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Valentyn Pozhydaiev, Cyprien Muller, Joseph Moran, David Lebœuf. Catalytic Synthesis of  $\beta$ -(Hetero)arylethylamines: Modern Strategies and Advances. *Angewandte Chemie International Edition*, 2023, 62 (41), 10.1002/anie.202309289 . hal-04564878

**HAL Id: hal-04564878**

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Submitted on 30 Apr 2024

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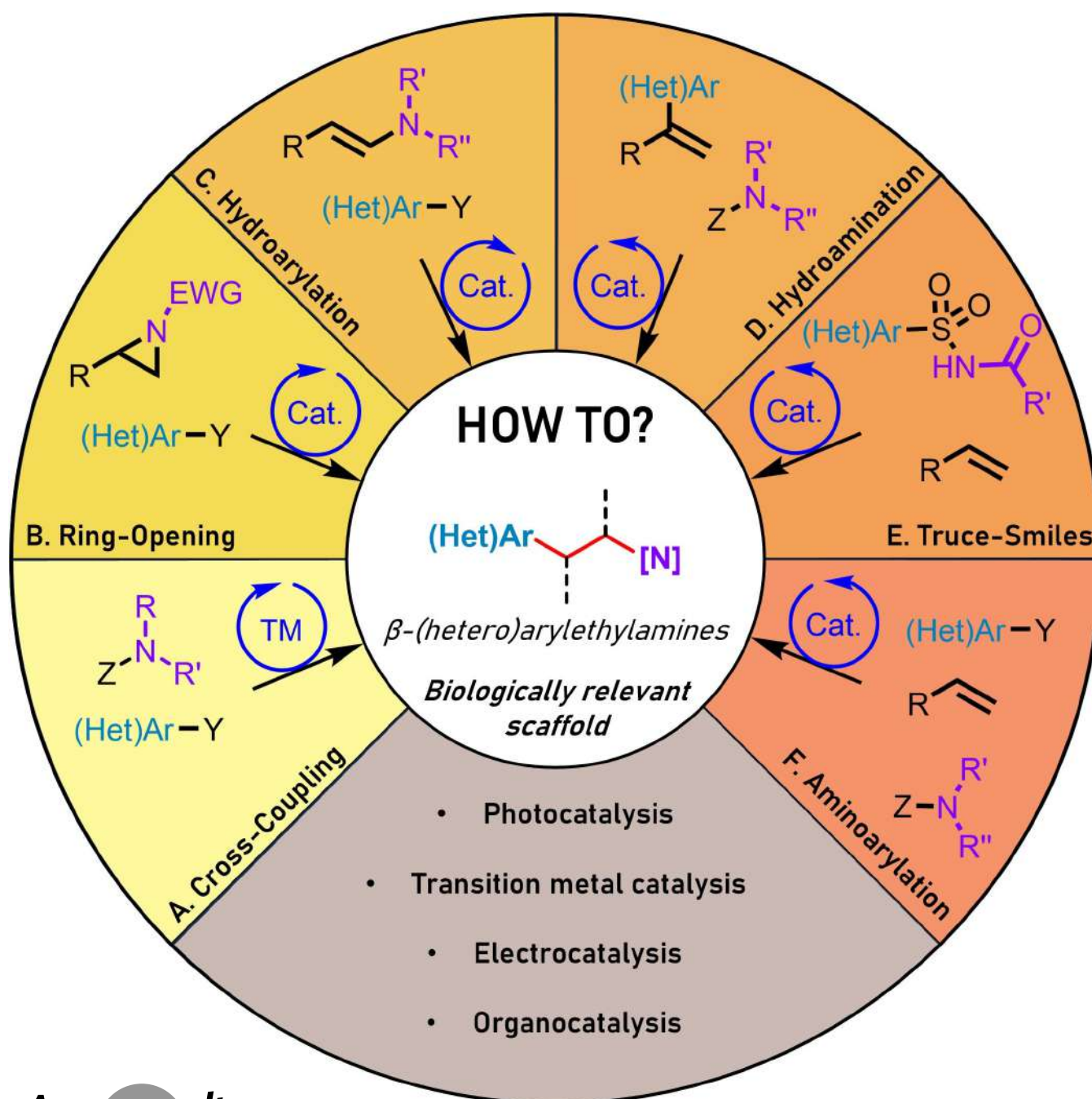


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## Synthetic Methods

# Catalytic Synthesis of $\beta$ -(Hetero)arylethylamines: Modern Strategies and Advances

Valentyn Pozhydaiev, Cyprien Muller, Joseph Moran,\* and David Lebœuf\*

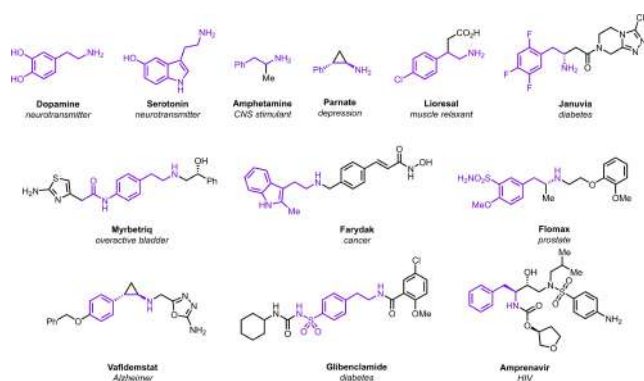


**Abstract:**  $\beta$ -(Hetero)arylethylamines appear in a myriad of pharmaceuticals due to their broad spectrum of biological properties, making them prime candidates for drug discovery. Conventional methods for their preparation often require engineered substrates that limit the flexibility of the synthetic routes and the diversity of compounds that can be accessed. Consequently, methods that provide rapid and versatile access to those scaffolds remain limited. To overcome these challenges, synthetic chemists have designed innovative and modular strategies to access the  $\beta$ -(hetero)arylethylamine motif, paving the way for their more extensive use in future pharmaceuticals. This review outlines recent progresses in the synthesis of (hetero)arylethylamines and emphasizes how these innovations have enabled new levels of molecular complexity, selectivity, and practicality.

## 1. Introduction

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).<sup>[1–3]</sup> 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  $\beta$ -(hetero)arylethylamines.<sup>[4]</sup> 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  $\beta$ -(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  $\beta$ -(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,<sup>[5–7]</sup> but our aim here is to provide a broader perspective on the synthesis of  $\beta$ -(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. Our goal is not to be

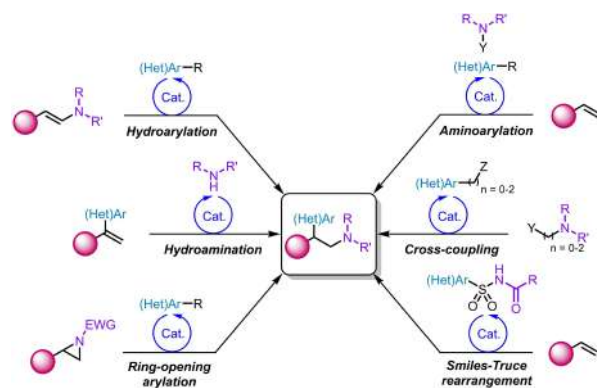


**Figure 1.** Selected examples of bioactive molecules incorporating  $\beta$ -(hetero)arylethylamine scaffolds.

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**Scheme 1.** Modern strategies to access  $\beta$ -(hetero)arylethylamines.

exhaustive but to highlight recent key examples that have shaped the field and opened new avenues for the future.

## 2. 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  $\beta$ -(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  $C(sp^2)$ – $C(sp^3)$  cross-couplings to include  $C(sp^3)$ – $C(sp^3)$  couplings and  $C(sp^3)$ –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,<sup>[8,9]</sup> 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.<sup>[10,11]</sup> 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  $\beta$ -(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,<sup>[10]</sup> the group extensively explored the reactivity of carbamate derivatives with (hetero)aryl halides bearing substitution patterns frequently encountered in medicinal chemistry (Scheme 2).<sup>[11]</sup> 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.

Organotrifluoroborate salts were also successfully used by Murphy, Barrett and co-workers to synthesize  $\beta$ -(hetero)arylethylamines through a less common palladium-catalyzed  $C(sp^3)$ – $C(sp^3)$  cross-coupling.<sup>[12]</sup> 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  $\beta$ -(hetero)arylethylamine in high yields, which supports the active role of the betaine in the catalytic cycle.

Most cross-coupling strategies for  $\beta$ -(hetero)arylethylamine synthesis led to products lacking substitution within the internal “ethylene” moiety, thereby



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Cyprien Muller obtained his BSc in physical chemistry at the Université de Strasbourg in 2018, before pursuing his studies in the Graduate School for Complex Systems Chemistry. Currently in the third year of his PhD in Pr. Joseph Moran's laboratory, his work focuses on elucidating new ways to influence chemical reactivity, ranging from catalysis to vibrational strong coupling.

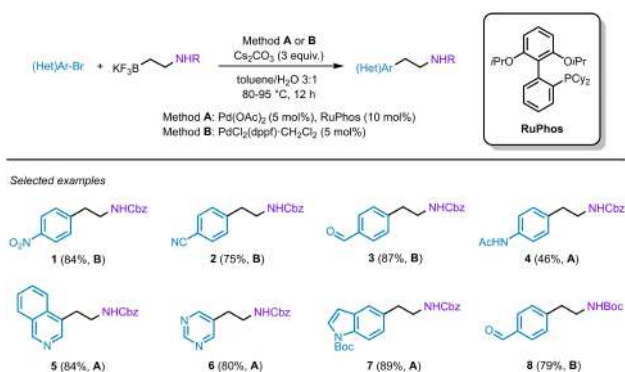


Joseph Moran completed his PhD in organic chemistry in 2009 (Ottawa) and did postdoctoral work in transition metal catalysis (Texas). He joined the ISIS institute (Université de Strasbourg) as an Assistant Professor in 2012 and was promoted to Professor in 2018. His research interests lie at the interfaces of catalysis with prebiotic chemistry, organic synthesis, and light-matter interactions. Selected awards include the Liebig-Lectureship (2022), the Forcheurs Jean-Marie Lehn Prize (2020), the C&EN Talented 12 (2018) and two ERC grants.

