Chiral arylsulfinylamides as reagents for visible light-mediated asymmetric alkene aminoarylations

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Abstract

Two- or one-electron mediated difunctionalizations of internal alkenes represent straightforward approaches to assemble molecular complexity by the simultaneous formation of two contiguous Csp^3-stereocenters. While racemic versions have been extensively explored, asymmetric variants, especially those involving open-shell C-centered radical species, are much more limited both in number and scope. In this work, we describe enantioenriched arylsulfinylamides as *all-in-one* reagents for the efficient asymmetric, intermolecular aminoarylation of alkenes. Under mild photoredox conditions, nitrogen addition of the arylsulfinylamide onto the double bond followed by 1,4-translocation of the aromatic ring produce, in a single operation, the corresponding aminoarylation adducts in enantiomerically enriched form. The sulfinyl group acts here as a traceless chiral auxiliary as it is eliminated *in situ* under the mild reaction conditions. Optically pure β,β-diarylethylamines, aryl-α,β-ethylenediamines, and α-aryl-β-aminoalcohols prominent motifs in pharmaceuticals, bioactive natural products, and

ligands for transition metals, are thereby accessible with excellent levels of regio-, relative and absolute stereocontrol.

Introduction

Nature's secondary metabolites as well as *de novo* designed small molecule probes are significantly populated with nitrogen atoms. HIV inhibitors[1], ion channel modulators[2], opioids[3,4] and endogenous neurotransmitters[5] (Figure 1a) are representative examples of relevant bioactive compounds showcasing N-containing motifs, many of which feature amines substituted with an aromatic group in β-position. Access to these prominent chemical blueprints in enantiomerically pure form is crucial, not only for accurate target engagement studies, but also for the optimization of their pharmacological profiles. A representative example is *R*-(+)-dinapsoline, a selective and efficient D_1 dopamine agonist[5], which was found to be 161-fold more potent than its *S*-(–)-enantiomer.

The asymmetric synthesis of β-arylethylamines has typically relied on additions[6-10] or hydrogenations of alkenes[11,12] as well as on ring opening[13-15] and condensation reactions[16]. These processes require multistep sequences encompassing highly tailored reaction conditions such as cryogenic temperatures and/or high pressures as well as precise metal/ligand combinations, which represents a significant limitation and hampers their broad applicability. In sharp contrast, two-[17-20] or one-electron[21-27] mediated multicomponent aminoarylation reactions featuring alkenes as highly abundant feedstocks represent a powerful, atom-economic alternative to access these ubiquitous motifs as two contiguous Csp^3–C and Csp^3–N bonds can be forged in a single operation [28-34]. Despite the intrinsic potential to impart both, relative and absolute stereocontrol in the newly formed stereocenters[35], asymmetric variants of these transformations, especially in intermolecular settings, are extremely scarce. Benzohydroxamic acid derivatives[18,36] and *ortho*-iodoanilines[37] have been showcased as non-cleavable C,N-tethered reagents to orchestrate asymmetric annulations with alkenes. Additionally, a handful

of examples featuring three-component reactions have been reported (Figure 1b). In 2017, the addition of *N*-fluoro-*N*-alkylsulfonamides (NFSA)-derived radicals and (hetero)arylboronic acids across the π-system in the presence of a chiral BOX-ligated copper catalyst to yield *β,β*-diarylethylamines with excellent levels of absolute stereocontrol was demonstrated[38]. More recently, an asymmetric Minisci reaction involving quinoline derivatives and *O*-acyl hydroxylmethylamine with *N*-vinylacetamide as radical acceptor was reported[39]. Notwithstanding the undisputable synthetic utility of these transformations, limitations regarding both, the type of nitrogen donors and the olefinic partners, justify the quest for alternative, more flexible strategies in this context.

An elegant light-mediated intermolecular aminoarylation of alkenes using arylsulfonylacetamides as bifunctional reagents has been demonstrated[40-43]. The reaction, only applicable to electron-rich styrenes, furnished the corresponding *β,β*-diarylethylamines in racemic form[40]. Recently, our group exploited the ability of chiral *N*-sulfinyl moieties to impart absolute stereocontrol in the challenging assembly of all-C quaternary centers[44].

