 3.9 Hz, 4H), 3.17 (dd, *J* = 12.7, 4.6 Hz, 1H), 3.02 (dd, *J* = 12.7, 6.4 Hz, 1H), 2.98–2.92 (m, 4H), 1.59 (brs, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 166.8 (C), 151.3 (C), 147.7 (C), 134.5 (C), 131.5 (CH), 128.7 (CH), 127.8 (CH), 119.5 (C), 112.8 (CH), 66.4 (CH₂), 60.5 (CH₂), 58.6 (CH), 48.3 (CH₂), 46.4 (CH₂), 14.6 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₂₁H₂₈N₃O₅S [M+H]⁺ 434.1744, found 434.1736.

Ethyl 4-((2-amino-1-(4-(morpholinosulfonyl)phenyl)ethyl)amino)benzoate 24



Chemical Formula: C₁₈H₂₃N₃O₄S

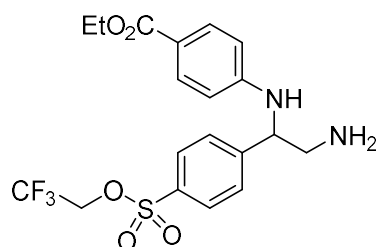
Exact Mass: 377.1409

General Procedure **A** was followed with *N*-methyl-4-vinylbenzenesulfonamide (65.1 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol,

10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzocaine (248 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **24** (64.0 mg, 0.170 mmol, 57% yield) as a yellow oil.

¹H NMR (400 MHz, CD₃OD): δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.9 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 6.56 (d, *J* = 8.9 Hz, 2H), 4.59 (dd, *J* = 8.2, 4.9 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.07–2.77 (m, 2H), 2.49 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), NH and NH₂ unobserved. **¹³C NMR (101 MHz, CD₃OD):** δ 168.7 (C), 153.4 (C), 148.3 (C), 139.6 (C), 132.2 (CH), 128.6 (2 CH), 119.1 (C), 113.2 (CH), 61.3 (CH₂), 60.8 (CH), 49.0 (CH₂), 29.3 (CH₃), 14.7 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₈H₂₄N₃O₄S [M+H]⁺ 378.1482, found 378.1470.

Ethyl 4-((2-amino-1-(4-((2,2,2-trifluoroethoxy)sulfonyl)phenyl)ethyl)amino)benzoate 25

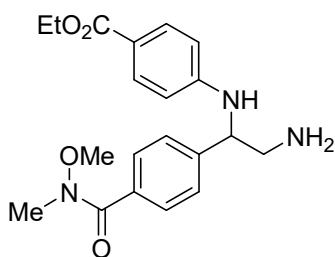


Chemical Formula: C₁₉H₂₁F₃N₂O₅S
Exact Mass: 446.1123

General Procedure **A** was followed with 2,2,2-trifluoroethyl 4-vinylbenzenesulfonate (79.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 1.50 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzocaine (248 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **25** (79.0 mg, 0.177 mmol, 59% yield) as an orange oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 6.48 (d, *J* = 8.8 Hz, 2H), 5.61 (d, *J* = 5.3 Hz, 1H), 4.52 (q, *J* = 5.4 Hz, 1H), 4.40 (qd, *J* = 7.9, 0.7 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.19 (dd, *J* = 12.7, 4.6 Hz, 1H), 3.02 (dd, *J* = 12.7, 6.3 Hz, 1H), 1.34 (brs, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 166.8 (C), 151.2 (C), 149.9 (C), 134.0 (C), 131.5 (CH), 128.8 (CH), 128.3 (CH), 122.4 (q, *J* = 277.6 Hz, CF₃), 119.7 (C), 112.8 (CH), 65.1 (q, *J* = 37.9 Hz, CH₂), 60.6 (CH₂), 58.8 (CH), 48.2 (CH₂), 14.6 (CH₃). **¹⁹F NMR (471 MHz, CD₂Cl₂):** δ -73.3 (m). **HRMS (ESI):** *m/z* calcd. for C₁₉H₂₂N₂O₅SF₃ [M+H]⁺ 447.1196, found 447.1184.

Ethyl 4-((2-amino-1-(4-(methoxy(methyl)carbamoyl)phenyl)ethyl)amino)benzoate 26



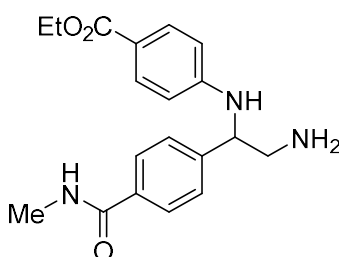
Chemical Formula: $C_{20}H_{25}N_3O_4$

Exact Mass: 371.1845

General Procedure **A** was followed with *N*-methoxy-*N*-methyl-4-vinylbenzamide (57.3 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzocaine (248 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **26** (54.0 mg, 0.145 mmol, 49% yield) as an orange oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.73 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 6.51 (d, *J* = 8.8 Hz, 2H), 5.58 (d, *J* = 5.7 Hz, 1H), 4.48 (q, *J* = 5.5 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.54 (s, 3H), 3.29 (s, 3H), 3.15 (dd, *J* = 12.6, 4.6 Hz, 1H), 3.02 (dd, *J* = 12.6, 6.3 Hz, 1H), 1.70 (s, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 169.8 (C), 166.8 (C), 151.6 (C), 144.3 (C), 133.9 (C), 131.5 (CH), 128.9 (CH), 126.6 (CH), 119.2 (C), 112.7 (CH), 61.3 (CH), 60.5 (CH₂), 58.8 (CH₃), 48.3 (CH₂), 34.0 (CH₃), 14.6 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₂₀H₂₆N₃O₄ [M+H]⁺ 372.1918, found 372.1907.

Ethyl 4-((2-amino-1-(4-(methylcarbamoyl)phenyl)ethyl)amino)benzoate 27



Chemical Formula: $C_{19}H_{23}N_3O_3$

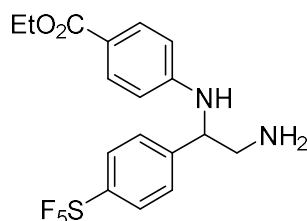
Exact Mass: 341.1739

General Procedure **A** was followed with *N*-methyl-4-vinylbenzamide (48.3 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in

HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzocaine (248 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **27** (69.5 mg, 0.204 mmol, 68% yield) as a yellow oil.

¹H NMR (400 MHz, CD₃OD): δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.69 (d, *J* = 8.9 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 6.56 (d, *J* = 8.9 Hz, 2H), 4.55 (dd, *J* = 7.8, 5.2 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.01–2.90 (m, 3H), 2.88 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), NH and NH₂ unobserved. **¹³C NMR (101 MHz, CD₃OD):** δ 170.4 (C), 168.6 (C), 153.5 (C), 146.6 (C), 134.7 (C), 132.2 (CH), 128.6 (CH), 127.9 (CH), 118.9 (C), 113.2 (CH), 61.3 (CH₂), 60.6 (CH), 48.8 (CH₂), 26.9 (CH₃), 14.7 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₉H₂₄N₃O₃ [M+H]⁺ 342.1812, found 342.1811.

Ethyl 4-((2-amino-1-(4-(pentafluoro-*I*⁶-sulfaneyl)phenyl)ethyl)amino)benzoate 28

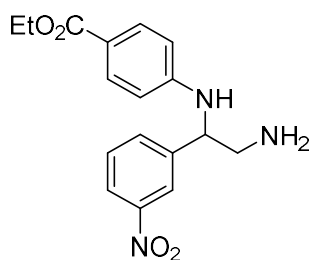


Chemical Formula: C₁₇H₁₉F₅N₂O₂S
Exact Mass: 410.1087

General Procedure **A** was followed with pentafluoro(4-vinylphenyl)-*I*⁶-sulfane (69.0 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzocaine (248 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 2 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 95/5) afforded **28** (52.0 mg, 0.126 mmol, 42% yield) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.75 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 6.48 (d, *J* = 8.8 Hz, 2H), 5.57 (d, *J* = 4.9 Hz, 1H), 4.48 (q, *J* = 5.3 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.25–3.10 (m, 1H), 3.01 (dd, *J* = 12.6, 6.2 Hz, 1H), 1.34 (brs, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 166.8 (C), 153.1 (m, C), 151.2 (C), 146.2 (C), 133.9 (C), 131.5 (CH), 127.4 (CH), 126.6 (m, CH), 119.5 (C), 112.8 (CH), 60.5 (CH₂), 58.4 (CH), 48.2 (CH₂), 14.6 (CH₃). **¹⁹F NMR (377 MHz, CD₂Cl₂):** δ 86.5 (m), 64.7 (d, *J* = 149.7 Hz). **HRMS (ESI):** *m/z* calcd. for C₁₇H₂₀F₅N₂O₂S [M+H]⁺ 411.1160, found 411.1148.

Ethyl 4-((2-amino-1-(3-nitrophenyl)ethyl)amino)benzoate 29

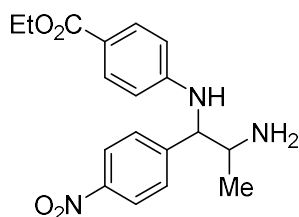


Chemical Formula: C₁₇H₁₉N₃O₄
Exact Mass: 329.1376

General Procedure **A** was followed with 3-nitrostyrene (44.7 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzocaine (248 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **29** (69.0 mg, 0.210 mmol, 70% yield) as an orange oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.21 (d, *J* = 1.9 Hz, 1H), 8.16–8.04 (m, 1H), 7.87–7.67 (m, 3H), 7.53 (t, *J* = 7.9 Hz, 1H), 6.51 (d, *J* = 8.8 Hz, 2H), 5.60 (d, *J* = 5.0 Hz, 1H), 4.52 (q, *J* = 5.4 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.19 (dd, *J* = 12.7, 4.6 Hz, 1H), 3.03 (dd, *J* = 12.7, 6.4 Hz, 1H), 1.37 (s, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 166.4 (C), 150.8 (C), 148.7 (C), 144.1 (C), 132.9 (CH), 131.2 (CH), 129.8 (CH), 122.4 (CH), 121.5 (CH), 119.3 (C), 112.5 (CH), 60.2 (CH₂), 58.2 (CH), 48.0 (CH₃), 14.2 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₇H₂₀N₃O₄ [M+H]⁺ 330.1448, found 330.1438.

Ethyl 4-((2-amino-1-(4-nitrophenyl)propyl)amino)benzoate 30



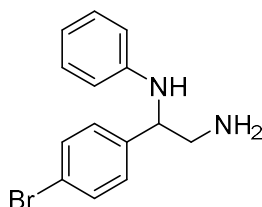
Chemical Formula: C₁₈H₂₁N₃O₄
Exact Mass: 343.1532

General Procedure **A** was followed with 1-nitro-4-(prop-1-en-1-yl)benzene (48.9 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzocaine (248 mg, 1.5

mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **30** (58.0 mg, 0.169 mmol, 56% yield, dr 4:1) as an orange oil.

Major Diastereoisomer. **¹H NMR (400 MHz, CD₂Cl₂):** δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 6.47 (d, *J* = 8.8 Hz, 2H), 5.66 (d, *J* = 6.2 Hz, 1H), 4.71–4.38 (m, 1H), 3.69–3.35 (m, 1H), 1.77 (brs, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 166.7 (C), 151.0 (C), 147.8 (2 C), 131.5 (CH), 129.0 (CH), 123.9 (CH), 119.5 (C), 112.8 (CH), 61.7 (CH), 60.5 (CH₂), 50.9 (CH), 21.1 (CH₃), 14.2 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₈H₂₂N₃O₄ [M+H]⁺ 344.1605, found 344.1595.

1-(4-Bromophenyl)-*N*'-phenylethane-1,2-diamine **31**

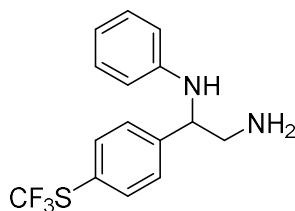


Chemical Formula: C₁₄H₁₅BrN₂
Exact Mass: 290.0419

General Procedure **B** was followed with 4-bromostyrene (55.0 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₂ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μL, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **31** (45.0 mg, 0.153 mmol, 51% yield) as a brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.46 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 7.10–7.03 (m, 2H), 6.62 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.53–6.48 (m, 2H), 4.88 (brs, 1H), 4.28 (dd, *J* = 7.0, 4.6 Hz, 1H), 3.08 (dd, *J* = 12.6, 4.6 Hz, 1H), 2.90 (dd, *J* = 12.6, 7.0 Hz, 1H), 1.27 (brs, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 147.9 (C), 142.0 (C), 132.0 (CH), 129.4 (CH), 128.9 (CH), 121.0 (C), 117.7 (CH), 113.9 (CH), 59.4 (CH), 48.9 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₄H₁₆BrN₂ [M+H]⁺ 291.0491, found 291.0486.

***N*'-phenyl-1-(4-((trifluoromethyl)thio)phenyl)ethane-1,2-diamine 33**

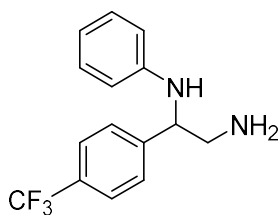


Chemical Formula: C₁₅H₁₅F₃N₂S
Exact Mass: 312.0908

General Procedure **B** was followed with (trifluoromethyl)(4-vinylphenyl)sulfane (61.2 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₂ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at 60 °C for 6 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 µL, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **33** (48.0 mg, 0.153 mmol, 51% yield) along traces of salt (93:7) as an orange oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.10–7.02 (m, 2H), 6.63 (t, *J* = 7.3 Hz, 1H), 6.51 (d, *J* = 7.7 Hz, 2H), 4.94 (brs, 1H), 4.39–4.32 (m, 1H), 3.13 (dd, *J* = 12.6, 4.6 Hz, 1H), 2.93 (dd, *J* = 12.6, 7.0 Hz, 1H), 1.26 (brs, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 147.8 (C), 146.4 (C), 137.0 (CH), 130.2 (q, *J* = 307.7 Hz, C), 129.4 (CH), 128.3 (CH), 122.9 (q, *J* = 2.1 Hz, CH), 117.8 (CH), 113.9 (CH), 59.6 (CH), 48.9 (CH₂). **¹⁹F NMR (471 MHz, CD₂Cl₂):** δ -41.4. **HRMS (ESI):** *m/z* calcd. for C₁₅H₁₆F₃N₂S [M+H]⁺ 313.0981, found 313.0968.

***N*'-phenyl-1-(4-(trifluoromethyl)phenyl)ethane-1,2-diamine 34**



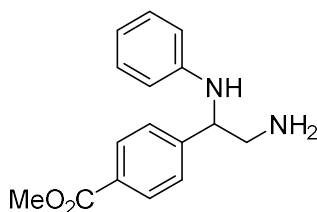
Chemical Formula: C₁₅H₁₅F₃N₂
Exact Mass: 280.1187

General Procedure **B** was followed with 4-(trifluoromethyl)styrene (51.6 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₂ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 µL, 0.06 mmol, 20 mol%)

were added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **34** (45.0 mg, 0.159 mmol, 53% yield) as a bright purple oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.60 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.07 (dd, *J* = 8.6, 7.3 Hz, 2H), 6.63 (t, *J* = 7.3 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 2H), 4.98 (brs, 1H), 4.39 (dd, *J* = 7.1, 4.6 Hz, 1H), 3.13 (dd, *J* = 12.6, 4.6 Hz, 1H), 2.94 (dd, *J* = 12.6, 7.1 Hz, 1H), 1.47 (brs, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 147.8 (C), 147.2 (C), 129.5 (q, *J* = 32.2 Hz, C), 129.4 (CH), 127.5 (CH), 125.9 (q, *J* = 3.8 Hz, CH), 124.8 (q, *J* = 272.2 Hz, C), 117.8 (CH), 113.9 (CH), 59.6 (CH), 48.8 (CH₂). **¹⁹F NMR (471 MHz, CD₂Cl₂):** δ -62.6. **HRMS (ESI):** *m/z* calcd. for C₁₅H₁₆F₃N₂ [M+H]⁺ 281.1260, found 281.1254.

Methyl 4-(2-amino-1-(phenylamino)ethyl)benzoate 35

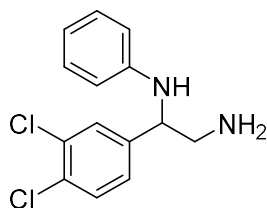


Chemical Formula: C₁₆H₁₈N₂O₂
Exact Mass: 270.1368

General Procedure **B** was followed with methyl 4-vinylbenzoate (48.6 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₃ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μL, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **35** (44.0 mg, 0.162 mmol, 54% yield) as an orange oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.07–7.01 (m, 2H), 6.61 (t, *J* = 7.3 Hz, 1H), 6.55–6.47 (m, 2H), 4.98 (brs, 1H), 4.41 (dd, *J* = 7.4, 4.6 Hz, 1H), 3.87 (s, 3H), 3.11 (dd, *J* = 12.7, 4.6 Hz, 1H), 2.94 (dd, *J* = 12.7, 7.4 Hz, 1H), 2.06 (brs, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 167.1 (C), 148.0 (C), 147.8 (C), 130.2 (CH), 129.7 (C), 129.4 (CH), 127.1 (CH), 117.8 (CH), 113.9 (CH), 59.5 (CH), 52.3 (CH₃), 48.5 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₆H₁₉N₂O₂ [M+H]⁺ 271.1441, found 271.1438.

1-(3,4-Dichlorophenyl)-N'-phenylethane-1,2-diamine 36

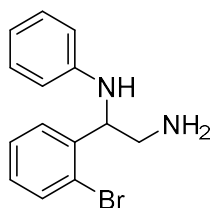


Chemical Formula: C₁₄H₁₄Cl₂N₂
Exact Mass: 280.0534

General Procedure **B** was followed with 3,4-dichlorostyrene (52.0 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₂ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μ L, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **36** (43.0 mg, 0.153 mmol, 51% yield) as a brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.49 (d, J = 2.0 Hz, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.24 (dd, J = 8.3, 2.1 Hz, 1H), 7.12–7.01 (m, 2H), 6.64 (t, J = 7.3 Hz, 1H), 6.57–6.44 (m, 2H), 4.93 (brs, 1H), 4.27 (dd, J = 7.2, 4.6 Hz, 1H), 3.08 (dd, J = 12.7, 4.6 Hz, 1H), 2.90 (dd, J = 12.7, 7.2 Hz, 1H), 1.62 (brs, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 147.6 (C), 143.6 (C), 132.9 (C), 131.1 (C), 130.9 (CH), 129.4 (CH), 129.0 (CH), 126.7 (CH), 117.9 (CH), 113.9 (CH), 59.0 (CH), 48.7 (CH₂). **HRMS (ESI):** m/z calcd. for C₁₄H₁₅Cl₂N₂ [M+H]⁺ 281.0607, found 281.0602.

1-(2-Bromophenyl)-N'-phenylethane-1,2-diamine 37



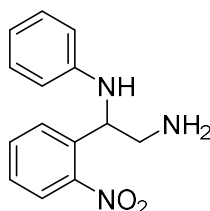
Chemical Formula: C₁₄H₁₅BrN₂
Exact Mass: 290.0419

General Procedure **B** was followed with 2-bromostyrene (55.0 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₂ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at RT for 16

h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μ L, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 $^{\circ}$ C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **37** (48.0 mg, 0.165 mmol, 55% yield) as a brown oil.

^1H NMR (400 MHz, CD_2Cl_2): δ 7.59 (dd, J = 8.0, 1.2 Hz, 1H), 7.42 (dd, J = 7.7, 1.7 Hz, 1H), 7.25 (td, J = 7.5, 1.2 Hz, 1H), 7.18–7.10 (m, 1H), 7.09–7.03 (m, 2H), 6.62 (t, J = 7.3 Hz, 1H), 6.49 (d, J = 7.7 Hz, 2H), 5.07 (brs, 1H), 4.80–4.73 (m, 1H), 3.20–3.09 (m, 1H), 2.90 (dd, J = 12.7, 7.1 Hz, 1H), 1.70 (brs, 2H). **^{13}C NMR (101 MHz, CD_2Cl_2):** δ 147.6 (C), 140.8 (C), 133.4 (CH), 129.4 (CH), 129.2 (CH), 128.4 (CH), 128.1 (CH), 123.8 (C), 117.8 (CH), 113.8 (CH), 58.6 (CH), 46.6 (CH_2). **HRMS (ESI):** m/z calcd. for $\text{C}_{14}\text{H}_{16}\text{BrN}_2$ $[\text{M}+\text{H}]^+$ 291.0491, found 291.0484.

1-(2-Nitrophenyl)- N^1 -phenylethane-1,2-diamine 38

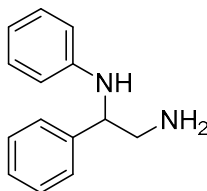


Chemical Formula: $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_2$
Exact Mass: 257.1164

General Procedure **B** was followed with 2-nitrostyrene (44.8 mg, 0.30 mmol), $[\text{PivO-NH}_3][\text{OTf}]$ (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and $\text{Fe}(\text{acac})_2$ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μ L, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 $^{\circ}$ C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **38** (36.0 mg, 0.138 mmol, 46% yield) as a brown oil.

^1H NMR (400 MHz, CD_2Cl_2): δ 7.94 (dd, J = 8.3, 1.3 Hz, 1H), 7.71 (dd, J = 8.0, 1.4 Hz, 1H), 7.55 (td, J = 7.6, 1.3 Hz, 1H), 7.41 (ddd, J = 8.3, 7.3, 1.4 Hz, 1H), 7.08–7.02 (m, 2H), 6.65–6.59 (m, 1H), 6.52–6.46 (m, 2H), 5.20–5.00 (m, 2H), 3.22 (dd, J = 12.8, 3.9 Hz, 1H), 2.95 (dd, J = 12.8, 6.6 Hz, 1H), 1.69 (brs, 2H). **^{13}C NMR (101 MHz, CD_2Cl_2):** δ 149.8 (C), 147.3 (C), 137.9 (C), 133.7 (CH), 129.5 (CH), 128.9 (CH), 128.5 (CH), 125.2 (CH), 118.1 (CH), 113.7 (CH), 55.1 (CH), 47.7 (CH_2). **HRMS (ESI):** m/z calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 258.1237, found 258.1233.

***N'*,1-diphenylethane-1,2-diamine 39**

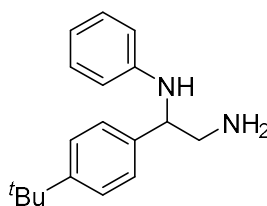


Chemical Formula: C₁₄H₁₆N₂
Exact Mass: 212.1313

General Procedure **B** was followed with styrene (31.2 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₂ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μL, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **39** (42.0 mg, 0.195 mmol, 65% yield) as a dark purple oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.37–7.30 (m, 4H), 7.27–7.23 (m, 1H), 7.07–7.01 (m, 2H), 6.60 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.57–6.52 (m, 2H), 4.94 (brs, 1H), 4.37 (dd, *J* = 7.3, 4.6 Hz, 1H), 3.08 (dd, *J* = 12.6, 4.6 Hz, 1H), 2.94 (dd, *J* = 12.6, 7.3 Hz, 1H), 2.27 (brs, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 148.1 (C), 142.6 (C), 129.4 (CH), 128.9 (CH), 127.5 (CH), 127.0 (CH), 117.5 (CH), 113.9 (CH), 59.8 (CH), 48.9 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₄H₁₇N₂ [M+H]⁺ 213.1386, found 213.1382.

***1*-(4-(*Tert*-butyl)phenyl)-*N'*-phenylethane-1,2-diamine 40**

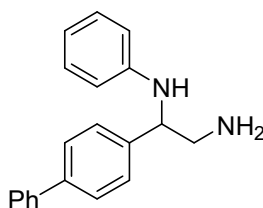


Chemical Formula: C₁₈H₂₄N₂
Exact Mass: 268.1939

General Procedure **B** was followed with 4-*tert*-butylstyrene (48.0 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₂ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μL, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **40** (41.0 mg, 0.150 mmol, 50% yield) as a brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.37 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.07 (t, *J* = 7.8 Hz, 2H), 6.61 (t, *J* = 7.3 Hz, 1H), 6.55 (d, *J* = 7.9 Hz, 2H), 4.81 (brs, 1H), 4.32 (dd, *J* = 7.0, 4.7 Hz, 1H), 3.06 (dd, *J* = 12.5, 4.7 Hz, 1H), 2.93 (dd, *J* = 12.6, 7.0 Hz, 1H), 1.43 (brs, 2H), 1.31 (s, 9H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 150.4 (C), 148.3 (C), 139.5 (C), 129.4 (CH), 126.6 (CH), 125.8 (CH), 117.4 (C), 113.8 (CH), 59.6 (CH), 49.1 (CH₂), 34.7 (C), 31.5 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₈H₂₅N₂ [M+H]⁺ 269.2012, found 269.2007.

1-([1,1'-biphenyl]-4-yl)-N'-phenylethane-1,2-diamine **41**

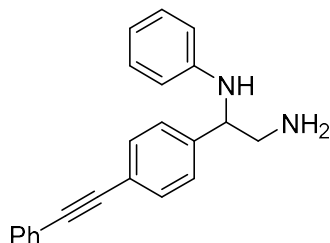


Chemical Formula: C₂₀H₂₀N₂
Exact Mass: 288.1626

General Procedure **B** was followed with 4-vinylbiphenyl (54.0 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₂ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μL, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **41** (40.0 mg, 0.138 mmol, 46% yield) as a brown oil.

¹H NMR (400 MHz, CD₃OD): δ 7.62–7.54 (m, 4H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.42–7.38 (m, 2H), 7.31 (dt, *J* = 8.1, 1.6 Hz, 1H), 7.02 (dd, *J* = 8.6, 7.3 Hz, 2H), 6.66–6.58 (m, 2H), 6.56 (t, *J* = 7.3 Hz, 1H), 4.53 (dd, *J* = 8.5, 4.9 Hz, 1H), 3.00 (qd, *J* = 13.1, 6.7 Hz, 2H), NH and NH₂ unobserved. **¹³C NMR (100 MHz, CD₃OD):** δ 149.2 (C), 142.3 (C), 142.2 (C), 141.6 (C), 129.9 (CH), 129.8 (CH), 128.4 (CH), 128.3 (2CH), 128.0 (CH), 118.2 (CH), 114.8 (CH), 60.2 (CH), 48.4 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₂₀H₂₁N₂ [M+H]⁺ 289.1699, found 289.1696.

***N'*-phenyl-1-(4-(phenylethynyl)phenyl)ethane-1,2-diamine 42**

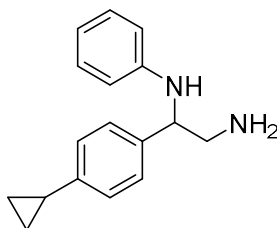


Chemical Formula: C₂₂H₂₀N₂
Exact Mass: 312.1626

General Procedure **B** was followed with 1-(phenylethynyl)-4-vinylbenzene (61.0 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₂ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μL, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **42** (45.0 mg, 0.144 mmol, 48% yield) as a brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.55–7.50 (m, 4H), 7.39–7.34 (m, 5H), 7.11–7.05 (m, 2H), 6.63 (t, *J* = 7.3 Hz, 1H), 6.55 (d, *J* = 7.9 Hz, 2H), 4.42–4.34 (m, 1H), 3.17–2.94 (m, 2H), 2.62 (brs, 2H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 147.4 (C), 142.6 (C), 131.7 (CH), 131.4 (CH), 128.9 (CH), 128.3 (CH), 128.2 (CH), 126.7 (CH), 123.1 (C), 121.9 (C), 117.3 (CH), 113.5 (CH), 89.0 (2C), 59.1 (CH), 48.1 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₂₂H₂₁N₂ [M+H]⁺ 313.1699, found 313.1699.

***1*-(4-Cyclopropylphenyl)-*N'*-phenylethane-1,2-diamine 43**



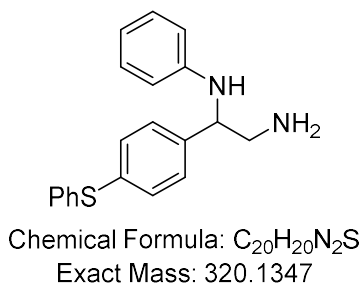
Chemical Formula: C₁₇H₂₀N₂
Exact Mass: 252.1626

General Procedure **B** was followed with 1-cyclopropyl-4-vinylbenzene (43.0 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₂ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was

stirred at RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μ L, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **43** (38.0 mg, 0.150 mmol, 50% yield) as a colorless oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.24 (d, J = 8.1 Hz, 2H), 7.07–7.04 (m, 4H), 6.62 (t, J = 7.3 Hz, 1H), 6.56 (d, J = 7.7 Hz, 2H), 4.42–4.31 (m, 1H), 3.13–2.90 (m, 2H), 2.30 (brs, 3H), 1.93–1.83 (m, 1H), 0.99–0.92 (m, 2H), 0.72–0.64 (m, 2H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 148.1 (C), 143.5 (C), 139.3 (C), 129.4 (CH), 126.9 (CH), 126.2 (CH), 117.6 (CH), 114.0 (CH), 59.4 (CH), 48.8 (CH₂), 15.3 (CH), 9.5 (CH₂), 9.4 (CH₂). **HRMS (ESI):** m/z calcd. for C₁₇H₂₁N₂ [M+H]⁺ 253.1699, found 253.1696.

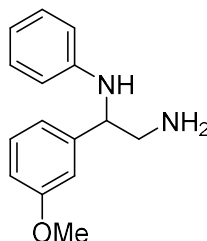
N*¹-phenyl-1-(4-(phenylthio)phenyl)ethane-1,2-diamine **44*



General Procedure **B** was followed with phenyl(4-vinylphenyl)sulfane (64.0 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₃ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μ L, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*PrOH: 100/0 to 90/10) afforded **44** (38.0 mg, 0.120 mmol, 40% yield) as a violet oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.31–7.13 (m, 9H), 7.00–6.94 (m, 2H), 6.53 (t, J = 7.3 Hz, 1H), 6.44 (d, J = 7.7 Hz, 2H), 4.26 (dd, J = 7.1, 4.6 Hz, 1H), 3.00 (dd, J = 12.6, 4.6 Hz, 1H), 2.85 (dd, J = 12.6, 7.1 Hz, 1H), 2.28 (brs, 3H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 147.9 (C), 141.5 (C), 136.0 (C), 135.0 (C), 131.6 (CH), 131.4 (CH), 129.6 (CH), 129.4 (CH), 128.0 (CH), 127.6 (CH), 117.8 (CH), 114.0 (CH), 59.1 (CH), 48.5 (CH₂). **HRMS (ESI):** m/z calcd. for C₂₀H₂₁N₂S [M+H]⁺ 321.1420, found 321.1407.

1-(3-methoxyphenyl)-N'-phenylethane-1,2-diamine 45



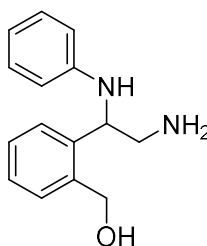
Chemical Formula: C₁₅H₁₈N₂O

Exact Mass: 242.1419

General Procedure **B** was followed with 3-methoxystyrene (40.0 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₂ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μL, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **45** (38.0 mg, 0.156 mmol, 52% yield) as a brown oil.

¹H NMR (400 MHz, CD₃OD): δ 7.22 (t, *J* = 8.1 Hz, 1H), 7.04–6.98 (m, 2H), 6.97–6.93 (m, 2H), 6.80–6.75 (m, 1H), 6.62–6.58 (m, 2H), 6.58–6.53 (m, 1H), 4.46 (dd, *J* = 8.4, 4.9 Hz, 1H), 3.74 (s, 3H), 2.97 (m, 2H), NH and NH₂ unobserved. **¹³C NMR (101 MHz, CD₃OD):** δ 161.5 (C), 149.1 (C), 144.7 (C), 130.7 (CH), 129.9 (CH), 120.1 (CH), 118.2 (CH), 114.8 (CH), 113.7 (CH), 113.3 (CH), 60.2 (CH₃), 55.6 (CH), 48.5 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₅H₁₉N₂O [M+H]⁺ 242.1492, found 242.1490.

(2-(2-Amino-1-(phenylamino)ethyl)phenyl)methanol 46



Chemical Formula: C₁₅H₁₈N₂O

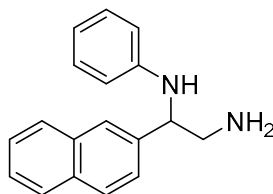
Exact Mass: 242.1419

General Procedure **B** was followed with (2-vinylphenyl)methanol (40.2 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₂ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at

RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μ L, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 $^{\circ}$ C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 70/30) afforded **46** (45.0 mg, 0.186 mmol, 62% yield) as an orange oil.

^1H NMR (400 MHz, CD_3OD): δ 7.46–7.41 (m, 1H), 7.39–7.35 (m, 1H), 7.25–7.15 (m, 2H), 6.98 (dd, J = 8.6, 7.3 Hz, 2H), 6.59 (dd, J = 8.6, 1.0 Hz, 2H), 6.55–6.49 (m, 1H), 4.82 (d, J = 2.0 Hz, 2H), 4.80–4.76 (m, 1H), 2.99 (dd, J = 13.2, 4.5 Hz, 1H), 2.87 (dd, J = 13.2, 8.6 Hz, 1H), OH, NH and NH_2 unobserved. **^{13}C NMR (100 MHz, CD_3OD):** δ 149.2 (C), 141.8 (C), 139.7 (C), 130.1 (CH), 129.8 (CH), 129.2 (CH), 128.2 (CH), 126.9 (CH), 118.0 (CH), 114.6 (CH), 63.2 (CH_2), 56.9 (CH), 48.5 (CH_2). **HRMS (ESI):** m/z calcd. for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 243.1492, found 243.1494.

1-(naphthalen-2-yl)- N^1 -phenylethane-1,2-diamine 47

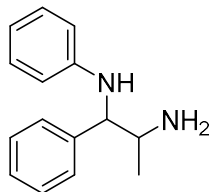


Chemical Formula: $\text{C}_{18}\text{H}_{18}\text{N}_2$
Exact Mass: 262,1470

General Procedure **B** was followed with 4-vinylnaphtalene (46.0 mg, 0.30 mmol), $[\text{PivO-NH}_3][\text{OTf}]$ (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and $\text{Fe}(\text{acac})_2$ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μ L, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 $^{\circ}$ C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **47** (44.0 mg, 0.168 mmol, 56% yield) as a brown oil.

^1H NMR (400 MHz, CD_3OD): δ 7.85–7.76 (m, 4H), 7.51 (dd, J = 8.5, 1.7 Hz, 1H), 7.42 (td, J = 7.5, 6.8, 3.8 Hz, 2H), 6.99 (dd, J = 8.6, 7.3 Hz, 2H), 6.63 (dd, J = 8.6, 1.0 Hz, 2H), 6.55–6.50 (m, 1H), 4.61 (dd, J = 8.3, 5.0 Hz, 1H), 3.10–2.96 (m, 2H), NH and NH_2 unobserved. **^{13}C NMR (100 MHz, CD_3OD):** δ 149.3 (C), 140.8 (C), 134.9 (C), 134.4 (C), 129.9 (CH), 129.5 (CH), 128.8 (CH), 128.7 (CH), 127.2 (CH), 126.7 (CH), 126.6 (CH), 125.8 (CH), 118.1 (CH), 114.8 (CH), 61.0 (CH), 47.5 (CH_2). **HRMS (ESI):** m/z calcd. for $\text{C}_{18}\text{H}_{19}\text{N}_2$ $[\text{M}+\text{H}]^+$ 263.1543, found 263.1544.

***N'*,1-diphenylpropane-1,2-diamine 48**



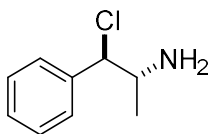
Chemical Formula: C₁₅H₁₈N₂

Exact Mass: 226.1470

General Procedure **B** was followed with trans- β -methylstyrene (36.0 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₂ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μ L, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **48** (39.0 mg, 0.171 mmol, 57% yield, dr 3.5:1) as a brown oil.

¹H NMR (400 MHz, CD₃OD, major diastereoisomer): δ 7.30–7.17 (m, 4H), 7.15–7.09 (m, 1H), 6.93–6.87 (m, 2H), 6.56–6.40 (m, 3H), 4.13 (d, J = 8.1 Hz, 1H), 3.19–3.12 (m, 1H), 1.04 (s, 1H), 0.94 (d, J = 6.1 Hz, 3H), NH₂ unobserved. **¹³C NMR (100 MHz, CD₃OD, major diastereoisomer):** δ 149.1 (C), 142.5 (C), 129.9 (CH), 129.6 (CH), 128.6 (CH), 128.5 (CH), 118.5 (CH), 115.2 (CH), 64.9 (CH), 53.1 (CH), 18.9 (CH₃). **HRMS (ESI):** m/z calcd. for C₁₅H₁₉N₂ [M+H]⁺ 227.1543, found 227.1540.