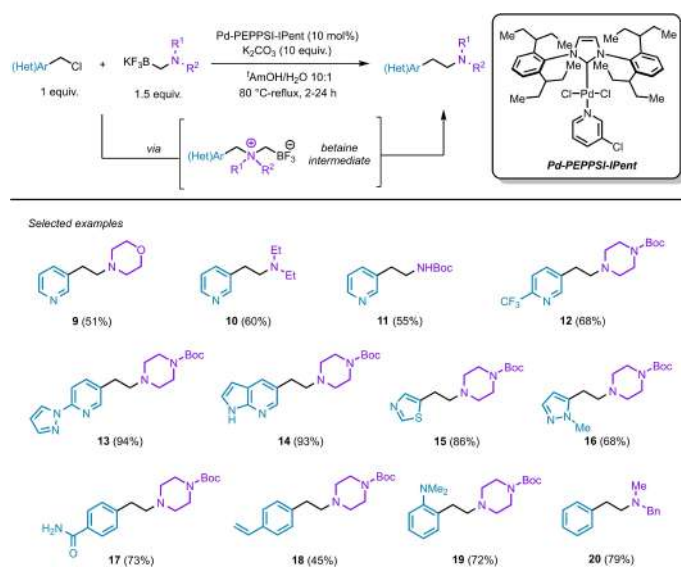


David Leboeuf obtained his PhD in organic chemistry in 2009 (UPMC, Paris VI). After completing two postdoctoral works at the University of Rochester with Pr. Alison J. Frontier (2010–2012) and at the ICIQ with Pr. Antonio M. Echavarren (2012–2013), he was appointed CNRS researcher at the Université Paris-Saclay in 2013. In 2019, he joined the ISIS institute (Université de Strasbourg), where his research interests focus on the application of supramolecular chemistry to catalysis, notably cultivating the use of hexafluoroisopropanol in synthesis.



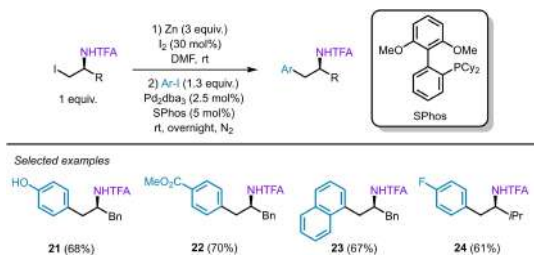


**Scheme 2.** Aminoethylation of (hetero)aryl bromides by Pd-catalyzed Suzuki–Miyaura cross-coupling.



**Scheme 3.** Synthesis of  $\beta$ -(hetero)arylethylamines via  $\text{C}(\text{sp}^3)\text{--C}(\text{sp}^3)$  Pd-catalyzed Suzuki–Miyaura cross-coupling.

excluding stereochemical issues. In 2010, the group of Jackson disclosed a modified version of the Negishi cross-coupling to access chiral  $\beta$ -(hetero)arylethylamines (Scheme 4).<sup>[13,14]</sup> Based on previous experimental evidence, the authors suggested that the presence of an electron-withdrawing TFA protecting group on the amine could hinder  $\beta$ -elimination of the Pd-alkyl intermediate, keeping

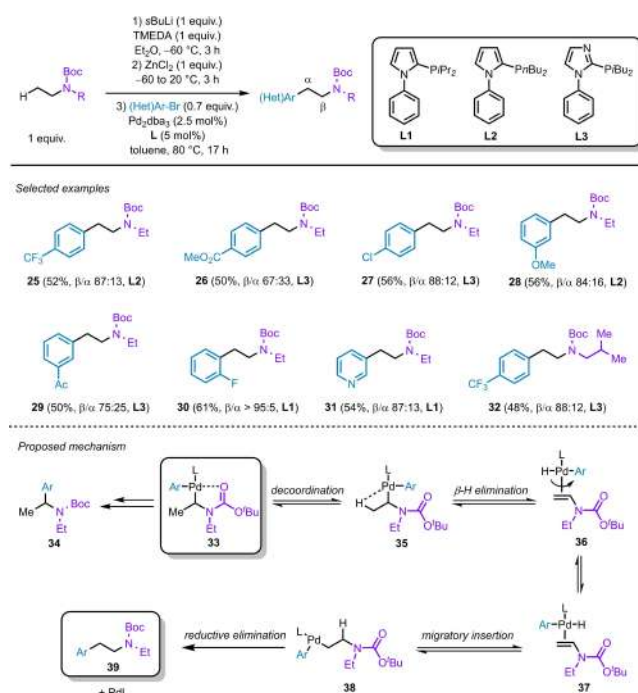


**Scheme 4.** Synthesis of chiral arylethylamines via Negishi cross-coupling.

the  $\beta$ -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  $\alpha$ -position of the amine.<sup>[31]</sup>

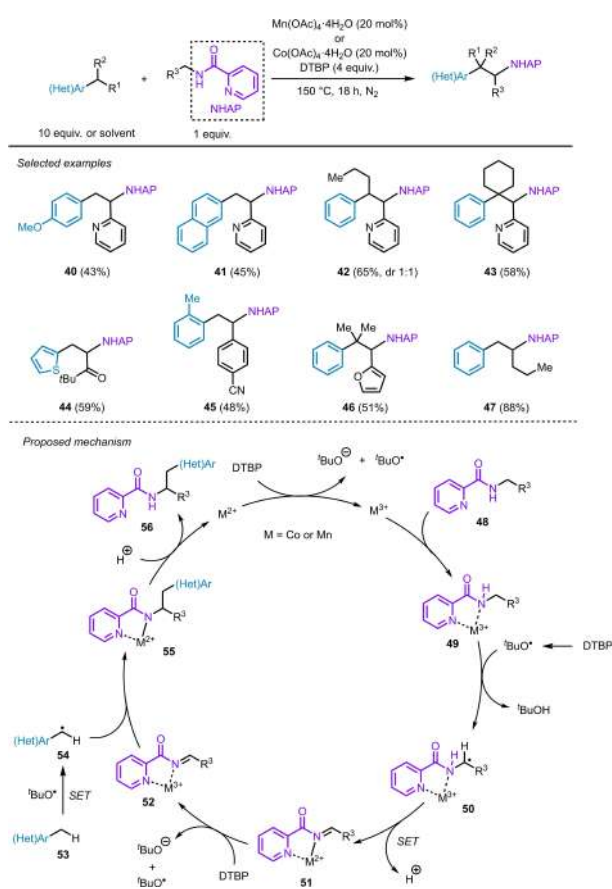
An alternative approach for the generation of alkylzinc intermediates for Negishi cross-coupling reactions, relying on simple ethylamines, was developed by the group of Baudoin (Scheme 5).<sup>[15]</sup> The presence of a Boc protecting group enables  $\alpha$ -lithiation of ethylamine followed by transmetalation with  $\text{ZnCl}_2$ . 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  $\beta$ -(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  $\beta$ -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  $\beta$ -carbon site may have a lower activation barrier over the  $\alpha$ -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.

Considering the previous example, the direct amination of inert  $\text{C}(\text{sp}^3)\text{--H}$  bonds is a highly attractive strategy to access  $\beta$ -(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  $\beta$ -arylethylamines.<sup>[16]</sup> Catalytic



**Scheme 5.** Ligand-controlled  $\beta$ -arylation of acyclic N-Boc amines.

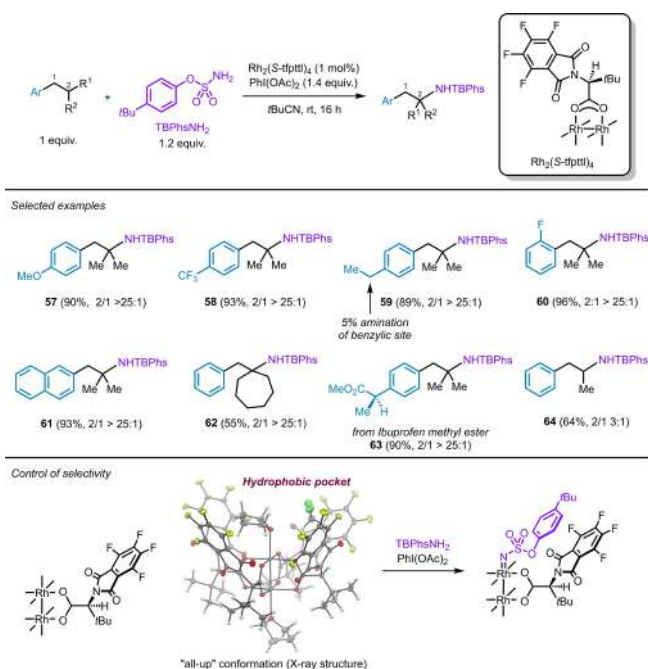
oxidative cross-coupling using abundant metals such as cobalt and manganese enabled the functionalization of various benzylic substrates in good yields to access  $\alpha$ -substituted  $\beta$ -arylethylamines via a coordination activating strategy (Scheme 6). An excess of di-*tert*-butyl peroxide (DTBP) 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(sp<sup>3</sup>)-C(sp<sup>3</sup>) bond and to construct the  $\beta$ -(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-tetramethylpiperidinyl-1-oxyl (TEMPO) or butylated hydroxytoluene (BHT), the reactivity was suppressed, supporting the involvement of radical intermediates. When



**Scheme 6.** Manganese/cobalt-catalyzed oxidative C(sp<sup>3</sup>)-C(sp<sup>3</sup>) cross-coupling between amines and benzylic substrates.

conducting a competition experiment between toluene and toluene-d<sub>8</sub>, a significant primary kinetic isotope effect ( $k_H/k_D = 6.14$  when R<sup>3</sup> = 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.

Another noteworthy approach for the synthesis of  $\beta$ -arylethylamines through site-selective amination of unactivated C(sp<sup>3</sup>)-H bonds was recently described by the group of Dauban (Scheme 7).<sup>[17]</sup> 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  $\alpha$ -*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(sp<sup>3</sup>)-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(sp<sup>3</sup>)-H bonds for a variety of substrates, affording  $\beta$ -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  $\beta$ -arylethylamines incorporat-



**Scheme 7.** Rh-catalyzed intermolecular selective C(sp<sup>3</sup>)-H amination of tertiary C-H bonds. X-ray structure reproduced from ref. [17]. Copyright (2021), with permission from American Chemical Society.

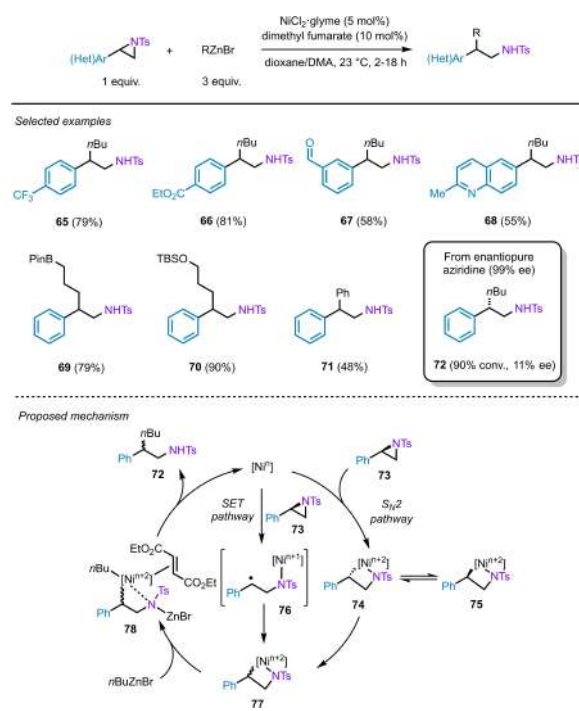
ing an  $\alpha$ -tertiary amine. Of note, the obtained products were easily deprotected with pyridine to give the free amine.