Inspired by these results, we hypothesized that addition of a nitrogen atom bound to a chiral arylsulfoxide group onto the terminal position of a 1,2-disubstituted alkene could control the absolute stereochemistry in the formation of the newly created Csp^3–N bond as well as on the neighbouring Csp^3–Csp^2 center generated upon a radical Truce-Smiles rearrangement of the corresponding aryl moiety. Here, we describe enantioenriched arylsulfinylamides as multifunctional *all-in-one* reagents able to forge, regio- and stereoselectively, two contiguous Csp^3–C and Csp^3–N bonds across a variety of π-systems. A photochemically-enabled addition of the nitrogen atom onto the terminal position of styrenes, vinyl amides, and vinyl ethers furnishes a C-radical intermediate which, upon translocation of the aromatic ring, delivers enantioenriched *β,β*-diarylethylamines, aryl-*α,β*-ethylenediamines, and *α*-aryl-*β*-aminoalcohols, respectively. The mild reaction conditions and broad functional group tolerance

combined with the excellent regio-, diastereo- and enantioselectivity, highlight both the generality and synthetic utility of these transformations in the assembly of relevant blueprints populating pharmaceuticals, bioactive natural products and ligands for transition metal catalysis.

Results

Reaction optimization. Enantiopure (S_S)-*N*-(*p*-tolylsulfinyl)butyramide **1a** and *trans*-anethole were chosen as model substrates for our initial investigations. Reactions under blue LED irradiation in the presence of different photocatalysts were performed combining these two starting materials in a 1:1.2 ratio (for experimental details, see Supplementary Table 1). Extensive screening revealed that, using 1 mol% of (Ir[dF(CF_3)ppy]$_2$(dtbpy))PF_6 and 0.3 equivalents of potassium benzoate as base in a isopropanol/trifluoroethanol/water mixture at ambient temperature, the desired *β,β*-diarylethylamine **2.1** could be produced in 53% yield, with excellent diasteroselectivity (>20:1 d.r.) and promising 89:11 enantiomeric ratio. Adjusting the stoichiometry between **1a** and the olefin to a 1:2 ratio and decreasing the reaction temperature to -20 °C furnished **2.1** in an improved 83% yield with almost perfect levels of both relative and absolute stereocontrol (>20:1 d.r.; >99:1 e.r.). Further, efficiency of stereochemical information transfer was maintained when the reaction was scaled up ten-fold, affording **2.1** in 58% yield (>20:1 d.r.; 98:2 e.r., for the experimental details, see Supplementary Figure 4). Additional experiments in the presence of radical inhibitors or excluding the photocatalyst, the light or the base resulted in the recovery of both unreacted starting materials (for the experimental details, see Supplementary Table 2).

Reaction scope. With the optimal conditions in hand, we set out to explore the compatibility of different N-atom donors and aryl migrating groups within the *all-in-one* arylsulfinylamide reagents. To this end, modifications on both, the N-atom donor and the aryl migrating group

were investigated. Alkyl amide derivatives featuring a diverse set of substitution patterns were also compatible with the standard reaction conditions furnishing the corresponding adducts (CH_2PMP, **2.2**; CHEtPh, **2.3**; Cy, **2.4**; $(CH_2)_2CO_2Et$, **2.5**; CH_2CH(OTBS)Me, **2.6**) with excellent levels of regio-, and both relative and absolute stereocontrol (Table 1). Furthermore, successful incorporation of aromatic and heteroaromatic substituted amides and even *tert*-butyl carbamate derivative (**2.7**-**2.9**) emphasizes the functional group compatibility of the method. Furthermore, carbamate derivative (**2.9**) could also be transformed under the standard conditions providing access to the corresponding free amine upon acid hydrolysis with complete retention of the stereochemical information (See Supporting Information, compound **2.39**).