***(1R,2R)*-1-Chloro-1-phenylpropan-2-amine 48'**



Chemical Formula: C₉H₁₂ClN

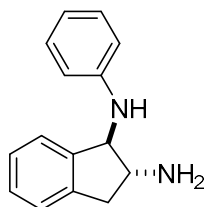
Exact Mass: 169.0658

Product isolated after the first step. Purification by FC over silica gel (DCM/*i*PrOH: 100/0 to 95/5) afforded **48'** (32.0 mg, 0.189 mmol, 63% yield, dr > 10:1) as a brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.30–7.17 (m, 4H), 7.15–7.09 (m, 1H), 6.93–6.87 (m, 2H), 6.56–6.40 (m, 3H), 4.13 (d, J = 8.1 Hz, 1H), 3.19–3.12 (m, 1H), 1.04 (s, 1H), 0.94 (d, J = 6.1 Hz, 3H),

NH₂ unobserved. ¹³C NMR (100 MHz, CD₂Cl₂): δ 149.1 (C), 142.5 (C), 129.9 (CH), 129.6 (CH), 128.6 (CH), 128.5 (CH), 118.5 (CH), 115.2 (CH), 64.9 (CH), 53.1 (CH), 18.9 (CH₃).

***N*¹-phenyl-2,3-dihydro-1*H*-indene-1,2-diamine 49**

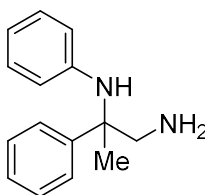


Chemical Formula: C₁₅H₁₆N₂
Exact Mass: 224.1313

General Procedure **B** was followed with indene (34.8 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₂ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μL, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **49** (29.0 mg, 0.129 mmol, 43% yield) as a brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.28–7.14 (m, 6H), 6.78–6.68 (m, 3H), 4.61 (d, *J* = 6.0 Hz, 1H), 4.00 (brs, 1H), 3.54 (m, 1H), 3.23 (dd, *J* = 15.6, 6.9 Hz, 1H), 2.69 (dd, *J* = 15.6, 7.1 Hz, 1H), 1.93 (brs, 2H). ¹³C NMR (101 MHz, CD₂Cl₂): δ 148.7 (C), 143.8 (C), 141.4 (C), 129.7 (CH), 128.3 (CH), 127.2 (CH), 125.4 (CH), 124.8 (CH), 117.8 (CH), 113.5 (CH), 67.2 (CH), 61.3 (CH), 40.0 (CH₂). HRMS (ESI): *m/z* calcd. for C₁₅H₁₇N₂ [M+H]⁺ 225.1386, found 225.1382.

***N*²,2-diphenylpropane-1,2-diamine 50**



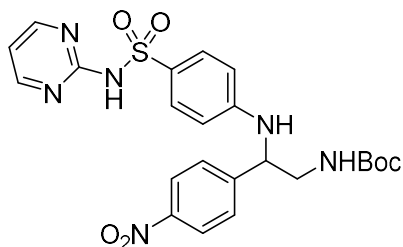
Chemical Formula: C₁₅H₁₈N₂
Exact Mass: 226.1470

General Procedure **B** was followed with α-methylstyrene (35.0 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₂ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μL, 0.06 mmol, 20 mol%) were added

to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 95/5) afforded **50** (28.0 mg, 0.123 mmol, 41% yield) as a brown oil.

¹H NMR (400 MHz, CD₃OD): δ 7.47–7.44 (m, 2H), 7.36–7.31 (m, 2H), 7.26–7.21 (m, 1H), 6.93–6.88 (m, 2H), 6.54–6.48 (m, 1H), 6.39–6.34 (m, 2H), 2.99 (d, *J* = 13.2 Hz, 1H), 2.93 (d, *J* = 13.2 Hz, 1H), 1.62 (s, 3H), NH and NH₂ unobserved. **¹³C NMR (101 MHz, CD₃OD):** δ 147.6 (C), 146.4 (C), 129.6 (CH), 129.4 (CH), 127.7 (CH), 127.5 (CH), 117.8 (CH), 116.5 (CH), 60.2 (C), 53.5 (CH₂), 24.3 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₅H₁₉N₂ [M+H]⁺ 227.1543, found 227.1537.

Tert-butyl (2-(4-nitrophenyl)-2-((4-(N-(pyrimidin-2-yl)sulfamoyl)phenyl)amino)ethyl)carbamate 51



Chemical Formula: C₂₃H₂₆N₆O₆S
Exact Mass: 514.1635

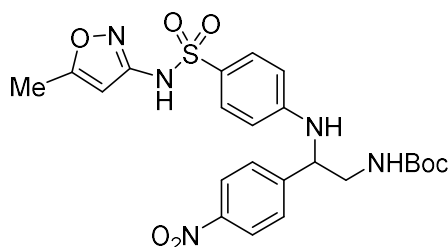
General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then sulfadiazine (226 mg, 0.9 mmol, 3.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h.

In this example, the product ends up being partially soluble in water. Thus, the reaction mixture was concentrated and directly purified by FC over silica gel (DCM/MeOH: 100/0 to 90/10) to afford target product in mixture with the corresponding salt. To get a full characterization, the mixture was Boc-protected.

The mixture was re-dissolved in DCM (5 mL) and cooled to 0 °C. Triethylamine (84 μL, 0.60 mmol, 2.0 equiv.) and Boc₂O (66 mg, 0.30 mmol, 1.0 equiv.) were then added, and the reaction mixture was stirred at rt for 4 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (15 mL) and then extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FC over silica gel (DCM/MeOH: 100/0 to 99/1) afforded **51** (80.2 mg, 0.156 mmol, 52% yield over 2 steps) as a yellow solid.

¹H NMR (400 MHz, CDCl₃): δ 11.64 (brs, 1H), 8.58 (d, J = 4.9 Hz, 2H), 8.17 (d, J = 8.6 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 6.90 (t, J = 4.9 Hz, 1H), 6.35 (d, J = 8.7 Hz, 2H), 6.27 (brs, 1H), 5.11 (t, J = 6.4 Hz, 1H), 4.57–4.47 (m, 1H), 3.57–3.37 (m, 2H), 1.43 (s, 9H). **¹³C NMR (101 MHz, CDCl₃):** δ 158.6 (CH), 158.0 (C), 157.0 (C), 151.0 (C), 148.7 (C), 148.6 (C), 130.5 (CH), 127.5 (CH), 126.7 (C), 124.4 (CH), 115.5 (CH), 112.0 (CH), 80.9 (C), 60.4 (CH), 46.8 (CH₂), 28.4 (CH₃). **HRMS (ESI):** m/z calcd. for C₂₃H₂₆N₆O₆SNa [M+Na]⁺ 537.1527, found 537.1508.

Tert-butyl (2-((4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)amino)-2-(4-nitrophenyl)ethyl)carbamate 52



Chemical Formula: C₂₃H₂₇N₅O₇S
Exact Mass: 517.1631

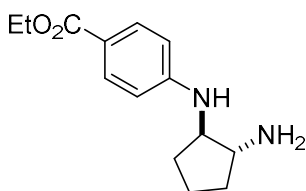
General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then sulfamethoxazole (228 mg, 0.9 mmol, 3.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h.

In this example, the product ends up being partially soluble in water. Thus, the reaction mixture was concentrated and directly purified by FC over silica gel (DCM/MeOH: 100/0 to 90/10) to afford target product in mixture with the corresponding salt. To get a full characterization, the mixture was Boc-protected.

The mixture was re-dissolved in DCM (5 mL) and cooled to 0 °C. Triethylamine (84 μ L, 0.60 mmol, 2.0 equiv.) and Boc₂O (66 mg, 0.30 mmol, 1.0 equiv.) were then added, and the reaction mixture was stirred at rt for 4 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (15 mL) and then extracted with DCM (10 mL $\times$ 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FC over silica gel (DCM/MeOH: 100/0 to 99/1) afforded **52** (77.6 mg, 0.150 mmol, 50% yield over 2 steps) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 8.21 (d, *J* = 8.4 Hz, 2H), 8.00 (brs, 1H), 7.51 (d, *J* = 8.6 Hz, 2 x 2H), 6.35 (d, *J* = 8.4 Hz, 2H), 6.34 (s, 1H), 6.16 (s, 1H), 4.96 (t, *J* = 6.4 Hz, 1H), 4.57–4.47 (m, 1H), 3.59–3.39 (m, 2H), 2.32 (s, 3H), 1.46 (s, 9H). **¹³C NMR (101 MHz, CDCl₃):** δ 170.9 (C), 158.1 (C), 157.9 (C), 151.2 (C), 147.8 (C), 147.5 (C), 129.2 (CH), 127.5 (CH), 126.2 (C), 124.5 (CH), 112.6 (CH), 95.6 (CH), 81.2 (C), 60.5 (CH), 46.9 (CH₂), 28.4 (CH₃), 12.9 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₂₃H₂₇N₅O₇SNa [M+Na]⁺ 540.1523, found 540.1507.

Ethyl 4-(2-aminocyclopentyl)amino)benzoate 53

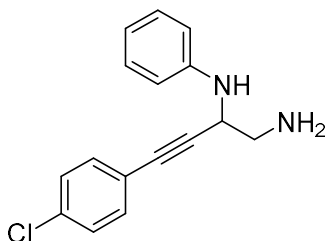


Chemical Formula: C₁₄H₂₀N₂O₂
Exact Mass: 248.1525

General Procedure **A** was followed with cyclopentene (20.5 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzocaine (248 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **53** (38.0 mg, 0.150 mmol, 50% yield) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.80 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 8.8 Hz, 2H), 4.54 (d, *J* = 6.6 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.46 (m, 1H), 3.11 (q, *J* = 7.0 Hz, 1H), 2.93 (brs, 2H), 2.31–2.18 (m, 1H), 2.04–1.92 (m, 1H), 1.73 (m, 2H), 1.49–1.36 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 166.9 (C), 152.5 (C), 131.6 (CH), 118.8 (C), 112.2 (CH), 62.0 (CH), 60.5 (CH₂), 59.2 (CH), 33.0 (CH₂), 31.4 (CH₂), 21.1 (CH₂), 14.6 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₄H₂₁N₂O₂ [M+H]⁺ 249.1598, found 249.1592.

4-(4-Chlorophenyl)-N2-phenylbut-3-yne-1,2-diamine 54

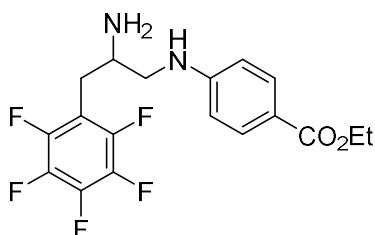


Chemical Formula: C₁₆H₁₅ClN₂
Exact Mass: 270.0924

General Procedure **B** was followed with 1-(but-3-en-1-yn-1-yl)-4-chlorobenzene (48.6 mg, 0.30 mmol), [PivO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.), NaCl (18.5 mg, 0.32 mmol, 1.05 equiv.) and Fe(acac)₃ (7.6 mg, 0.03 mmol, 10 mol%) in MeOH/DCM 3:1 (0.5 mL). The reaction mixture was stirred at RT for 16 h, then aniline (140 mg, 1.5 mmol, 5.0 equiv.) and HOTf (6 μ L, 0.06 mmol, 20 mol%) were added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 95/5) afforded **54** (44.5 mg, 0.165 mmol, 55% yield) as a brown oil.

¹H NMR (400 MHz, CD₃OD): δ 7.36–7.25 (m, 4H), 7.19–7.12 (m, 2H), 6.80 (dd, J = 8.6, 1.0 Hz, 2H), 6.74–6.65 (m, 1H), 4.39 (t, J = 6.3 Hz, 1H), 3.02 (d, J = 6.3 Hz, 2H), NH and NH₂ unobserved. **¹³C NMR (100 MHz, CD₃OD):** δ 148.8 (C), 135.3 (C), 134.1 (CH), 130.0 (CH), 129.7 (CH), 122.9 (C), 119.3 (CH), 115.4 (CH), 90.7 (C), 83.3 (C), 49.7 (CH), 46.7 (CH₂). **HRMS (ESI):** m/z calcd. for C₁₆H₁₆ClN₂ [M+H]⁺ 271.0997, found 271.0998.

Ethyl 4-((2-amino-3-(perfluorophenyl)propyl)amino)benzoate **55**



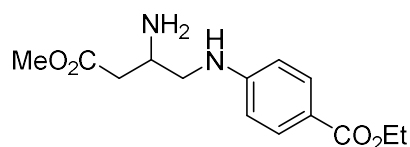
Chemical Formula: C₁₈H₁₇F₅N₂O₂
Exact Mass: 388.1210

General Procedure **A** was followed with 1-allyl-2,3,4,5,6-pentafluorobenzene (62.4 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzocaine (248 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/*i*-PrOH: 100/0 to 85/15) afforded **55** (88.5 mg, 0.23 mmol, 76% yield) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.82 (d, J = 8.8 Hz, 2H), 6.58 (d, J = 8.9 Hz, 2H), 4.86 (t, J = 5.7 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.33–3.19 (m, 2H), 3.03–2.86 (m, 2H), 2.80–2.71 (m, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.27 (s, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 166.9 (C), 152.4 (C), 145.7 (dm, J = 242.8 Hz, 2C), 140.3 (dm, J = 250.2 Hz, C), 137.7 (dm, J = 246.6 Hz, 2C), 131.6 (CH), 119.1 (C), 112.6 (td, J = 19.0, 4.2 Hz, C), 111.9 (CH), 60.5 (CH₂), 51.1 (CH), 49.4 (CH₂), 29.8 (CH₂),

14.6 (CH₃). **¹⁹F NMR (471 MHz, CD₂Cl₂):** -142.2 (m), -159.3 (m), -164.0 (m). **HRMS (ESI):** *m/z* calcd. for C₁₈H₁₈N₂F₅O₂ [M+H]⁺ 389.1283, found 389.1285.

Ethyl 4-((2-amino-4-methoxy-4-oxobutyl)amino)benzoate 56

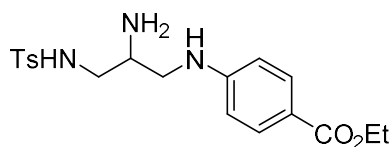


Chemical Formula: C₁₄H₂₀N₂O₄
Exact Mass: 280.1423

General Procedure **A** was followed with methyl but-3-enoate (30.0 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzocaine (248 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **56** (36.0 mg, 0.126 mmol, 42% yield) as a yellow oil.

¹H NMR (400 MHz, DMSO-d₆): δ 7.68 (d, *J* = 8.8 Hz, 2H), 6.61 (d, *J* = 8.8 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.58 (s, 3H), 3.25–3.17 (m, 1H), 3.10–2.93 (m, 2H), 2.54–2.47 (m, 1H), 2.27 (dd, *J* = 15.4, 8.4 Hz, 1H), 1.79 (brs, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), NH₂ unobserved. **¹³C NMR (101 MHz, DMSO-d₆):** δ 172.3 (C), 165.8 (C), 152.8 (C), 130.9 (CH), 116.1 (C), 110.9 (CH), 59.5 (CH₂), 51.2 (CH), 48.9 (CH₂), 48.8 (CH₂), 47.5 (CH), 14.4 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₄H₂₁N₂O₄ [M+H]⁺ 281.1496, found 281.1490.

Ethyl 4-((2-amino-3-((4-methylphenyl)sulfonamido)propyl)amino)benzoate 57



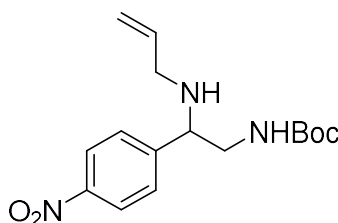
Chemical Formula: C₁₉H₂₅N₃O₄S
Exact Mass: 391.1566

General Procedure **A** was followed with *N*-allyl-4-methylbenzenesulfonamide (63.3 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzocaine

(248 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **57** (53.0 mg, 0.135 mmol, 45% yield) as dark brown oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 7.80 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 6.53 (d, *J* = 8.8 Hz, 2H), 4.70 (t, *J* = 5.2 Hz, 1H), 4.27 (t, *J* = 7.1 Hz, 2H), 3.19 (dt, *J* = 11.3, 5.0 Hz, 1H), 3.15–2.97 (m, 4H), 2.87 (dd, *J* = 13.0, 6.6 Hz, 1H), 2.41 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), NH and NH₂ unobserved. **¹³C NMR (101 MHz, CD₂Cl₂):** δ 166.9 (C), 152.2 (C), 144.2 (C), 137.1 (C), 131.7 (CH), 130.2 (CH), 127.3 (CH), 119.3 (C), 11.9 (CH), 60.5 (CH₂), 50.2 (CH), 47.3 (CH₂), 47.2 (CH₂), 21.6 (CH₃), 14.6 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₉H₂₆N₃O₄S [M+H]⁺ 392.1639, found 392.1627.

Tert-butyl (2-(allylamino)-2-(4-nitrophenyl)ethyl)carbamate 61



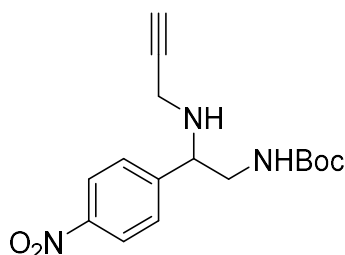
Chemical Formula: C₁₆H₂₃N₃O₄
Exact Mass: 321.1689

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then allylamine (86 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 2 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 80/20) afforded target product in mixture with the corresponding salt. To get a full characterization, the mixture was Boc-protected.

The mixture was re-dissolved in DCM (5 mL) and cooled to 0 °C. Triethylamine (84 μL, 0.60 mmol, 2.0 equiv.) and Boc₂O (66 mg, 0.30 mmol, 1.0 equiv.) were then added, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (15 mL) and then extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FC over silica gel (DCM/MeOH: 100/0 to 99/1) afforded **61** (42.0 mg, 0.131 mmol, 44% yield over 2 steps) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.18 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 5.85 (dddd, *J* = 16.9, 10.3, 6.3, 5.4 Hz, 1H), 5.19–5.00 (m, 2H), 4.85 (brs, 1H), 3.94 (t, *J* = 6.2 Hz, 1H), 3.28 (t, *J* = 5.9 Hz, 1H), 3.12 (ddt, *J* = 14.2, 5.3, 1.5 Hz, 1H), 3.04 (ddt, *J* = 14.3, 6.4, 1.3 Hz, 1H), 1.64 (s, 1H), 1.39 (s, 5H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 156.2 (C), 150.1 (C), 147.8 (C), 136.9 (CH), 128.7 (CH), 124.0 (CH), 116.1 (CH₂), 79.7 (C), 62.1 (CH), 50.2 (CH₂), 47.0 (CH₂), 28.4 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₆H₂₄N₃O₄ [M+H]⁺ 322.1761, found 322.1753.

Tert-butyl (2-(4-nitrophenyl)-2-(prop-2-yn-1-ylamino)ethyl)carbamate 62



Chemical Formula: C₁₆H₂₁N₃O₄
Exact Mass: 319.1532

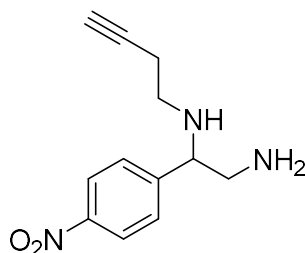
General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then propargylamine (83 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 2 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 80/20) afforded target product in mixture with the corresponding salt. To get a full characterization, the mixture was Boc-protected.

The mixture was re-dissolved in DCM (5 mL) and cooled to 0 °C. Triethylamine (84 µL, 0.60 mmol, 2.0 equiv.) and Boc₂O (66 mg, 0.30 mmol, 1.0 equiv.) were then added, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (15 mL) and then extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FC over silica gel (DCM/MeOH: 100/0 to 99/1) afforded **62** (40.0 mg, 0.125 mmol, 42% yield over 2 steps) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 4.81 (brs, 0H), 4.17 (t, *J* = 6.1 Hz, 1H), 3.42 (dd, *J* = 17.3, 2.4 Hz, 1H), 3.36–3.22 (2H), 3.12 (dd, *J* = 17.3, 2.4 Hz, 1H), 2.26 (t, *J* = 2.4 Hz, 1H), 1.83 (brs, 1H), 1.39 (s, 9H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 156.3 (C), 149.0 (C), 148.0 (C), 129.0 (CH), 124.0 (CH), 81.9 (C), 79.8 (C), 72.0 (CH), 60.7 (CH),

46.9 (CH₂), 36.2 (CH₂), 28.4 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₆H₂₂N₃O₄ [M+H]⁺ 320.1605, found 320.1597.

***N'*-(but-3-yn-1-yl)-1-(4-nitrophenyl)ethane-1,2-diamine 63**

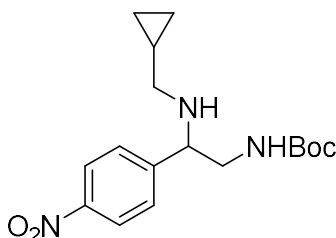


Chemical Formula: C₁₂H₁₅N₃O₂
Exact Mass: 233.1164

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then but-3-yn-1-amine (104 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 80/20) afforded **63** (29.0 mg, 0.123 mmol, 41% yield) as an orange oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 2H), 3.82 (dd, *J* = 8.2, 4.6 Hz, 1H), 2.98 (dd, *J* = 12.7, 4.6 Hz, 1H), 2.78 (dd, *J* = 12.7, 8.3 Hz, 1H), 2.68-2.55 (m, 5H), 2.37-2.30 (m, 2H), 2.04 (t, *J* = 2.6 Hz, 1H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 145.7 (C), 142.9 (C), 123.8 (CH), 119.1 (CH), 78.1 (C), 64.9 (CH), 59.3 (CH), 43.5 (CH₂), 41.3 (CH₂), 15.2 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₂H₁₆N₃O₂ [M+H]⁺ 234.1237, found 234.1237.

***Tert*-butyl (2-((cyclopropylmethyl)amino)-2-(4-nitrophenyl)ethyl)carbamate 64**



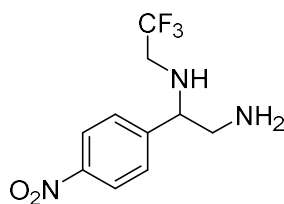
Chemical Formula: C₁₇H₂₅N₃O₄
Exact Mass: 335.1845

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then cyclopropylmethylamine (107 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 2 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 80/20) afforded target product in mixture with the corresponding salt. To get a full characterization, the mixture was Boc-protected.

The mixture was re-dissolved in DCM (5 mL) and cooled to 0 °C. Triethylamine (84 µL, 0.60 mmol, 2.0 equiv.) and Boc₂O (66 mg, 0.30 mmol, 1.0 equiv.) were then added, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (15 mL) and then extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FC over silica gel (DCM/MeOH: 100/0 to 99/1) afforded **64** (39.0 mg, 0.116 mmol, 39% yield over 2 steps) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 4.87 (brs, 1H), 3.94 (t, *J* = 6.2 Hz, 1H), 3.27 (t, *J* = 6.2 Hz, 1H), 2.39–2.24 (m, 2H), 1.64 (s, 1H), 1.39 (s, 9H), 0.94–0.85 (m, 1H), 0.48–0.37 (m, 1H), 0.08–0.02 (m, 1H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 156.2 (C), 150.5 (C), 147.7 (C), 128.6 (CH), 123.9 (CH), 79.6 (C), 62.6 (CH), 52.9 (CH₂), 47.1 (CH₂), 28.4 (CH₃), 11.6 (CH), 3.7 (CH₂), 3.24 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₇H₂₆N₃O₄ [M+H]⁺ 336.1918, found 336.1910.

1-(4-Nitrophenyl)-N¹-(2,2,2-trifluoroethyl)ethane-1,2-diamine **65**

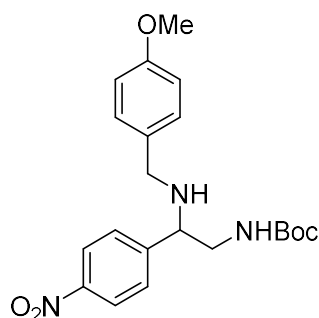


Chemical Formula: C₁₀H₁₂F₃N₃O₂
Exact Mass: 263.0882

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2,2,2-trifluoroethylamine (150 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 3 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **65** (39.0 mg, 0.150 mmol, 50% yield) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 3.83 (dd, *J* = 8.4, 4.4 Hz, 1H), 3.13–2.94 (m, 3H), 2.70 (dd, *J* = 12.7, 8.4 Hz, 1H), 1.40 (brs, 2H), NH unobserved. **¹³C NMR (101 MHz, CD₂Cl₂):** δ 149.7 (C), 148.0 (C), 128.7 (CH), 126.0 (q, *J* = 279.3 Hz, C), 124.1 (CH), 64.2 (CH), 48.9 (CH₂), 48.5 (q, *J* = 31.5 Hz, CH₂). **¹⁹F NMR (471 MHz, CD₂Cl₂):** δ -71.96. **HRMS (ESI):** *m/z* calcd. for C₁₀H₁₃F₃N₃O₂ [M+H]⁺ 264.0954, found 264.0952.

Tert-butyl (2-((4-methoxybenzyl)amino)-2-(4-nitrophenyl)ethyl)carbamate 66



Chemical Formula: C₂₁H₂₇N₃O₅
Exact Mass: 401.1951

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 4-methoxybenzylamine (210 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 95/5) afforded target product in mixture with the corresponding salt.

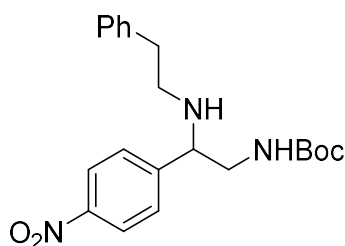
To get a full characterization, the mixture was Boc-protected. The mixture was re-dissolved in DCM (5 mL) and cooled to 0 °C. Triethylamine (84 µL, 0.60 mmol, 2.0 equiv.) and Boc₂O (66 mg, 0.30 mmol, 1.0 equiv.) were then added, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (15 mL) and then extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FC over silica gel (*n*-pentane/EtOAc: 100/0 to 50/50) afforded **66** (49.0 mg, 0.123 mmol, 41% yield over 2 steps as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 8.22 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 2H), 7.16 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.77 (s, 1H), 3.95 (t, *J* = 5.8 Hz, 1H), 3.79 (s, 3H), 3.62 (d, *J* = 13.0 Hz, 1H), 3.50 (d, *J* = 13.0 Hz, 1H), 3.37–3.22 (m, 2H), 1.75 (s, 1H), 1.41 (s, 9H). **¹³C NMR (101 MHz, CDCl₃):** δ 158.9 (C), 156.1 (C), 149.5 (C), 147.6 (C), 131.9 (C), 129.3 (CH), 128.4

(CH), 124.0 (CH), 114.0 (CH), 79.9 (C), 61.7 (CH), 55.4 (CH₃), 50.9 (CH₂), 46.9 (CH₂), 28.5 (CH₃).

HRMS (ESI): *m/z* calcd. for C₂₁H₂₈N₃O₅ [M+H]⁺ 402.2024, found 402.2017.

Tert-butyl (2-(4-nitrophenyl)-2-(phenethylamino)ethyl)carbamate 67



Chemical Formula: C₂₁H₂₇N₃O₄

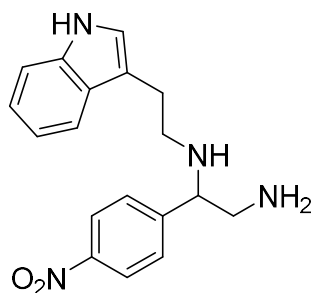
Exact Mass: 385.2002

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-phenylethylamine (182 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 2 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 80/20) afforded target product in mixture with the corresponding salt. To get a full characterization, the mixture was Boc-protected.

The mixture was re-dissolved in DCM (5 mL) and cooled to 0 °C. Triethylamine (84 μL, 0.60 mmol, 2.0 equiv.) and Boc₂O (66 mg, 0.30 mmol, 1.0 equiv.) were then added, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (15 mL) and then extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FC over silica gel (DCM/MeOH: 100/0 to 99/1) afforded **67** (47.0 mg, 0.122 mmol, 41% yield over 2 steps) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 7.37–7.26 (m, 2H), 7.25–7.20 (m, 1H), 7.17–7.12 (m, 2H), 4.81 (t, *J* = 5.9 Hz, 1H), 3.94 (t, *J* = 6.0 Hz, 1H), 3.49–3.16 (m, 2H), 2.88–2.56 (m, 4H), 1.82 (brs, 1H), 1.42 (s, 9H). **¹³C NMR (101 MHz, CDCl₃):** δ 156.0 (C), 149.4 (C), 147.5 (C), 139.6 (C), 128.7 (CH), 128.6 (CH), 128.2 (CH), 126.4 (CH), 123.8 (CH), 79.7 (C), 62.3 (CH), 48.7 (CH₂), 46.7 (CH₂), 36.3 (CH₂), 28.4 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₇H₂₈N₃O₄ [M+H]⁺ 386.2074, found 386.2064.

N'*-(2-(1*H*-indol-3-yl)ethyl)-1-(4-nitrophenyl)ethane-1,2-diamine **68*

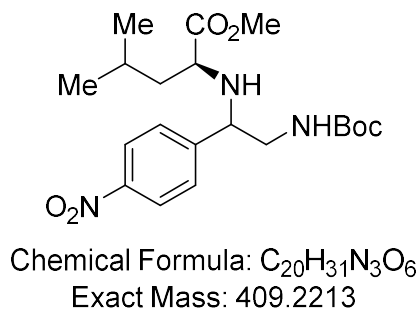


Chemical Formula: C₁₈H₂₀N₄O₂
Exact Mass: 324.1586

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then tryptamine (240 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 1 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 70/30) afforded **68** (54.0 mg, 0.167 mmol, 56% yield) along traces of salt (95:5) as an orange oil.

¹H NMR (400 MHz, CD₃OD): δ 8.09 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.08–7.02 (m, 1H), 7.01 (s, 1H), 6.94–6.88 (m, 1H), 3.77 (t, *J* = 6.5 Hz, 1H), 2.97–2.67 (m, 7H), NH (indole) and NH₂ unobserved. **¹³C NMR (101 MHz, CD₃OD):** δ 151.1 (C), 148.6 (C), 138.2 (C), 129.5 (CH), 128.6 (C), 124.5 (CH), 123.5 (CH), 122.3 (CH), 119.5 (CH), 119.3 (CH), 113.5 (C), 112.3 (CH), 65.9 (CH), 48.7 (CH₂), 48.5 (CH₂), 26.5 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₈H₂₁N₄O₂ [M+H]⁺ 325.1659, found 325.1662.

Methyl (2-((tert-butoxycarbonyl)amino)-1-(4-nitrophenyl)ethyl)-L-leucinate **69**



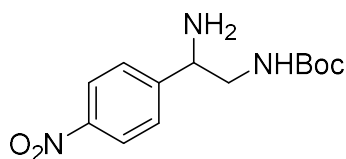
Of note, HCl salts of amino esters cannot be used in this reaction sequence as they mainly afford the aminochlorination product.

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then methyl *L*-leucinate (218 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 3 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 80/20) afforded target product in mixture with the corresponding salt. To get a full characterization, the mixture was Boc-protected.

The mixture was re-dissolved in DCM (5 mL) and cooled to 0 °C. Triethylamine (84 µL, 0.60 mmol, 2.0 equiv.) and Boc₂O (66 mg, 0.30 mmol, 1.0 equiv.) were then added, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (15 mL) and then extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FC over silica gel (Pentane/EtOAc: 100/0 to 95/5) afforded **69** (52.0 mg, 0.127 mmol, 42% yield over 2 steps, dr 1.8:1) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 8.19 (d, *J* = 8.7 Hz, 3.6H), 8.18 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 3.6H), 7.48 (d, *J* = 8.7 Hz, 2H), 4.83 (brs, 1.8H), 4.80 (brs, 1H), 3.93–3.85 (m, 1H), 3.82 (t, *J* = 6.3 Hz, 1.8H), 3.70 (s, 5.4H), 3.53 (s, 3H), 3.34–3.19 (m, 6.6H), 2.96 (dd, *J* = 8.9, 5.5 Hz, 1.8H), 2.03 (brs, 2.8H), 1.86–1.79 (m, 1.8H), 1.77–1.70 (m, 1H), 1.49–1.42 (m, 5.6H), 1.42 (s, 16.2H), 1.40 (s, 9H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 5.4H), 0.72 (d, *J* = 6.6 Hz, 5.4H). **¹³C NMR (101 MHz, CDCl₃):** δ 176.3 (C), 175.7 (C), 156.0 (C), 155.9 (C), 149.1 (C), 149.0 (C), 147.6 (C), 147.4 (C), 128.5 (CH), 128.2 (CH), 123.7 (2CH), 79.8 (C), 79.7 (C), 61.0 (CH), 60.9 (CH), 57.9 (CH), 57.4 (CH), 51.8 (CH₃), 51.7 (CH₃), 47.3 (CH₂), 45.7 (CH₂), 43.1 (CH₂), 42.7 (CH₂), 28.3 (2CH₃), 24.8 (CH), 24.6 (CH), 23.0 (CH₃), 22.7 (CH₃), 22.3 (CH₃), 21.7 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₂₀H₃₂N₃O₆ [M+H]⁺ 410.2286, found 410.2278.

Tert-butyl (2-amino-2-(4-nitrophenyl)ethyl)carbamate 72



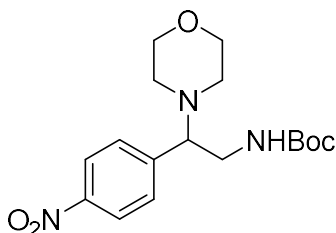
Chemical Formula: $C_{13}H_{19}N_3O_4$
Exact Mass: 281.1376

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then cyclopropylamine (86 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 2 h. The crude product was directly engaged in the Boc-protection step.

The mixture was re-dissolved in DCM (5 mL) and cooled to 0 °C. Triethylamine (84 µL, 0.60 mmol, 2.0 equiv.) and Boc₂O (66 mg, 0.30 mmol, 1.0 equiv.) were then added, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (15 mL) and then extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FC over silica gel (DCM/MeOH: 100/0 to 99/1) afforded **72** (32.0 mg, 0.114 mmol, 38% yield over 2 steps) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 4.90 (brs, 1H), 4.30–4.15 (m, 1H), 3.40–3.29 (m, 1H), 3.26–3.12 (m, 1H), 1.76 (brs, 1H), 1.41 (s, 9H). **¹³C NMR (101 MHz, CDCl₃):** δ 156.2 (C), 151.0 (C), 147.4 (C), 127.6 (CH), 123.9 (CH), 79.9 (C), 55.4 (CH), 48.3 (CH₂), 28.4 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₃H₂₀N₃O₄ [M+H]⁺ 282.1448, found 282.1441.

Tert-butyl (2-morpholino-2-(4-nitrophenyl)ethyl)carbamate 73



Chemical Formula: $C_{17}H_{25}N_3O_5$
Exact Mass: 351.1794

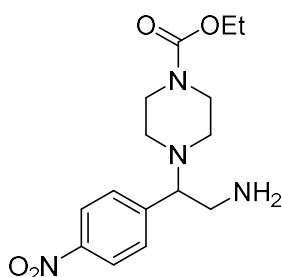
General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5

mL). The reaction mixture was stirred at 60 °C for 1 h, then morpholine (131 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 2 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 80/20) afforded target product in mixture with the corresponding salt. To get a full characterization, the mixture was Boc-protected.

The mixture was re-dissolved in DCM (5 mL) and cooled to 0 °C. Triethylamine (84 μ L, 0.60 mmol, 2.0 equiv.) and Boc₂O (66 mg, 0.30 mmol, 1.0 equiv.) were then added, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (15 mL) and then extracted with DCM (10 mL $\times$ 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FC over silica gel (DCM/MeOH: 100/0 to 99/1) afforded **73** (44.0 mg, 0.125 mmol, 42% yield over 2 steps) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.19 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 4.71 (brs, 1H), 3.67–3.64 (m, 4H), 3.57 (dt, J = 23.4, 6.3 Hz, 2H), 3.39 (dt, J = 13.3, 5.6 Hz, 1H), 2.42 (t, J = 4.7 Hz, 4H), 1.36 (s, 9H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 155.9 (C), 147.9 (C), 146.7 (C), 79.6 (C), 69.1 (CH), 67.3 (CH₂), 51.3 (CH₂), 41.9 (CH₂), 28.4 (CH₃). **HRMS (ESI):** m/z calcd. for C₁₇H₂₆N₃O₅ [M+H]⁺ 352.1867, found 352.1857.

Ethyl 4-(2-amino-1-(4-nitrophenyl)ethyl)piperazine-1-carboxylate 74

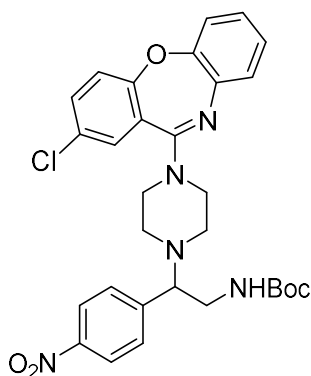


Chemical Formula: C₁₅H₂₂N₄O₄
Exact Mass: 322.1641

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then ethyl 1-piperazinecarboxylate (235 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 95/5) afforded **74** (50.0 mg, 0.155 mmol, 52% yield) as an orange oil.