Classical transition metal-catalyzed cross-coupling reactions are a reliable and efficient tool for the synthesis of  $\beta$ -(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  $\beta$ -(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  $C(sp^3)$ -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  $\beta$ -(hetero)arylethylamines are certainly forthcoming thanks to recent developments in photocatalysis and electrocatalysis.

### 3. Ring-opening of aziridines

Aziridine ring-opening represents another efficient way of constructing  $\beta$ -(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.<sup>[18]</sup> Furthermore, aziridines are readily accessible from feedstock alkenes and their reactivity can be easily fine-tuned in accordance with their substitution pattern.<sup>[19]</sup> 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  $Ni^0$  and  $Pd^0$  could undergo  $S_N2$ -type oxidative addition to one of the aziridine C–N bonds to form a 4-membered azametallacycle.<sup>[20,21]</sup> However, these findings did not translate into efficient cross-coupling methodologies due to the strong preference to undergo  $\beta$ -elimination to form imines.<sup>[21]</sup> 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).<sup>[22–25]</sup> During the reaction development, classical ligands such as  $PPh_3$ ,  $PCy_3$ , 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

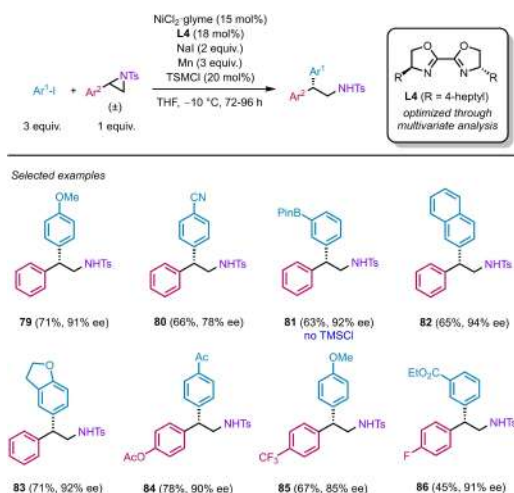


**Scheme 8.** Ni-catalyzed Negishi cross-coupling between styrenyl aziridines and alkylzinc bromides.

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.

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).<sup>[26]</sup> 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. Not-

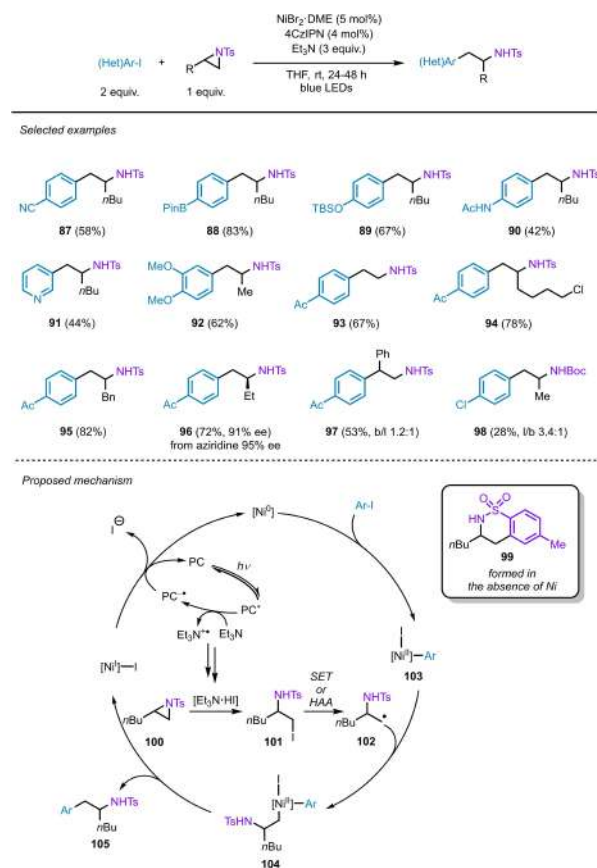




**Scheme 9.** Ni-catalyzed enantioselective reductive cross-coupling of styrenyl aziridines with aryl iodides.

withstanding these major improvements, the methodology remained limited in that  $\beta,\beta$ -diarylethylamines could be accessed only from aromatic aziridines.<sup>[25]</sup>

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).<sup>[28]</sup> 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  $\beta$ -(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 <sup>1</sup>H 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<sub>3</sub>N to form a radical cation, which generates the [Et<sub>3</sub>N·HI] species. Based on previous studies on the ring-opening of epoxides with [Et<sub>3</sub>N·HI], the authors suggested that a nucleophilic addition would occur at the less hindered site to

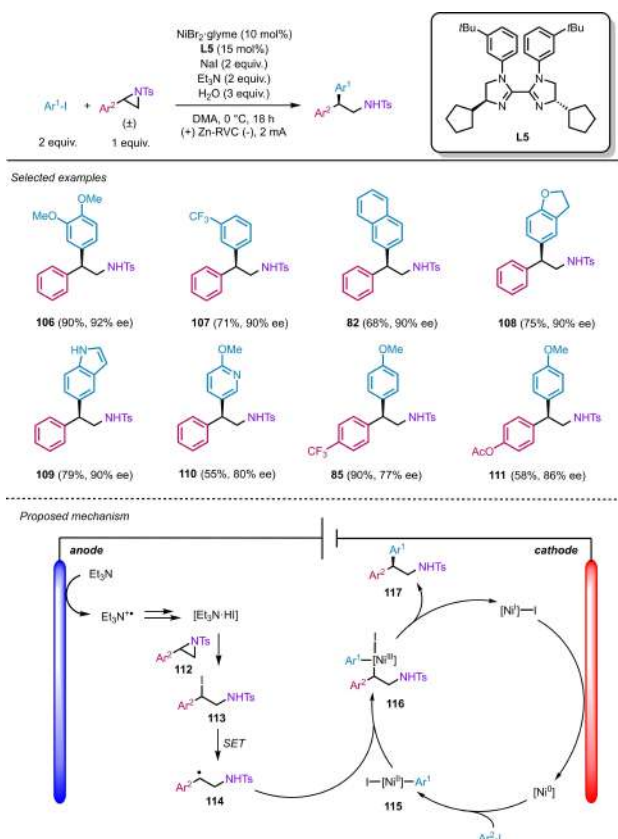


**Scheme 10.** Ni/Photoredox electrophilic cross-coupling of aliphatic aziridines with (hetero)aryl iodides.

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.

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).<sup>[29]</sup> This transformation enables electrophilic cross-coupling of arylaziridines with (hetero)aryl iodides at the benzylic position to afford  $\beta$ -(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<sup>0</sup> species can undergo oxidative addition to aryl iodides but not with aziridines. A control experiment





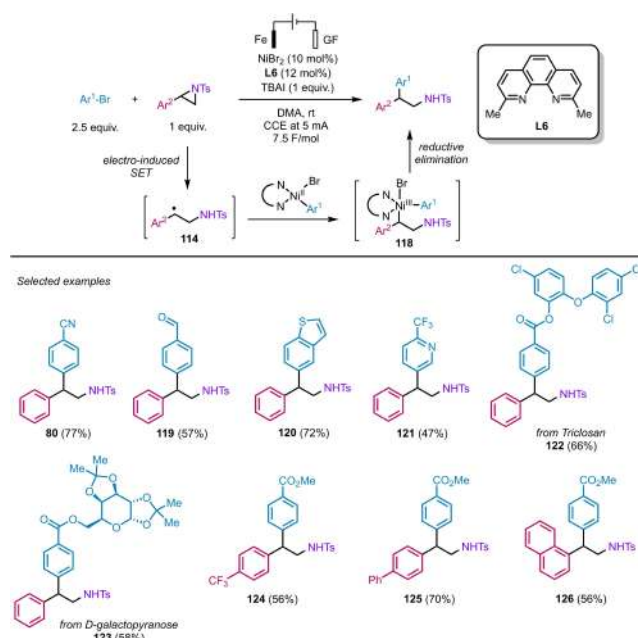
**Scheme 11.** Ni/biimidazole-catalyzed electrochemical enantioselective reductive cross-coupling of styrenyl aziridines with aryl iodides.

without electric current completely halted the reaction. This result indicates that the electrochemical reduction of the Ni<sup>I</sup> 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<sub>3</sub>N to a radical cation followed by formation of [Et<sub>3</sub>N·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<sub>2</sub>Pin<sub>2</sub>, 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.<sup>[30]</sup> The comparison between the two models revealed profound differences in the way the ligand induced enantioselectivity in electrochemical and photocatalytic cross-coupling reac-

tions. 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.

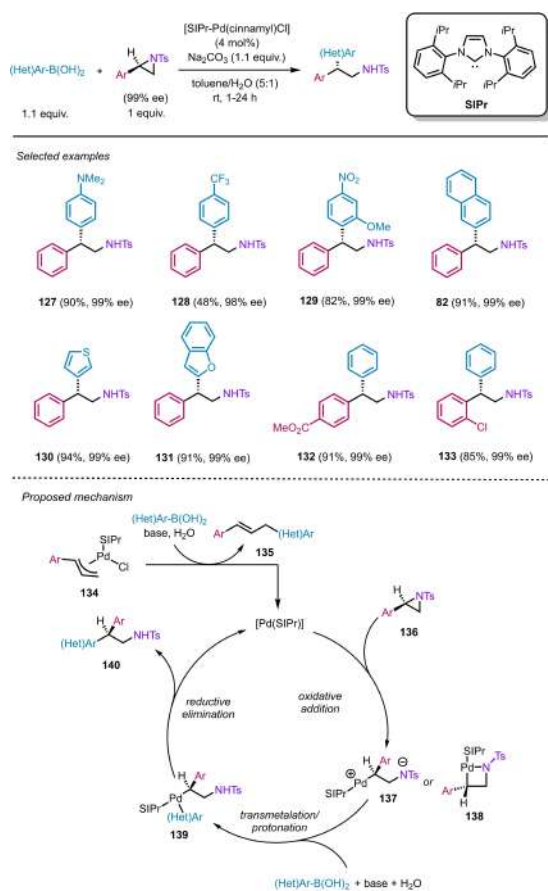
The Qiu group disclosed a similar electroreductive nickel-catalyzed cross-coupling of aziridines with aryl bromides (Scheme 12).<sup>[31,32]</sup> The protocol was compatible with a large variety of electron-deficient (hetero)aryl bromides incorporating cyano, trifluoromethyl, aldehyde, ester, amide, 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



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

reaction in the presence of tetrabutylammonium tetrafluoroborate (TBABF<sub>4</sub>), 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.

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,<sup>[33]</sup> the group of Minaka reported in 2014 a stereospecific version between styrenyl aziridines and readily available and bench-stable (hetero)arylboronic acids (Scheme 13).<sup>[34]</sup> 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  $\beta$ -elimination as a side

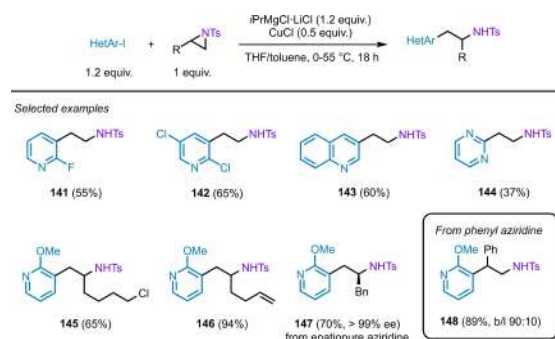


**Scheme 13.** Pd/NHC-catalyzed enantiospecific arylation of styrenyl aziridines with (hetero)arylboronic acids.

reaction. The reaction is proposed to proceed via initial S<sub>N</sub>2-type oxidative addition with inversion at the benzylic carbon (**137** or **138**), followed by transmetalation (**139**) and reductive elimination with retention of stereochemistry (**140**).

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).<sup>[35,36]</sup> 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.

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.<sup>[37–39]</sup> In the context of synthesizing  $\beta$ -(hetero)arylethylamine scaffolds, several other shortcomings



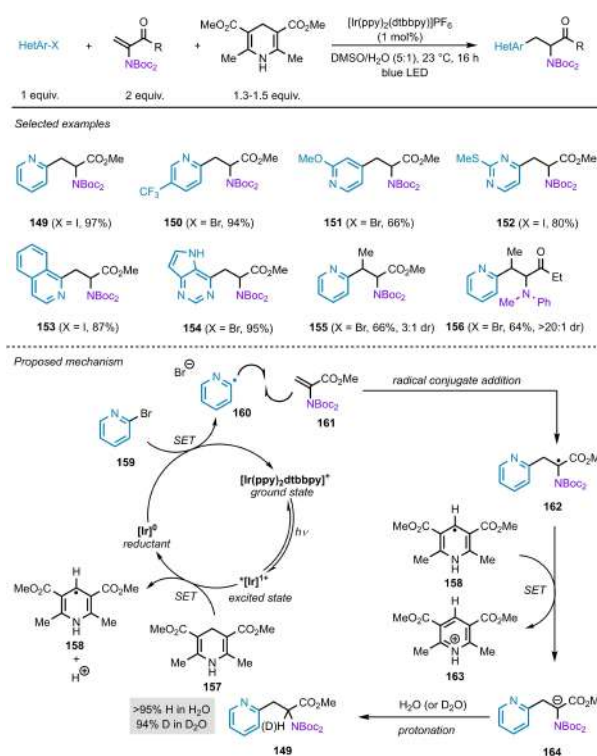
**Scheme 14.** Cu-catalyzed regioselective and stereospecific ring-opening arylation of aziridines with pyridyl Grignard reagents.

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  $\beta$ -(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.

#### 4. Hydroarylation of enamides

When it comes to the construction of the  $\beta$ -(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.<sup>[40]</sup> 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).<sup>[41]</sup> 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  $\alpha$ -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  $\alpha$ -carbonyl radical, which can then capture a proton from water. Based on these mechanistic experiments, the authors proposed the following



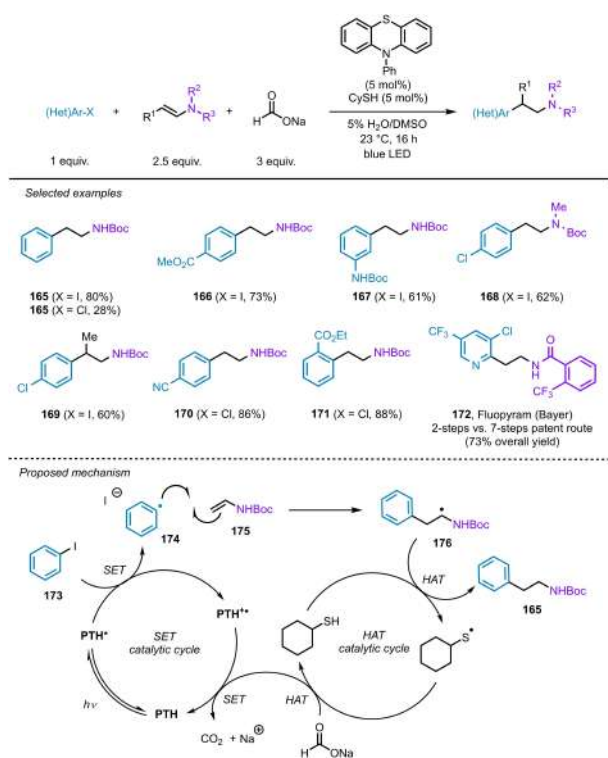
**Scheme 15.** Synthesis of  $\beta$ -heteroarylethylamine derivatives via photocatalytic radical conjugate addition.

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  $\alpha$ -dehydroamino ester **161** via a radical conjugate addition process to form the corresponding  $\alpha$ -carbonyl radical **162**. Subsequent SET with the Hantzsch ester radical **158** and protonation by water delivers unnatural amino acids bearing nitrogen-containing heterocycles.

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 ( $\leq 2.0$  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).<sup>[42]</sup> The authors hypothesized that the use of CySH would preclude undesired HAT reduction of the photogenerated aryl radicals,





**Scheme 16.** Synthesis of  $\beta$ -(hetero)arylethylamine via dual-catalytic radical hydroarylation of enamides.

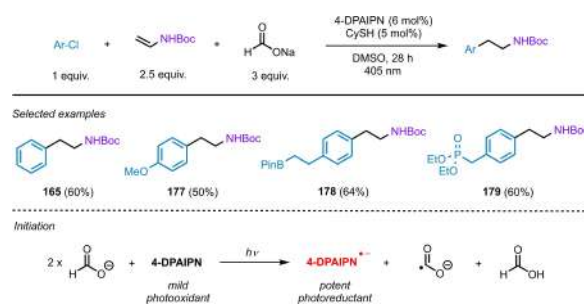
a process which interferes with the desired addition of the aryl radical to the enamide. The reaction mechanism would initially proceed through the formation of a neutral phenyl radical **174** from phenyl iodide **173** and its subsequent anti-Markovnikov addition to enamide **175** to form  $\alpha$ -carbamoyl radical **176**. This electrophilic intermediate would finally undergo a HAT from the electrophilic cyclohexanethiol to deliver the corresponding  $\beta$ -(hetero)arylethylamine. Here, the excess sodium formate would regenerate the photocatalyst and thyl species ( $\text{CyS}^\bullet$ ) 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  $\beta$ -(hetero)arylethylamine skeleton.

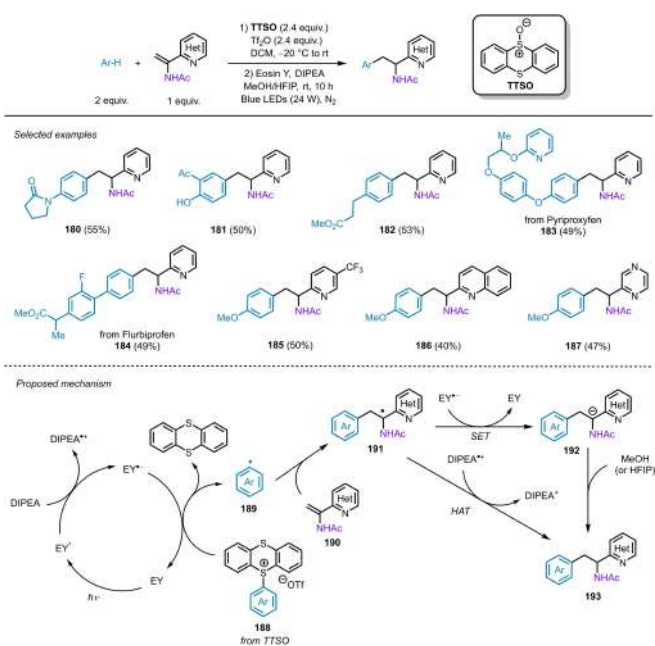
As it was emphasized by the group of Jui during their investigations, operating with aryl halides having reduction potentials inferior to  $-2.0$  V vs SCE, as it is the case with aryl chlorides, is a challenging task under traditional photoredox catalysis. The group of Wickens approached the problem from a different angle by using electron-primed photocatalysis to generate aryl radicals from aryl chlorides (Scheme 17).<sup>[43]</sup> 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<sup>-•</sup> 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  $\beta$ -arylethylamines bearing medically 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.

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).<sup>[44]</sup> 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  $\beta$ -arylethylamine framework. A wide array of electron-rich arenes were amenable to the transformation, including examples of late-stage functionalization of pyriproxyfen and



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



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

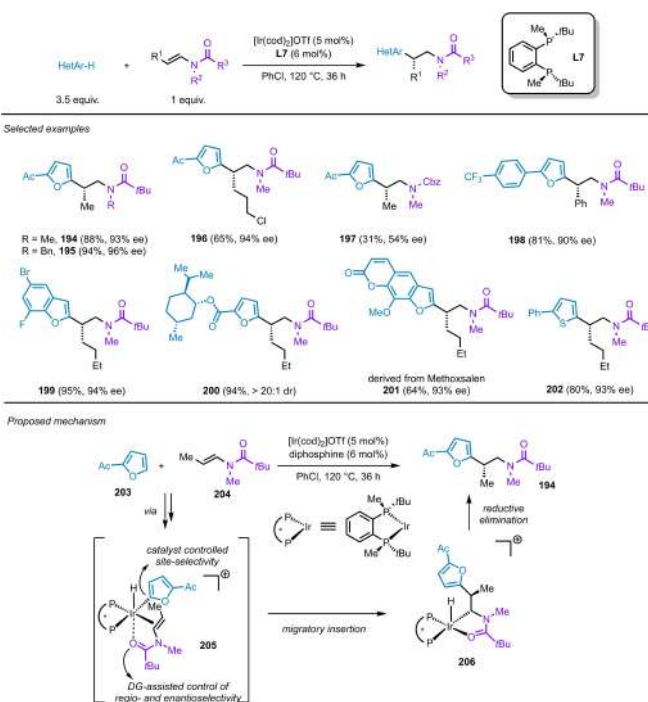
flurbiprofen. Unfortunately, the heteroarene scope was not examined. The reaction mechanism is thought to involve the trifluoromethanesulfonylation of thianthrene S-oxide, followed by reaction with a given arene to generate the corresponding aryl thianthrenium salt **188** in situ. In a second step, 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  $\alpha$ -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).