¹H NMR (400 MHz, CDCl₃): δ 8.18 (d, *J* = 8.7 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 4.26 (dd, *J* = 9.9, 4.1 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.48 (m, 4H), 2.59 (m, 2H), 2.46–2.35 (m, 4H), 1.90 (brs, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). **¹³C NMR (101 MHz, CDCl₃):** δ 155.6 (C), 151.8 (C), 147.3 (C), 127.7 (CH), 123.8 (CH), 66.4 (CH₂), 61.5 (CH₂), 53.2 (CH₂), 52.3 (CH), 43.9 (CH₂), 14.8 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₅H₂₃N₄O₄ [M+H]⁺ 323.1719, found 323.1783.

Tert-butyl (2-(4-(2-chlorodibenzo[*b,f*][1,4]oxazepin-11-yl)piperazin-1-yl)-2-(4-nitrophenyl)ethyl)carbamate 75



Chemical Formula: C₃₀H₃₂ClN₅O₅
Exact Mass: 577.2092

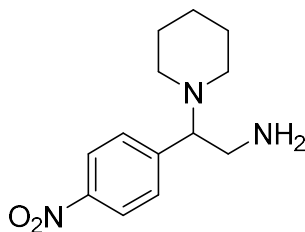
General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol) and [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then amoxapine (376 mg, 1.2 mmol, 4.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 95/5) afforded target product in mixture with amoxapine. To get a full characterization, the mixture was Boc-protected.

The mixture was re-dissolved in DCM (5 mL) and cooled to 0 °C. Triethylamine (168 μL, 1.20 mmol, 4.0 equiv.) and Boc₂O (264 mg, 1.20 mmol, 4.0 equiv.) were then added, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (15 mL) and then extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure.

Purification by FC over silica gel (*n*-pentane/EtOAc: 100/0 to 50/50) afforded **75** (81.0 mg, 0.141 mmol, 47% yield over 2 steps as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 8.23 (d, *J* = 8.8 Hz, 2H), 7.46 (m, *J* = 8.8 Hz, 2H), 7.36 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.23 (d, *J* = 2.6 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 1H), 7.12–7.05 (m, 3H), 7.00–6.96 (m, 1H), 4.69 (s, 1H), 3.73–3.64 (m, 2H), 3.58–3.42 (m, 5H), 2.57 (brs, 4H), 1.41 (s, 9H). **¹³C NMR (100 MHz, CDCl₃):** δ 159.2 (C), 158.7 (C), 155.7 (C), 151.7 (C), 147.5 (C), 145.9 (C), 139.9 (C), 132.5 (CH), 130.2 (C), 129.2 (CH), 128.9 (CH), 127.0 (CH), 125.8 (CH), 124.7 (CH), 124.6 (C), 123.7 (CH), 122.7 (CH), 120.1 (CH), 79.7 (C), 68.3 (CH), 50.0 (CH₂), 47.4 (CH₂), 41.7 (CH₂), 28.3 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₃₀H₃₃ClN₅O₅ [M+H]⁺ 578.2165, found 578.2156.

2-(4-nitrophenyl)-2-(piperidin-1-yl)ethan-1-amine **76**

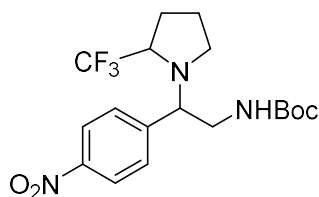


Chemical Formula: C₁₃H₁₉N₃O₂
Exact Mass: 249.1477

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then piperidine (128 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 18 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 80/20) afforded **76** (30.0 mg, 0.120 mmol, 40% yield) as an orange oil.

¹H NMR (400 MHz, CD₃OD): δ 8.25 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 3.76 (dd, *J* = 9.1, 5.7 Hz, 1H), 3.40 (dd, *J* = 13.0, 9.1 Hz, 1H), 2.99 (dd, *J* = 13.0, 5.7 Hz, 1H), 2.53–2.44 (m, 2H), 2.29 (brs, 2H), 1.65–1.56 (m, 4H), 1.40–1.33 (m, 2H), NH₂ unobserved. **¹³C NMR (101 MHz, CD₃OD):** δ 149.0 (C), 145.0 (C), 131.0 (CH), 124.2 (CH), 70.2 (CH), 51.9 (CH₂), 41.6 (CH₂), 27.3 (CH₂), 25.5 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₃H₂₀N₃O₂ [M+H]⁺ 250.1548, found 250.1550.

Tert-butyl (2-(4-nitrophenyl)-2-(2-(trifluoromethyl)pyrrolidin-1-yl)ethyl)carbamate **77**



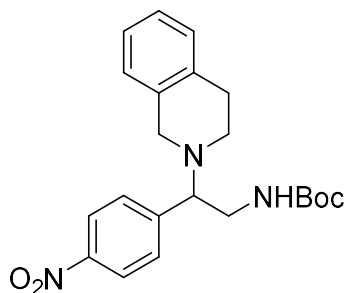
Chemical Formula: $C_{18}H_{24}F_3N_3O_4$
Exact Mass: 403.1719

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol) and $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-(trifluoromethyl)pyrrolidine (209 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 95/5) afforded target product in mixture with the corresponding salt.

To get a full characterization, the mixture was Boc-protected. The mixture was re-dissolved in DCM (5 mL) and cooled to 0 °C. Triethylamine (84 μ L, 0.60 mmol, 2.0 equiv.) and Boc_2O (66 mg, 0.30 mmol, 1.0 equiv.) were then added, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with a solution of sat. $NaHCO_3$ (15 mL) and then extracted with DCM (10 mL $\times$ 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. Purification by FC over silica gel (*n*-pentane/EtOAc: 100/0 to 90/10) afforded **77** (56.0 mg, 0.138 mmol, 46% yield over 2 steps, dr 1:1) as a yellow oil.

1H NMR (400 MHz, $CDCl_3$): δ 8.21 (m, 4H), 7.51 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 4.75 (s, 1H), 4.59 (s, 1H), 4.24 (t, J = 7.1 Hz, 1H), 4.12 (dd, J = 8.1, 6.7 Hz, 1H), 3.68–3.52 (m, 4H), 3.49–3.37 (m, 2H), 3.02–2.95 (m, 1H), 2.94–2.82 (m, 2H), 2.50–2.40 (m, 1H), 2.00–1.91 (m, 2H), 1.87–1.64 (m, 6H), 1.42 (s, 9H), 1.41 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 156.1 (C), 155.8 (C), 147.7 (C), 147.4 (C), 147.3 (C), 145.2 (C), 129.5 (CH), 129.0 (CH), 126.93 (q, J = 280.8 Hz, C), 126.89 (q, J = 282.2 Hz, C), 123.8 (2 CH), 80.0 (C), 79.7 (C), 64.7 (CH), 63.5 (CH), 61.8 (q, J = 21.9, CH), 60.8 (q, J = 21.9, CH), 49.0 (CH_2), 48.9 (CH_2), 43.4 (CH_2), 40.8 (CH_2), 28.5 (CH_3), 28.4 (CH_3), 26.8 (CH_2), 26.6 (CH_2), 24.4 (CH_2), 23.9 (CH_2). **^{19}F NMR (471 MHz, $CDCl_3$):** δ -75.2 (d, J = 7.1 Hz), -75.7 (d, J = 7.7 Hz). **HRMS (ESI):** m/z calcd. for $C_{18}H_{25}F_3N_3O_4$ $[M+H]^+$ 404.1797, found 404.1852.

Tert-butyl (2-(3,4-dihydroisoquinolin-2(1H)-yl)-2-(4-nitrophenyl)ethyl)carbamate 78



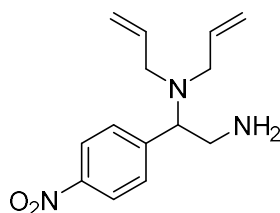
Chemical Formula: $C_{22}H_{27}N_3O_4$
Exact Mass: 397.2002

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) and $FeSO_4 \cdot 7H_2O$ (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 1,2,3,4-tetrahydroisoquinoline (200 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 80/20) afforded target product in mixture with the corresponding salt. To get a full characterization, the mixture was Boc-protected.

The mixture was re-dissolved in DCM (5 mL) and cooled to 0 °C. Triethylamine (84 μ L, 0.60 mmol, 2.0 equiv.) and Boc_2O (66 mg, 0.30 mmol, 1.0 equiv.) were then added, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with a solution of sat. $NaHCO_3$ (15 mL) and then extracted with DCM (10 mL $\times$ 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. Purification by FC over silica gel (DCM/MeOH: 100/0 to 99/1) afforded **78** (56.0 mg, 0.141 mmol, 47% yield over 2 steps) as a yellow oil.

1H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.17–7.09 (m, 3H), 7.00–6.98 (m, 1H), 4.80 (brs, 1H), 3.80–3.63 (m, 4H), 3.56–3.49 (m, 1H), 2.94–2.82 (m, 3H), 2.65–2.59 (m, 1H), 1.39 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 155.9 (C), 147.6 (C), 146.6 (C), 134.2 (C), 129.3 (CH), 128.8 (CH), 126.8 (CH), 126.5 (CH), 126.0 (CH), 123.8 (CH), 79.8 (C), 67.9 (CH), 53.2 (CH_2), 47.9 (CH_2), 42.1 (CH_2), 29.3 (CH_2), 28.5 (CH_3). **HRMS (ESI):** m/z calcd. for $C_{22}H_{28}N_3O_4$ $[M+H]^+$ 398.2073, found 398.2074.

***N',N'*-diallyl-1-(4-nitrophenyl)ethane-1,2-diamine 79**

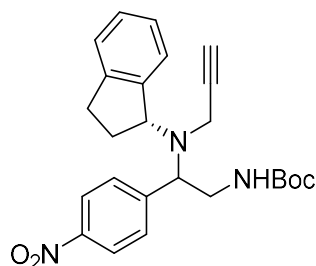


Chemical Formula: C₁₄H₁₉N₃O₂
Exact Mass: 261.1477

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then diallylamine (146 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 3 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 75/25) afforded **79** (36.0 mg, 0.135 mmol, 45% yield) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 5.84 (dddd, *J* = 17.6, 10.2, 7.6, 5.0 Hz, 2H), 5.22–5.12 (m, 4H), 3.91 (dd, *J* = 7.8, 5.9 Hz, 1H), 3.30 (ddt, *J* = 14.5, 4.9, 1.8 Hz, 2H), 3.19 (dd, *J* = 13.1, 7.8 Hz, 1H), 2.96 (dd, *J* = 13.1, 5.9 Hz, 1H), 2.81 (dd, *J* = 14.5, 7.6 Hz, 2H), 1.86 (brs, 2H). **¹³C NMR (101 MHz, CD₃OD):** δ 148.8 (C), 146.3 (C), 137.4 (CH), 131.0 (CH), 124.4 (CH), 118.2 (CH₂), 64.8 (CH), 53.9 (CH₂), 42.6 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₄H₂₀N₃O₂ [M+H]⁺ 262.1550, found 262.1543.

Tert-butyl (2-(((R)-2,3-dihydro-1H-inden-1-yl)(prop-2-yn-1-yl)amino)-2-(4-nitrophenyl)ethyl)carbamate 80



Chemical Formula: C₂₅H₂₉N₃O₄
Exact Mass: 435.2158

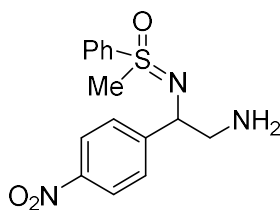
General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then rasagiline (257 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 6 h. Purification by FC

over silica gel (DCM/MeOH: 100/0 to 90/10) afforded target product in mixture with the corresponding salt. To get a full characterization, the mixture was Boc-protected.

The mixture was re-dissolved in DCM (5 mL) and cooled to 0 °C. Triethylamine (84 µL, 0.60 mmol, 2.0 equiv.) and Boc₂O (66 mg, 0.30 mmol, 1.0 equiv.) were then added, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (15 mL) and then extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FC over silica gel (DCM/MeOH: 100/0 to 99/1) afforded **80** (57.0 mg, 0.131 mmol, 44% yield over 2 steps, dr 1:1) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 8.25–8.20 (m, 2H), 7.67–7.61 (m, 2H), 7.35–7.31 (m, 0.5H), 7.24–7.12 (m, 3.5H), 4.81–4.58 (m, 1.5H), 4.48–4.43 (m, 0.5H), 4.39–4.30 (m, 1H), 3.91–3.78 (m, 1H), 3.66–3.53 (m, 1H), 3.41 (dd, *J* = 17.8, 2.5 Hz, 0.5H), 3.30 (dd, *J* = 17.8, 2.3 Hz, 0.5H), 3.28 (dd, *J* = 17.9, 2.3 Hz, 0.5H), 3.10 (dd, *J* = 17.9, 2.3 Hz, 0.5H), 3.05–2.94 (m, 0.5H), 2.90–2.74 (m, 1H), 2.68–2.58 (m, 0.5H), 2.32–2.14 (m, 1H), 2.29 (t, *J* = 2.4 Hz, 0.5H), 2.18 (t, *J* = 2.4 Hz, 0.5H), 2.01–1.92 (m, 0.5H), 1.79–1.70 (m, 0.5H), 1.41 (s, 4.5H), 1.39 (s, 4.5H). **¹³C NMR (101 MHz, CDCl₃):** δ 155.8 (2C), 148.5 (C), 148.3 (C), 147.6 (C), 147.5 (C), 143.8 (C), 143.4 (C), 143.2 (C), 142.9 (C), 129.5 (CH), 129.3 (CH), 127.9 (2CH), 126.8 (CH), 126.6 (CH), 125.1 (CH), 124.9 (CH), 124.7 (CH), 124.5 (CH), 123.9 (CH), 123.8 (CH), 81.8 (C), 81.7 (C), 79.9 (C), 79.7 (C), 73.0 (CH), 72.7 (CH), 65.2 (CH), 65.1 (CH), 63.4 (CH), 62.9 (CH), 43.1 (CH₂), 42.6 (CH₂), 36.0 (2CH₂), 30.6 (CH₂), 30.4 (CH₂), 28.5 (2CH₃), 27.9 (CH₂), 25.6 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₂₅H₂₉N₃O₄Na [M+Na]⁺ 458.2050, found 458.2028.

((2-Amino-1-(4-nitrophenyl)ethyl)imino)(methyl)(phenyl)-λ⁶-sulfanone 81



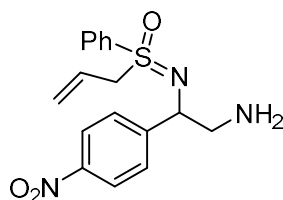
Chemical Formula: C₁₅H₁₇N₃O₃S
Exact Mass: 319.0991

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then (±)-imino(methyl)(phenyl)-λ⁶-sulfanone (233 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for

16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **81** (56.0 mg, 0.174 mmol, 58% yield, dr 1:1) as a dark orange oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.14 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H), 7.97–7.95 (m, 2H), 7.68–7.56 (m, 7H), 7.51 (m, 1H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.38 (m, 2H), 4.17 (dd, *J* = 7.1, 4.8 Hz, 1H), 4.13 (dd, *J* = 7.6, 4.4 Hz, 1H), 3.18 (s, 3H), 3.09 (s, 3H), 2.89–2.78 (m, 4H), 2.26 (brs, 4H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 152.7 (C), 151.7 (C), 147.3 (C), 147.2 (C), 139.9 (C), 139.8 (C), 133.5 (CH), 133.3 (CH), 129.8 (CH), 129.5 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 128.2 (CH), 123.6 (CH), 123.5 (CH), 61.0 (CH), 60.9 (CH), 51.1 (CH₂), 51.0 (CH₂), 45.7 (CH₃), 45.3 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₅H₁₈N₃O₃S [M+H]⁺ 320.1063, found 320.1057.

Allyl((2-amino-1-(4-nitrophenyl)ethyl)imino)(phenyl)-I⁶-sulfanone 82



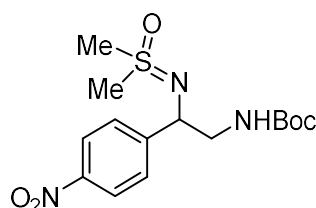
Chemical Formula: C₁₇H₁₉N₃O₃S

Exact Mass: 345.1147

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then allyl(imino)(phenyl)-I⁶-sulfanone (270 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 2 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **82** (58.0 mg, 0.168 mmol, 56% yield, dr 1.5:1) along traces of products arising from the isomerization of the double bond as an orange oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.15 (d, *J* = 8.7 Hz, 3H), 8.10 (d, *J* = 8.7 Hz, 2H), 7.91–7.87 (m, 3H), 7.67–7.63 (m, 1.5H), 7.61–7.55 (m, 8H), 7.53–7.46 (m, 3H), 7.40–7.36 (m, 2H), 5.88–5.77 (m, 1H), 5.73–5.62 (m, 1.5H), 5.28 (d, *J* = 10.2 Hz, 1H), 5.20 (d, *J* = 10.1 Hz, 1.5H), 5.13–5.05 (m, 1H), 5.02–4.94 (m, 1.5H), 4.28 (dd, *J* = 6.7, 4.9 Hz, 1.5H), 4.16 (dd, *J* = 7.3, 4.4 Hz, 1H), 4.00–3.81 (m, 5H), 2.90–2.72 (m, 5H), 1.86 (brs, 5H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 152.9 (C), 152.0 (C), 147.3 (C), 147.2 (C), 137.7 (2C), 133.5 (CH), 133.4 (CH), 129.8 (CH), 129.7 (CH), 129.5 (CH), 129.3 (CH), 128.3 (CH), 128.2 (CH), 126.0 (CH), 124.3 (CH₂), 124.1 (CH₂), 123.6 (2CH), 61.7 (CH₂), 61.3 (CH+CH₂), 60.8 (CH), 51.4 (2CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₇H₂₀N₃O₃S [M+H]⁺ 346.1215, found 346.1220.

Tert-butyl (2-((dimethyl(oxo)-*l*⁶-sulfaneylidene)amino)-2-(4-nitrophenyl)ethyl)carbamate 83



Chemical Formula: C₁₅H₂₃N₃O₅S

Exact Mass: 357.1358

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then dimethylsulfoximine (140 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 2 h. The crude product was directly engaged in the Boc-protection step.

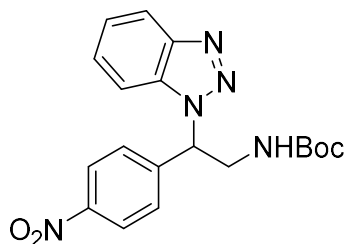
The mixture was re-dissolved in DCM (5 mL) and cooled to 0 °C. Triethylamine (84 µL, 0.60 mmol, 2.0 equiv.) and Boc₂O (66 mg, 0.30 mmol, 1.0 equiv.) were then added, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (15 mL) and then extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FC over silica gel (DCM/MeOH: 100/0 to 99/1) afforded **83** (55.0 mg, 0.154 mmol, 51% yield over 2 steps) as a yellow oil.

Because of the presence of sulfoximine and Boc group, the product appears as a mixture 7:3.

¹H NMR (400 MHz, CDCl₃): δ 8.15 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 1.4H), 7.48 (d, *J* = 8.6 Hz, 0.6H), 5.76 (brs, 0.3H), 5.12 (brs, 0.7H), 4.80 (brs, 0.3H), 4.62–4.52 (m, 0.7H), 3.47–3.38 (m, 1H), 3.18–3.05 (m, 1H), 3.08 (s, 2.1H), 2.96 (s, 0.9H), 2.88 (s, 0.9H), 2.86 (s, 2.1H), 1.40 (s, 9H).

¹³C NMR (101 MHz, CDCl₃): δ 156.0 (C), 155.5 (C), 150.9 (C), 147.2 (C), 147.1 (C), 127.9 (CH), 127.6 (CH), 123.7 (CH), 123.5 (CH), 79.9 (C), 79.5 (C), 57.1 (CH), 49.0 (CH₂), 48.3 (CH₂), 43.1 (CH₃), 42.5 (CH₃), 28.5 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₅H₂₄N₃O₅S [M+H]⁺ 358.1431, found 358.1420.

Tert-butyl (2-(1H-benzo[d][1,2,3]triazol-1-yl)-2-(4-nitrophenyl)ethyl)carbamate 84



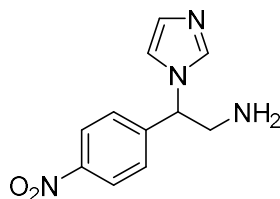
Chemical Formula: $C_{19}H_{21}N_5O_4$
Exact Mass: 383.1594

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) and $FeSO_4 \cdot 7H_2O$ (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then benzotriazole (179 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 2 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded target product in mixture with the corresponding salt. To get a full characterization, the mixture was Boc-protected.

The mixture was re-dissolved in DCM (5 mL) and cooled to 0 °C. Triethylamine (84 μ L, 0.60 mmol, 2.0 equiv.) and Boc_2O (66 mg, 0.30 mmol, 1.0 equiv.) were then added, and the reaction mixture was stirred at rt for 1 h. The reaction mixture was quenched with a solution of sat. $NaHCO_3$ (15 mL) and then extracted with DCM (10 mL $\times$ 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. Purification by FC over silica gel (DCM/MeOH: 100/0 to 99/1) afforded **84** (71.0 mg, 0.185 mmol, 62% yield over 2 steps) as a yellow oil.

1H NMR (400 MHz, CD_2Cl_2): δ 8.17 (d, J = 8.8 Hz, 2H), 8.06 (d, J = 8.2 Hz, 1H), 7.62–7.32 (m, 5H), 6.18 (dd, J = 8.8, 4.5 Hz, 1H), 5.30 (t, J = 5.5 Hz, 1H), 4.33–4.25 (m, 1H), 4.22–4.14 (m, 1H), 1.33 (s, 9H). **^{13}C NMR (101 MHz, CD_2Cl_2):** δ 156.1 (C), 148.4 (C), 146.5 (C), 144.4 (C), 133.8 (C), 128.4 (CH), 128.2 (CH), 124.8 (CH), 124.4 (CH), 120.3 (CH), 109.9 (CH), 80.1 (C), 62.2 (CH), 45.2 (CH_2), 28.3 (CH_3). **HRMS (ESI):** m/z calcd. for $C_{19}H_{22}N_5O_4$ $[M+H]^+$ 384.1666, found 384.1654.

2-(1H-imidazol-1-yl)-2-(4-nitrophenyl)ethan-1-amine 85

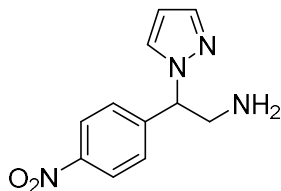


Chemical Formula: $C_{11}H_{12}N_4O_2$
Exact Mass: 232.0960

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) and $FeSO_4 \cdot 7H_2O$ (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then imidazole (103 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 80/20) afforded **85** (36.0 mg, 0.153 mmol, 51% yield) as a yellow oil.

1H NMR (400 MHz, CD_2Cl_2): δ 8.19 (d, J = 8.8 Hz, 2H), 7.66 (s, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 15.5 Hz, 2H), 5.28 (dd, J = 8.2, 5.6 Hz, 1H), 3.51–3.40 (m, 2H), 1.50 (brs, 2H). **^{13}C NMR (101 MHz, CD_2Cl_2):** δ 148.1 (C), 146.4 (C), 137.2 (CH), 130.3 (CH), 128.0 (CH), 124.4 (CH), 118.0 (CH), 64.0 (CH), 46.6 (CH_2). **HRMS (ESI):** m/z calcd. for $C_{11}H_{13}N_4O_2$ $[M+H]^+$ 233.1033, found 233.1031.

2-(4-nitrophenyl)-2-(1H-pyrazol-1-yl)ethan-1-amine 86



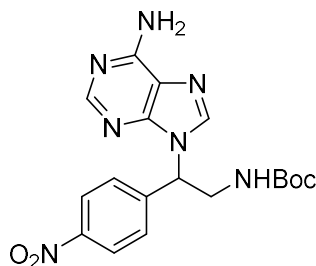
Chemical Formula: $C_{11}H_{12}N_4O_2$
Exact Mass: 232.0960

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) and $FeSO_4 \cdot 7H_2O$ (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then pyrazole (103 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 4 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 95/5) afforded **86** (41.0 mg, 0.177 mmol, 59% yield) as a yellow oil.

1H NMR (400 MHz, CD_2Cl_2): δ 8.14 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 1.6 Hz, 1H), 7.55 (d, J = 2.3 Hz, 1H), 7.40 (d, J = 8.8 Hz, 2H), 6.34 (t, J = 2.1 Hz, 1H), 5.38 (dd, J = 9.1, 4.8 Hz, 1H), 3.65 (dd,

$J = 13.5, 9.1$ Hz, 1H), 3.32 (dd, $J = 13.5, 4.7$ Hz, 1H), 1.36 (brs, 2H). **^{13}C NMR (101 MHz, CD_2Cl_2):** δ 147.8 (C), 147.3 (C), 140.3 (CH), 130.4 (CH), 128.1 (CH), 124.0 (CH), 106.2 (CH), 68.5 (CH), 47.0 (CH_2). **HRMS (ESI):** m/z calcd. for $\text{C}_{11}\text{H}_{13}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ 233.1033, found 233.1026.

Tert-butyl (2-(6-amino-9H-purin-9-yl)-2-(4-nitrophenyl)ethyl)carbamate 87



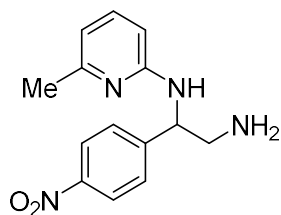
Chemical Formula: $\text{C}_{18}\text{H}_{21}\text{N}_7\text{O}_4$
Exact Mass: 399.1655

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), $[\text{MsO-NH}_3][\text{OTf}]$ (120 mg, 0.45 mmol, 1.5 equiv.) and $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then adenine (203 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 2 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 60/40) afforded target product in mixture with the corresponding salt. To get a full characterization, the mixture was Boc-protected.

The mixture was re-dissolved in DMF (5 mL) and cooled to 0 °C. Triethylamine (84 μL , 0.60 mmol, 2.0 equiv.) and Boc_2O (66 mg, 0.30 mmol, 1.0 equiv.) were then added, and the reaction mixture was stirred at rt for 4 h. The reaction mixture was quenched with a solution of sat. NaHCO_3 (15 mL) and then extracted with DCM (10 mL $\times$ 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **87** (50.0 mg, 0.126 mmol, 42% yield over 2 steps) as a yellow solid.

^1H NMR (400 MHz, DMSO-d_6): δ 8.44 (s, 1H), 8.21 (d, $J = 8.7$ Hz, 2H), 8.09 (s, 1H), 7.64 (d, $J = 8.8$ Hz, 2H), 7.32–7.24 (m, 3H), 5.91 (dd, $J = 8.9, 6.1$ Hz, 1H), 4.06–3.97 (m, 1H), 3.94–3.86 (m, 1H), 1.30 (s, 9H). **^{13}C NMR (101 MHz, DMSO-d_6):** δ 156.1 (C), 155.7 (C), 152.5 (CH), 149.6 (C), 147.2 (C), 145.6 (C), 139.7 (CH), 128.6 (CH), 123.9 (CH), 118.9 (C), 78.3 (C), 57.2 (CH), 42.7 (CH_2), 28.1 (CH_3). **HRMS (ESI):** m/z calcd. for $\text{C}_{20}\text{H}_{24}\text{N}_5\text{O}_4$ $[\text{M}+\text{H}]^+$ 400.1728, found 400.1718.

N¹-(6-methylpyridin-2-yl)-1-(4-nitrophenyl)ethane-1,2-diamine 88



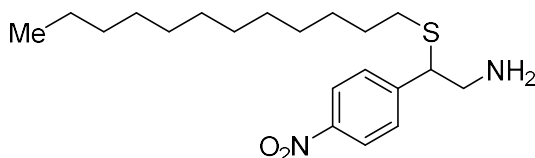
Chemical Formula: $C_{14}H_{16}N_4O_2$
Exact Mass: 272.1273

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) and $FeSO_4 \cdot 7H_2O$ (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 6-methylpyridin-2-amine (162 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 6 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 80/20) afforded **88** (24.0 mg, 0.088 mmol, 29% yield) as a yellow oil. **Of note**, the product is rather unstable on silica and must be rapidly purified.

1H NMR (400 MHz, CD_2Cl_2): δ 8.15 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 8.7 Hz, 2H), 7.22 (t, J = 7.8 Hz, 1H), 6.42 (d, J = 7.3 Hz, 1H), 6.06 (d, J = 8.3 Hz, 1H), 5.73 (brs, 1H), 4.80 (s, 1H), 3.18-3.06 (m, 2H), 2.38 (brs, 2H), 2.27 (s, 3H). **^{13}C NMR (101 MHz, CD_2Cl_2):** δ 157.7 (C), 157.2 (C), 150.5 (C), 147.6 (C), 138.2 (CH), 128.0 (CH), 124.0 (CH), 113.1 (CH), 104.5 (CH), 57.7 (CH), 47.8 (CH₂), 24.3 (CH₃). **HRMS (ESI):** m/z calcd. for $C_{14}H_{17}N_4O_2$ $[M+H]^+$ 373.1346, found 373.1342.

3.5 Characterization Data of Aminothiolation Products

2-(Dodecylthio)-2-(4-nitrophenyl)ethan-1-amine **90**

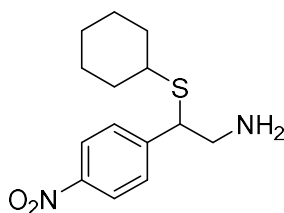


Chemical Formula: $C_{20}H_{34}N_2O_2S$
Exact Mass: 366.2341

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) and $FeSO_4 \cdot 7H_2O$ (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 1-dodecanethiol (305 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 95/5) afforded **90** (58.0 mg, 0.156 mmol, 52% yield) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 3.87 (t, *J* = 6.9 Hz, 1H), 3.10–2.98 (m, 2H), 2.40–2.31 (m, 2H), 1.51–1.43 (m, 2H), 1.33–1.20 (m, 20H), 0.89–0.84 (m, 3H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 150.1 (C), 147.4 (C), 129.4 (CH), 124.0 (CH), 53.8 (CH), 47.8 (CH₂), 32.3 (CH₂), 31.5 (CH₂), 30.03 (CH₂), 30.02 (CH₂), 29.96 (CH₂), 29.9 (CH₂), 29.8 (CH₂), 29.7 (CH₂), 29.5 (CH₂), 29.2 (CH₂), 23.1 (CH₂), 14.3 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₂₀H₃₅N₂O₂S [M+H]⁺ 367.2414, found 367.2405.

2-(Cyclohexylthio)-2-(4-nitrophenyl)ethan-1-amine **91**



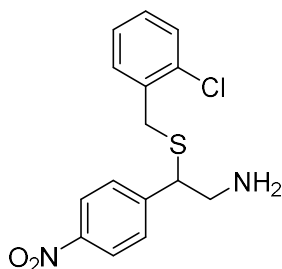
Chemical Formula: C₁₄H₂₀N₂O₂S

Exact Mass: 280.1245

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then cyclohexanethiol (175 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 95/5) afforded **91** (51.0 mg, 0.180 mmol, 60% yield) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H), 3.94 (t, *J* = 6.9 Hz, 1H), 3.01 (m, 2H), 2.46 (m, 1H), 1.97–1.91 (m, 1H), 1.77–1.62 (m, 3H), 1.57–1.51 (m, 1H), 1.45 (brs, 2H), 1.36–1.15 (m, 5H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 150.7 (C), 147.4 (C), 129.3 (CH), 124.0 (CH), 52.3 (CH), 48.3 (CH₂), 43.7 (CH), 34.3 (CH₂), 34.1 (CH₂), 26.4 (CH₂), 26.2 (CH₂), 26.1 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₄H₂₁N₂O₂S [M+H]⁺ 281.1318, found 281.1311.

2-((2-Chlorobenzyl)thio)-2-(4-nitrophenyl)ethan-1-amine **92**

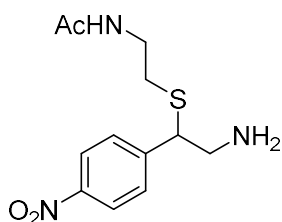


Chemical Formula: $C_{15}H_{15}ClN_2O_2S$
Exact Mass: 322.0543

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) and $FeSO_4 \cdot 7H_2O$ (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then 2-chlorobenzenemethanethiol (240 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 95/5) afforded **92** (62.0 mg, 0.192 mmol, 64% yield) as a yellow oil.

1H NMR (400 MHz, CD_3OD): δ 8.17 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.33–7.25 (m, 2H), 7.20–7.16 (m, 2H), 3.98 (t, J = 7.2 Hz, 1H), 3.78 (d, J = 13.3 Hz, 1H), 3.72 (d, J = 13.3 Hz, 1H), 3.06–2.94 (m, 2H), NH and NH_2 unobserved. **^{13}C NMR (101 MHz, CD_3OD):** δ 150.1 (C), 148.5 (C), 136.9 (C), 135.0 (C), 132.1 (CH), 130.7 (CH), 130.4 (CH), 129.8 (CH), 128.1 (CH), 124.7 (CH), 53.9 (CH), 47.6 (CH_2), 34.1 (CH_2). **HRMS (ESI):** m/z calcd. for $C_{15}H_{16}ClN_2O_2S$ $[M+H]^+$ 323.0616, found 323.0607.

***N*-(2-((2-amino-1-(4-nitrophenyl)ethyl)thio)ethyl)acetamide 93**



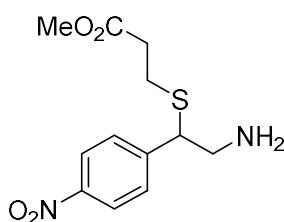
Chemical Formula: $C_{12}H_{17}N_3O_3S$
Exact Mass: 283.0991

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), $[MsO-NH_3][OTf]$ (120 mg, 0.45 mmol, 1.5 equiv.) and $FeSO_4 \cdot 7H_2O$ (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then *N*-acetylcysteamine (180 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification

by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **93** (43.0 mg, 0.150 mmol, 50% yield) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.18 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 2H), 5.95 (brs, 1H), 3.93 (m, 1H), 3.30 (q, *J* = 6.5 Hz, 2H), 3.06 (m, 2H), 2.51 (m, 2H), 1.89 (s, 3H), 1.46 (brs, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 170.2 (C), 149.5 (C), 147.6 (C), 129.4 (CH), 124.2 (CH), 53.4 (CH), 47.7 (CH₂), 38.9 (CH₂), 31.4 (CH₂), 23.3 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₂H₁₇N₃O₃Na [M+Na]⁺ 306.0883, found 306.0874.

Methyl 3-((2-amino-1-(4-nitrophenyl)ethyl)thio)propanoate **94**

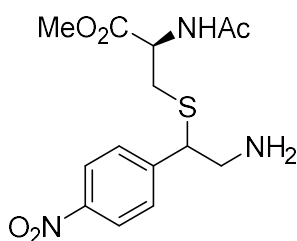


Chemical Formula: C₁₂H₁₆N₂O₄S
Exact Mass: 284.0831

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then methyl 3-mercaptopropionate (180 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **94** (35.0 mg, 0.123 mmol, 41% yield) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H), 3.92 (m, 1H), 3.63 (s, 3H), 3.10–3.00 (m, 2H), 2.67–2.58 (m, 2H), 2.53–2.46 (m, 2H), 1.48 (brs, 2H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 172.3 (C), 149.5 (C), 147.6 (C), 129.4 (CH), 124.1 (CH), 53.9 (CH), 52.0 (CH₃), 47.7 (CH₂), 34.7 (CH₂), 26.5 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₂H₁₇N₂O₄S [M+H]⁺ 285.0904, found 285.0897.

Methyl *N*-acetyl-*S*-(2-amino-1-(4-nitrophenyl)ethyl)-*L*-cysteinate **95**



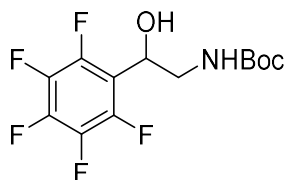
Chemical Formula: C₁₄H₁₉N₃O₅S
Exact Mass: 341.1045

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then *N*-acetyl-*L*-cysteine methyl ester (266 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 16 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 90/10) afforded **95** (38.0 mg, 0.111 mmol, 37% yield, dr 1.2:1) as an orange oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.20–8.17 (m, 4.4H), 7.53–7.50 (m, 4.4H), 6.74 (d, *J* = 7.7 Hz, 1H), 6.33 (d, *J* = 7.4 Hz, 1.2H), 4.79–4.74 (m, 1H), 4.72–4.67 (m, 1.2H), 3.97 (t, *J* = 7.1 Hz, 1H), 3.92 (t, *J* = 6.9 Hz, 1.2H), 3.74 (s, 3.6H), 3.67 (s, 3H), 3.08–3.04 (m, 4.4H), 2.90–2.76 (m, 4.4H), 2.01 (s, 3H), 1.92 (s, 3.6H), 1.39 (brs, 4.4H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 171.4 (2C), 170.2 (C), 169.9 (C), 149.1 (C), 148.9 (C), 147.7 (2C), 129.4 (CH), 129.3 (CH), 124.2 (2CH), 54.0 (CH), 53.9 (CH), 53.0 (CH₃), 52.9 (CH₃), 52.3 (2CH), 47.6 (CH₂), 47.5 (CH₂), 34.0 (CH₂), 33.6 (CH₂), 23.2 (2CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₄H₂₀N₃O₅S [M+H]⁺ 342.1117, found 342.1118.