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.<sup>[45]</sup> However, this approach is limited to terminal alkenes, which restricts the diversity of accessible  $\beta$ -(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  $\beta$ -(hetero)arylethylamine scaf-

folds. 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  $\beta$ -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).<sup>[46]</sup> 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 heteroarene 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  $\beta$ -heteroarylation did not exceed 21% (86% ee) when the amide methyl group was replaced with a H.

Despite recent progress, the hydroarylation of enamides still requires further research, including enantioselective



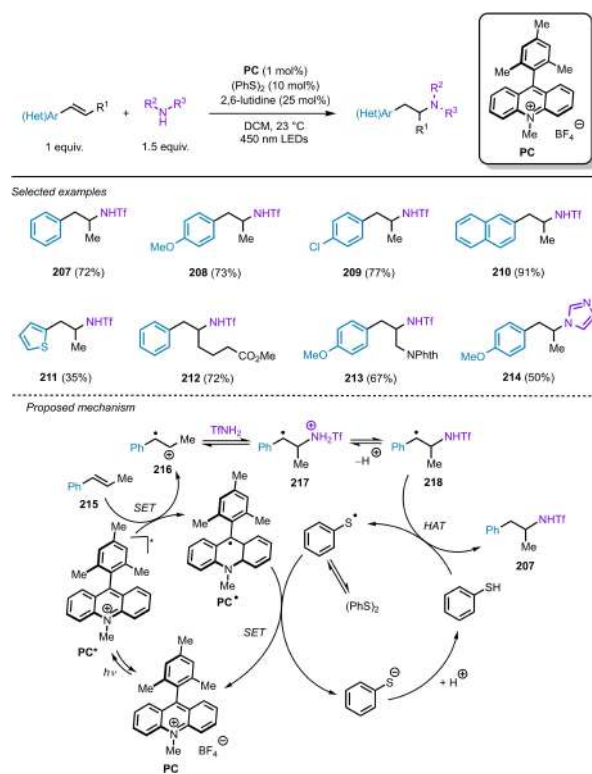
**Scheme 19.** Ir-catalyzed enantioselective functionalization of heteroarene C–H bonds with internal enamides.

processes, which are currently limited to specific heterocycles, and the underexplored reactivity of internal enamides. Moreover, in all these examples, the  $\beta$ -(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  $\beta$ -(hetero)arylamines.

### 5. Hydroamination and hydroamidation of vinyl (hetero)arenes

For the assembly of  $\beta$ -(hetero)arylamines, the anti-Markovnikov hydroamination and hydroamidation of vinyl (hetero)arenes brings several advantages compared to the hydroarylation of enamides.<sup>[47]</sup> The disconnection of a single C–N bond breaks down the  $\beta$ -(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.<sup>[48–53]</sup> Other indirect strategies involve two-step one-pot procedures such as the hydroboration/amination of styrenes or the Wacker oxidation/reductive amination of styrenes.<sup>[54,55]</sup> 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).<sup>[56]</sup> 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  $\text{TsNH}_2$ ,  $\text{NsNH}_2$  and  $\text{BocNH}_2$  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 under-



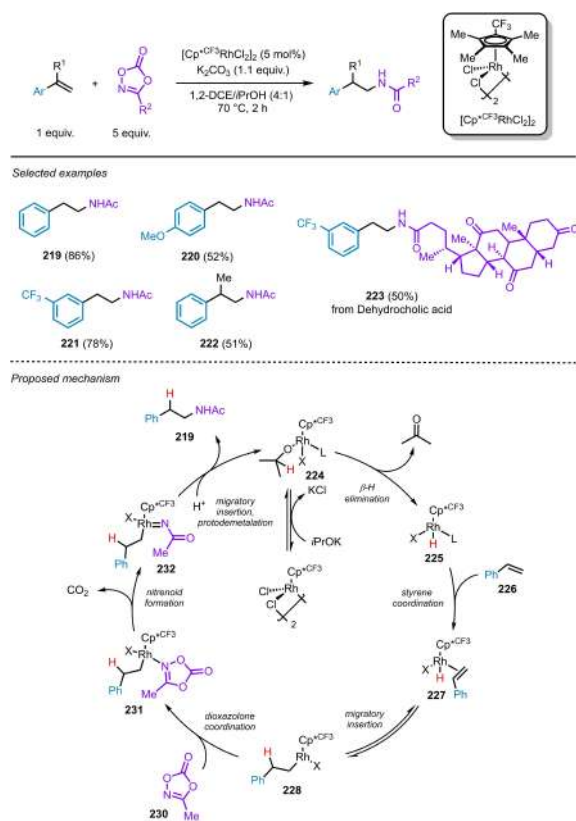
**Scheme 20.** Anti-Markovnikov hydroamidation and -amination of styrene derivatives catalyzed by a two-component organic photoredox system.

goes 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  $(\text{PhS})_2$  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.

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).<sup>[57]</sup> While mostly aliphatic alkenes were reported, mono- and 1,1-disubstituted styrenes were also compatible with their standard conditions to afford the corresponding  $\beta$ -(hetero)arylethylamides in yields ranging from 50 to 86%. The mechanistic studies conducted suggest the formation of key rhodium nitrenoid species **232** upon  $\text{CO}_2$  extrusion from coordinated dioxazolone **231**. Subsequent alkyl migratory insertion into a  $[\text{Rh}]$ -nitrenoid and protodemetalation would deliver hydroamidation product **219**.

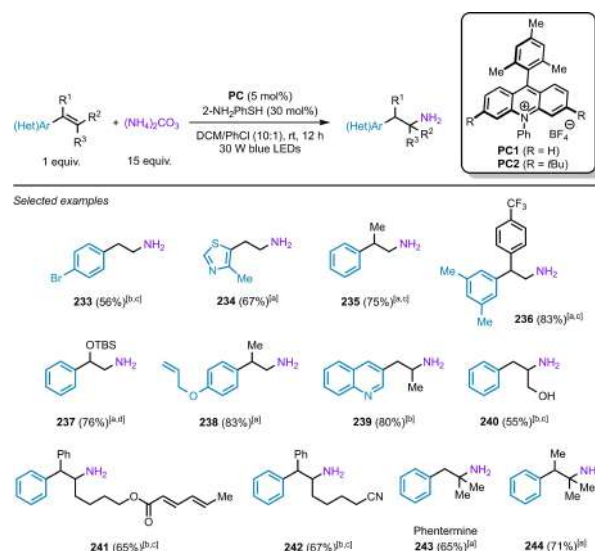
Despite several advances in the anti-Markovnikov hydroamination of vinyl (hetero)arenes, few reports tackled





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

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,<sup>[58]</sup> the group of Shu succeeded to solve this problem by devising an expedient strategy to access unprotected primary  $\beta$ -(hetero)arylethylamines (Scheme 22).<sup>[59]</sup> 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

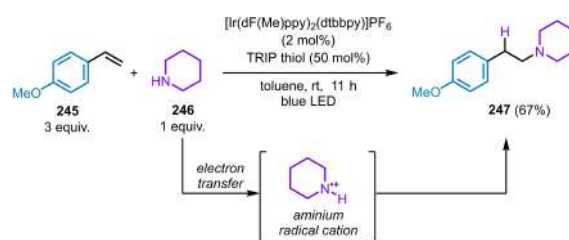


**Scheme 22.** Synthesis of primary aliphatic amines via photocatalytic hydroamination of styrene derivatives using ammonium carbonate as amine source. [a] PC1. [b] PC2 in DCM/MeCN (10:1). [c] Isolated yield of NHBoc.

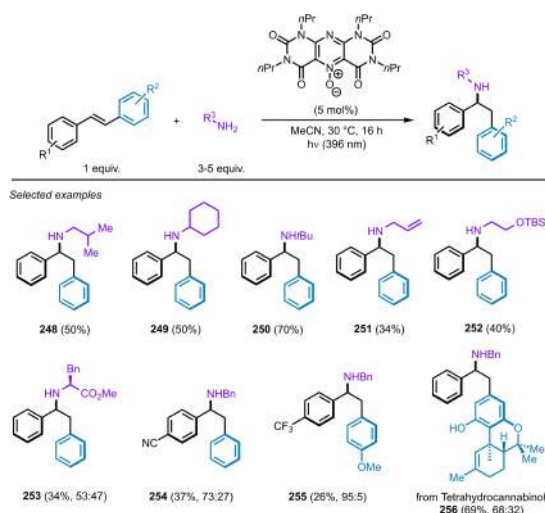
addition, the authors demonstrated that the radical intermediate could be trapped by TEMPO. Thus, the reaction likely operates with a similar mechanism as the one described by the group of Nicewicz (see Scheme 20).

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.<sup>[60]</sup>

To tackle this issue, the group of Pospesch reported the use of a highly potent pyrimidopyridine-*N*-oxide photocatalyst, whose excited state has a high reduction potential ( $E_{1/2}(\text{PC}^*/\text{PC}^-) = +2.29 \text{ V vs SCE}$ ), 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).<sup>[61]</sup> Atypically,



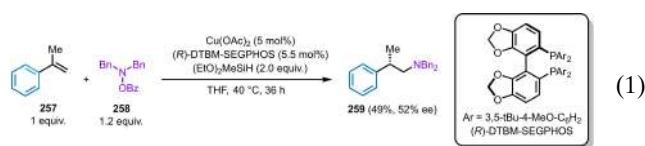
**Scheme 23.** Photocatalytic hydroamination of *p*-methoxystyrene with piperidine. TRIP thiol = 2,4,6-triisopropylbenzenethiol.



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

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  $[\text{Ru}(\text{dtbbpy})_3](\text{PF}_6)_2$  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  $\alpha$ -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.