3.6 Characterization Data of Aminohydroxylation Product

Tert*-butyl (2-hydroxy-2-(perfluorophenyl)ethyl)carbamate **96*



Chemical Formula: C₁₃H₁₄F₅NO₃
Exact Mass: 327.0894

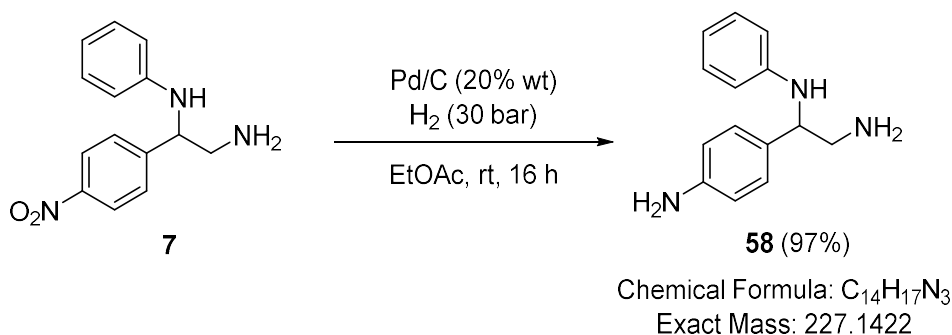
General Procedure **A** was followed with 2,3,4,5,6-pentafluorostyrene (58.2 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h.

Upon completion of the first step, the reaction mixture was diluted by DCM and extracted with aqueous HCl 1 M (2 × 15 mL). The combined aqueous phases were concentrated *in vacuo* and re-dissolved in DCM (5 mL). The reaction mixture was cooled to 0 °C, triethylamine (84 µL, 0.60 mmol, 2.0 equiv.) and Boc₂O (132 mg, 0.60 mmol, 2.0 equiv.) were added, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched with water and then extracted with DCM (10 mL × 3). The combined organic layers were washed with a solution of sat. NaHCO₃ (15 mL), brine (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by FC over silica gel (*n*-pentane/EtOAc: 90/10) afforded **96** (48.0 mg, 0.153 mmol, 49% yield) as a yellow oil.

¹H NMR (500 MHz, CDCl₃): δ 5.20–5.14 (m, 1H), 5.04 (s, 1H), 4.04 (s, 1H), 3.62–3.53 (m, 1H), 3.52–3.40 (m, 1H), 1.43 (s, 9H). **¹³C NMR (101 MHz, CDCl₃):** δ 157.5 (C), 145.1 (dm, *J* = 251.7 Hz), 140.9 (dm, *J* = 253.8 Hz), 137.7 (d, *J* = 253.1 Hz), 115.1 (m, C), 80.8 (C), 67.2 (CH), 46.0 (CH₂), 28.3 (CH₃). **¹⁹F NMR (471 MHz, CDCl₃):** δ -142.9 (m), -154.6 (m), -161.8 (m). **HRMS (ESI):** *m/z* calcd. for C₁₃H₁₅F₅NO₃ [M+H]⁺ 328.0967, found 328.0960.

4. Derivatization of Diamination Products

Reduction of **7** to aniline **58**

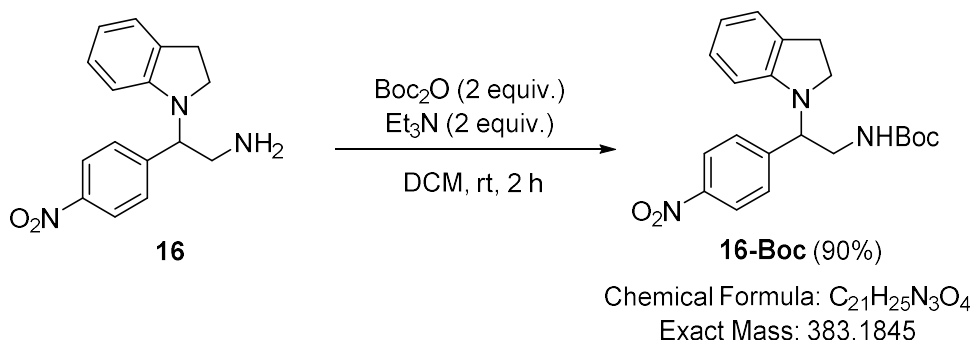


A glass vial (8 mL) with a Teflon-coated magnetic stir bar was charged with amine **7** (100 mg, 0.39 mmol), Pd/C (20 mg, 20% wt) and EtOAc (5 mL). The reaction mixture was placed under H₂ gas at 30 bar for 16 h. Then, the reaction mixture was filtered over a pad of celite (rinsed with DCM). The crude product was purified by FC over silica gel (DCM/MeOH: 100/0 to 85/15) to afford **58** (86.0 mg, 0.38 mmol, 97% yield) as a purple oil.

¹H NMR (400 MHz, CD₃OD): δ 7.10 (d, *J* = 8.4 Hz, 2H), 7.02–6.97 (m, 2H), 6.68 (d, *J* = 8.4 Hz, 2H), 6.60–6.51 (m, 3H), 4.28 (t, *J* = 6.7 Hz, 1H), 2.86 (d, *J* = 6.7 Hz, 2H), NH and NH₂ unobserved. **¹³C NMR (101 MHz, CD₃OD):** δ 149.4 (C), 147.6 (C), 132.8 (C), 129.8 (CH), 128.6 (CH), 117.8

(CH), 116.8 (CH), 114.8 (CH), 60.6 (CH), 49.1 (CH₂). **HRMS (ESI):** m/z calcd. for C₁₄H₁₈N₃ [M+H]⁺ 228.1495, found 228.1491.

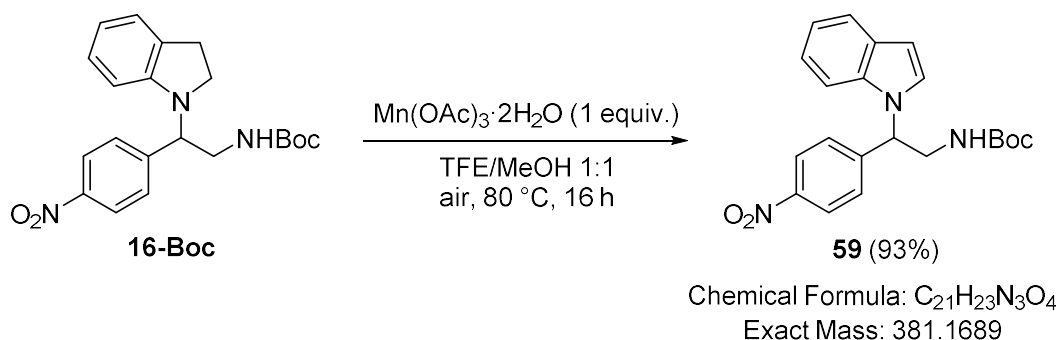
Boc-protection of **16**



To a solution of **16** (99.5 mg, 0.35 mmol) in DCM (3.5 mL) were added triethylamine (98 μ L, 0.7 mmol, 2.0 equiv.) and Boc₂O (153 mg, 0.7 mmol, 2.0 equiv.) at 0 °C, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched with a solution of sat. NaHCO₃ (15 mL) and then extracted with DCM (10 mL $\times$ 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FC over silica gel (*n*-pentane/EtOAc: 100/0 to 80/20) to afford **16-Boc** (120.0 mg, 0.31 mmol, 90% yield) as a yellow oil.

¹H NMR (400 MHz, CD₂Cl₂): δ 8.17 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.01 (ddd, J = 32.7, 7.4, 1.3 Hz, 2H), 6.61 (td, J = 7.4, 1.0 Hz, 1H), 6.43 (d, J = 7.9 Hz, 1H), 4.87 (dd, J = 8.9, 5.6 Hz, 2H), 3.82–3.63 (m, 2H), 3.56–3.47 (m, 1H), 3.28 (q, J = 8.6 Hz, 1H), 3.03–2.93 (m, 2H), 1.40 (s, 9H). **¹³C NMR (101 MHz, CD₂Cl₂):** δ 156.0 (C), 151.2 (C), 147.8 (C), 146.5 (C), 130.1 (C), 129.0 (CH), 127.6 (CH), 125.1 (CH), 124.0 (CH), 118.2 (CH), 107.2 (CH), 79.8 (C), 58.8 (CH), 47.9 (CH₂), 41.8 (CH₂), 28.6 (CH₂), 28.4 (CH₃). **HRMS (ESI):** m/z calcd. for C₂₁H₂₆N₃O₄ [M+H]⁺ 384.1918, found 384.1908.

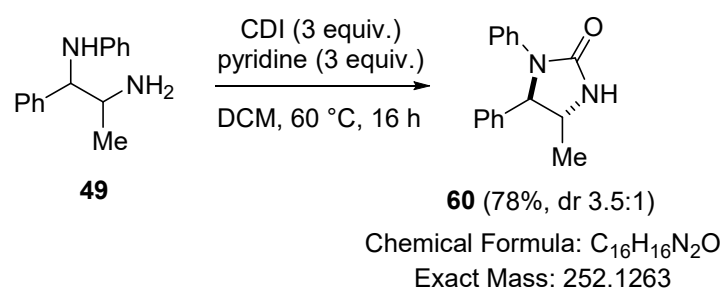
Oxidation of **16-Boc** to indole **59**



Indoline **16-Boc** (120.0 mg, 0.31 mmol), $\text{Mn(OAc)}_3 \cdot 2\text{H}_2\text{O}$ (83.0 mg, 1 equiv.) and TFE/MeOH 1:1 (3 mL) were placed in an oven-dried 25 mL tube equipped with a Teflon-coated magnetic stir bar under air atmosphere. The reaction mixture was stirred at 80 °C for 16 h. It was then cooled to room temperature, diluted with H_2O (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by FC over silica gel (*n*-pentane/EtOAc: 100/0 to 75/25) to afford **59** (110.0 mg, 0.288 mmol, 93% yield) as a yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 8.12 (d, J = 8.8 Hz, 2H), 7.69–7.65 (m, 1H), 7.31–7.27 (m, 3H), 7.21–7.13 (m, 3H), 6.68 (d, J = 3.3 Hz, 1H), 5.85 (m, 1H), 4.76 (m, 1H), 4.21–4.11 (m, 1H), 3.88–3.79 (m, 1H), 1.41 (s, 9H). **^{13}C NMR (101 MHz, CDCl_3):** δ 155.9 (C), 147.6 (C), 146.2 (C), 136.5 (C), 128.9 (C), 127.5 (CH), 124.6 (CH), 124.1 (CH), 122.4 (CH), 121.4 (CH), 120.4 (CH), 109.8 (CH), 103.5 (CH), 80.3 (C), 58.8 (CH), 44.2 (CH_2), 28.4 (CH_3). **HRMS (ESI):** m/z calcd. for $\text{C}_{21}\text{H}_{24}\text{N}_3\text{O}_4$ $[\text{M}+\text{H}]^+$ 382.1761, found 382.1773.

Reaction of **49** with CDI

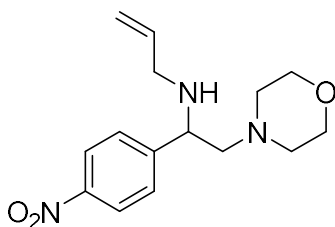


A 10 mL tube equipped with a Teflon-coated magnetic stir bar was charged with diamine **49** (100 mg, 0.45 mmol, 1.0 equiv.), carbonyldiimidazole (218 mg, 1.35 mmol, 3 equiv.), pyridine (108 μL , 1.35 mmol, 3 equiv.) and DCM (3 mL). Then, the reaction mixture was stirred at 60 °C for 16 h. It

was then cooled to room temperature, diluted with H₂O (20 mL) and extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by FC over silica gel (pentane/EtOAc, 100/0 to 70/30, gradient) to afford **60** (88 mg, 0.35 mmol, 78% yield, dr 3.5:1) as a yellow solid. The product was then recrystallized in dichloromethane for X-Ray analysis.

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.40–7.23 (m, 7H), 7.20–7.15 (m, 2H), 6.92–6.86 (m, 1H), 4.95 (d, *J* = 5.8 Hz, 1H), 3.40 (pd, *J* = 6.1, 1.1 Hz, 1H), 1.28 (d, *J* = 6.2 Hz, 3H), NH unobserved. **¹³C NMR (100 MHz, DMSO-*d*₆):** δ 158.3 (C), 140.4 (C), 139.4 (C), 128.8 (CH), 128.2 (CH), 127.7 (CH), 126.4 (CH), 122.3 (CH), 119.9 (CH), 66.2 (CH), 54.2 (CH), 20.6 (CH₃).

N*-(2-morpholino-1-(4-nitrophenyl)ethyl)prop-2-en-1-amine **89*



Chemical Formula: C₁₅H₂₁N₃O₃
Exact Mass: 291.1583

General Procedure **A** was followed with 4-nitrostyrene (44.8 mg, 0.30 mmol), [MsO-NH₃][OTf] (120 mg, 0.45 mmol, 1.5 equiv.) and FeSO₄·7H₂O (8.4 mg, 0.03 mmol, 10 mol%) in HFIP (0.5 mL). The reaction mixture was stirred at 60 °C for 1 h, then allylamine (86 mg, 1.5 mmol, 5.0 equiv.) was added to the reaction mixture which was stirred at 80 °C for 2 h. Purification by FC over silica gel (DCM/MeOH: 100/0 to 80/20) afforded target product in mixture with the corresponding salt.

The mixture was re-dissolved in acetonitrile (1 mL). Potassium carbonate (104 mg, 0.75 mmol), potassium iodide (4.2 mg, 0.025 mmol, 0.10 equiv.) and 2-bromoethyl ether (38 μL, 0.30 mmol) were then added, and the reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was quenched with a solution of sat. NH₄Cl (15 mL) and then extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by FC over silica gel (DCM/*i*PrOH: 100/0 to 95/5) afforded **89** (40.0 mg, 0.137 mmol, 46% yield over 2 steps) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 5.82 (dddd, *J* = 17.3, 10.3, 7.1, 4.9 Hz, 1H), 5.18–5.02 (m, 2H), 3.93 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.78–3.65 (m,

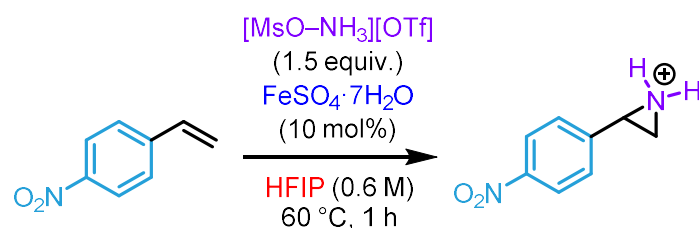
4H), 3.16 (ddt, $J = 14.4, 4.9, 1.6$ Hz, 1H), 2.96 (ddt, $J = 14.4, 7.1, 1.1$ Hz, 1H), 2.65–2.54 (m, 2H), 2.50–2.27 (m, 5H). **^{13}C NMR (101 MHz, CDCl_3):** δ 150.7 (C), 147.4 (C), 136.6 (CH), 128.4 (CH), 123.8 (CH), 116.3 (CH_2), 67.1 (CH_2), 65.7 (CH_2), 58.2 (CH), 53.7 (CH_2), 50.0 (CH_2). **HRMS (ESI):** m/z calcd. for $\text{C}_{15}\text{H}_{22}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$ 292.1656, found 292.1658.

5. Crystal data and structure refinement for compound 60.

Identification code	jmdl240610
Empirical formula	C ₁₆ H ₁₆ N ₂ O
Formula weight	252.31
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P b c a
Unit cell dimensions	a = 9.9702(7) Å alpha = 90 deg. b = 9.4694(6) Å beta = 90 deg. c = 26.7296(18) Å gamma = 90 deg.
Volume	2523.6(3) Å ³
Z, Calculated density	8, 1.328 Mg/m ³
Absorption coefficient	0.084 mm ⁻¹
F(000)	1072
Crystal size	0.160 x 0.100 x 0.040 mm
Theta range for data collection	2.549 to 30.068 deg.
Limiting indices	-13<=h<=14, -10<=k<=13, -37<=l<=37
Reflections collected / unique	32879 / 3696 [R(int) = 0.0834]
Completeness to theta = 25.242	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7460 and 0.6298
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3696 / 0 / 177
Goodness-of-fit on F ²	1.042
Final R indices [I>2sigma(I)]	R1 = 0.0563, wR2 = 0.1229
R indices (all data)	R1 = 0.0924, wR2 = 0.1395
Extinction coefficient	n/a
Largest diff. peak and hole	0.421 and -0.278 e.Å ⁻³

6. Kinetic Studies of the Aziridination of *p*-Nitrostyrene in HFIP

To obtain insights into the mechanism of the aziridination of *p*-nitrostyrene (Scheme 1), kinetic studies were performed using *in-situ* IR spectroscopy. Following the kinetics of this transformation is challenging due to multiple factors which drastically limits the means with which the reaction can be followed. The main issue is the heterogeneous nature of the reaction due to limited solubilities of [MsO–NH₃][OTf] and FeSO₄·7H₂O in HFIP.



Scheme 1. Aziridination of 4-nitrostyrene.

When *p*-nitrostyrene is added to a suspension of [MsO–NH₃][OTf] and FeSO₄·7H₂O in HFIP at 60 °C, various changes were observed in the IR spectra. The most pronounced changes were found in the region between 1450–1650 cm^{–1}, which correspond to the C–C bond vibrations of the aryl rings (Figure 1A). The three observed IR vibrations for *p*-nitrostyrene within this region could be assigned to the three possible C–C stretching modes of the aryl ring by comparison to an IR spectrum simulated computationally. Additionally, it was observed that the IR spectrum computed for the aziridine product shows C–C vibrations which are shifted with respect to *p*-nitrostyrene in a similar way (Figure 1B) as observed experimentally (Figure 1A).

Following the kinetics of the disappearance of *p*-nitrostyrene resulted in a curve, which could be analyzed by a single-exponential decay function to yield first-order rates k_{obs} (Figure 2, grey curve and fit). The formation of the vibration that was assigned to the aziridine (Figure 2, blue curve) showed a sigmoidal profile. Such sigmoidal profiles are characteristics of induction events, e.g. one of the formed products (TfOH or MsOH) being able to catalyze the reaction. The kinetics of product formation, however, cannot be analyzed in a straightforward way and, accordingly, the kinetic analysis was based on the first-order rates for the disappearance of *p*-nitrostyrene, k_{obs} .

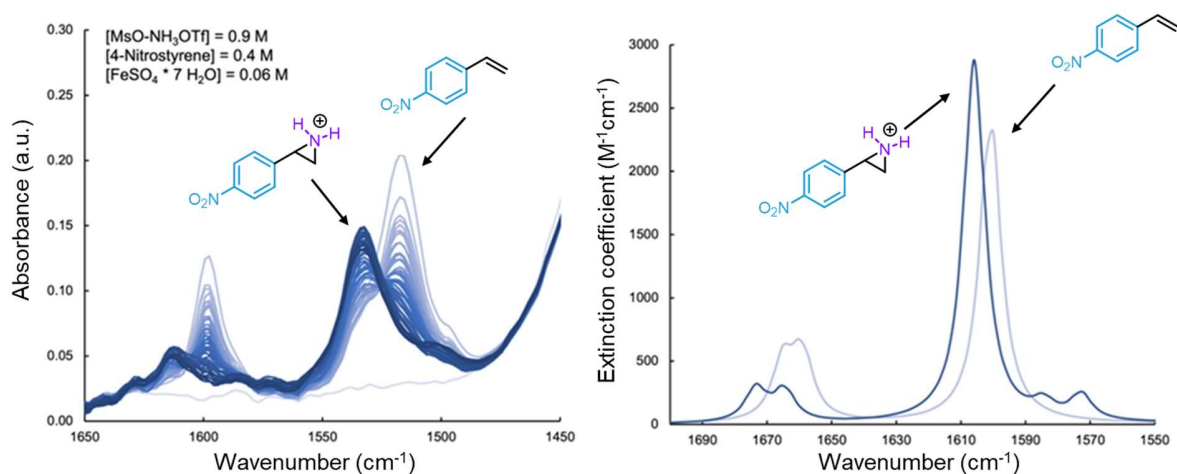


Figure 1. Left: Experimental IR Spectra during the reaction indicating the conversion from *p*-nitrostyrene (NS) to the reaction product which is assumed to be mostly the aziridine. Right: DFT-calculated IR spectra (SMD(HFIP)/MN15/def2-TZVP) for reactant (light blue curve) and product (blue curve).

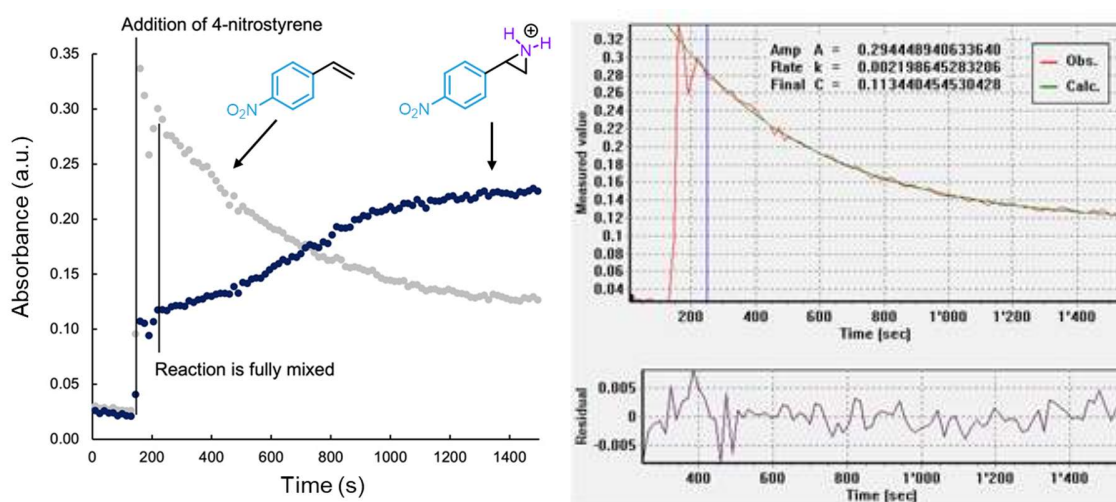


Figure 2. Left: Time-dependent absorbances of *p*-nitrostyrene (blue) and product (grey) for the reaction of $[\text{MsO-NH}_3][\text{OTf}] = 0.9 \text{ M}$, $[\text{p-nitrostyrene}] = 0.8 \text{ M}$ and $\text{FeSO}_4 \cdot 7\text{H}_2\text{O} = 0.06 \text{ M}$ in HFIP, 60°C . Right: Mono-exponential fit of the concentration of *p*-nitrostyrene indicating a first-order decay.

When varying the concentrations of *p*-nitrostyrene while keeping the concentrations $[\text{MsO-NH}_3][\text{OTf}]$ and $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ constant, identical rates k_{obs} were observed within the error of the measurements (Figure 3). This indicates that the reaction order in *p*-nitrostyrene is zero.

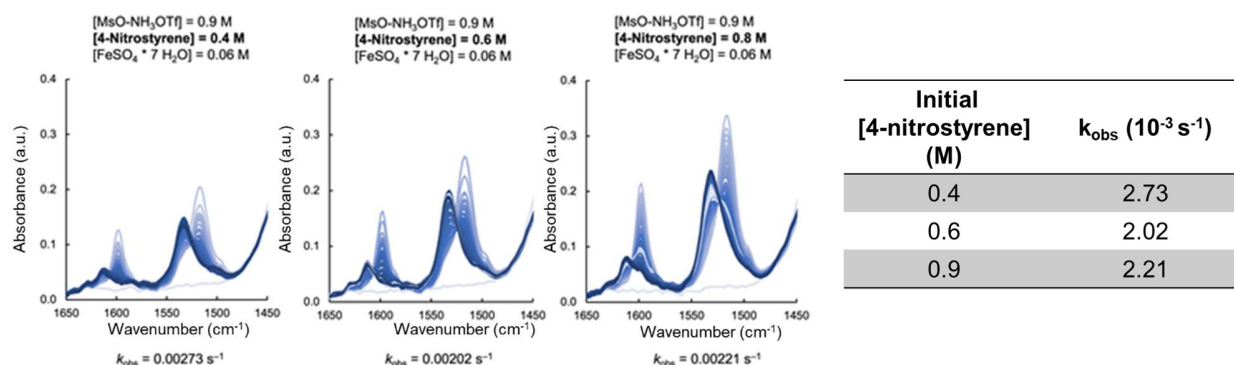


Figure 3. In-situ IR spectra for three reaction of with different concentrations of 4-nitrostyrene at constants concentrations of $[\text{MsO-NH}_3][\text{OTf}]$ and $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ in HFIP at 60 °C.

The reaction could analogously be followed in the absence of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$. However, the IR spectra in the absence of catalytic amounts of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ did not show the appearance of the clearly shifted new species observed in the reactions in the presence of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (Figure 1), and instead the disappearance of the C–C vibration of *p*-nitrostyrene was only associated with the appearance of a small shoulder (Figure 4).

Similarly to the iron-containing reaction, the kinetics for the disappearance of *p*-nitrostyrene showed first-order decays. In the absence of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$, variation of the concentration of *p*-nitrostyrene did - as with the reaction containing $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ - not result in differences in the observed rate of disappearance of *p*-nitrostyrene (Figure 4; cf. Figure 3).

Additionally, the rates k_{obs} of the reactions in the absence of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ are almost identical compared to the reaction containing $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (Figures 3 and 4), implying that the disappearance of *p*-nitrostyrene is unaffected by $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (zero-order).

Though the rates of consumption of *p*-nitrostyrene are unaffected by the presence of 10 mol% $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$, iron has a pronounced effect on the reaction but mostly on product formation: Only in the presence of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$, was the new band assigned to the aziridine observed (Figure 1 vs. Figure 4). Additionally, the reaction in the absence of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ was visually found to be incomplete as large amounts of $[\text{MsO-NH}_3][\text{OTf}]$ remained undissolved even after no more progress was observed kinetically (Figure 5, left). This was found to be in contrast to the reaction containing $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ where complete dissolution of $[\text{MsO-NH}_3][\text{OTf}]$ was observed (Figure 5, right).

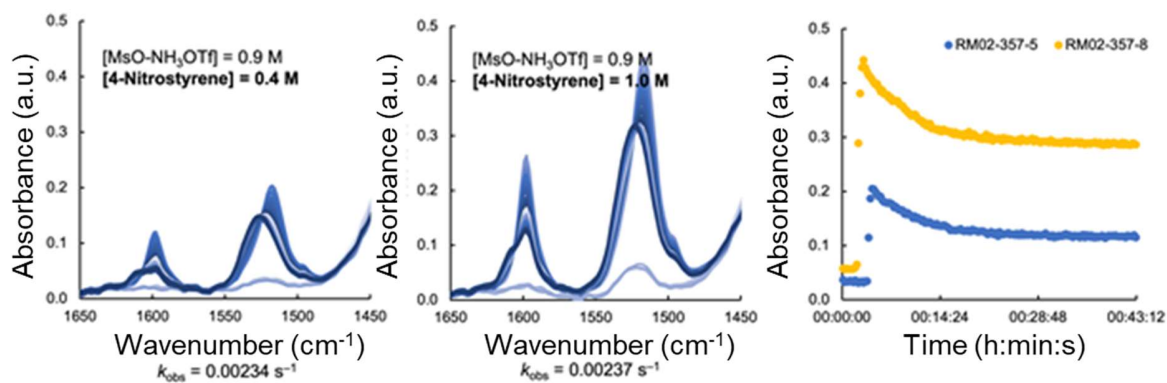


Figure 4. In-situ IR spectra for two reaction with different concentrations of *p*-nitrostyrene at constant concentrations of [MsO–NH₃][OTf] in HFIP at 60 °C.

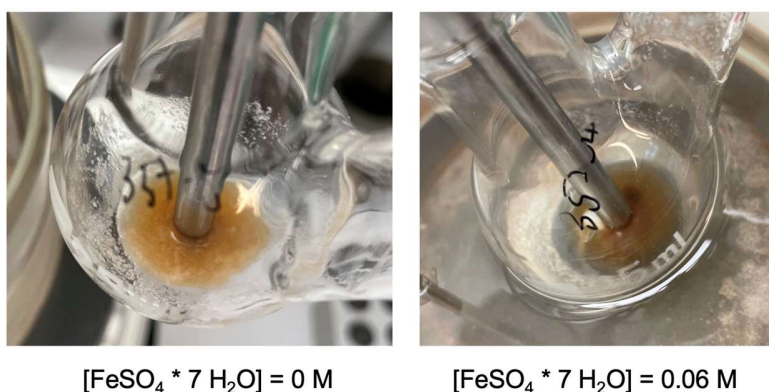


Figure 5. Reactions after completion according to *in-situ* kinetics indicating remaining [MsO–NH₃][OTf] in the absence of FeSO₄·7H₂O.

Analysis of the reaction products in the iron-free reaction is directly possible by ¹H NMR spectroscopy and indicated that, besides the aziridine, large amounts of the dimerization product of *p*-nitrostyrene are formed (Figure 6).

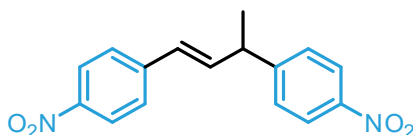


Figure 6. Dimerization product of *p*-nitrostyrene detected by ¹H NMR spectroscopy in the absence of FeSO₄·7H₂O.

Although large amounts of FeSO₄·7H₂O do not seem to impact the consumption of *p*-nitrostyrene, the role of Fe might also lie within the steps following the initial N–O bond homolysis. However, on a preparative scale the yields of the full reaction sequence (including the subsequent arylation

or amination) in the absence of iron are not reproducible and differ largely (this might imply that trace amounts of metal have an influence in these reactions).

It cannot be excluded, however, that traces of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ efficiently catalyze the reaction, as Ritter and co-workers have shown that a similar reaction that involves cleavage of $[\text{MsO}-\text{NH}_3][\text{OTf}]$ still proceeds with iron at amounts < 1 ppm where the reactions times were only a factor of 20 smaller. As the IR probe, which is directly in contact with the reaction medium, is metallic (Hastelloy C22, Ni 58, Cr 22, Mo 13.0, Fe 3.0, W 3.0), it is reasonable to assume that even the experiments without added $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ contain significant amounts of Fe that might catalyze the reaction.

Conclusions

Under the limitations of the kinetic approach (heterogeneous mixture that gradually dissolves, mixing difficult to reproduce, signal/noise of IR) the following results were obtained:

- Reaction order in *p*-nitrostyrene is **zero**
- Reaction order in iron (for the consumption of *p*-nitrostyrene) is *likely zero*. An alternative which cannot be excluded: the reaction has a positive order in iron because already in the “iron-free” reaction, due to trace amounts, the reaction reaches its maximum velocity.
- Kinetics for product formation show induction kinetics (only with Fe)
- With or without iron, the reaction reaches a different product distribution after completion of the initial phase.

The observation of a first-order decay of *p*-nitrostyrene as well as the observation of the reaction being zero-order in *p*-nitrostyrene would suggest the reaction to proceed via rate-determining N–O bond homolysis (which would be a process showing first-order kinetics) followed by fast attack of the aminium radicals at *p*-nitrostyrene.

7. Electrochemical Investigation of H-bonding of HFIP

While the chemistry of hexafluoroisopropanol (HFIP) is rich and well-developed, the understanding of its mechanism of activation of substrates is scarce and is mostly of qualitative nature.^[1] This study is an attempt to approach the problem from a quantitative standpoint by means of electrochemistry. Cyclic voltammetry has been successfully employed for investigating non-covalent interactions such as halogen bonds or hydrogen bonds.^[2-4] Since the reduction or oxidation of certain species can make them more or less susceptible to participate in such interactions, changes in their redox behavior can be directly observed on voltammograms in the presence of a complexing partner. It is therefore interesting to quantify interactions of HFIP with model molecules and compare its effect with other H-bonding donors. A good candidate for such studies is tetrachlorobenzoquinone (known as TCQ or chloranil) (Figure 1). Cyclic voltammetry (CV) of TCQ reveals two well-defined reversible waves corresponding to two consecutive one-electron reductions to radical monoanion and dianion. Chemical structures suggest that reduced versions of quinone are better acceptors of hydrogen bonds than the neutral form. Hence, progressive shifts of the second wave towards positive potential are expected upon gradual addition of HFIP due to its stabilization of negatively charged species with H-bonds. As lone pairs of the neutral quinone are poor acceptors of H-bonding, the first wave should not be impacted to the same extent as the second wave.

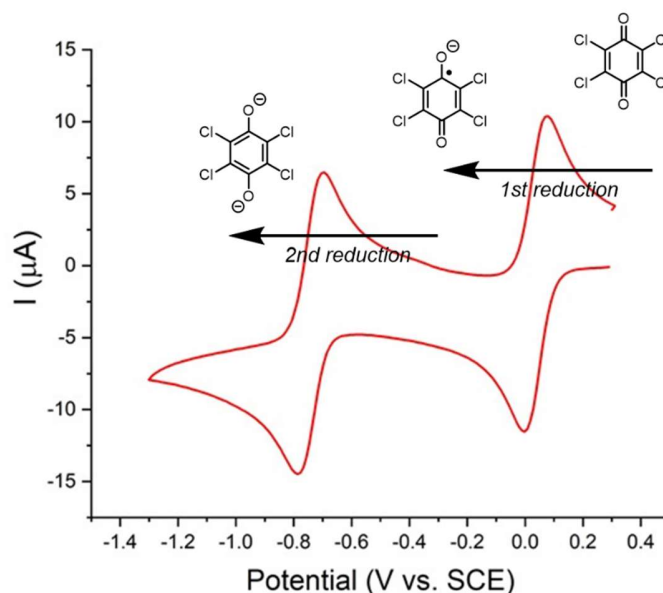


Figure 1. Cyclic voltammogram of TCQ in MeCN in the absence of HFIP.

At the beginning of addition of HFIP, the second wave becomes strongly shifted towards positive potentials (Figure 2, left). The wave becomes quasi-reversible at the beginning of the titration and progressively loses reversibility, while the anodic peak steadily becomes broader. The dianion likely undergoes quick side reactions prior to re-oxidation to the radical anion. The plateau of the shift of a half-wave potential of the second wave is reached upon addition of 80 equivalents of HFIP. $E_{1/2}'$ of the first wave does not shift, suggesting the H-bonding of HFIP with neutral TCQ is not significant. Once the addition of HFIP was complete, the competition experiment with tetrabutylammonium chloride (TBACl) was carried out. Chloride anions are potential acceptors of hydrogen bonds and can divert HFIP molecules from coordinating with reduced forms of chloranil. The second wave is expected to shift back to lower potentials, which is indeed observed during gradual addition of TBACl (Figure 2, right).

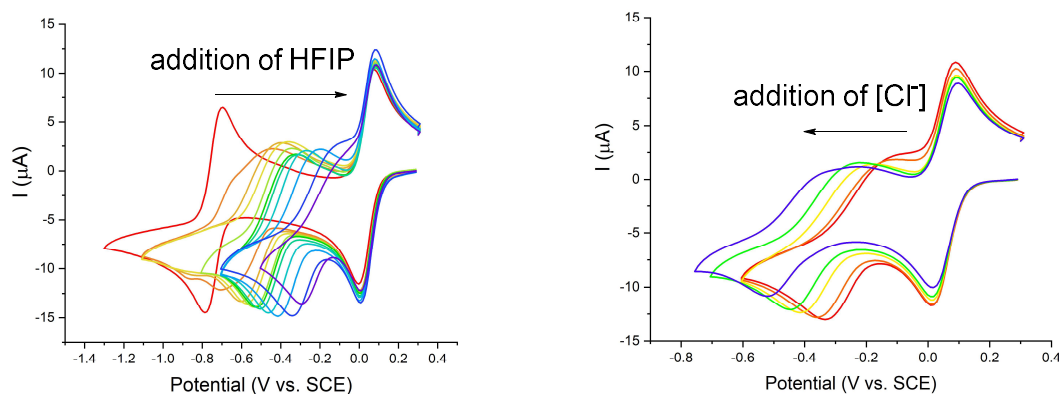


Figure 2. Cyclic voltammograms of TCQ during titration with HFIP (left) and TBACl (right).

The same experiment was performed with another widely used fluorinated alcohol trifluoroethanol (TFE) (Figure 3). TFE induces a much smaller shift of the second wave $E_{1/2}'$ compared to HFIP, which is consistent with its weaker H-bonding donor ability. Moreover, the second wave remains reversible throughout titration. The reverse titration with chloride anions slightly shifts the second wave back to more negative potentials. The new wave appearing between the two waves of TCQ was already observed by other lab members when working with TCQ and is ascribed to some side reactions in the presence of TBACl. Since HFIP and TFE are alcohols, we can hypothesize that the observed differences in shifts and shapes of waves could be due to different amounts of trace water in both solvents. The control titration with up to 200 equivalents of distilled water reveals the maximum shift of the second wave $E_{1/2}'$ by 110 mV, which cannot explain the observed changes upon addition of HFIP and TFE.

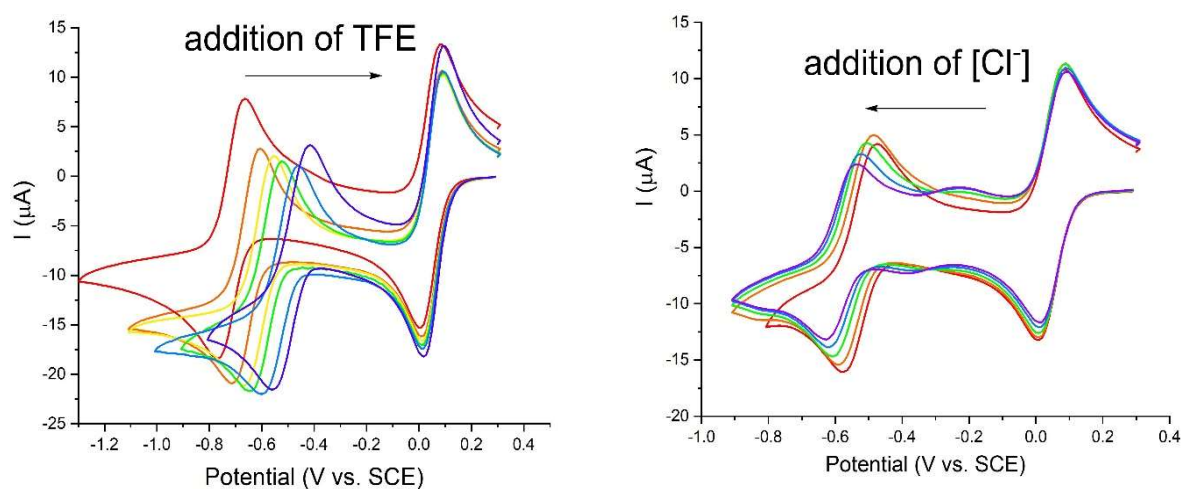


Figure 3. Cyclic voltammograms of TCQ during titration with TFE (left) and TBACl (right).

The plot of $\Delta E_{1/2}'$ against the number of added equivalents of the alcohol (Figure 4) reveals a sharp shift at the beginning the titration and a plateau when more and more alcohol is added. Due to time constraints, experiments could not be performed at least three times to check for reproducibility. Yet, no significant differences were observed after two consecutive titrations with each alcohol.

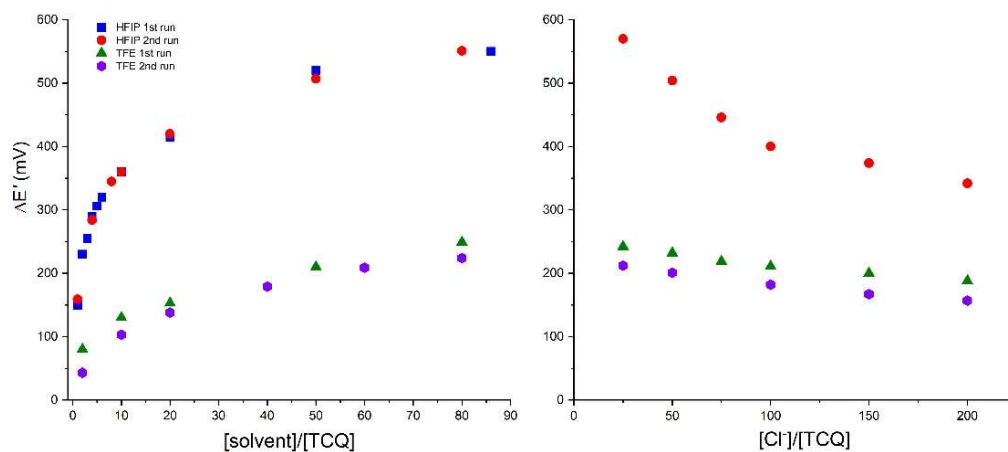
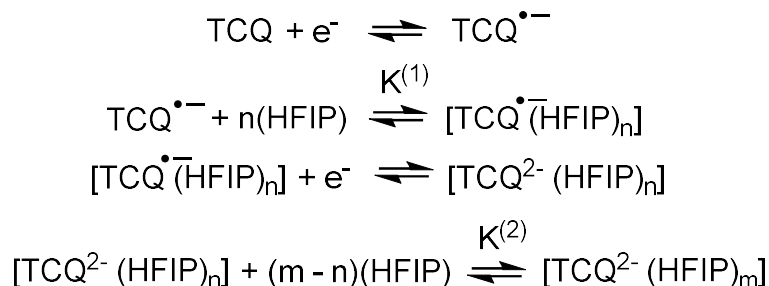


Figure 4. Dependence of the potential shift of the second wave of TCQ reduction on the increasing concentrations of fluorinated alcohols (left) and TBACl (right).

Taken together, the above observations allow us to conclude that the observed potential shifts are due to fast hydrogen-bonding equilibria which are coupled to reductions of TCQ (Scheme 1).



Scheme 1. Possible equilibria during the reduction of TCQ. HFIP is shown as an example.

The values of $\Delta E'_{1/2}$ can be quantitatively related to equilibrium constants of formation of H-bonded complexes with reduced versions of TCQ and their stoichiometry (Equation 1).^[5]

$$e^{\left(\frac{F}{RT}\Delta E'_{1/2}\right)} = \frac{1 + K^{(2)}[\text{HFIP}]^m}{1 + K^{(1)}[\text{HFIP}]^n} \quad (1)$$

Since the first wave does not shift during titrations, $K^{(1)}$ should be negligibly small and could be neglected, which eliminates the denominator. If we assume $K^{(2)} \gg 1$, then the equation 1 is simplified to equation 2.

$$e^{\left(\frac{F}{RT}\Delta E'_{1/2}\right)} = K^{(2)}[\text{HFIP}]^m \quad (2)$$

After some rearrangements, we obtain the equation 3. We are interested in a limiting case where the titrating agent is introduced in large excess with respect to [TCQ] and therefore $[\text{HFIP}]_{\text{eq}} \approx [\text{HFIP}]_{\text{added}}$. By plotting $\Delta E'_{1/2}$ against the decimal logarithm of added [HFIP], we obtain a linear plot. The slope contains the average number of alcohol molecules forming the H-bonding complex with TCQ^{2-} , while the equilibrium constant $K^{(2)}$ can be extracted from the intercept.

$$\Delta E'_{1/2} = 0.059 \cdot \lg K^{(2)} + 0.059 \cdot m \cdot \lg [\text{HFIP}] \quad (3)$$

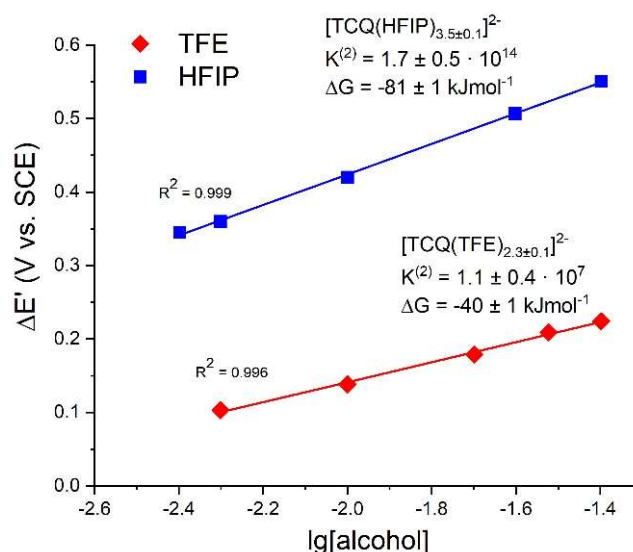
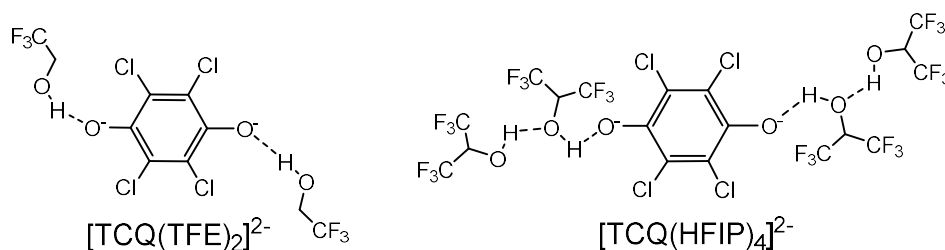


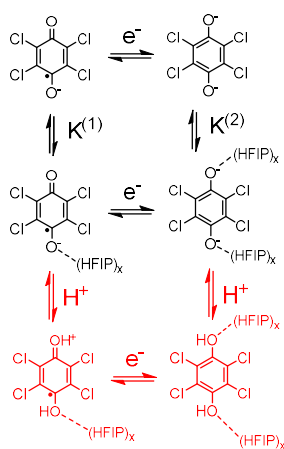
Figure 5. Linear fit of experimental $\Delta E'_{1/2}$ to equation 3.

The regression analysis provides a perfect fit of experimental data to equation 3 (Figure 5). Experimental errors of estimated equilibrium constants, Gibbs energies and the complex stoichiometries were obtained through propagation of standard errors of intercept and slope obtained from regression models. The magnitude of estimated errors of equilibrium constants (~30%) is consistent with previous studies on the subject.^[5] The calculated values represented on Figure 5 constitute the most important result of this study. The obtained data is in line with the known behavior of HFIP and TFE. HFIP is a very strong H-bond donor and so far, much stronger than TFE. Such low Gibbs energy of formation of H-bonded complex can explain the extraordinary activating ability of HFIP towards challenging and unreactive substrates. The average H-bond complex with TCQ dianion contains 2 TFE molecules and 4 HFIP molecules (Scheme 2). As HFIP is bulkier than TFE, two additional HFIP molecules likely coordinate to the HFIP molecule directly H-bonded to TCQ oxygen.



Scheme 2. Possible structures of TCQ-fluorinated alcohol complexes.

The above analysis holds if the Nernstian equilibrium is operating at the electrode surface, yet we have observed the progressive loss of reversibility upon addition of HFIP. Such behavior has been already reported in the literature during the titration with TFA.^[4,5] Since the dianion becomes more basic than the neutral TCQ and HFIP is an acidic solvent, the reduction to dianion likely becomes coupled with the proton transfer. Once the dianion is protonated, a higher potential is required to oxidize it, hence the strong positive shift of the anodic peak of the second wave. The gradual loss of reversibility and broadening of the second wave is likely due to the complex interplay of H-bond assisted and proton-coupled reductions. Scheme 3 gives an approximative outline of events that could happen at the electrode surface once HFIP is added. The reality must be more complex with a variable number of protons transferred or HFIP molecules forming H-bonded complex. The more HFIP that is added, the more the proton-coupled path starts dominating. Although the obtained numerical values of titration with HFIP are fully consistent with the chemistry of this solvent and are not anomalous, they should be considered with caution. Since the Nernstian behavior is progressively lost during the titration, the full validity of equation 3 can be questioned in such case. Such a problem does not arise with TFE; the second wave stays reversible at the end of experiment.



Scheme 3. Simplified square-scheme of reactions taking place in the presence of HFIP.

Cyclic voltammogram of TCQ in bulk HFIP reveals that two reduction waves of TCQ collapse into one with the complete loss of reversibility (Figure 6). The intensity of the cathodic peak is higher than that of the anodic peak. This result corresponds to the two-electron reduction coupled with the proton transfer from HFIP,^[4,5] which supports conclusions made from titration experiments. The neutral TCQ is likely strongly H-bonded in bulk HFIP given the large ~1 V shift of the anodic peak to positive potentials. This observation also corroborates our previous mechanistic proposals that were backed up by DFT calculations and might explain why HFIP was the only

solvent enabling those transformations. In most cases, HFIP was suggested to play a dual role as a strong H-bonding catalyst and as a proton donor towards strongly deactivated substrates.

After the initial studies of H-bonding between HFIP and the model molecule TCQ, we moved to

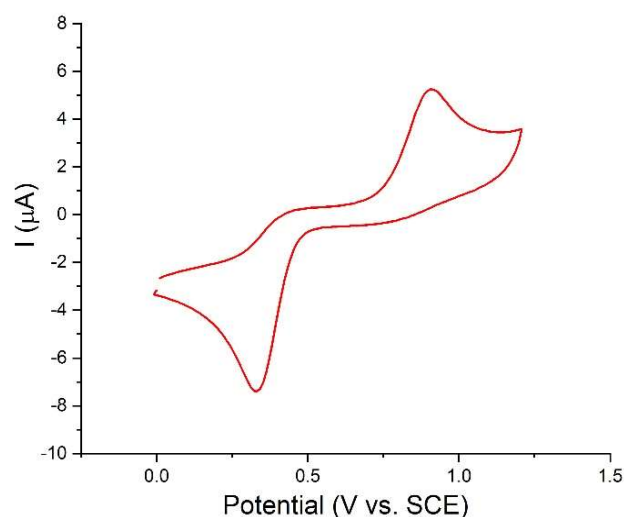


Figure 6. Cyclic voltammogram of TCQ in bulk HFIP.

electrochemical investigation of our current reaction of interest: amination of styrenes with $[\text{MsO-NH}_3][\text{OTf}]$ under $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ catalysis in HFIP. To avoid unnecessary coordination of MeCN to iron(II), we switched to DCM for experiments. Unfortunately, the electrochemical behavior of neither the iron salt nor the hydroxylammonium could be studied in this solvent due to solubility issues. However, $[\text{MsO-NH}_3][\text{OTf}]$ was titrated alone in MeCN with up to 80 equivalents of HFIP (Figure 7). Since the reductive homolysis of hydroxylammonium is a chemically irreversible reaction, we could only observe a cathodic peak in the voltammogram. This peak progressively shifts towards positive potentials as more HFIP is added, suggesting H-bonding of HFIP with $[\text{MsO-NH}_3][\text{OTf}]$ facilitates the activation of the salt to generate aminyl radicals. The obtained voltammograms presented undesired reduction waves, likely resulting from the slow degradation of hydroxylammonium salt during its transportation and exposure to air.

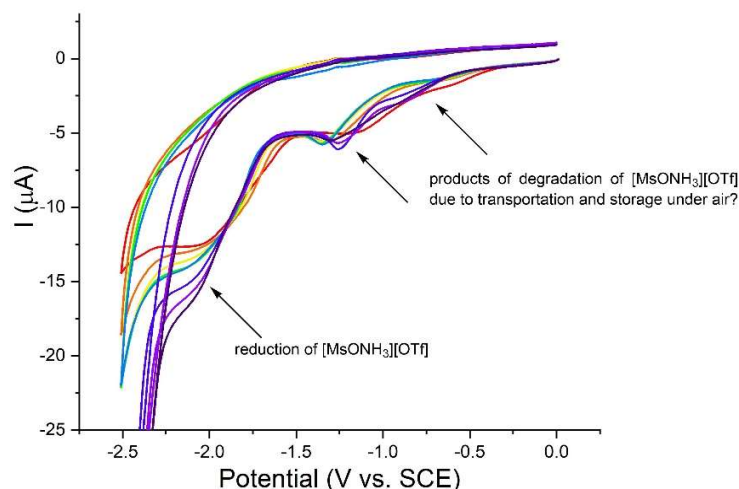


Figure 7. Cyclic voltammograms of $[\text{MsO-NH}_3][\text{OTf}]$ during titration with HFIP.

Conclusion

The effect of H-bonding of HFIP on the reduction potential of a model molecule TCQ was successfully studied in a series of titration experiments. Interactions were quantified and compared with another fluorinated alcohol TFE. On average, 4 molecules of HFIP coordinate to the dianion of TCQ forming very strong hydrogen bonds with $K_{\text{eq}} = 1.7 \pm 0.5 \cdot 10^{14}$ and $\Delta G = -81 \pm 1 \text{ kJmol}^{-1}$. Although the numerical analysis does not reveal anomalous values with respect to what is already known about properties of HFIP, the calculated values should be considered with caution due to the progressive loss of reversibility during the titration and hence breakdown of the Nernst equation. The shape of the second wave at the end of the titration with HFIP suggests the presence of complex equilibria and likely the interplay between H-bond assisted and proton-coupled electron transfers. In bulk HFIP, the proton-coupled transfer seems to dominate.

Experimental Part

The measurements were performed in a standard one-compartment three electrode cell containing 0.1 M solution of TBAPF_6 in anhydrous acetonitrile thermostated at 25 °C. Mechanically polished glassy carbon disk electrodes (carbon rod of 3 mm diameter, embedded in an insoluble polymer matrix) were employed as working electrodes and a platinum wire as auxiliary electrode. A salt bridge containing the electrolyte was used to connect the electrochemical cell with a saturated calomel reference electrode (SCE). Electrolyte and solvent were added to the electrochemical cell equipped with working, reference and auxiliary electrode protected under anhydrous argon atmosphere. The solvent was degassed by purging with

acetonitrile saturated argon for a few minutes. After taking a background scan, the quinone and internal reference were added and a cyclic voltammogram was performed. The difference in the measured formal standard potentials of the second reduction wave of the quinone relative to the first reduction wave (and the internal standard) ΔE° was then calculated.

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Chapter 3: A Povarov-Type Reaction to Access Tetrahydroquinolines from *N*-Benzylhydroxylamines and Alkenes

Introduction

State-of-the-art in synthesis of 1,2,3,4-tetrahydroquinolines

Despite the widespread prevalence of pharmaceuticals and natural products containing the tetrahydroquinoline core (Figure 1), the number of reliable synthetic methods for its rapid construction remains surprisingly scarce. The two most common routes are the partial reduction of quinolines and the three-component Povarov reaction between an aniline, aldehyde, and alkene. The main strengths of the Povarov reaction lie in the rapid and modular construction of a heterocyclic core as well as the use of readily available feedstocks, which is exemplified by a surge of reaction modifications published in recent years.^[1] However, most of existing protocols of the Povarov reaction are only compatible with electron-rich alkenes, with the reactivity of strongly deactivated alkenes being completely unexplored due to intrinsic mechanistic limitations. On the other hand, the main shortcoming of the partial reduction of quinolines is the necessity of constructing the heterocycle skeleton beforehand, which adds additional synthetic steps. In recent years, many novel approaches for the synthesis of tetrahydroquinolines based on radical chemistry have emerged, which offers an attractive alternative to well-established protocols. Several selected works which illustrate recent advances in the field will be discussed in the following paragraphs.

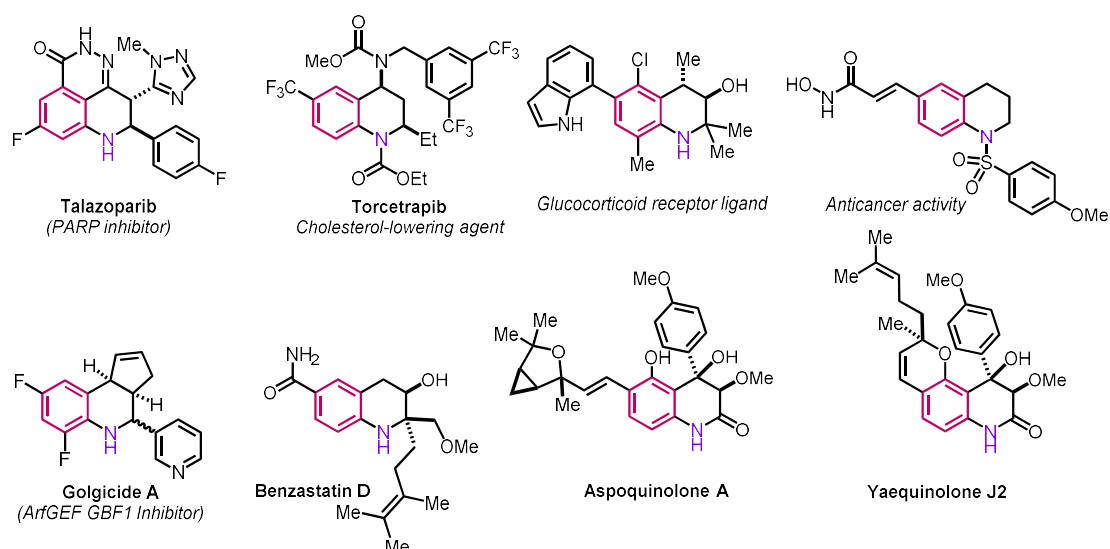
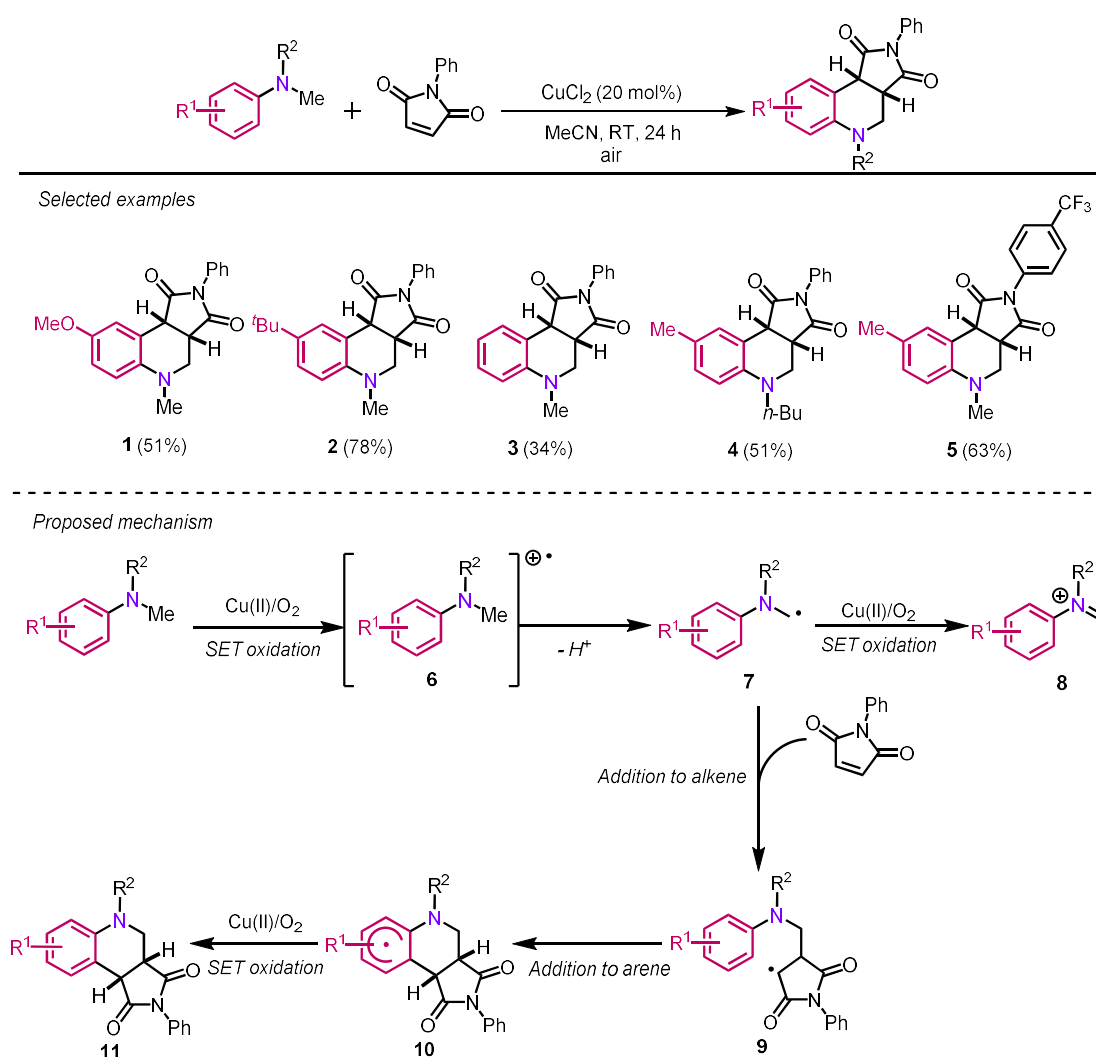


Figure 1. Selected examples of drugs and natural products incorporating a tetrahydroquinoline core.

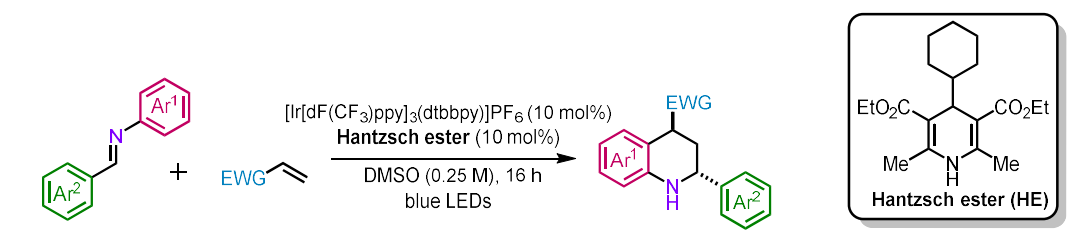
In 2011, the group of Miura reported a copper-catalyzed oxidative cyclization of *N*-methylanilines with various maleimides to form tricyclic tetrahydroquinolines (Scheme 1).^[2] Although the scope

of alkenes was not explored beyond maleimides, this work is a good illustration of how radical chemistry offers an efficient way to bypass existing substrate limitations of the classical Povarov reaction in which maleimides are too electron-poor to react. The proposed mechanism involves initial SET oxidation of *N*-methylaniline by copper(II)/O₂ to the transient radical cation **6**, which upon deprotonation leads to the key reactive α -amino radical **7**. **7** can then either add to the maleimide double bond and cyclize to **10** or undergo an off-pathway second SET oxidation to iminium **8** which then quickly decomposes. This work later inspired Murarka and co-workers to develop a similar transformation where **7** is obtained from a precursor bearing a photocleavable leaving group.^[3]

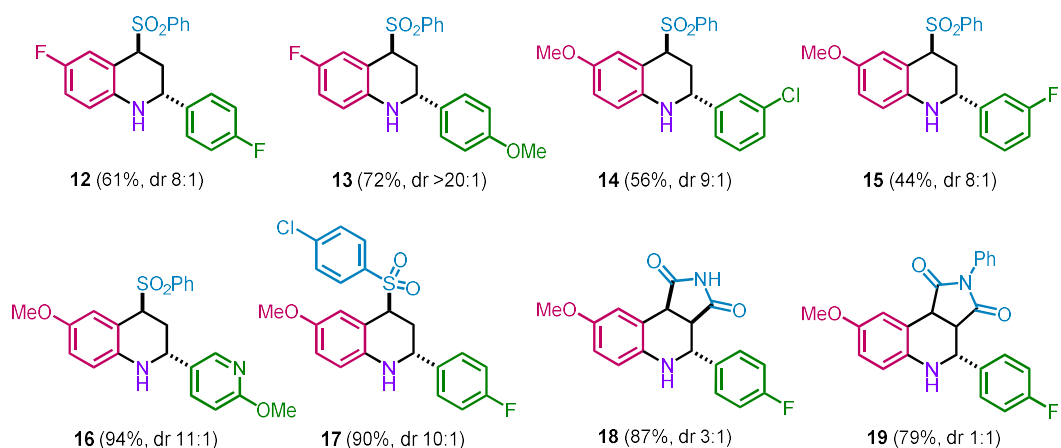


Scheme 1. Copper-catalyzed oxidative direct cyclization of *N*-methylanilines.

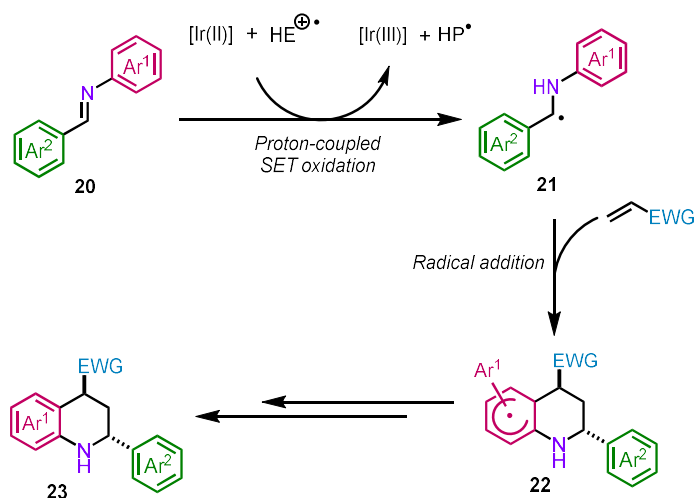
The strategy relying on the reactivity of α -amino radicals was later further developed by the group of Dixon in a more general photocatalyzed reverse polarity Povarov reaction (Scheme 2).^[4] This new protocol expanded the scope of electron-poor alkenes and afforded the corresponding tetrahydroquinolines with a high control of the diastereoselectivity. In-depth mechanistic investigations ruled out the direct oxidative SET of imine **20** to α -amino radical **21** and point towards a more complex proton-coupled electron transfer mechanism. The Hantzsch ester is presumably initially oxidized by the Ir photocatalyst to the corresponding radical cation, which is more acidic than the neutral molecule, making it a suitable partner for the proton-coupled oxidation of imine **20**. The α -amino radical **21** then adds to the alkene before cyclizing to **22**. Kinetic isotope effect experiments with a fully deuterated Ar¹ ring indicate that a loss of H in **22** towards re-aromatization of the ring takes place after the rate-determining step. Additionally, the reaction protocol was shown to operate in a three-component version with the corresponding aniline, aldehyde and alkene mixed at the beginning of the reaction.



Selected examples



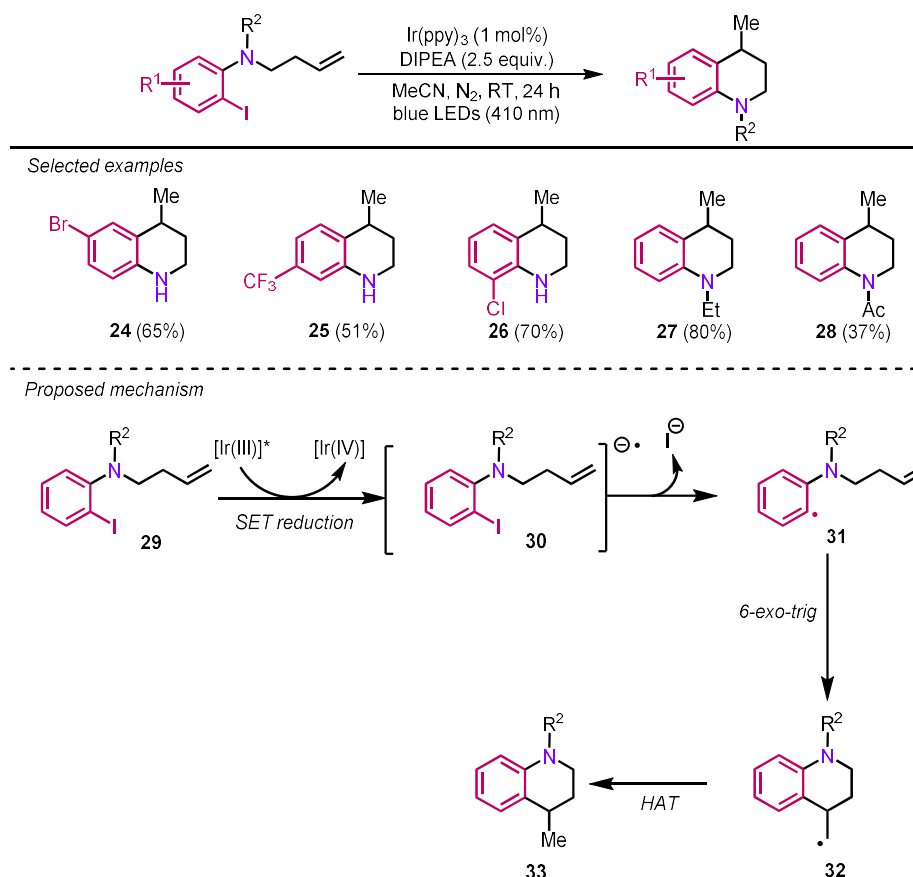
Proposed mechanism



Scheme 2. Photocatalytic reverse polarity Povarov reaction.

Numerous strategies based on intramolecular radical cyclizations have been recently reported as well, although they often require engineered substrates, which renders them less synthetically useful compared to multi-component approaches. In 2020, Alemán and co-workers disclosed a photocatalyzed intramolecular cyclization of aryl radicals to tetrahydroquinolines, which alleviates the use of stoichiometric quantities of Bu₃SnH - a previously irreplaceable reagent to initiate this

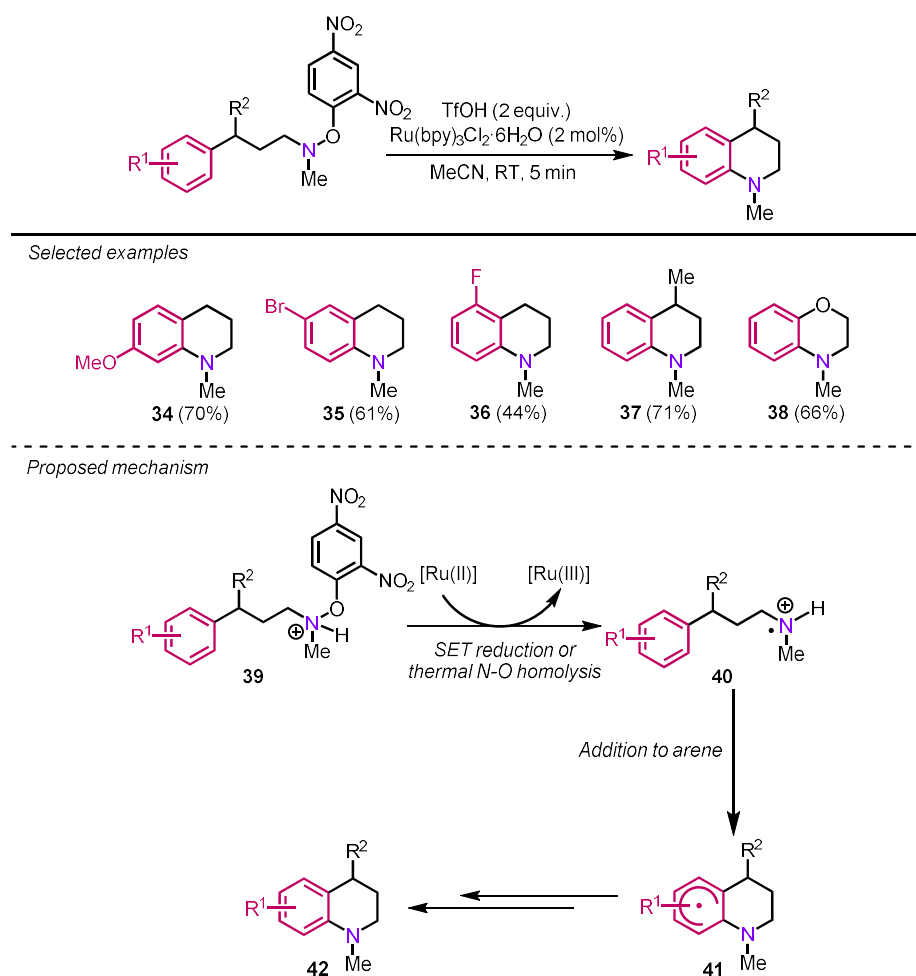
transformation (Scheme 3).^[5] Aryl iodide **29** is suggested to undergo SET reduction to radical anion **30**, which decomposes to the reactive aryl radical **31**. The double bond in the starting material is well poised for the 6-exo-trig cyclization to afford the corresponding tetrahydroquinolines **24-28**.



Scheme 3. Synthesis of tetrahydroquinolines via photocatalytic cyclization.

The cyclization problem can be tackled from a different angle by forming a C–N bond instead of a C–C bond - a strategy recently depicted by the group of Murphy (Scheme 4).^[6] The overall reaction design of these cyclizations follows similar principles, while the cleavable group X of the labile N–X bond can be always tailored to meet individual needs for the desired reactivity. The group of Murphy leveraged the reactivity of *N*-2,4-dinitrophenoxy derivatives as precursors of N-centered radicals. Initial screening of reaction conditions in the dark showed that the cyclization could take place under non-photochemical conditions. The addition of $\text{Ru(bpy)}_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ in catalytic quantities was beneficial; yet its role was not clear apart from the potential reductive SET of the substrate. Of note, the reaction could be performed without adding $\text{Ru(bpy)}_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$. The

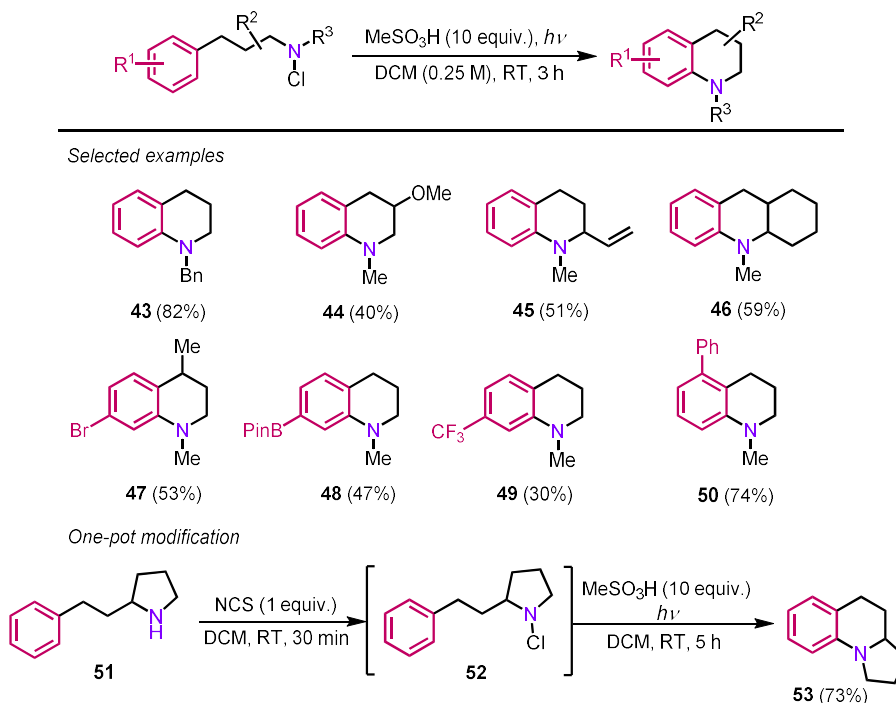
main mechanistic hypothesis suggests the initial protonation of substrate to a *N*-2,4-dinitrophenoxy derivative **40**, which becomes more prone to thermal homolysis or reductive SET. Newly formed aminium radical **40** is close enough to add to the aryl ring to form the 6-membered cycle of a tetrahydroquinoline core **41**. Importantly, the presence of oxygen as a potential terminal oxidant of **41** was crucial for obtaining higher yields.