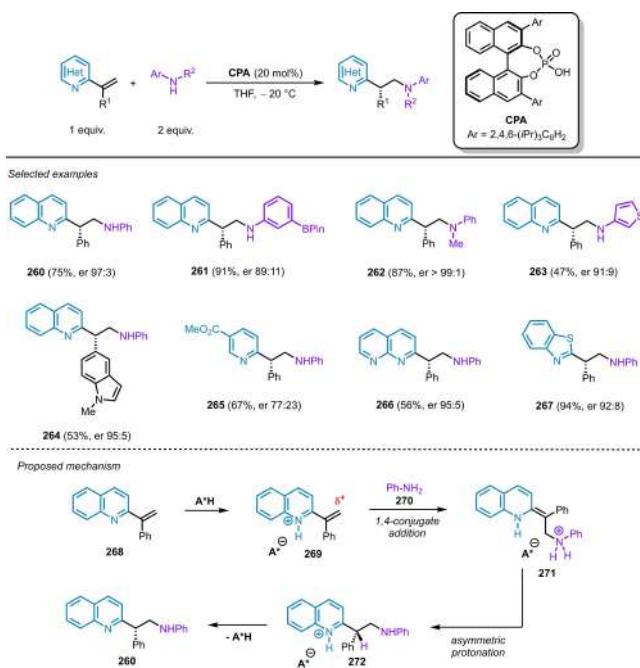
The asymmetric hydroamination of vinyl (hetero)arenes represents an open challenge. The Buchwald group reported an efficient copper-catalyzed enantioselective anti-Markovnikov hydroamination of aliphatic alkenes but obtained only moderate success with styrenes. For example, in the case of  $\alpha$ -methylstyrene,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



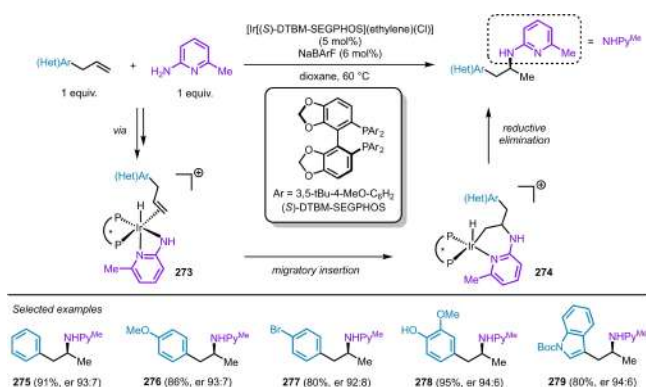
In 2018, the group of Watson reported an intriguing strategy to achieve enantioselective anti-Markovnikov hydroamination. Their idea revolves around the introduction of a nitrogen heterocycle on the alkene with the aim of triggering 1,4-conjugate additions in the presence of a Brønsted acid catalyst. They exploited a chiral phosphoric

acid (CPA) for highly enantioselective conjugate addition of anilines to 1,1-vinyl aza-heterocycles (Scheme 25).<sup>[63]</sup> 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  $\alpha$ -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.

An alternative to the asymmetric synthesis of  $\beta$ -(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).<sup>[64]</sup> 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 isomer-



**Scheme 25.** Chiral phosphoric acid-catalyzed enantioselective synthesis of  $\alpha$ -chiral azaheteroaryl ethylamines.



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

ization 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.

In the past years, photocatalysis and transition metal catalysis have become prominent tools for the synthesis of  $\beta$ -(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  $\beta$ -(hetero)arylamines.

## 6. Truce-Smiles rearrangement

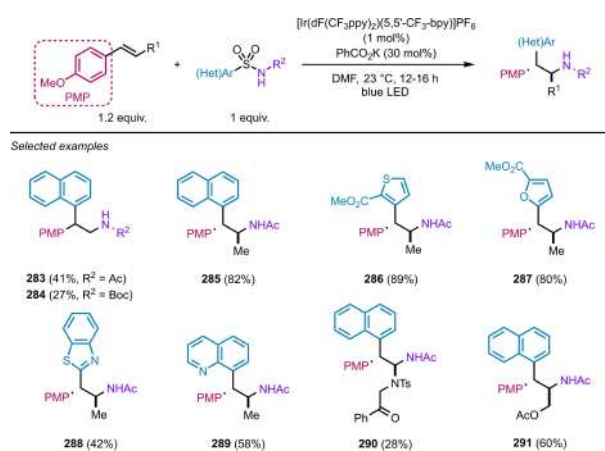
Another elegant way to forge  $\beta$ -(hetero)arylethylamine scaffolds is the Truce-Smiles rearrangement, which consists in the intramolecular migration of an aryl group via formal

*ipso* substitution through typically radical or anionic pathways (Scheme 27).<sup>[65]</sup> The driving force of this process is the release of SO<sub>2</sub> 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  $\beta$ -(hetero)arylethylamine along with the introduction of a variety pharmacophores would not be commented as they were recently reviewed by the group of Greaney.<sup>[6]</sup>

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).<sup>[66]</sup> 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, intermolecu-



**Scheme 27.** Radical Truce-Smiles rearrangement.



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



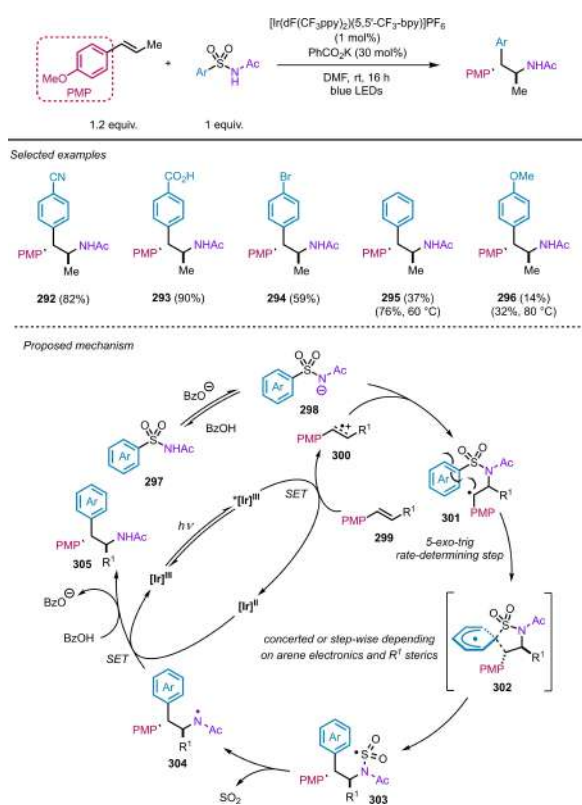
lar reactions of this type might simply be inherently challenging since *N*-acylsulfonamidyl radicals form phenols through rapid homolytic cleavage of the aryl–S bond, a process that is more competitive when less reactive alkenes are employed.

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).<sup>[67]</sup> 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

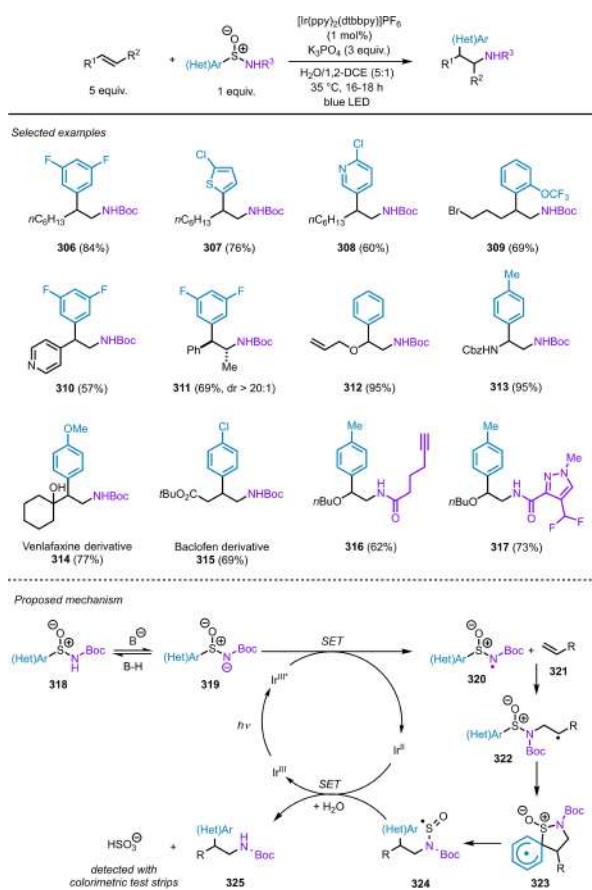
an antiperiplanar arrangement of the *para*-methoxyphenyl and the methyl groups. The subsequent extrusion of SO<sub>2</sub> ensures the irreversibility of migration (**304**). Insights gained from the mechanistic studies are clearly reflected in the extended scope of the transformation. A series of substrates 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.

Despite this breakthrough, the starting alkenes that could be used lacked diversity, limiting the synthetic utility of this method to access  $\beta$ -(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(sp<sup>2</sup>)–S–N bond angle of  $\approx 96^\circ$  in a sulfinamide, compared to the  $109^\circ$  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).<sup>[68]</sup> 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.

In parallel with the studies of the group of Stephenson, the Nevado group recently devised a photocatalytic asymmetric aminoarylation via the Truce–Smiles rearrangement



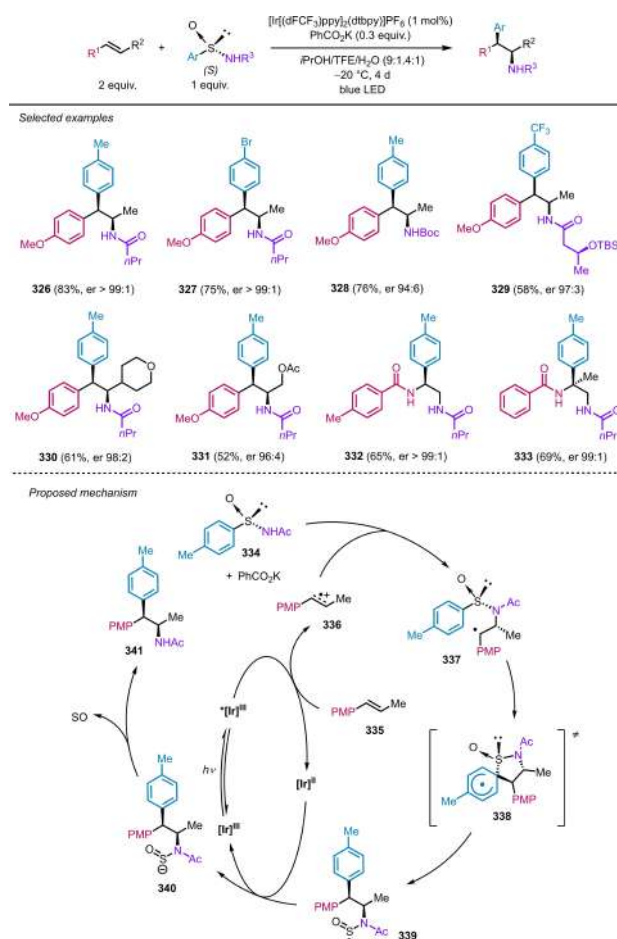
**Scheme 29.** Mechanistic understanding and resulting extended scope for photocatalytic 1,2-aminoarylation of styrenes with arylsulfonylacetamides.