Scheme 4. Synthesis of tetrahydroquinolines via cyclization of aminium radicals.

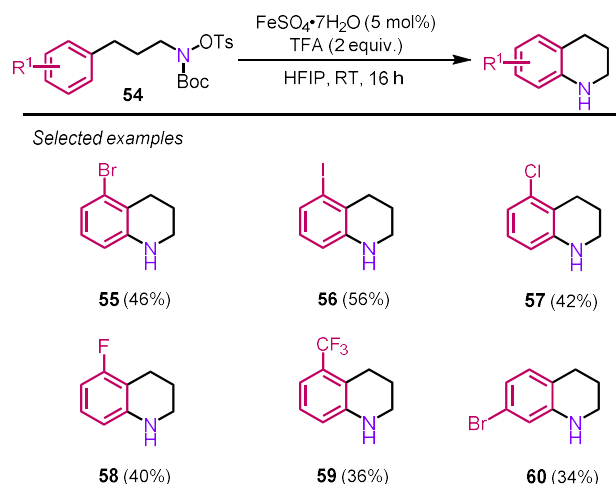
An alternative version of the intramolecular cyclization of the aminium radical formed from a chloroamine precursor was reported by the group of Marsden (Scheme 5).^[7] Upon protonation by methanesulfonic acid, chloroamine undergoes photolysis followed by homolysis of N–Cl bond to generate the key reactive aminium radical. The presence of electron-withdrawing substituents on the aryl ring such as Br (**47**) or CF₃ (**49**) drastically decreased the yield, pointing towards the electrophilic nature of the generated N-centered radical. A more practical one-pot version of the protocol was developed as well. In the first step, a secondary amine is chlorinated by *N*-

chlorosuccinimide to form the chloroamine **52**. In the second step, MeOH is added, and the reaction mixture is irradiated to trigger the cyclization to the target tetrahydroquinoline **53**.



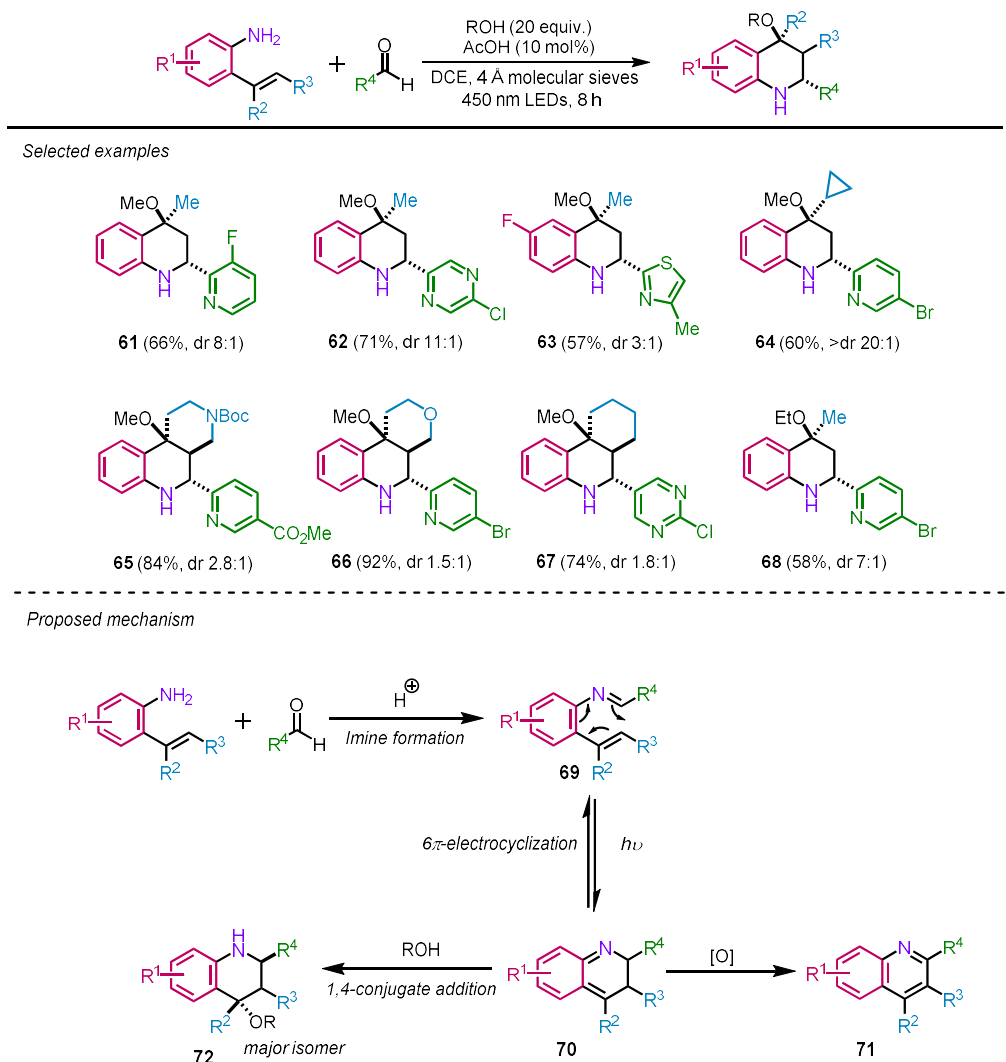
Scheme 5. Synthesis of tetrahydroquinolines starting from chloroamines as radical precursors.

A conceptually similar cyclization to tetrahydroquinolines from *O*-tosylhydroxylamine precursors **54** was developed by the group of Morandi (Scheme 6).^[8] In contrast to the previous example, the reaction did not require any photoactivation, only taking place in HFIP. Due to its strong H-bond donor ability, HFIP is suggested to facilitate the homolysis of the N–O bond. The synthetic utility of the method is rather limited since target tetrahydroquinolines **55–60** were obtained in moderate yields, and precursors **54** required a multi-step synthesis. Nonetheless, Boc-protected *O*-tosylhydroxylamine derivatives proved a promising platform for accessing aminium radicals in HFIP.



Scheme 6. Intramolecular cyclization to tetrahydroquinolines from O-tosylhydroxylamines.

An elegant diastereoselective visible-light mediated synthesis of tetrahydroquinolines was reported by AstraZeneca in 2022 (Scheme 7).^[9] Their protocol accommodated a broad range of medicinally relevant moieties such as pyrimidines **62**, **67** or thiazoles **63**, notably bearing a halide substituent ready for further Pd-catalyzed functionalizations. Tricyclic scaffolds **65-67** were obtained as well, albeit with a lower diastereoselectivity. Mechanistic studies suggest the initial formation of imine **69** by a reaction between the aniline and the aldehyde. Upon irradiation, **69** is brought to an excited state that can undergo a conrotatory 6π -electrocyclization. This mechanistic proposal is supported by the analysis of stereochemistry of the final product obtained from *E*- and *Z*-alkenes. Cyclized intermediate **70** is unstable and is trapped by the alcohol additive to afford the final tetrahydroquinoline **72**. Trapping by an alcohol is critical to divert the intermediate **70** from slow oxidation to the corresponding quinoline **71** observed in the absence of the added alcohol. The alkoxy group in **72** could then be easily removed by Pd/C-catalyzed hydrogenation.



Scheme 7. Synthesis of tetrahydroquinolines via photochemical 6 π -electrocyclization.

The analysis of recent literature has shown that Povarov-type reactions remain the most flexible and versatile methods to access tetrahydroquinolines starting from cheap and available starting materials. Despite major progress in the field of photocatalyzed/mediated cyclization reactions for the synthesis of the tetrahydroquinoline core, they lack the desired generality and require engineered substrates with reactive functional groups introduced in the correct positions beforehand. Expanding the alkene scope of the Povarov reaction to include strongly deactivated alkenes is still a major challenge, but the solution to it will unlock the access to the chemical space of tetrahydroquinolines bearing electron-withdrawing substituents, which are often found in bioactive substances.

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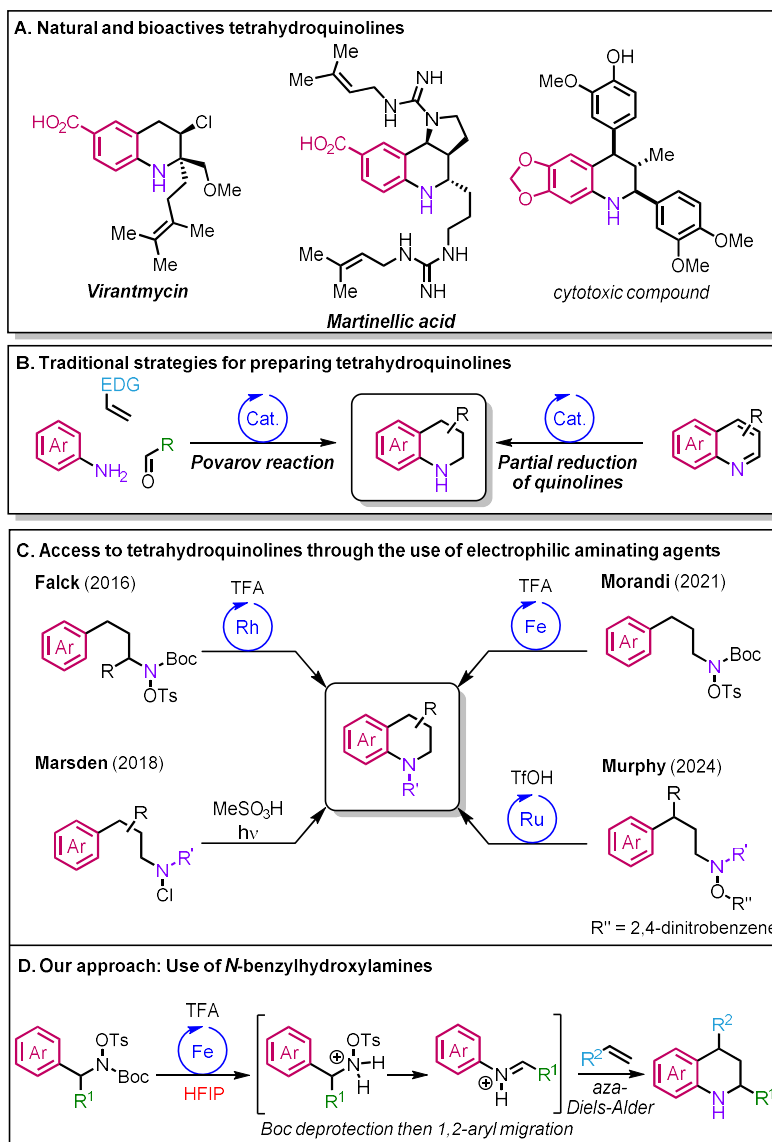
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Main Text

Introduction

Tetrahydroquinolines assume a pivotal role across diverse industrial sectors as building blocks for the synthesis of pharmaceuticals, agrochemicals, and materials (Scheme 1A).^[1,2] Currently, the Povarov reaction and the partial reduction of quinolines are among the most popular approaches to synthesise tetrahydroquinolines (Scheme 1B).^[1-3] Both have nevertheless their own limitations. In the case of the Povarov reaction, the transformation is mainly limited to alkenes bearing electron-donating groups (EDGs),^[4] while the reduction of quinolines requires the pre-installation of the desired functionalities through multi-steps synthesis. More recently, new elegant strategies for the preparation of tetrahydroquinolines have appeared that rely on the intramolecular C–H amination of arenes via nitrogen-centered radicals formed from electrophilic aminating agents,^[5,6] as exemplified by the groups of Marsden, Morandi and Murphy (Scheme 1C).^[7-9] Other relevant variants to access tetrahydroquinolines were also reported by the groups of Falck and Bower via rhodium catalysis and Brønsted acid-promoted reactions.^{10,11} However, overall, the scaffolds attainable are limited, and engineered substrates are often required to access more complex molecules.

In this context, hydroxylammonium salts serve as promising sources for the incorporation of nitrogen in feedstock compounds.^[12,13] These reagents have attracted the attention of researchers owing to their chemical properties and versatility. Hydroxylammonium salts are prepared from relatively inexpensive and commercially available starting material which makes their synthesis straightforward. These reagents grant access to a variety of free unprotected amines; their nitrogen-oxygen bond can be homolytically cleaved to generate a nitrogen-centered radical that adds to C–C double bonds. Their use has been remarkably exploited by the group of Morandi in several iron(II)-catalysed alkene aminofunctionalisations.^[14-16] Our group has recently described efficient methods for the 1,2-aminoarylation and 1,2-diamination of highly electronically deactivated styrenes, affording unprotected amines in a one-pot sequence while displaying broad functional group compatibility.^[17,18] During our investigations, we noted that the reactions only occurred when hexafluoroisopropanol (HFIP) was used as a solvent,^[19-21] which we attributed to its ability to enhance the reactivity of the various reactive intermediates.



Scheme 1. Importance of tetrahydroquinoline motif and synthetic approaches to access them.

To exploit these reagents in intermolecular processes, we aimed to develop a new set of readily available and bench-stable hydroxylamine reagents that could react with alkenes to provide complex tetrahydroquinolines. By relying on the unique properties of HFIP, we hypothesised that we might unlock the reactivity of highly electronically deactivated styrenes to complement the scope of the Povarov reaction. Our design plan relied on the use *N*-benzylhydroxylamine derivatives that could be easily obtained by a Mitsunobu reaction (Scheme 1D). Following a Boc deprotection under acidic conditions, a 1,2-aryl migration could occur to give an *N*-aryliminium; this intermediate could then engage in an aza-Diels-Alder reaction to yield the corresponding

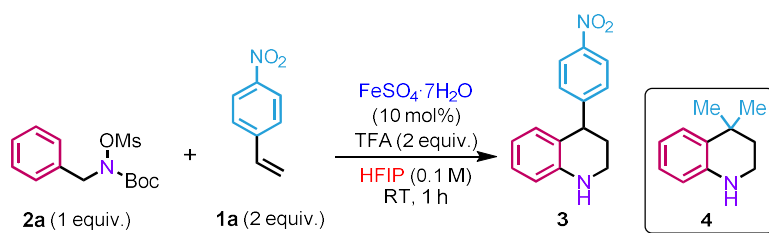
tetrahydroquinoline. Here, we disclose our research efforts in the development of this transformation.

Results and Discussion

Optimization Studies

In our initial investigations, we evaluated the reaction between hydroxylamine **2a** and an excess of *p*-nitrostyrene **1a** (2 equiv.) in the presence of a catalytic amount of iron(II) sulfate heptahydrate and trifluoroacetic acid (TFA) using HFIP (0.1 M) as a solvent. The role of TFA is to promote the *in situ* deprotection of the Boc group. Attempts to prepare the corresponding hydroxylammonium salt [MsO-NH₂Bn][OTf] from hydroxylamine **2a** and triflic acid led to rapid decomposition of the product. Under the reaction conditions mentioned above, the target product **3** was isolated in 50% isolated yield (Table 1, Entry 1). Other iron(II) salts were tested but did not improve the yields (Table 1, Entries 2 and 3). As observed in our previous studies, the reaction only took place in HFIP (Table 1, Entries 4-7). In the absence of either TFA or FeSO₄·7H₂O, a significant drop in yield was observed (Table 1, Entries 8 and 9). In the same vein, decreasing the amount of styrene, operating at higher concentration or higher temperature proved detrimental for the reactivity (Table 1, Entries 10-12). Using an excess of **2a** also led to a decrease in efficacy (Table 1, Entry 13). Replacing the mesyl group by a tosyl one on **2a** did not affect the reactivity, delivering **3** in 52% yield (Table 1, Entry 14). Some of the mass balance of the reaction was found to be diverted to the formation of side product **4** (10% yield), resulting from the reaction with the isobutene produced *in situ* during Boc group deprotection of hydroxylamine **2a**.

Thus, two different alkenes in the reaction medium compete to react with the hydroxylammonium salt. A similar side-product was observed by the group of Falck during their studies on amination of benzyl alcohols.^[22] Although we failed to completely suppress its formation, bubbling argon in the reaction mixture slightly improved the yield (60%) (Table 1, Entry 15).



Entry	Variation from standard conditions ^[a]	Yield ^[b]
1	none	52% (50%)
2	$\text{Fe}(\text{OTf})_2$ instead of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$	41% (38%)
3	$\text{Fe}(\text{OAc})_2$ instead of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$	44% (41%)
4	MeNO_2 instead of HFIP	n.r.
5	TFE instead of HFIP	n.r.
6	1,2-DCE instead of HFIP	n.r.
7	DCM instead of HFIP	n.r.
8	without TFA	32%
9	without $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$	17%
10	1 equiv. 1a	24%
11	0.2 M	19%
12	40 °C	19%
13	1 equiv. 1a , 3 equiv. 2a	36%
14	TsO instead of MsO	55% (52%) ^[c]
16	TsO instead of MsO and argon bubbling	63% (60%)

[a] Standard reaction conditions: **1a** (0.4 mmol), **2** (0.2 mmol), $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (10 mol%) and TFA (0.4 mmol) in HFIP (0.1 M), rt, 1 h (in a sealed tube). [b] NMR yield using triethylsilane as an external standard (isolated yield in parentheses). [c] Product **4** obtained in 10% yield. n.r. = no reaction.

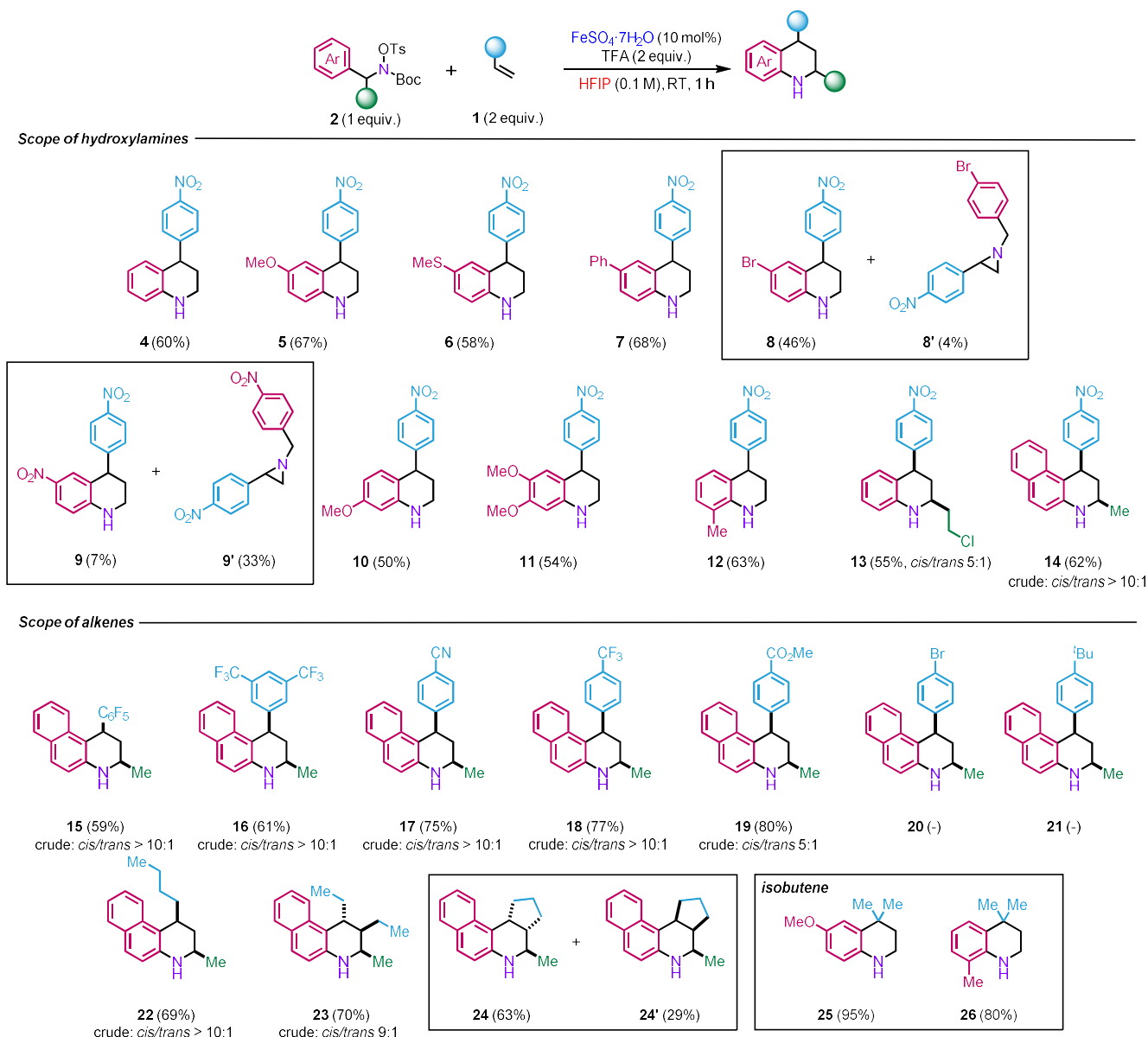
Table 1. Optimization of reaction conditions.

Reaction Scope

We then began to explore the scope of the reaction by using electronically varied hydroxylamines **2d-2l** in reaction with *p*-nitrostyrene **1a** (Scheme 2). The transformation tolerates the presence of various electron-donating and moderate electron-withdrawing groups at the *para*-position, including ether, thioether, aryl, and halide, to afford the corresponding tetrahydroquinolines **5-8** in 46-68% yields. On the other hand, in the case of the more electron-deficient nitro-containing hydroxylamine **2g**, aziridine **9'** was obtained, as a major product (33% yield) with only traces of tetrahydroquinoline **9** (7% yield). The formation of product **9'** seems to indicate that the migration of the aryl does not occur in the presence of a strong electron-withdrawing group. Therefore, the reaction between the styrene and hydroxylammonium takes place to form, instead, the aziridine as observed in our previous studies.^[17,18]

The reaction is also compatible with the presence of electron-rich substituents at the *ortho*- and *meta*-position (**10-12**, 50-63%). The reaction is not limited to primary benzyl alcohols but could also be extended to secondary ones such as **13** (55%). Tetrahydrobenzo[f]quinoline scaffolds such as **14** (62%) are also accessible using this methodology from naphthyl hydroxylamine **2I**. In these different examples, the reaction did not produce observable by-products, suggesting that some of the moderate yields result from the partial decomposition of the hydroxylamines during the reaction.

Regarding the reactivity of various alkenes, naphthyl hydroxylamine **2I** was used as a model hydroxylamine. The functional group tolerance of this method was studied towards styrenes incorporating strong electron-withdrawing groups as they show limited reactivity in the existing Povarov reaction. To our delight, electron-deficient styrene derivatives afforded products **15-19** in high yields (59-80% yields). The *cis* configuration for the major products was ascertained by NOESY analyses. However, in the case of styrene bearing a moderate electron-withdrawing group (Br, **20**), or electron-donating group (*t*-Bu, **21**), oligomerisation of the styrene was observed. The versatility of the method was also tested with electron-rich aliphatic alkenes. For instance, product **22** was obtained from 1-hexene in 70% yield. In the case of *trans*-3-hexene, product **23** was obtained in 70% yield as major diastereoisomer. Its structure was evidenced by NOESY analyses (see SI). The fact that the stereochemistry of the starting material was retained in the product implies that the reaction might involve a concerted mechanism. We next examined cyclic alkenes. Satisfyingly, cyclopentene was well-tolerated in the reaction, yielding two diastereoisomers **24** and **24'** in a combined yield of 92%. Finally, different hydroxylamines were tested with isobutene generated *in situ*. First, *para*-substituted methoxy hydroxylamine afforded product **25** in a nearly quantitative yield (95%). Second, *ortho*-methyl substituted hydroxylamine led to the formation of **26** in 80% yield. However, no product was observed with naphthyl hydroxylamine **2I**. In that case, it seems that the hydrolysis of the postulated iminium intermediate is faster than the reaction with isobutene since only 2-naphthylamine was recovered from the reaction.

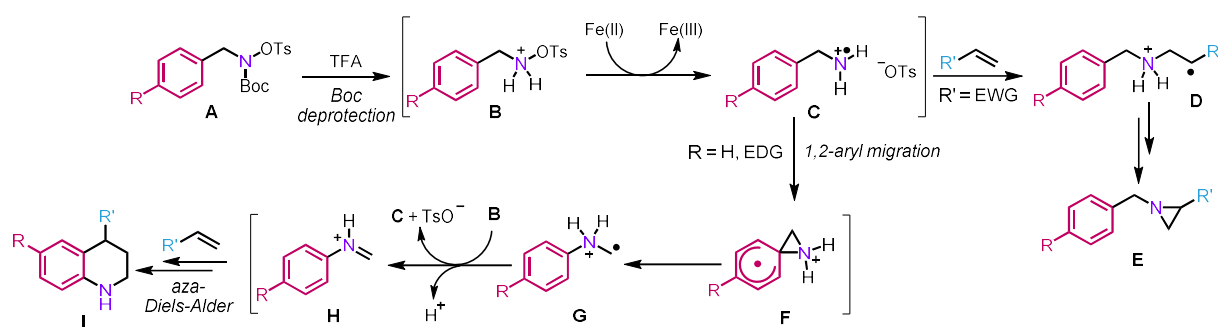


Scheme 2. Scope of the transformation. [a] Aziridine was obtained in 4% yield.

Regarding this transformation, various observations make us lean towards a radical cation crossover mechanism: (1) In the presence of TEMPO, the reaction is completely inhibited, which strongly suggests the involvement of radical species; (2) As mentioned above, in the absence of an alkene partner, naphthyl hydroxylamine **21** led to 2-naphthylamine, which is consistent with the 1,2-aryl migration proposed; (3) The fact that the stereochemistry of the alkene is retained in the product implies that the reaction likely involves a concerted mechanism.

We thus propose the following mechanism (Scheme 3): Initially, the Boc group is deprotected in the presence of TFA, generating the corresponding ammonium **B**. Then, a classical homolytic

cleavage of the N-O bond occurs to provide aminium radical cation **C**. At this point, the reaction can diverge depending on the substitution pattern of the hydroxylamine. In the presence of an electron-withdrawing group (EWG), the 1,2-aryl migration is disfavoured and the aminium radical cation can directly add across the double bond (**D**) to finally provide aziridine **E**.^[23] On the other hand, in the presence of an EDG, a rare but not unprecedented radical 1,2-aryl migration can occur to provide α -aminomethyl radical **G**.^[24] From there, **G** can regenerate **C** by single electron transfer to **B**, a mechanism consistent with a precedent report by the group of Phipps.^[25] Lastly, iminium **H** would engage in a classical aza-Diels-Alder to deliver tetrahydroquinoline **I**. Regarding the positive effect of HFIP on the reactivity, it might be explained by its ability to strongly donate H-bonds, thereby increasing the electrophilicity of various intermediates such as **C** or **H** to facilitate the key steps of the process, namely the 1,2-aryl migration and aza-Diels-Alder.



Scheme 3. Plausible mechanistic pathway.

Conclusion

In conclusion, through exploring the reactivity of new hydroxylamine reagents, we have demonstrated their efficacy in generating tetrahydroquinolines with different substitution patterns. In contrast to the classical Povarov reaction, our methodology accommodates electron-deficient and aliphatic alkenes, thereby expanding the chemical space of available tetrahydroquinoline scaffolds. The ability of these reagents to react with isobutene without the need to directly handle this hazardous compound also represents a significant advantage. Ongoing investigations are focusing on deciphering the mechanism of this transformation.

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Supporting Information

It should be noted that only the characterization of the different products of the scope was kept inside of the thesis. All NMR spectra were not included but are available online.

1. General Remarks

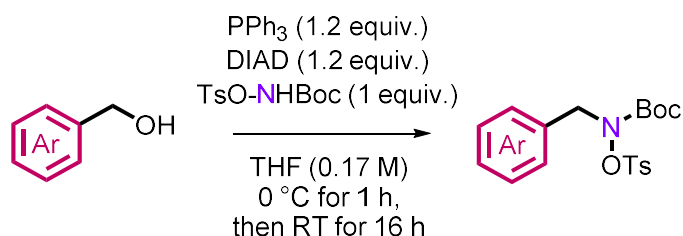
Materials: All commercial materials were purchased from Sigma-Aldrich, TCI and FluoroChem, and were used as received, without further purification. HFIP (CAS: 920-66-1) was purchased from FluoroChem. The other starting materials were prepared according to known protocols.

Reactions were monitored by thin layer chromatography (TLC) performed on aluminum plates coated with silica gel F₂₅₄ with 0.2 mm thickness. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm and/or by staining using potassium permanganate. Flash column chromatography (FC) was performed using silica gel 60 (230-400 mesh, Merck and co.). Yields refer to chromatographically and spectroscopically pure compounds. When stated, NMR yields were calculated by using mesitylene as an external standard.

¹H NMR, ¹³C NMR, ¹⁹F NMR, ³¹P NMR spectra were recorded using a Bruker UltraShield 400 or 500 at 300K. ¹H NMR chemical shifts are reported in ppm using residual solvent peak as reference (CDCl₃: δ = 7.26 ppm; CD₂Cl₂: 5.32 ppm; CD₃OD: 3.31 ppm). Data for ¹H NMR are presented as follows: chemical shift δ (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constant *J* (Hz) and integration; ¹³C NMR spectra were recorded at 100, 126 MHz using broadband proton decoupling and chemical shifts are reported in ppm using residual solvent peaks as reference (CDCl₃: δ = 77.16 ppm; CD₂Cl₂: 53.84 ppm; CD₃OD: 49.00 ppm). Multiplicity was defined by recorded a ¹³C NMR spectra using the attached proton test (APT). ¹⁹F NMR spectra were recorded at 471 MHz at ambient temperature. ³¹P NMR spectra were recorded at 162 MHz at ambient temperature. High-resolution mass spectrometry (HRMS) analysis was performed on instruments GCT 1er Waters (EI and IC), MicroTOF-Q Bruker (ESI) and a GC Thermo Scientific Trace 1300 GC unit coupled to an APPI MasCom source mounted on a Thermo Scientific Exactive Plus EMR mass unit (Orbitrap FT-HRMS analyzer).

2. Synthesis of New Hydroxylamine Reagents

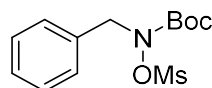
2.1 General procedure (A) for the Mitsunobu reaction to synthesize new hydroxylamine reagents



To a stirring solution of triphenylphosphine (1.2 equiv.) and TsO-NHBoc (1.0 equiv.) in anhydrous THF (0.17 M) at 0 °C were added the corresponding benzylic alcohol (1.0 equiv.) and DIAD (1.2 equiv.). After stirring at 0 °C for 1 h, the reaction was allowed to warm to RT and was stirred for another 16 h. Upon completion, all volatiles were removed under reduced pressure and the residue was purified by flash column chromatography (FC) over silica gel to furnish target hydroxylamine reagents **2a-2l**.

2.2 Characterization data of new hydroxylamine reagents 2a-2l

tert-butyl benzyl((methylsulfonyl)oxy)carbamate **2a**

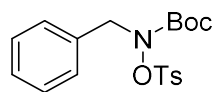


Chemical Formula: C₁₃H₁₉NO₅S
Exact Mass: 301.0984

General Procedure **A** was followed with MsO-NHBoc (1.10 g, 5.2 mmol, 1.0 equiv.), benzyl alcohol (560 mg, 5.2 mmol, 1.0 equiv.), PPh₃ (1.63 g, 6.2 mmol, 1.2 equiv.), and DIAD (1.22 mL, 6.2 mmol, 1.2 equiv.) in THF (30 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **2a** (1.26 g, 4.2 mmol, 80% yield) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ 7.32–7.21 (m, 5H), 4.76 (brs, 2H), 3.02 (s, 3H), 1.40 (s, 9H). **¹³C NMR (100 MHz, CDCl₃):** δ 155.3 (C), 134.7 (C), 129.0 (CH), 128.6 (CH), 128.3 (CH), 84.5 (C), 56.9 (CH₂), 36.9 (CH₃), 28.0 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₃H₁₉NO₅SNa [M+Na]⁺ 324.0876, found 324.0879.

tert*-butyl benzyl(tosyloxy)carbamate **2b*

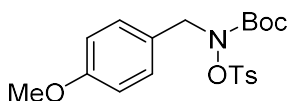


Chemical Formula: C₁₉H₂₃NO₅S
Exact Mass: 377.1297

General Procedure **A** was followed with TsO-NHBoc (1.50 g, 5.2 mmol, 1.0 equiv.), benzyl alcohol (560 mg, 5.2 mmol, 1.0 equiv.), PPh₃ (1.63 g, 6.2 mmol, 1.2 equiv.), and DIAD (1.22 mL, 6.2 mmol, 1.2 equiv.) in THF (30 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **2b** (1.48 g, 4.4 mmol, 85% yield) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ 7.90 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.34–7.28 (m, 5H), 4.79 (brs, 2H), 2.48 (s, 3H), 1.21 (s, 9H). **¹³C NMR (100 MHz, CDCl₃):** δ 155.2 (C), 145.8 (C), 134.8 (C), 131.2 (C), 129.7 (CH), 129.6 (CH), 128.9 (CH), 128.5 (CH), 128.1 (CH), 83.5 (C), 56.3 (CH₂), 27.6 (CH₃), 21.8 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₉H₂₃NO₅Na [M+Na]⁺ 400.1189, found 400.1185.

tert*-butyl (4-methoxybenzyl)(tosyloxy)carbamate **2c*

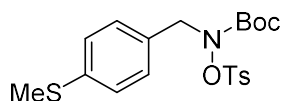


Chemical Formula: C₂₀H₂₅NO₆S
Exact Mass: 407.1403

General Procedure **A** was followed with TsO-NHBoc (1.50 g, 5.2 mmol, 1.0 equiv.), 4-methoxybenzyl alcohol (720 mg, 5.2 mmol, 1.0 equiv.), PPh₃ (1.63 g, 6.2 mmol, 1.2 equiv.), and DIAD (1.22 mL, 6.2 mmol, 1.2 equiv.) in THF (30 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 80/20) afforded **2c** (1.62 g, 4.0 mmol, 77% yield) as a brown solid.

¹H NMR (400 MHz, CDCl₃): δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.72 (brs, 2H), 3.81 (s, 3H), 2.48 (s, 3H), 1.21 (s, 9H). **¹³C NMR (100 MHz, CDCl₃):** δ 159.5 (C), 155.3 (C), 145.7 (C), 131.3 (C), 130.6 (CH), 129.7 (CH), 129.5 (CH), 126.9 (C), 113.8 (CH), 83.4 (C), 55.8 (CH₂), 55.2 (CH₃), 27.6 (CH₃), 21.7 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₂₀H₂₅NO₆Na [M+Na]⁺ 430.1295, found 430.1289.

***tert*-butyl (4-(methylthio)benzyl)(tosyloxy)carbamate 2d**

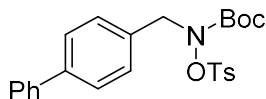


Chemical Formula: C₂₀H₂₅NO₅S₂
Exact Mass: 423.1174

General Procedure **A** was followed with TsO-NHBoc (1.50 g, 5.2 mmol, 1.0 equiv.), 4-methylthiobenzyl alcohol (800 mg, 5.2 mmol, 1.0 equiv.), PPh₃ (1.63 g, 6.2 mmol, 1.2 equiv.), and DIAD (1.22 mL, 6.2 mmol, 1.2 equiv.) in THF (30 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **2d** (1.60 g, 3.8 mmol, 73% yield) as a bright brown solid.

¹H NMR (400 MHz, CDCl₃): δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.26–7.19 (m, 4H), 4.75 (brs, 2H), 2.49 (s, 3H), 2.48 (s, 3H), 1.21 (s, 9H). **¹³C NMR (100 MHz, CDCl₃):** δ 155.2 (C), 145.8 (C), 138.5 (C), 131.5 (C), 131.2 (C), 129.7 (CH), 129.6 (CH), 129.5 (CH), 126.5 (CH), 83.6 (C), 55.8 (CH₂), 27.6 (CH₃), 21.7 (CH₃), 15.7 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₂₀H₂₅NO₅S₂K [M+K]⁺ 462.0806, found 462.0799.

***tert*-butyl ([1,1'-biphenyl]-4-ylmethyl)(tosyloxy)carbamate 2e**

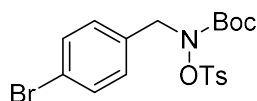


Chemical Formula: C₂₅H₂₇NO₅S
Exact Mass: 453.1610

General Procedure **A** was followed with TsO-NHBoc (1.50 g, 5.2 mmol, 1.0 equiv.), 4-phenylbenzyl alcohol (960 mg, 5.2 mmol, 1.0 equiv.), PPh₃ (1.63 g, 6.2 mmol, 1.2 equiv.), and DIAD (1.22 mL, 6.2 mmol, 1.2 equiv.) in THF (30 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **2e** (2.10 g, 4.6 mmol, 88% yield) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.59–7.53 (m, 4H), 7.44 (ddd, *J* = 7.8, 6.5, 1.2 Hz, 2H), 7.39–7.34 (m, 5H), 4.82 (brs, 2H), 2.45 (s, 3H), 1.21 (s, 9H). **¹³C NMR (100 MHz, CDCl₃):** δ 155.4 (C), 145.9 (C), 141.1 (C), 140.8 (C), 134.0 (C), 131.4 (C), 129.9 (CH), 129.7 (CH), 129.6 (CH), 128.9 (CH), 127.5 (C), 127.4 (CH), 127.2 (CH), 83.7 (C), 56.1 (CH₂), 27.7 (CH₃), 21.8 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₂₅H₂₇NO₅SNa [M+Na]⁺ 476.1502, found 476.1501.

***tert*-butyl (4-bromobenzyl)(tosyloxy)carbamate 2f**

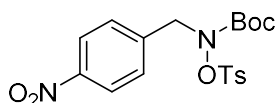


Chemical Formula: C₁₉H₂₂BrNO₅S
Exact Mass: 455.0402

General Procedure **A** was followed with TsO-NHBoc (1.50 g, 5.2 mmol, 1.0 equiv.), 4-bromobenzyl alcohol (970 mg, 5.2 mmol, 1.0 equiv.), PPh₃ (1.63 g, 6.2 mmol, 1.2 equiv.), and DIAD (1.22 mL, 6.2 mmol, 1.2 equiv.) in THF (30 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **2f** (1.77 g, 3.9 mmol, 75% yield) as a bright purple solid.

¹H NMR (400 MHz, CDCl₃): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 4.65 (brs, 2H), 2.38 (s, 3H), 1.11 (s, 9H). **¹³C NMR (100 MHz, CDCl₃):** δ 155.1 (C), 145.9 (C), 133.8 (C), 131.7 (CH), 131.1 (C), 130.8 (CH), 129.7 (CH), 129.6 (CH), 122.3 (C), 83.8 (C), 55.7 (CH₂), 27.6 (CH₃), 21.8 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₉H₂₂NO₅BrSNa [M+Na]⁺ 478.0294, found 478.0299.

***tert*-butyl (4-nitrobenzyl)(tosyloxy)carbamate 2g**

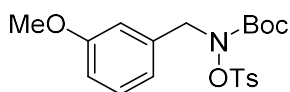


Chemical Formula: C₂₀H₂₅NO₅S₂
Exact Mass: 423.1174

General Procedure **A** was followed with TsO-NHBoc (1.50 g, 5.2 mmol, 1.0 equiv.), 4-nitrobenzyl alcohol (795 mg, 5.2 mmol, 1.0 equiv.), PPh₃ (1.63 g, 6.2 mmol, 1.2 equiv.), and DIAD (1.22 mL, 6.2 mmol, 1.2 equiv.) in THF (30 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **2g** (2.00 g, 4.8 mmol, 92% yield) as a yellow solid.

¹H NMR (400 MHz, CDCl₃): δ 8.16 (d, *J* = 8.8 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.87 (s, 2H), 2.45 (s, 3H), 1.17 (s, 9H). **¹³C NMR (100 MHz, CDCl₃):** δ 155.0 (C), 147.7 (C), 146.3 (C), 142.3 (C), 130.9 (C), 129.8 (2CH), 129.7 (CH), 123.8 (CH), 84.3 (C), 55.6 (CH₂), 27.6 (CH₃), 21.8 (CH₃).

***tert*-butyl (3-methoxybenzyl)(tosyloxy)carbamate 2h**

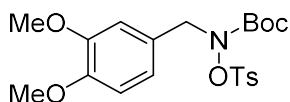


Chemical Formula: C₂₀H₂₅NO₆S
Exact Mass: 407.1403

General Procedure **A** was followed with TsO-NHBoc (1.50 g, 5.2 mmol, 1.0 equiv.), 3-methoxybenzyl alcohol (720 mg, 5.2 mmol, 1.0 equiv.), PPh₃ (1.63 g, 6.25 mmol, 1.2 equiv.), and DIAD (1.22 mL, 6.25 mmol, 1.2 equiv.) in THF (30 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **2h** (1.75 g, 4.3 mmol, 83% yield) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.26–7.21 (m, 1H), 6.91–6.87 (m, 1H), 6.86–6.83 (m, 2H), 4.77 (brs, 2H), 3.80 (s, 3H), 2.48 (s, 3H), 1.23 (s, 9H). **¹³C NMR (100 MHz, CDCl₃):** δ 159.7 (C), 155.2 (C), 145.7 (C), 136.3 (C), 131.3 (C), 129.7 (CH), 129.6 (CH), 129.5 (CH), 121.2 (CH), 114.1 (CH), 113.9 (CH), 83.5 (C), 56.2 (CH₂), 55.2 (CH₃), 27.6 (CH₃), 21.7 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₂₀H₂₅NO₆SNa [M+Na]⁺ 430.1295, found 430.1310.

***tert*-butyl (3,4-dimethoxybenzyl)(tosyloxy)carbamate 2i**

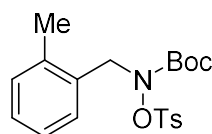


Chemical Formula: C₂₁H₂₇NO₇S
Exact Mass: 437.1508

General Procedure **A** was followed with TsO-NHBoc (1.50 g, 5.2 mmol, 1.0 equiv.), 3,4-dimethoxybenzyl alcohol (870 mg, 5.2 mmol, 1.0 equiv.), PPh₃ (1.63 g, 6.2 mmol, 1.2 equiv.), and DIAD (1.22 mL, 6.2 mmol, 1.2 equiv.) in THF (30 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **2i** (1.61 g, 3.7 mmol, 71% yield) as a dark brown solid.

¹H NMR (400 MHz, CDCl₃): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 6.83–6.71 (m, 3H), 4.67 (brs, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 2.39 (s, 3H), 1.12 (s, 9H). **¹³C NMR (100 MHz, CDCl₃):** δ 155.4 (C), 148.9 (C), 148.8 (C), 145.7 (C), 131.2 (C), 129.7 (CH), 129.5 (CH), 127.2 (CH), 122.0 (CH), 112.1 (CH), 110.8 (CH), 83.4 (C), 56.1 (CH₂), 55.9 (CH₃), 55.8 (CH₃), 27.6 (CH₃), 21.7 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₂₁H₂₈NO₇S [M+H]⁺ 438.1581, found 438.1586.

tert*-butyl (2-methylbenzyl)(tosyloxy)carbamate **2j*

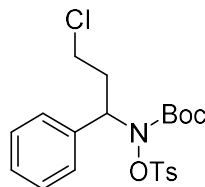


Chemical Formula: C₂₀H₂₅NO₅S
Exact Mass: 391.1453

General Procedure **A** was followed with TsO-NHBoc (1.50 g, 5.2 mmol, 1.0 equiv.), 2-methylbenzyl alcohol (635 mg, 5.2 mmol, 1.0 equiv.), PPh₃ (1.63 g, 6.2 mmol, 1.2 equiv.), and DIAD (1.22 mL, 6.2 mmol, 1.2 equiv.) in THF (30 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **2j** (1.83 g, 4.7 mmol, 90% yield) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.13–7.03 (m, 4H), 4.78 (brs, 2H), 2.38 (s, 3H), 2.25 (s, 3H), 1.14 (s, 9H). **¹³C NMR (100 MHz, CDCl₃):** δ 155.3 (C), 145.7 (C), 136.6 (C), 133.3 (C), 131.2 (C), 130.5 (CH), 129.7 (CH), 129.6 (CH), 128.4 (CH), 127.8 (CH), 126.0 (CH), 83.5 (C), 53.4 (CH₂), 27.6 (CH₃), 21.7 (CH₃), 19.4 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₂₀H₂₆NO₅S [M+H]⁺ 392.1526, found 392.1524.

tert*-butyl (3-chloro-1-phenylpropyl)(tosyloxy)carbamate **2k*

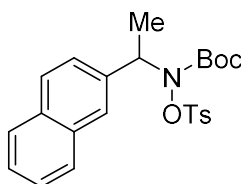


Chemical Formula: C₂₁H₂₆ClNO₅S
Exact Mass: 439.1220

General Procedure **A** was followed with TsO-NHBoc (1.50 g, 5.2 mmol, 1.0 equiv.), 3-chloro-1-phenylpropan-1-ol (880 mg, 5.2 mmol, 1.0 equiv.), PPh₃ (1.63 g, 6.25 mmol, 1.2 equiv.), and DIAD (1.22 mL, 6.25 mmol, 1.2 equiv.) in THF (30 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **2k** (1.49 g, 3.4 mmol, 65% yield) as a dark brown solid.

¹H NMR (400 MHz, CDCl₃): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.28–7.21 (m, 7H), 5.20 (brs, 1H), 3.74–3.63 (m, 1H), 3.48–3.39 (m, 1H), 2.74–2.65 (m, 1H), 2.36 (s, 3H), 2.35–2.25 (m, 1H), 1.10 (s, 9H). **¹³C NMR (100 MHz, CDCl₃):** δ 155.9 (C), 145.8 (C), 136.7 (C), 131.5 (C), 129.6 (CH), 129.5 (CH), 128.5 (2CH), 128.4 (CH), 84.0 (C), 42.1 (CH₂), 35.0 (CH₂), 27.5 (CH₃), 21.7 (CH₃), one CH unobserved. **HRMS (ESI):** *m/z* calcd. for C₂₁H₂₆NO₅ClSNa [M+Na]⁺ 462.1112, found 462.1102.

tert*-butyl (1-(naphthalen-2-yl)ethyl)(tosyloxy)carbamate **2I*



Chemical Formula: C₂₄H₂₇NO₅S

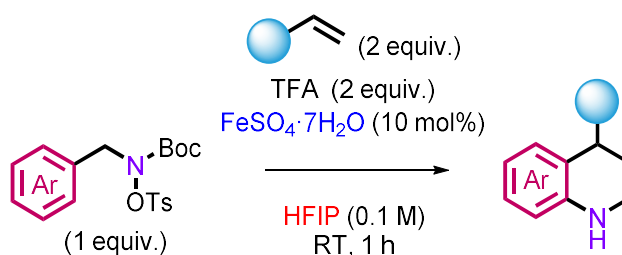
Exact Mass: 441.1610

General Procedure **A** was followed with TsO-NHBoc (1.50 g, 5.2 mmol, 1.0 equiv.), 1-(naphthalen-2-yl)ethan-1-ol (895 mg, 5.2 mmol, 1.0 equiv.), PPh₃ (1.63 g, 6.2 mmol, 1.2 equiv.), and DIAD (1.22 mL, 6.2 mmol, 1.2 equiv.) in THF (30 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **2I** (1.19 g, 2.7 mmol, 52% yield) as a bright purple solid.

¹H NMR (400 MHz, DMSO-*d*₆): δ 7.91–7.84 (m, 3H), 7.82–7.69 (m, 3H), 7.53–7.50 (m, 2H), 7.47 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 5.25 (q, *J* = 7.0 Hz, 1H), 2.37 (s, 3H), 1.64 (d, *J* = 7.0 Hz, 3H), 1.15 (s, 9H). **¹³C NMR (100 MHz, DMSO-*d*₆):** δ 160.5 (C), 151.1 (C), 142.0 (C), 137.9 (C), 137.7 (C), 136.2 (C), 135.0 (CH), 134.3 (CH), 133.1 (CH), 133.0 (CH), 132.6 (CH), 131.4 (CH), 131.4 (CH), 131.2 (CH), 130.7 (CH), 88.6 (C), 68.1 (CH), 32.4 (CH₃), 26.3 (CH₃), 22.5 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₂₄H₂₇NO₅SNa [M+Na]⁺ 464.1502, found 464.1486.

3. Synthesis of Tetrahydroquinolines

3.1 General procedure (B) for the synthesis of tetrahydroquinolines

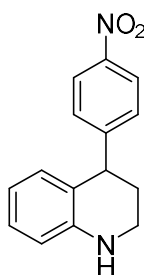


A 5 ml vial equipped with a Teflon-coated magnetic stir bar was charged with FeSO₄·7H₂O (10 mol%) under air and HFIP (0.1 M) was added. The mixture was purged by Ar by bubbling the gas through the solution for 5 min. Then, hydroxylamine reagent (1 equiv.), alkene (2 equiv.) and TFA (2 equiv.) were sequentially added. The reaction mixture was stirred at RT for 1 h while maintaining the bubbling of Ar through the solution. Upon completion, the reaction mixture was quenched with a solution of sat. NaHCO₃ (10 mL) and then extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and concentrated

under reduced pressure. The crude mixture was purified by flash column chromatography (FC) over silica gel to furnish the target products **3-25**.

3.2 Characterization data of tetrahydroquinolines **3-25**

4-(4-nitrophenyl)-1,2,3,4-tetrahydroquinoline **3**

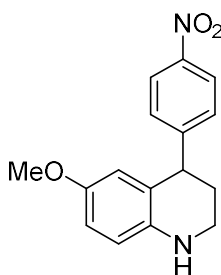


Chemical Formula: $C_{15}H_{14}N_2O_2$
Exact Mass: 254.1055

General Procedure **B** was followed with 4-nitrostyrene (59.8 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2b** (75.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μ L, 0.40 mmol, 2.0 equiv.) and $FeSO_4 \cdot 7H_2O$ (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **3** (31.0 mg, 0.12 mmol, 60% yield) as a yellow oil.

1H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.7 Hz, 2H), 6.99–6.94 (m, 1H), 6.60 (d, J = 7.4 Hz, 1H), 6.52–6.47 (m, 2H), 4.19 (t, J = 6.0 Hz, 1H), 3.93 (brs, 1H), 3.24 (ddd, J = 10.9, 6.9, 3.6 Hz, 1H), 3.11 (ddd, J = 11.7, 8.5, 3.4 Hz, 1H), 2.22–2.14 (m, 1H), 1.99–1.91 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 154.5 (C), 146.5 (C), 144.9 (C), 130.3 (CH), 129.5 (CH), 128.0 (CH), 123.6 (CH), 121.5 (C), 117.3 (CH), 114.5 (CH), 42.8 (CH), 38.8 (CH_2), 30.9 (CH_2). **HRMS (ESI):** m/z calcd. for $C_{15}H_{15}N_2O_2$ $[M+H]^+$ 255.1134, found 255.1177.

6-methoxy-4-(4-nitrophenyl)-1,2,3,4-tetrahydroquinoline **5**



Chemical Formula: $C_{16}H_{16}N_2O_3$
Exact Mass: 284.1161

General Procedure **B** was followed with 4-nitrostyrene (59.8 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2c** (81.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μ L, 0.40 mmol, 2.0 equiv.) and

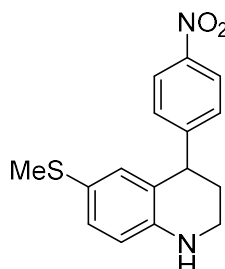
FeSO₄·7H₂O (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **5** (38.0 mg, 0.13 mmol, 67% yield) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 8.08 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.61 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.49 (d, *J* = 8.7 Hz, 1H), 6.19 (d, *J* = 2.8 Hz, 1H), 4.18 (t, *J* = 6.2 Hz, 1H), 3.69 (s, 1H), 3.55 (s, 3H), 3.24–3.18 (m, 1H), 3.13–3.07 (m, 1H), 2.23–2.15 (m, 1H), 1.98–1.90 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 154.4 (C), 151.9 (C), 146.5 (C), 139.1 (C), 129.5 (CH), 123.7 (CH), 122.8 (C), 115.9 (CH), 115.4 (CH), 114.4 (CH), 55.7 (CH₃), 43.1 (CH), 39.3 (CH₂), 31.4 (CH₂).

HRMS (ESI): *m/z* calcd. for C₁₆H₁₇N₂O₃ [M+H]⁺ 285.1234, found 285.1229.

6-(methylthio)-4-(4-nitrophenyl)-1,2,3,4-tetrahydroquinoline **6**

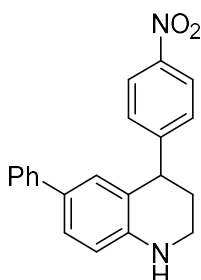


Chemical Formula: C₁₆H₁₆N₂O₂S
Exact Mass: 300.0932

General Procedure **B** was followed with 4-nitrostyrene (59.8 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2d** (85.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μL, 0.40 mmol, 2.0 equiv.) and FeSO₄·7H₂O (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **6** (35.0 mg, 0.12 mmol, 58% yield) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 8.09 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.02 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 4.17 (t, *J* = 5.9 Hz, 1H), 3.96 (s, 1H), 3.29–3.20 (m, 1H), 3.12 (ddd, *J* = 11.8, 8.7, 3.4 Hz, 1H), 2.25 (s, 3H), 2.20–2.14 (m, 1H), 2.00–1.90 (m, 1H). **¹³C NMR (100 MHz, CDCl₃):** δ 153.9 (C), 146.6 (C), 143.7 (C), 132.2 (CH), 130.2 (CH), 129.5 (CH), 124.1 (C), 123.7 (CH), 122.1 (C), 115.2 (CH), 42.7 (CH), 38.7 (CH₂), 30.7 (CH₂), 19.1 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₆H₁₇N₂O₂S [M+H]⁺ 301.1005, found 301.0996.

4-(4-nitrophenyl)-6-phenyl-1,2,3,4-tetrahydroquinoline 7

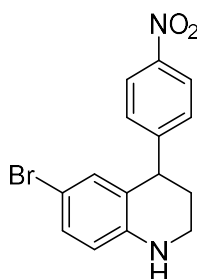


Chemical Formula: $C_{21}H_{18}N_2O_2$
Exact Mass: 330.1368

General Procedure **B** was followed with 4-nitrostyrene (59.8 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2e** (91.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μ L, 0.40 mmol, 2.0 equiv.) and $FeSO_4 \cdot 7H_2O$ (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **7** (45.0 mg, 0.136 mmol, 68% yield) as a yellow oil.

1H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 8.8 Hz, 2H), 7.43–7.39 (m, 2H), 7.36–7.30 (m, 5H), 7.24–7.19 (m, 1H), 6.97–6.95 (m, 1H), 6.66 (d, J = 8.3 Hz, 1H), 4.34 (t, J = 5.9 Hz, 1H), 4.14 (brs, 1H), 3.36 (ddd, J = 10.6, 6.8, 3.5 Hz, 1H), 3.22 (ddd, J = 11.8, 8.7, 3.4 Hz, 1H), 2.34–2.27 (m, 1H), 2.12–2.03 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 154.3 (C), 146.7 (C), 144.5 (C), 141.1 (C), 130.4 (C), 129.6 (CH), 128.9 (CH), 128.7 (CH), 126.9 (CH), 126.3 (CH), 126.2 (CH), 123.8 (CH), 121.8 (C), 115.0 (CH), 43.0 (CH), 38.9 (CH_2), 31.0 (CH_2). **HRMS (ESI):** m/z calcd. for $C_{21}H_{19}N_2O_2$ $[M+H]^+$ 331.1441, found 331.1443.

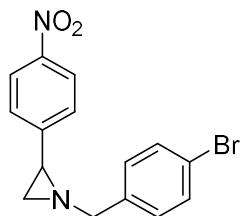
6-bromo-4-(4-nitrophenyl)-1,2,3,4-tetrahydroquinoline 8



Chemical Formula: $C_{15}H_{13}BrN_2O_2$
Exact Mass: 332.0160

General Procedure **B** was followed with 4-nitrostyrene (59.8 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2f** (91.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μ L, 0.40 mmol, 2.0 equiv.) and $FeSO_4 \cdot 7H_2O$ (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel

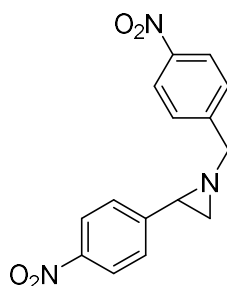
(pentane/EtOAc: 100/0 to 85/15) afforded **8** in mixture with aziridine **8'** (ratio 10:1, 33.0 mg, 0.10 mmol, 50% global yield, 46% corrected yield for **8**) as a yellow oil.



Chemical Formula: $C_{15}H_{13}BrN_2O_2$
Exact Mass: 332.0160

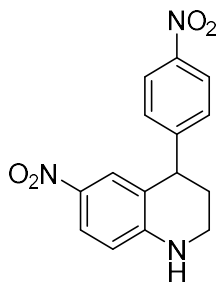
1H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8.7 Hz, 2H), 7.21 (d, J = 8.7 Hz, 2H), 7.05 (dd, J = 8.6, 2.2 Hz, 1H), 6.72 (d, J = 2.2 Hz, 1H), 6.39 (d, J = 8.6 Hz, 1H), 4.15 (t, J = 5.9 Hz, 1H), 3.97 (s, 1H), 3.24 (ddd, J = 10.7, 6.6, 3.6 Hz, 1H), 3.10 (ddd, J = 11.9, 8.7, 3.4 Hz, 1H), 2.19–2.10 (m, 1H), 2.00–1.90 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 153.4 (C), 146.7 (C), 143.8 (C), 132.5 (CH), 130.8 (CH), 129.4 (CH), 123.8 (CH), 123.4 (C), 116.0 (CH), 108.5 (C), 42.6 (CH), 38.6 (CH₂), 30.4 (CH₂). **HRMS (ESI):** m/z calcd. for $C_{15}H_{14}N_2O_2Br$ [M+H]⁺ 333.0233, found 333.0226.

1-(4-nitrobenzyl)-2-(4-nitrophenyl)aziridine **9'**



Chemical Formula: $C_{15}H_{13}N_3O_4$
Exact Mass: 299.0906

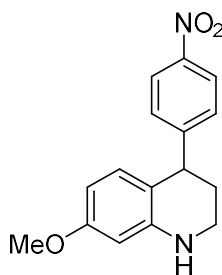
General Procedure **B** was followed with 4-nitrostyrene (59.8 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2g** (85.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μ L, 0.40 mmol, 2.0 equiv.) and $FeSO_4 \cdot 7H_2O$ (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 40/60) afforded **9'** in mixture with 1,2,3,4-tetrahydroquinoline **9** (ratio 5:1, 24.0 mg, 0.08 mmol, 40% global yield, 7% corrected yield for **9**) as a yellow oil.



Chemical Formula: $C_{15}H_{13}N_3O_4$
Exact Mass: 299.0906

1H NMR (400 MHz, $CDCl_3$): δ 8.17 (m, 4H), 7.53 (d, J = 8.9 Hz, 2H), 7.43 (d, J = 8.8 Hz, 2H), 3.84 (d, J = 14.8 Hz, 1H), 3.71 (d, J = 14.8 Hz, 1H), 2.61 (dd, J = 6.5, 3.2 Hz, 1H), 2.06 (d, J = 3.2 Hz, 1H), 2.01 (d, J = 6.5 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 147.6 (2C), 146.3 (2C), 128.4 (CH), 126.9 (CH), 123.9 (CH), 123.8 (CH), 63.7 (CH_2), 40.9 (CH), 39.5 (CH_2). **HRMS (ESI):** m/z calcd. for $C_{15}H_{14}N_3O_4$ $[M+H]^+$ 300.0979, found 300.0962.

7-methoxy-4-(4-nitrophenyl)-1,2,3,4-tetrahydroquinoline 10

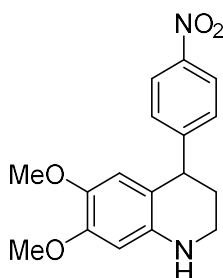


Chemical Formula: $C_{16}H_{16}N_2O_3$
Exact Mass: 284.1161

General Procedure **B** was followed with 4-nitrostyrene (59.8 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2h** (81.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μ L, 0.40 mmol, 2.0 equiv.) and $FeSO_4 \cdot 7H_2O$ (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **10** (29.0 mg, 0.10 mmol, 50% yield) as a yellow oil.

1H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.7 Hz, 2H), 6.51 (dd, J = 8.4, 0.6 Hz, 1H), 6.11 (dd, J = 8.4, 2.5 Hz, 1H), 6.05 (d, J = 2.5 Hz, 1H), 4.14 (t, J = 6.0 Hz, 1H), 3.68 (s, 3H), 3.26–3.20 (m, 1H), 3.14–3.08 (m, 1H), 2.21–2.15 (m, 1H), 1.98–1.92 (m, 1H), NH unobserved. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 159.6 (C), 154.7 (C), 146.5 (C), 145.8 (C), 131.1 (CH), 129.4 (CH), 123.6 (CH), 114.4 (C), 103.6 (CH), 99.3 (CH), 55.1 (CH_3), 42.2 (CH), 38.8 (CH_2), 31.1 (CH_2). **HRMS (ESI):** m/z calcd. for $C_{16}H_{17}N_2O_3$ $[M+H]^+$ 285.1234, found 285.1231.

6,7-dimethoxy-4-(4-nitrophenyl)-1,2,3,4-tetrahydroquinoline **11**

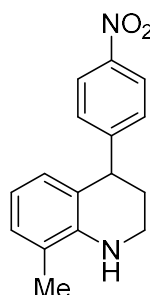


Chemical Formula: C₁₇H₁₈N₂O₄
Exact Mass: 314.1267

General Procedure **B** was followed with 4-nitrostyrene (59.8 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2i** (87.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μ L, 0.40 mmol, 2.0 equiv.) and FeSO₄·7H₂O (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **11** (34.0 mg, 0.11 mmol, 54% yield) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 8.08 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.7 Hz, 2H), 6.15 (s, 1H), 6.12 (s, 1H), 4.14 (t, J = 5.9 Hz, 1H), 3.77 (s, 3H), 3.68 (brs, 1H), 3.57 (s, 3H), 3.18 (ddd, J = 10.2, 6.7, 3.4 Hz, 1H), 3.07 (ddd, J = 11.7, 8.9, 3.1 Hz, 1H), 2.25-2.15 (m, 1H), 1.95-1.85 (m, 1H). **¹³C NMR (100 MHz, CDCl₃):** δ 154.9 (C), 149.2 (C), 146.5 (C), 141.7 (C), 139.2 (C), 129.4 (CH), 123.6 (CH), 114.0 (CH), 112.6 (C), 99.4 (CH), 56.6 (CH₃), 55.8 (CH₃), 42.3 (CH), 38.9 (CH₂), 31.6 (CH₂). **HRMS (ESI):** m/z calcd. for C₁₇H₁₉N₂O₄ [M+H]⁺ 315.1339, found 315.1333.

8-methyl-4-(4-nitrophenyl)-1,2,3,4-tetrahydroquinoline **12**

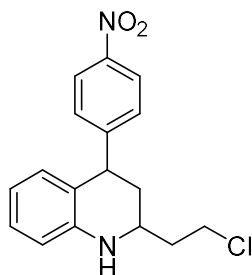


Chemical Formula: C₁₆H₁₆N₂O₂
Exact Mass: 268.1212

General Procedure **B** was followed with 4-nitrostyrene (59.8 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2j** (78.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μ L, 0.40 mmol, 2.0 equiv.) and FeSO₄·7H₂O (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **12** (34.0 mg, 0.13 mmol, 63% yield) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 8.06 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.91–6.87 (m, 1H), 6.53–6.43 (m, 2H), 4.22 (t, *J* = 6.0 Hz, 1H), 3.76 (s, 1H), 3.31 (ddd, *J* = 10.7, 6.7, 3.6 Hz, 1H), 3.18 (ddd, *J* = 11.8, 8.7, 3.3 Hz, 1H), 2.24–2.14 (m, 1H), 2.07 (s, 3H), 2.01–1.91 (m, 1H). **¹³C NMR (100 MHz, CDCl₃):** δ 154.7 (C), 146.4 (C), 142.9 (C), 129.5 (CH), 129.0 (CH), 128.2 (CH), 123.6 (CH), 121.5 (C), 121.0 (C), 116.6 (CH), 43.0 (CH), 39.0 (CH₂), 30.8 (CH₂), 17.4 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₆H₁₇N₂O₂ [M+H]⁺ 269.1285, found 269.1285.

2-(2-chloroethyl)-4-(4-nitrophenyl)-1,2,3,4-tetrahydroquinoline 13

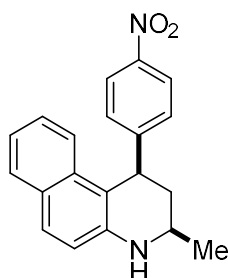


Chemical Formula: C₁₇H₁₇ClN₂O₂
Exact Mass: 316.0979

General Procedure **B** was followed with 4-nitrostyrene (59.8 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2k** (88.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μL, 0.40 mmol, 2.0 equiv.) and FeSO₄·7H₂O (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **13** (35.0 mg, 0.11 mmol, 55% yield, *cis/trans* 5:1) as a yellow oil.

¹H NMR (400 MHz, CDCl₃, major): δ 8.11 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 6.98–6.93 (m, 1H), 6.50 (ddd, *J* = 14.0, 7.7, 1.0 Hz, 2H), 6.42 (d, *J* = 7.7 Hz, 1H), 4.25 (dd, *J* = 12.1, 5.5 Hz, 1H), 3.92 (s, 1H), 3.71–3.51 (m, 3H), 2.14 (ddd, *J* = 12.8, 5.6, 2.4 Hz, 1H), 1.97–1.92 (m, 2H), 1.83–1.74 (m, 1H). **¹³C NMR (100 MHz, CDCl₃, major):** δ 153.6 (C), 146.8 (C), 144.9 (C), 129.5 (2CH), 127.8 (CH), 124.0 (CH), 123.3 (C), 118.2 (CH), 115.0 (CH), 49.6 (CH), 44.1 (CH), 41.3 (CH₂), 38.9 (CH₂), 38.7 (CH₂). **HRMS (ESI):** *m/z* calcd. for C₁₇H₁₈N₂O₂Cl [M+H]⁺ 317.1051, found 317.1070.

3-methyl-1-(4-nitrophenyl)-1,2,3,4-tetrahydrobenzo[f]quinoline 14

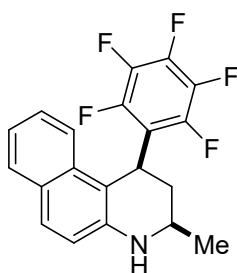


Chemical Formula: $C_{20}H_{18}N_2O_2$
Exact Mass: 318.1368

General Procedure **B** was followed with 4-nitrostyrene (59.8 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2I** (88.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μ L, 0.40 mmol, 2.0 equiv.) and $FeSO_4 \cdot 7H_2O$ (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **14** (40.0 mg, 0.12 mmol, 62% yield) as a yellow oil.

1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 8.8 Hz, 2H), 7.59–7.56 (m, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 8.7 Hz, 2H), 7.06–6.96 (m, 3H), 6.80 (d, J = 8.7 Hz, 1H), 4.65 (dd, J = 10.0, 7.9 Hz, 1H), 3.88 (s, 1H), 3.36 (dtt, J = 12.6, 6.3, 3.2 Hz, 1H), 2.40 (ddd, J = 13.3, 7.8, 2.5 Hz, 1H), 1.69–1.59 (m, 1H), 1.12 (d, J = 6.3 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 156.3 (C), 146.1 (C), 144.9 (C), 132.7 (C), 128.9 (CH), 128.8 (C), 128.6 (CH), 128.1 (CH), 126.2 (CH), 124.1 (CH), 123.4 (CH), 121.8 (CH), 118.6 (CH), 112.5 (C), 47.1 (CH), 43.9 (CH_2), 41.2 (CH), 22.0 (CH_3). **HRMS (ESI):** m/z calcd. for $C_{20}H_{19}N_2O_2$ $[M+H]^+$ 319.1441, found 319.1444.

3-methyl-1-(perfluorophenyl)-1,2,3,4-tetrahydrobenzo[f]quinoline 15



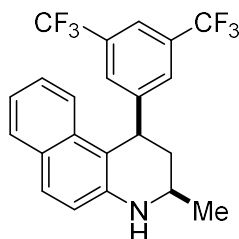
Chemical Formula: $C_{20}H_{14}F_5N$
Exact Mass: 363.1046

General Procedure **B** was followed with 2,3,4,5,6-pentafluorostyrene (77.6 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2I** (88.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μ L, 0.40 mmol, 2.0 equiv.) and $FeSO_4 \cdot 7H_2O$ (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica

gel (pentane/EtOAc: 100/0 to 90/10) afforded **15** (43.0 mg, 0.12 mmol, 59% yield) as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ 7.59 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.16–7.04 (m, 3H), 6.78 (d, *J* = 8.7 Hz, 1H), 4.93 (dd, *J* = 10.5, 8.4 Hz, 1H), 3.57 (brs, 1H), 3.32 (dtt, *J* = 12.4, 6.1, 3.1 Hz, 1H), 2.38 (ddd, *J* = 12.9, 8.1, 2.1 Hz, 1H), 1.77 (q, *J* = 11.3 Hz, 1H), 1.22 (d, *J* = 6.2 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃):** δ 144.6 (dm, *J* = 245 Hz, C), 144.2 (C), 139.6 (dm, *J* = 251 Hz, C), 137.6 (dm, *J* = 249 Hz, C), 132.3 (C), 128.9 (CH), 128.7 (C), 128.6 (CH), 126.4 (CH), 121.9 (CH), 121.2 (CH), 120.9 (m, C), 118.5 (CH), 111.9 (C), 47.3 (CH), 40.3 (CH₂), 30.9 (CH), 21.6 (CH₂). **¹⁹F NMR (376 MHz, CDCl₃):** δ -157.7 (t, *J* = 21.0 Hz), -162.2 (brs). **HRMS (ESI):** *m/z* calcd. for C₂₀H₁₅NF₅ [M+H]⁺ 364.1119, found 364.1113.

1-(3,5-bis(trifluoromethyl)phenyl)-3-methyl-1,2,3,4-tetrahydrobenzo[*ff*]quinoline 16

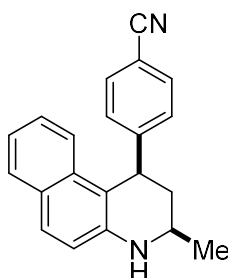


Chemical Formula: C₂₂H₁₇F₆N
Exact Mass: 409.1265

General Procedure **B** was followed with 3,5-bis(trifluoromethyl)styrene (96.0 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2l** (88.0 mg, 0.2 mmol, 1.0 equiv.), TFA (32.0 μL, 0.40 mmol, 2.0 equiv.) and FeSO₄·7H₂O (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 90/10) afforded **16** (50.0 mg, 0.12 mmol, 61% yield) as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ 7.62–7.57 (m, 2H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.43 (s, 2H), 7.08–7.02 (m, 2H), 6.98–6.94 (m, 1H), 6.83 (d, *J* = 8.8 Hz, 1H), 4.69 (dd, *J* = 10.0, 7.9 Hz, 1H), 3.95 (brs, 1H), 3.42–3.36 (m, 1H), 2.44 (ddd, *J* = 13.4, 7.8, 2.5 Hz, 1H), 1.71–1.64 (m, 1H), 1.14 (d, *J* = 6.3 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃):** δ 150.8 (C), 144.9 (C), 132.5 (C), 131.8 (q, *J* = 33.0 Hz, C), 129.2 (CH), 128.9 (C), 128.7 (CH), 127.4 (m, CH), 126.3 (CH), 123.4 (q, *J* = 271.0 Hz, C), 123.2 (CH), 121.9 (CH), 120.0 (m, CH), 118.6 (CH), 11.8 (C), 47.1 (CH), 44.2 (CH₂), 41.1 (CH), 22.0 (CH₃). **¹⁹F NMR (376 MHz, CDCl₃):** δ -62.7. **HRMS (ESI):** *m/z* calcd. for C₂₂H₁₈NF₆ [M+H]⁺ 410.1338, found 410.1332.