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

by employing chiral sulfinylamides (Scheme 31).<sup>[69]</sup> 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<sup>-1</sup> 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.

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



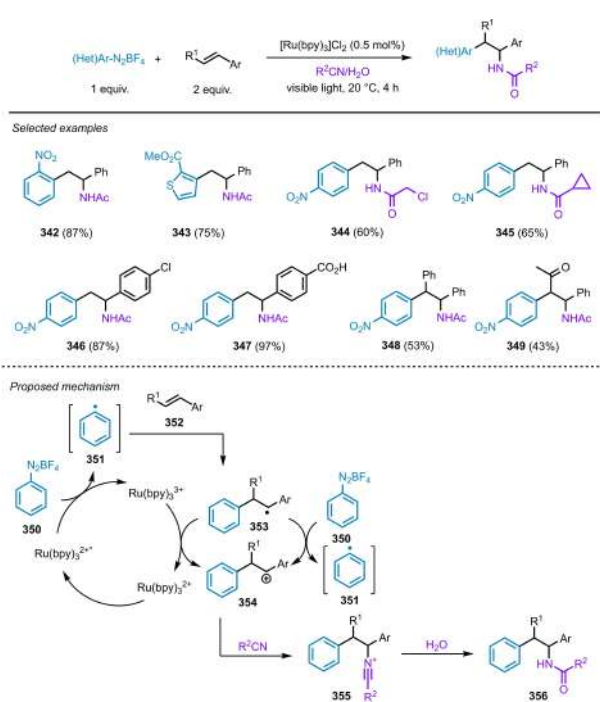
**Scheme 31.** Visible light-mediated asymmetric aminoarylation of alkenes with chiral arylsulfinylamides.

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.

## 7. (Hetero)arylamination of alkenes

Of the various approaches for the preparation of  $\beta$ -(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.

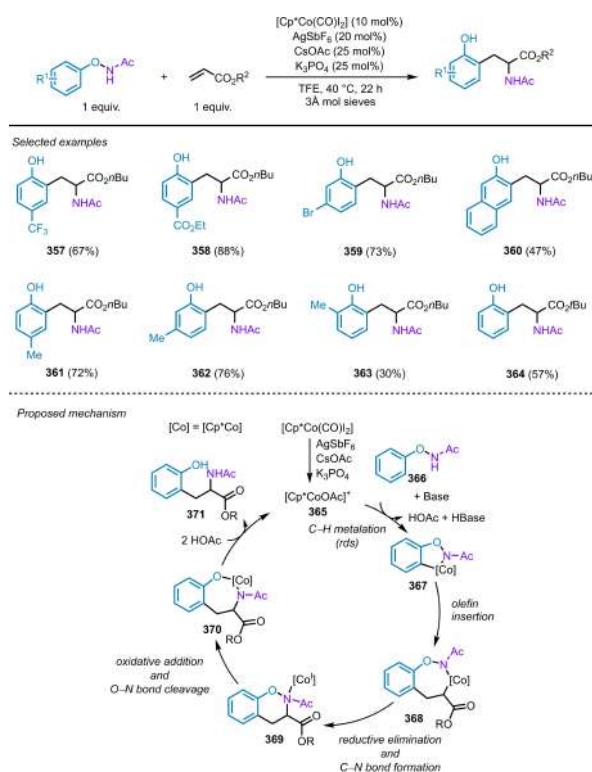
In 2014, following seminal studies by the group of Greaney,<sup>[70]</sup> the König group drove the growth of this area, unveiling the first example of a synergistic combination of a photo-Meerwein addition with a Ritter reaction to formally implement a 2,1-aminoarylation of styrenes (Scheme 32).<sup>[71]</sup> 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



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

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.

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).<sup>[72–74]</sup> 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,<sup>[75]</sup> the authors explored an analogous Cp\*Co(III) complex with the hope that it might overcome the  $\beta$ -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

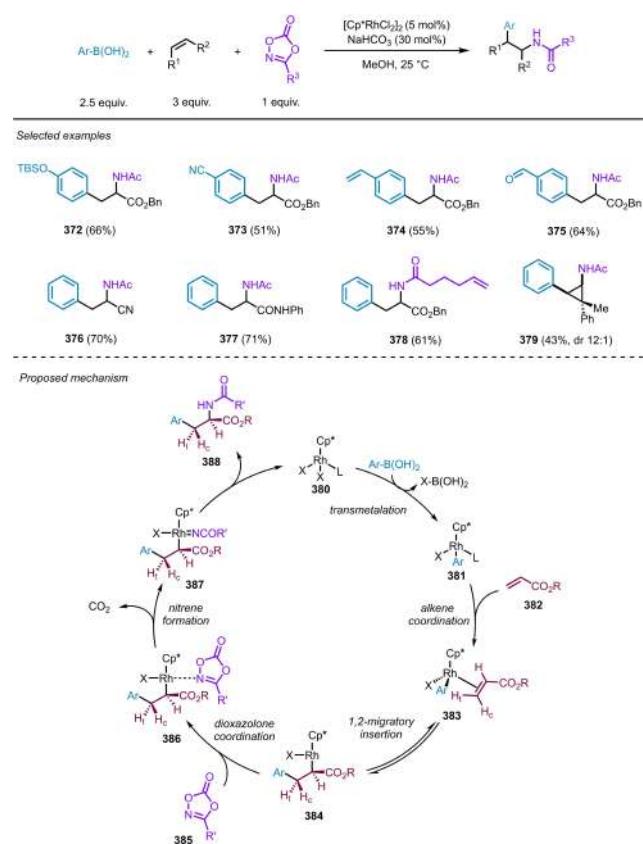


**Scheme 33.** Synthesis of unnatural amino acids via Co-catalyzed intermolecular arylation of acrylates.



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  $\beta$ -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).<sup>[76]</sup> 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.<sup>[77]</sup> Based on their experiments, they proposed the following mechanism: rhodium complex **380** would first undergo transmetalation with arylboronic acid to form **381**,



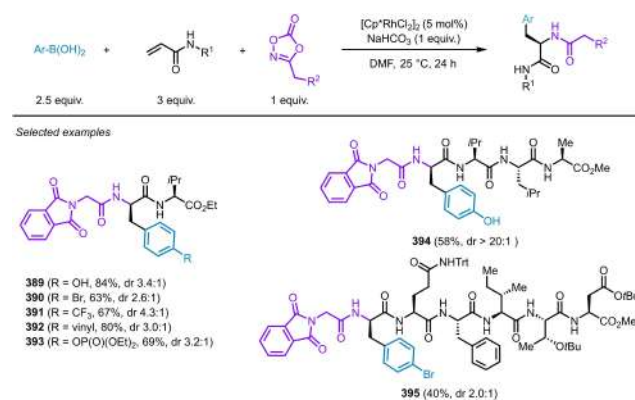
**Scheme 34.** Rh-catalyzed three component *syn*-aminoarylation of alkenes.

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 dioxazolone **385** onto the Rh center, would generate Rh(V)-nitrene **387** along with extrusion of CO<sub>2</sub>. Finally, reductive elimination and proto-demetalation would yield the desired *syn*-carboamination product and regenerate the catalyst.

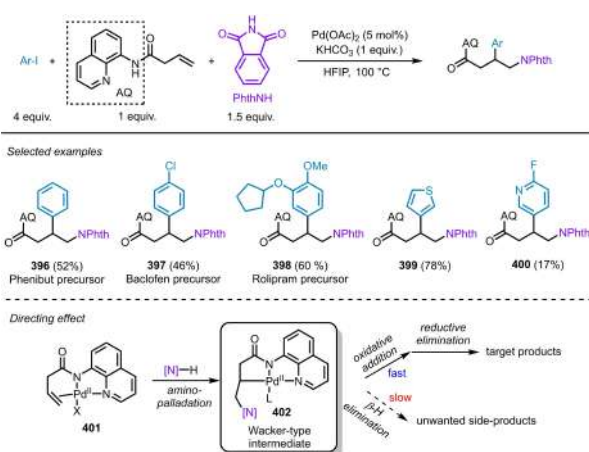
Whereas most interest in aminoarylation reactions have come from chemists interested in the preparation of small molecules, the Rovis group has recently further extended their three-component arylamidation reaction to biomolecules (Scheme 35).<sup>[78]</sup> For instance, they showed that by using peptides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

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).<sup>[79]</sup> 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 out-



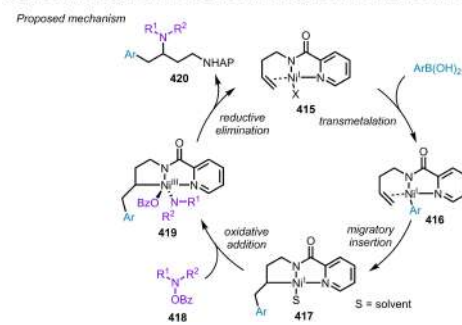
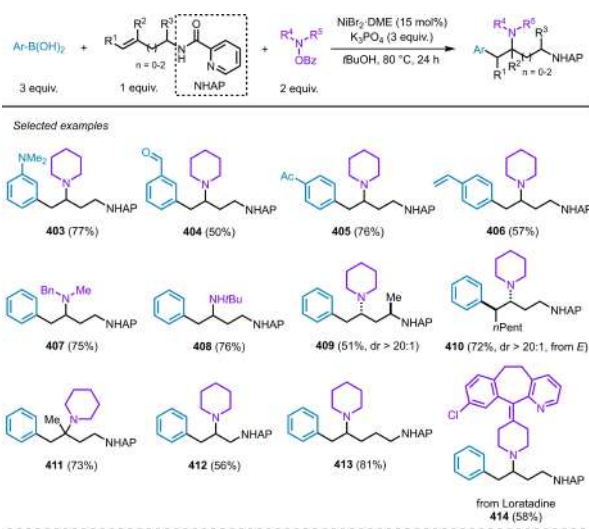
**Scheme 35.** Synthesis of unnatural peptides via diastereoselective aminoarylation of alkenes.



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

compete  $\beta$ -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.