3-methyl-1,2,3,4-tetrahydrobenzo[f]quinolin-1-yl)benzonitrile 17

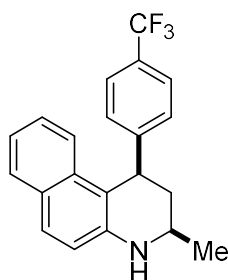


Chemical Formula: C₂₁H₁₈N₂
Exact Mass: 298.1470

General Procedure **B** was followed with 4-cyanostyrene (51.6 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2I** (88.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μ L, 0.40 mmol, 2.0 equiv.) and FeSO₄·7H₂O (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 80/20) afforded **17** (45.0 mg, 0.150 mmol, 75% yield) as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ 7.61–7.55 (m, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H), 7.06–6.96 (m, 3H), 6.80 (d, J = 8.8 Hz, 1H), 4.60 (dd, J = 10.0, 7.8 Hz, 1H), 3.89 (s, 1H), 3.41–3.32 (m, 1H), 2.40 (ddd, J = 13.3, 7.8, 2.5 Hz, 1H), 1.69–1.61 (m, 1H), 1.12 (d, J = 6.3 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃):** δ 154.0 (C), 144.9 (C), 132.7 (C), 132.6 (CH), 128.8 (CH), 128.7 (C), 128.6 (CH), 128.1 (CH), 126.1 (CH), 123.5 (CH), 121.8 (CH), 119.1 (C), 118.5 (CH), 112.5 (C), 109.6 (C), 47.1 (CH), 43.9 (CH₂), 41.4 (CH), 22.0 (CH₃). **HRMS (ESI):** m/z calcd. for C₂₁H₁₉N₂ [M+H]⁺ 299.1543, found 299.1537.

3-methyl-1-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydrobenzo[f]quinoline 18



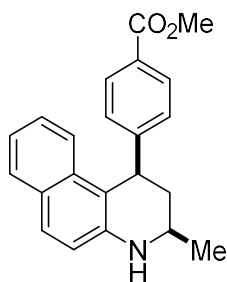
Chemical Formula: C₂₁H₁₈F₃N
Exact Mass: 341.1391

General Procedure **B** was followed with 4-trifluoromethylstyrene (69.0 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2I** (88.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μ L, 0.40 mmol, 2.0 equiv.) and

FeSO₄·7H₂O (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 90/10) afforded **18** (53.0 mg, 0.154 mmol, 77% yield) as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ 7.60–7.54 (m, 1H), 7.53–7.49 (m, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.12–6.98 (m, 5H), 6.80 (d, *J* = 8.7 Hz, 1H), 4.60 (dd, *J* = 9.9, 7.9 Hz, 1H), 3.83 (s, 1H), 3.40–3.31 (m, 1H), 2.39 (ddd, *J* = 13.3, 7.8, 2.6 Hz, 1H), 1.72–1.63 (m, 1H), 1.11 (d, *J* = 6.3 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃):** δ 152.4 (C), 144.8 (C), 132.9 (C), 128.8 (C), 128.7 (CH), 128.5 (CH), 128.0 (q, *J* = 32 Hz, C), 127.6 (CH), 126.0 (CH), 125.7 (q, *J* = 3.2 Hz, CH), 124.4 (q, *J* = 270 Hz, C), 123.8 (CH), 121.7 (CH), 118.5 (CH), 113.2 (C), 47.1 (CH), 44.2 (CH₂), 41.1 (CH), 22.1 (CH₃). **¹⁹F NMR (376 MHz, CDCl₃):** δ -62.2. **HRMS (ESI):** *m/z* calcd. for C₂₁H₁₉NF₃ [M+H]⁺ 342.1464, found 342.1466.

methyl 4-(3-methyl-1,2,3,4-tetrahydrobenzo[f]quinolin-1-yl)benzoate **19**

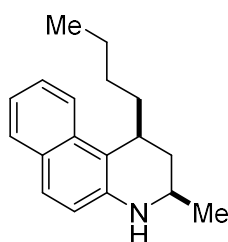


Chemical Formula: C₂₂H₂₁NO₂
Exact Mass: 331.1572

General Procedure **B** was followed with methyl 4-vinylbenzoate (65.0 mg, 0.40 mmol, 2 equiv.), hydroxylamine **2I** (88.0 mg, 0.2 mmol, 1 equiv.), TFA (32.0 μL, 0.40 mmol, 2.0 equiv.) and FeSO₄·7H₂O (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 80/20) afforded **19** (53.0 mg, 0.160 mmol, 80% yield) as a colorless oil.

¹H NMR (400 MHz, CDCl₃): δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.66–7.62 (m, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.18–7.05 (m, 5H), 6.88 (d, *J* = 8.8 Hz, 1H), 4.68 (dd, *J* = 10.0, 7.8 Hz, 1H), 3.92 (s, 1H), 3.86 (s, 3H), 3.50–3.41 (m, 1H), 2.49 (ddd, *J* = 13.3, 7.7, 2.5 Hz, 1H), 1.82–1.74 (m, 1H), 1.20 (d, *J* = 6.3 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃):** δ 167.4 (C), 154.1 (C), 145.0 (C), 133.2 (C), 130.3 (CH), 129.0 (C), 128.8 (CH), 128.6 (CH), 127.9 (C), 127.6 (CH), 126.1 (CH), 124.0 (CH), 121.9 (CH), 118.7 (CH), 113.6 (C), 52.2 (CH₃), 47.4 (CH), 44.3 (CH₂), 41.6 (CH), 22.3 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₂₂H₂₂NO₂ [M+H]⁺ 332.1645, found 332.1650.

1-butyl-3-methyl-1,2,3,4-tetrahydrobenzo[f]quinoline 22

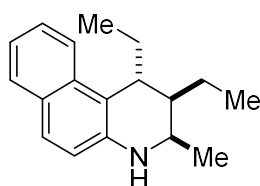


Chemical Formula: $C_{18}H_{23}N$
Exact Mass: 253.1830

General Procedure **B** was followed with 1-hexene (34.0 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2I** (88.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μ L, 0.40 mmol, 2.0 equiv.) and $FeSO_4 \cdot 7H_2O$ (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 90/10) afforded **21** (35.0 mg, 0.14 mmol, 69% yield) as a colorless oil.

1H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8.6 Hz, 1H), 7.61 (dd, J = 8.1, 1.3 Hz, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.33 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.14 (ddd, J = 8.0, 6.8, 1.1 Hz, 1H), 6.74 (d, J = 8.6 Hz, 1H), 3.72 (brs, 1H), 3.38 (q, J = 8.6 Hz, 1H), 3.18-3.08 (m, 1H), 2.30 (ddd, J = 13.3, 8.5, 3.4 Hz, 1H), 1.95–1.84 (m, 1H), 1.59–1.51 (m, 1H), 1.40–1.23 (m, 5H), 1.21 (d, J = 6.3 Hz, 3H), 0.82 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 143.8 (C), 132.7 (C), 129.0 (C), 128.7 (CH), 127.0 (CH), 125.8 (CH), 122.5 (CH), 121.6 (CH), 118.6 (C), 118.5 (CH), 47.6 (CH), 39.5 (CH_2), 37.5 (CH_2), 32.3 (CH), 29.5 (CH_2), 22.9 (CH_2), 22.7 (CH_3), 14.2 (CH_3). **HRMS (ESI):** m/z calcd. for $C_{18}H_{24}N$ $[M+H]^+$ 254.1903, found 254.1899.

1,2-diethyl-3-methyl-1,2,3,4-tetrahydrobenzo[f]quinoline 23

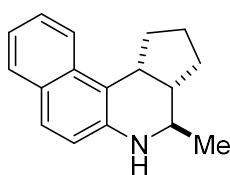


Chemical Formula: $C_{18}H_{23}N$
Exact Mass: 253.1830

General Procedure **B** was followed with *trans*-3-hexene (34.0 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2I** (88.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μ L, 0.40 mmol, 2.0 equiv.) and $FeSO_4 \cdot 7H_2O$ (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 90/10) afforded **22** (36.0 mg, 0.14 mmol, 70% yield) as a colorless oil.

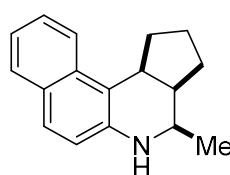
¹H NMR (400 MHz, CDCl₃): δ 7.67 (d, J = 8.6 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 8.7 Hz, 1H), 7.31 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 6.62 (d, J = 8.7 Hz, 1H), 3.80–3.50 (m, 2H), 3.05 (d, J = 10.0 Hz, 1H), 1.88 (dt, J = 15.1, 7.5, 3.8 Hz, 1H), 1.53–1.36 (m, 3H), 1.17 (d, J = 6.6 Hz, 3H), 1.01 (t, J = 7.4 Hz, 3H), 0.88–0.77 (m, 4H). **¹³C NMR (100 MHz, CDCl₃):** δ 140.8 (C), 133.8 (C), 128.8 (CH), 128.3 (C), 127.3 (CH), 126.2 (CH), 121.5 (CH), 121.2 (CH), 117.8 (CH), 114.7 (C), 44.8 (CH), 39.3 (CH), 38.1 (CH), 29.5 (CH₂), 19.1 (CH₃), 18.5 (CH₂), 12.5 (CH₃), 12.2 (CH₃). **HRMS (ESI):** m/z calcd. for C₁₈H₂₄N [M+H]⁺ 254.1903, found 254.1889.

4-methyl-2,3,3a,4,5,11c-hexahydro-1H-benzo[f]cyclopenta[c]quinoline 24 and 24'



Chemical Formula: C₁₇H₁₉N
Exact Mass: 237.1517

major



Chemical Formula: C₁₇H₁₉N
Exact Mass: 237.1517

minor

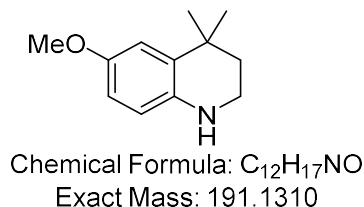
General Procedure **B** was followed with cyclopentene (28.0 mg, 0.40 mmol, 2.0 equiv.), hydroxylamine **2I** (88.0 mg, 0.20 mmol, 1 equiv.), TFA (32.0 μ L, 0.40 mmol, 2.0 equiv.) and FeSO₄·7H₂O (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL). Purification by FC over silica gel (pentane/EtOAc: 100/0 to 90/10) afforded **23** (30.0 mg, 0.13 mmol, 63% yield) as a colorless oil and **23'** (14.0 mg, 0.06 mmol, 29% yield) as a colorless oil.

¹H NMR (400 MHz, CDCl₃, major): δ 7.76 (d, J = 8.5 Hz, 1H), 7.58 (dd, J = 8.0, 1.1 Hz, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.32 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.14–7.07 (m, 1H), 6.71 (d, J = 8.7 Hz, 1H), 3.84 (brs, 1H), 3.35–3.27 (m, 1H), 3.00–2.92 (m, 1H), 2.57–2.49 (m, 1H), 1.97–1.82 (m, 2H), 1.70–1.60 (m, 3H), 1.40–1.32 (m, 1H), 1.17 (d, J = 6.2 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃, major):** δ 140.9 (C), 133.8 (C), 128.5 (CH), 128.0 (C), 127.2 (CH), 126.1 (CH), 122.3 (CH), 121.4 (CH), 117.8 (CH), 115.9 (C), 47.3 (CH), 42.6 (CH), 39.1 (CH), 34.2 (CH₂), 28.2 (CH₂), 22.8 (CH₂), 20.4 (CH₃). **HRMS (ESI):** m/z calcd. for C₁₇H₂₀N [M+H]⁺ 238.1590, found 238.1601.

¹H NMR (400 MHz, CDCl₃, minor): δ 7.76–7.72 (m, 1H), 7.62–7.58 (m, 1H), 7.40 (d, J = 8.7 Hz, 1H), 7.33 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.15 (ddd, J = 8.0, 6.8, 1.1 Hz, 1H), 6.71 (d, J = 8.7 Hz, 1H), 3.79–3.70 (m, 1H), 3.47 (brs, 1H), 3.34–3.26 (m, 1H), 2.45–2.34 (m, 2H), 1.66–1.38 (m, 5H), 1.18 (d, J = 6.5 Hz, 3H). **¹³C NMR (100 MHz, CDCl₃, minor):** δ 143.0 (C), 133.1 (C), 129.0 (C), 128.6 (CH), 126.6 (CH), 125.8 (CH), 123.1 (CH), 121.8 (CH), 119.9 (C), 118.3 (CH), 49.4 (CH),

46.5 (CH), 37.2 (CH), 35.9 (CH₂), 25.4 (CH₂), 25.3 (CH₂), 20.0 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₇H₂₀N [M+H]⁺ 238.1590, found 238.1601.

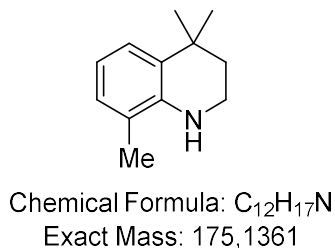
6-methoxy-4,4-dimethyl-1,2,3,4-tetrahydroquinoline 25



The modified general procedure **B** was followed with hydroxylamine **2c** (81.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μL, 0.40 mmol, 2.0 equiv.) and FeSO₄·7H₂O (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL) without the addition of alkene and purging with Ar. Purification by FC over silica gel (pentane/EtOAc: 100/0 to 85/15) afforded **24** (37.0 mg, 0.19 mmol, 95% yield) as a yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 6.72 (d, *J* = 2.9 Hz, 1H), 6.52 (dd, *J* = 8.6, 2.9 Hz, 1H), 6.38 (d, *J* = 8.6 Hz, 1H), 3.67 (s, 3H), 3.32 (brs, 1H), 3.18 (s, 2H), 1.67 (dd, *J* = 6.4, 5.0 Hz, 2H), 1.22 (s, 6H). **¹³C NMR (100 MHz, CDCl₃):** δ 151.9 (C), 137.8 (C), 132.1 (C), 115.4 (CH), 112.9 (CH), 112.2 (CH), 55.9 (CH₃), 38.8 (CH₂), 37.7 (CH₂), 32.1 (C), 31.4 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₂H₁₈NO [M+H]⁺ 192.1383 found 192.1389.

4,4,8-trimethyl-1,2,3,4-tetrahydroquinoline 26

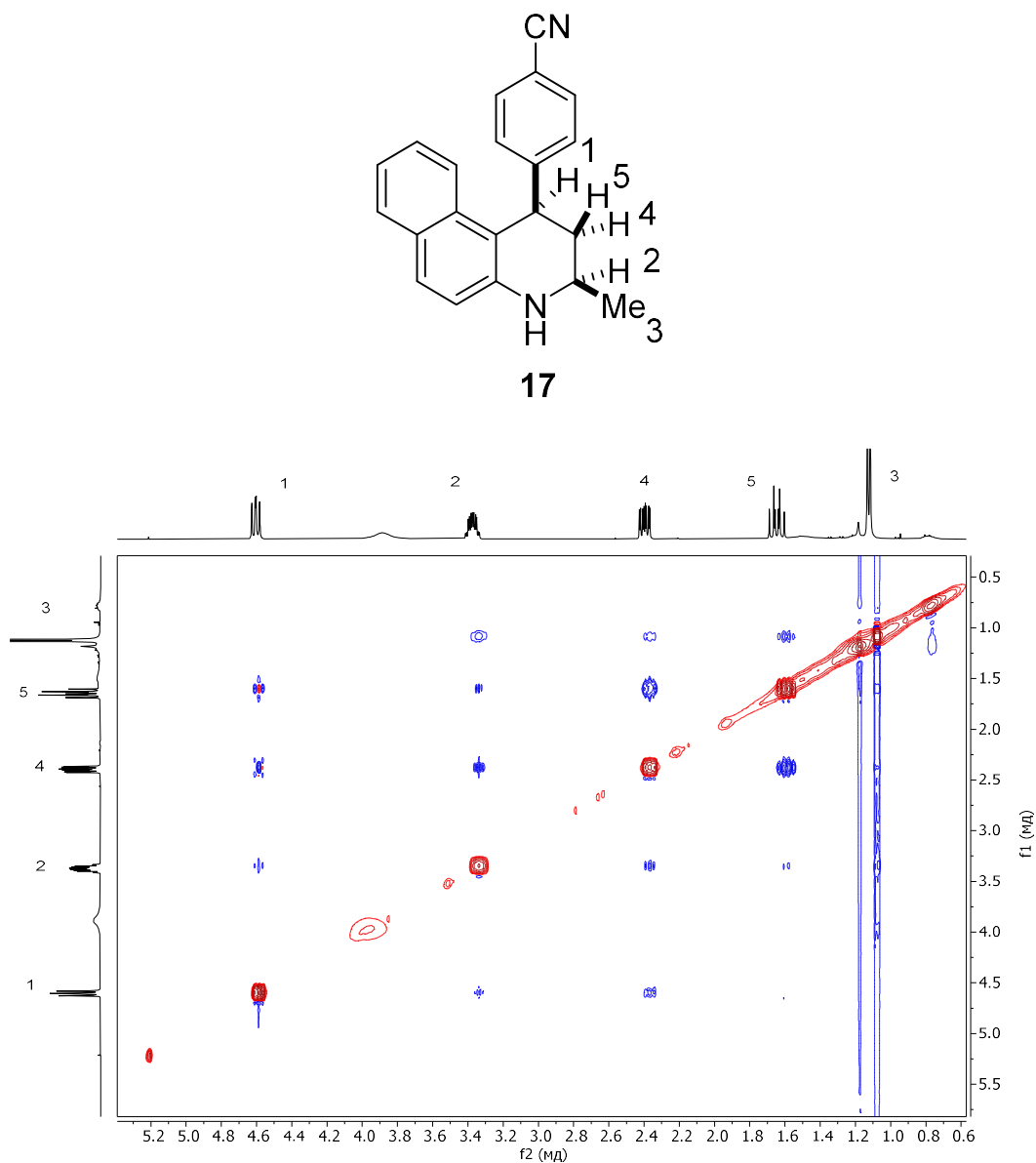


The modified general procedure **B** was followed with hydroxylamine **2j** (78.0 mg, 0.20 mmol, 1.0 equiv.), TFA (32.0 μL, 0.40 mmol, 2.0 equiv.) and FeSO₄·7H₂O (5.5 mg, 0.02 mmol, 0.1 equiv.) in HFIP (2 mL) without the addition of alkene and purging with Ar. Purification by FC over silica gel (pentane/EtOAc: 100/0 to 90/10) afforded **25** (28.0 mg, 0.16 mmol, 80% yield) as a colorless oil.

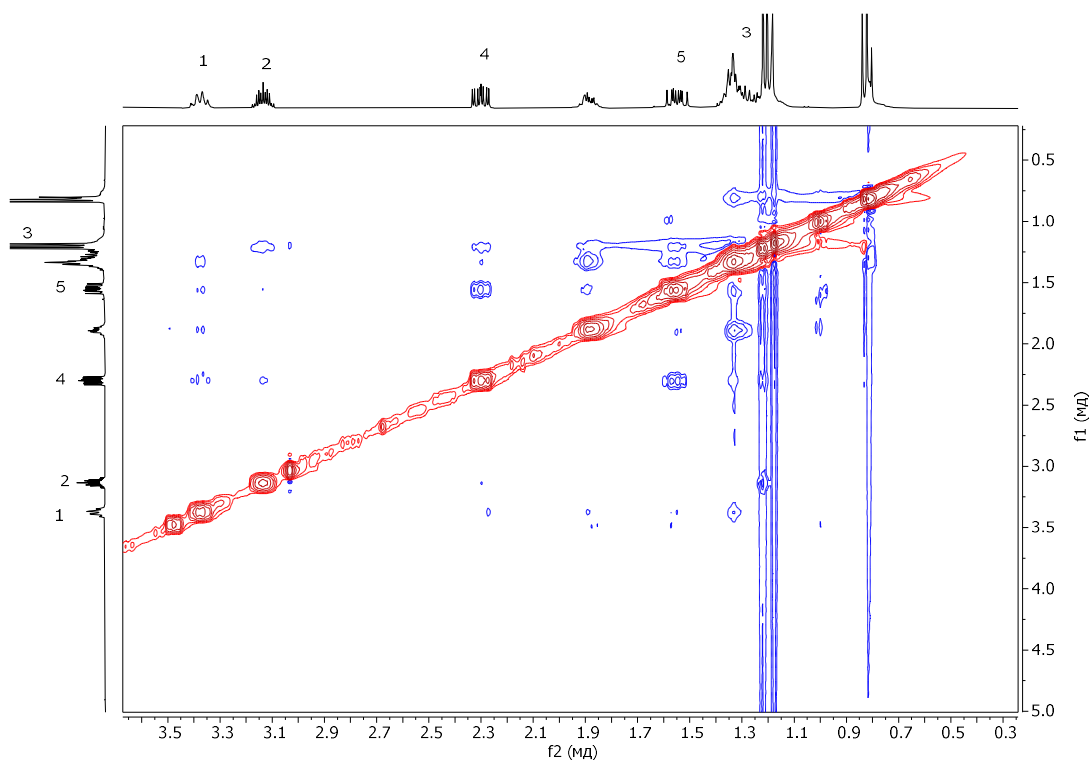
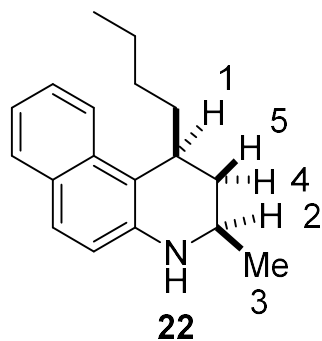
¹H NMR (400 MHz, CD₂Cl₂): δ 7.08–7.04 (m, 1H), 6.82 (ddd, *J* = 7.3, 1.4, 0.7 Hz, 1H), 6.53 (t, *J* = 7.5 Hz, 1H), 3.77 (s, 1H), 3.38–3.34 (m, 2H), 2.05 (s, 3H), 1.74–1.71 (m, 2H), 1.28 (s, 6H). **¹³C NMR (100 MHz, CD₂Cl₂):** δ 142.3 (C), 130.1 (C), 128.0 (CH), 124.7 (CH), 121.4 (C), 116.6 (CH),

39.0 (CH₂), 37.8 (CH₂), 32.2 (C), 31.5 (CH₃), 17.8 (CH₃). **HRMS (ESI):** *m/z* calcd. for C₁₂H₁₈N [M+H]⁺ 176.1439 found 176.2060.

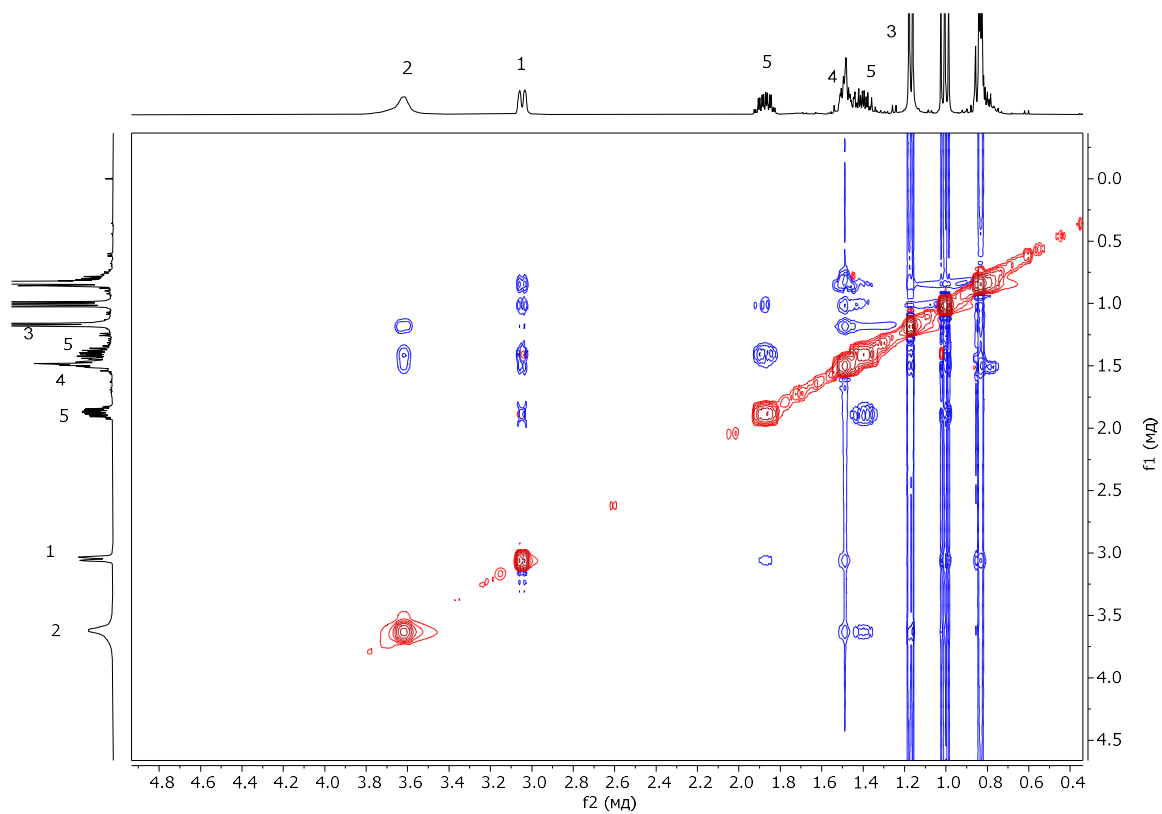
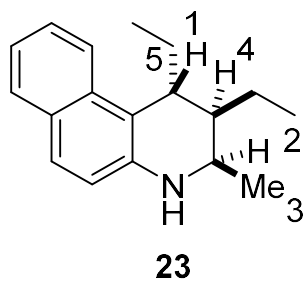
4. NOESY Analyses



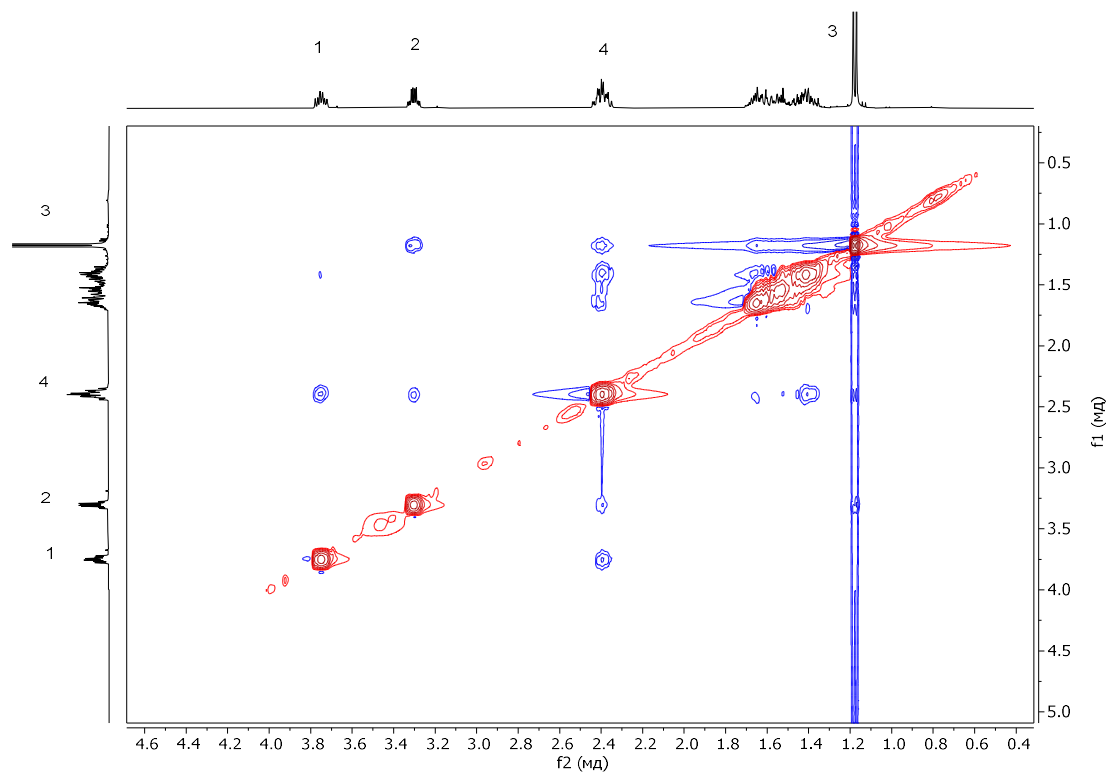
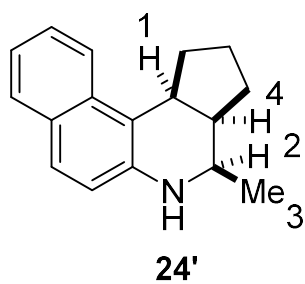
Analysis: proton **1** correlates with proton **2** but does not correlate with protons of the methyl group **3**. Proton **4** correlates with both proton **1** and proton **2**. These observations confirm a *cis* relative configuration.



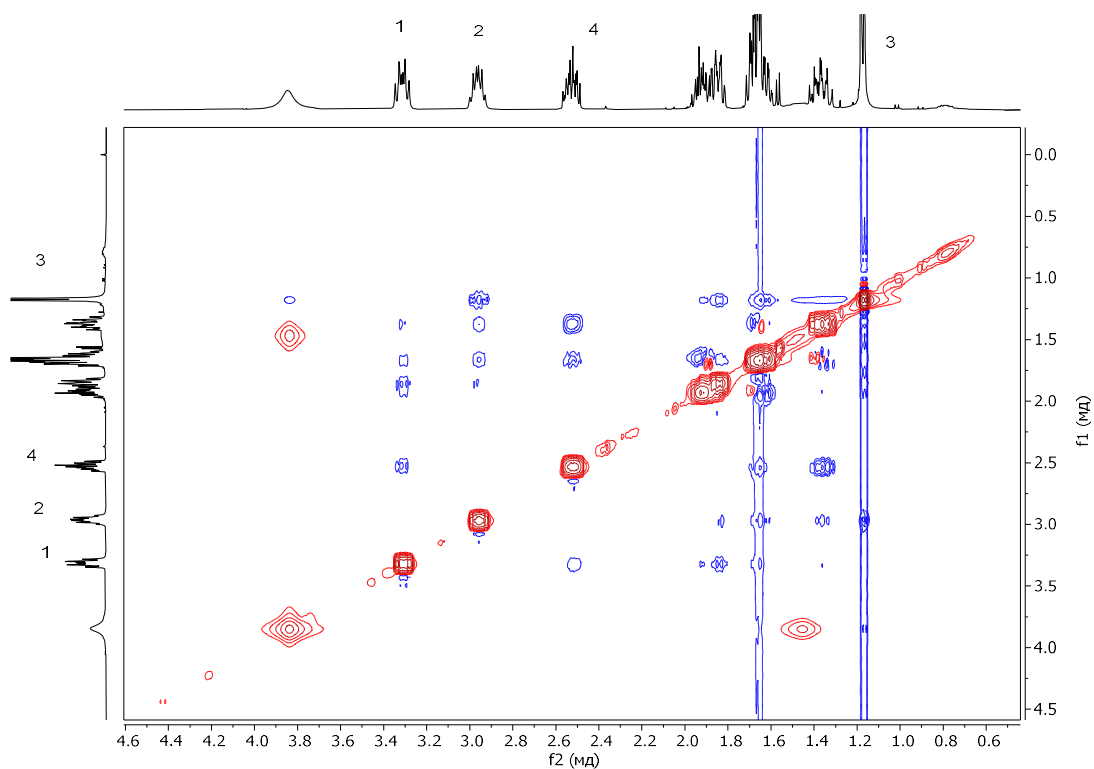
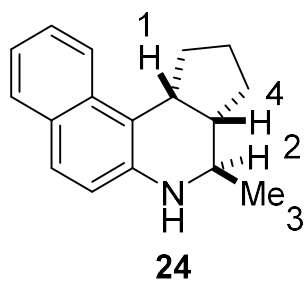
Analysis: Proton **1** correlates with proton **4**. Protons **1** and **2** do not correlate with each other. Proton **4** correlates with proton **2**. These observations suggest the relative configuration shown on the scheme above.



Analysis: Proton **1** does not correlate with proton **2**. Protons **1** and **2** correlate with protons **5**. These observations confirm the relative configuration shown on the scheme above.



Analysis: Proton **1** correlates with proton **4**. Proton **4** correlates with both proton **1** and proton **2**. These observations suggest the relative configuration shown on the scheme above.



Analysis: Proton **1** correlates with proton **4**. Protons **1** and **4** do not correlate with proton **2**. These observations suggest the relative configuration shown on the scheme above.

General Conclusion

During my doctoral studies, I have developed two new protocols for one-pot sequential aminoarylation and 1,2-diamination of alkenes. These operationally simple, user-friendly and scalable methods enable quick construction of biologically relevant scaffolds such as β -(hetero)arylethylamines and 1,2-vicinal diamines. By harnessing unique properties of HFIP as a reaction medium, numerous strongly deactivated alkenes incorporating a broad range of functional groups of medicinal relevance that were hitherto never described, including nitro, cyano, amide, sulfonamide, sulfonate ester, pentafluorosulfanyl, phosphonate, and morpholine groups, were successfully di-functionalized. The 1,2-diamination protocol was found to be general towards any type of *N*-nucleophiles including primary/secondary anilines, primary/secondary aliphatic amines, sulfoximines or *N*-heterocycles irrespective of their electronic properties. More importantly, both new reactions introduce an unprotected primary amine which is immediately available for further functionalizations. Additional kinetic and electrochemical studies were performed to get a deeper understanding of the role of HFIP in these reactions. The work described in chapters 1 and 2 resulted in two first-author publications in *Angewandte Chemie*.

In the second part of my PhD, I have designed and synthesized a series of new *N*-benzylhydroxylamine radical precursors. These reagents reacted with alkenes in HFIP in a Povarov-type reaction to afford diverse tetrahydroquinolines. The new protocol pushes the limits of the classical Povarov reaction and unlocks the reactivity of strongly deactivated alkenes, which were completely unreactive in this transformation so far. The behavior of new reagents in HFIP was studied which will allow using them in a more rational way. It was found that, upon deprotection by TFA and homolysis of the N–O bond, the formed aminium radicals underwent an unexpected radical 1,2-aryl shift. The work described in chapter 3 resulted in another first-author publication in *Chemical Communications*.

However, several serious limitations remained unsolved and require further research efforts. It is currently challenging to achieve enantioselective aminations of alkenes and ring-opening of aziridines in HFIP due to the preferential H-bonding of chiral Brønsted acids with the solvent molecules. Secondly, the use of HFIP was critical to unlock the reactivity of strongly deactivated alkenes, but it was detrimental to electron-rich alkenes in all three developed reactions in which they immediately polymerized. In the case of 1,2-diamination, a second set of conditions in MeOH/DCM mixture was developed, yet very electron-rich vinyl heterocycles were quickly trapped by methanol and remained unreactive. No such alternative method was found for the

aminoarylation or the Povarov-type reaction which worked exclusively in HFIP. Thirdly, despite recent advances in HFIP-promoted transformations, its precise role is still a matter of debates and requires deeper mechanistic understanding. The heterogeneous nature of new reactions and the presence of paramagnetic iron species make mechanistic investigations a challenging endeavor. The combination of advanced computational approaches and electrochemical methods should unveil the role of the solvent in these reactions, which will allow chemists to rationally design new transformations by consciously choosing HFIP as a solvent.

New Reactions of Aminofunctionalization of Alkenes

Résumé en français

Les amines aliphatiques sont au cœur de la chimie fine. Elles sont présentes dans plus de 40% des molécules pharmaceutiques mais sont également des précurseurs clés pour la construction de molécules bioactives complexes, de produits naturels et de polymères. Cette thèse décrit le développement d'une méthode générale pour l'accès rapide aux motifs β -aryléthylamines et 1,2-diamines à partir de styrènes, de sels de triflate d'hydroxylammonium et de divers nucléophiles. Contrairement aux approches précédentes, le nouveau protocole en un pot/deux étapes permet une construction modulaire de molécules densément fonctionnalisées où l'une des fonctionnalités azotées est une amine aliphatique primaire. L'une des caractéristiques de cette transformation est sa capacité à incorporer de nombreuses classes des nucléophiles (hétéro)arènes, des amines et de nucléophiles soufrés, y compris des molécules bioactives. Cette thèse décrit également la synthèse de divers tétrahydroquinolines à partir de nouveaux précurseurs des radicaux centrés sur l'azote de type N-benzylhydroxylamine et des alcènes appauvris en électrons qui a ainsi élargi le champ d'application de la réaction de Povarov classique.

Mots-clés: amines primaires, radicaux centrés sur l'azote, catalyse de fer, hexafluoroisopropanol, β -aryléthylamines, aziridine, 1,2-diamines, alcènes appauvris en électrons

Summary in English

Aliphatic amines are at the core of fine chemical synthesis. They feature in more than 40 % of drug molecules but are also versatile precursors for constructing more complex bioactive molecules, natural products, and polymers. This dissertation describes the development of a general method for the rapid construction of β -arylethylamine and 1,2-vicinal diamine scaffolds from styrenes, hydroxylammonium triflate salts and different nucleophiles. Compared to previous approaches, this new sequential one pot/two-step protocol enables the modular construction of densely functionalized molecules in which one of the nitrogen functionalities is a primary aliphatic amine. This method accommodates a broad range of nucleophiles such as (hetero)aromatics, amines or thiols as well as bioactive molecules. This thesis also describes the development of new precursors of N-centered radicals such as N-benzylhydroxylamines and their application in the synthesis of tetrahydroquinolines. In contrast to the classical Povarov reaction, the new methodology accommodates electron-deficient and aliphatic alkenes, thereby expanding the chemical space of available tetrahydroquinoline scaffolds.

Keywords: primary amines, N-centered radicals, iron catalysis, hexafluoroisopropanol, β -arylethylamines, aziridine, 1,2-diamines, electron-poor alkenes