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).<sup>[80]</sup> 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,  $\alpha$ -substituted homoallylamines or internal alkenes also underwent the reaction to provide the arylamination products with excellent control of the diastereoselectivity. Finally, this transformation proceeded smoothly with biologically relevant compounds



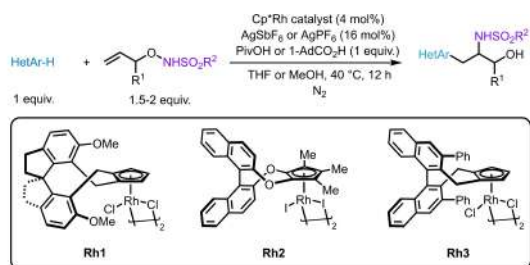
**Scheme 37.** Ni-catalyzed directed aminoarylation of unactivated alkenes.

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.

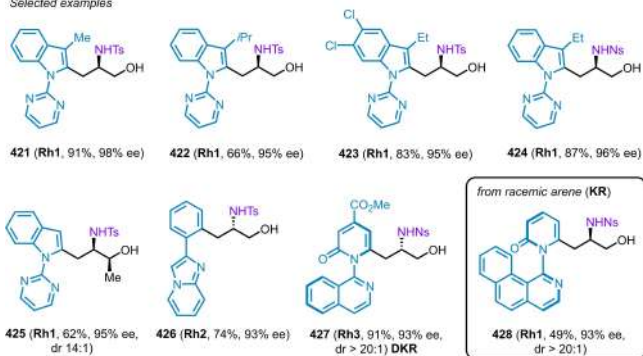
Remarkably, further studies by Engle group demonstrated that such type of directing group was not even necessary as simple alcohols or amines could be effectively used to control the regioselectivity of aminoarylation of aliphatic alkenes using arylboronate esters as arene components.<sup>[81,82]</sup>

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

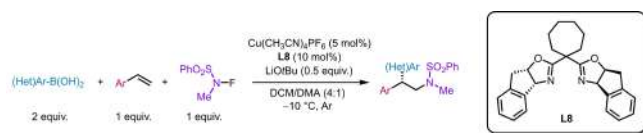
process proved highly stereoselective with various Cp\*Rh catalysts (Scheme 38).<sup>[83]</sup> The use of a bifunctional alkene favored specific chelation of the metal to induce stereocontrol. The reaction was compatible with a variety of bis-heterocyclic arene moieties bearing halide and alkyl groups. Various sulfonamides could be installed on the olefin to produce the desired aminoarylated products in excellent



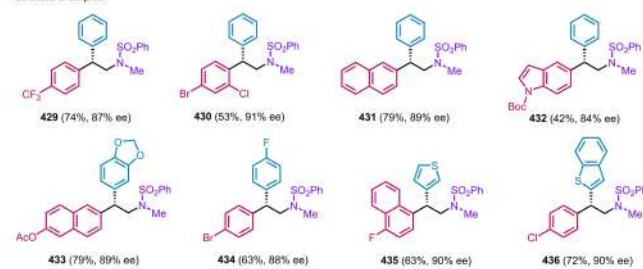
Selected examples



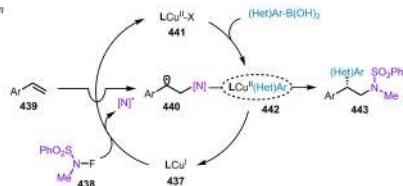
**Scheme 38.** Access to axially and centrally chiral compounds through bifunctional alkene (hetero)arylamidation.



Selected examples



Proposed mechanism



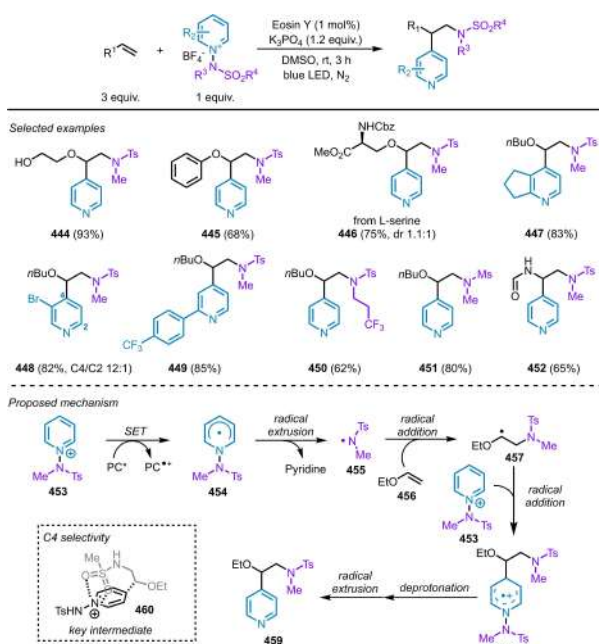
**Scheme 39.** Cu-catalyzed enantioselective synthesis of  $\beta,\beta$ -diarylethylamines.

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.

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  $\beta,\beta$ -diarylethylamines from styrenes (electron-rich or poor, including trifluoromethyl substitution), arylboronic acids, and *N*-fluoro-*N*-alkylsulfonamide as the amine source (Scheme 39).<sup>[84]</sup> 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  $\beta$ -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.

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).<sup>[85]</sup> 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



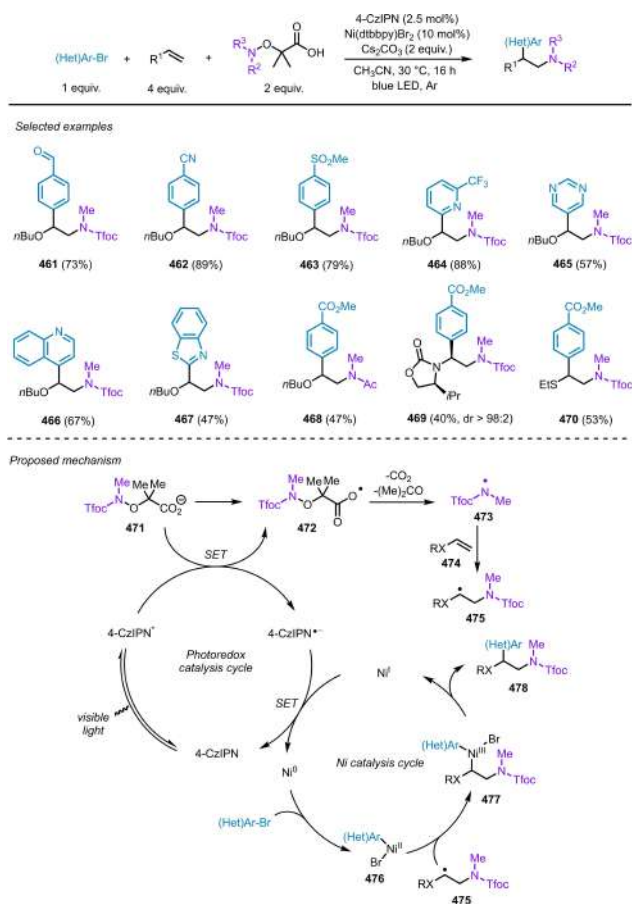


**Scheme 40.** Photocatalytic C4-aminopyridylation of alkenes using *N*-aminopyridinium salts.

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.

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.<sup>[86]</sup> 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).<sup>[87]</sup> They reported a three-component 1,2-amino(hetero)arylation acting on electron-rich vinyl ethers, enamides, encarbamates 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



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

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  $\beta$ -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. A recent report from our group addressed both limitations.<sup>[88]</sup> Based on prior work from the Morandi group regarding the aminofunctionalization of alkenes,<sup>[89–91]</sup> we expected that the reaction of a hydroxylamine derivative and a styrene could result in the formation of an aziridine in

situ. Moreover, based on our work on ring-opening arylation of epoxides in HFIP,<sup>[92]</sup> we anticipated that the aziridine could be opened using a (hetero)arene nucleophile to yield an aminoarylated product. As it is well-known for HFIP,<sup>[93]</sup> we envisioned that the unique properties of that solvent might allow strongly electronically deactivated styrenes to participate in the reaction. Indeed, iron (II) sulfate was found to be a promising catalyst for the reaction, which was compatible with indoles, pyrroles, and other electron-rich arene nucleophiles (Scheme 42).<sup>[88,94]</sup> In turn, the use of more electron-poor carbon nucleophiles proved less efficient. However, the method was compatible with extremely electron-poor styrene derivatives such as perfluorostyrene and *p*-nitrostyrene. As expected, the method proved incompatible with the use of electron-rich styrenes, which are well-known to oligomerize under acidic conditions. Aliphatic alkenes could also participate in the reaction, albeit with inverted regioselectivity. This is a rare method to directly obtain unprotected amines from alkene aminoarylation, which facilitates the rapid derivatization of the reaction products. In support of the mechanistic hypothesis, the proposed aziridine intermediate could be isolated at the end of the first step before adding the aromatic nucleophile. Here, it is important to stress that the reaction had to be carried out in a one-pot/two-step process to prevent the amination of the electron-rich (hetero)arene nucleophile under the reaction conditions.

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  $\beta$ -(hetero)arylamines 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.

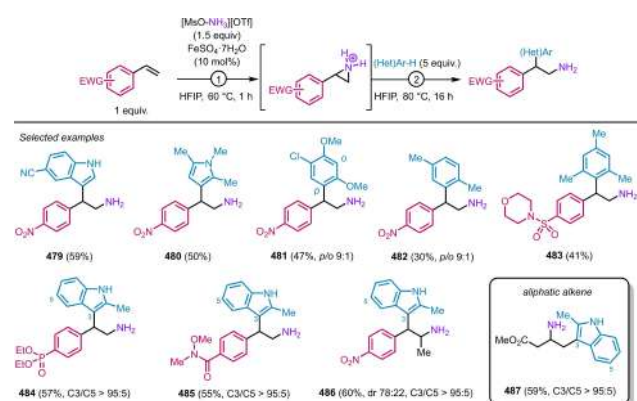
## 8. Summary and Outlook

Over the past decade, the advances made in the design of new methods to access  $\beta$ -(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  $\beta$ -(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  $\beta$ -(hetero)arylamines scaffolds, interest in the development of versatile and broadly applicable methodologies for their synthesis is not likely to wane.

## Acknowledgements

This work was supported by the Interdisciplinary Thematic Institute ITI-CSC via the IdEx Unistra (ANR-10-IDEX-0002) within the program Investissement d'Avenir. V.P. and C. M. thank the CSC Graduate School funded by the French



**Scheme 42.** Fe-catalyzed direct access to unprotected  $\beta$ -(hetero)arylethylamines in HFIP.

National Research Agency (CSC-IGS ANR-17-EURE-0016). D.L. and J.M thank the CNRS.

### Conflict of Interest

The authors declare no conflict of interest.

### Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Keywords:** C–H Activation ·  $\beta$ -(Hetero)Arylamine · Hydrofunctionalization · Photocatalysis · Rearrangement

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Manuscript received: June 30, 2023

Accepted manuscript online: August 20, 2023

Version of record online: August 31, 2023