The scope with respect to the migrating aromatic groups was investigated next. Transposition of a simple phenyl group proceeded smoothly under standard conditions to give **2.10** in high yield. Interestingly, substrates bearing both electron-withdrawing as well as electron-donating groups in the *para* position of the arene proved to be suitable precursors, furnishing the corresponding *β,β*-diarylethylamines (**2.11**-**2.14**) in good yields with outstanding levels of stereocontrol. *meta*-Methoxy and *meta*-bromo derivatives also delivered the desired products (*m*-OMe, **2.15**; *m*-Br, **2.16**) although with slightly lower stereoinduction. In contrast, more sterically hindered substrates bearing *ortho*-substituted aromatic rings (*o*-Me, **2.17**; *o*-Br, **2.18**) were obtained with excellent enantioselectivities. To our delight, the *ortho*-bromo adduct **2.18** was quantitatively converted into the corresponding indoline in presence of Pd catalyst with retention of configuration, highlighting the synthetic potential of the obtained aminoarylation products (See Supporting Information, compound **2.40**). Moreover, heteroaryl migration also took place under the standard conditions furnishing the corresponding thiophene derivatives **2.19** and **2.20** in good yields with excellent levels of both relative and absolute stereocontrol.

X-ray crystallographic analysis of compounds **2.3** and **2.11** confirmed the *syn* addition of the N-atom and the arene across the π-system. Adduct **2.11**, stemming from an (S_S)-arylsulfinylamide precursor containing a bromine atom, enabled us to assign the absolute configuration of the major diastereoisomer produced in this reaction as (1*S*,2*R*). It is important to note that the substitution pattern in the aromatic ring affects the priority of the groups at the new asymmetric carbon atom. As a result, a (1*R*,2*R*) configuration can be assigned to most of the obtained compounds. The reaction proved to be stereospecific: when the (*R*)-enantiomer of the arylsulfinylamide (R_S)-**1a'** was used as a precursor, the opposite enantiomer of the *β,β*-diarylethylamine product (1*S*,2*S*)-**2.1'** could be obtained in similar yield and enantiomeric ratio (for the experimental details, see Supplementary Figure 28).

The compatibility of the reaction between (S_S)-*N*-(*p*-tolylsulfinyl)butyramide **1a** with different styrene partners was also explored (Table 2). While simple styrenes (R^3 = H) were not competent substrates, phenethyl, cyclohexyl, 4-tetrahydropyranyl and carbinyl acetate groups at the terminal position of the double bond were effectively accommodated in the aminoarylation process. The corresponding *β,β*-diarylethylamines (**2.21**-**2.25**) were obtained in moderate to good yields with high enantioselectivity. Moreover, a chiral *para*-methoxy styrene derived from (*R*)-citronellal provided the corresponding aminoarylation adduct **2.26** in moderate yield but with excellent levels of regio-, and both relative and absolute stereocontrol.

To further expand the scope of this multicomponent radical cascade, different electron-rich olefins were surveyed. To our delight, aromatic vinyl amides turned out to be suitable partners providing efficient access to aryl-*α,β*-ethylenediamines. These motifs are not only present in biologically active compounds[2,45] but have also been prominently used as bidentate ligands in transition metal complexes[46,47]. Thus, *α,β*-diamine derivatives (*p*-OMe, **2.27;** *p*-Me, **2.28;** *o*-OMe, **2.29;** *o*-Me, **2.30**) were accessed in good yields and with moderate to excellent enantioselectivities. Furthermore, *α*- and *β*-methyl-substituted vinyl benzamides were

efficiently transformed into the corresponding adducts (β-Me, **2.31**-**2.33**, α-Me, **2.34**) featuring an even more sterically demanding quaternary stereocenter with perfect stereochemical information transfer. Finally, vinyl ethers could be successfully engaged in the reaction, providing access to protected α-aryl-β-aminoalcohols (**2.35**-**2.38**) in good yields with moderate to excellent enantioselectivities.

Mechanistic investigations. Having demonstrated the synthetic utility of this methodology, we focused our investigations on the underlying reaction mechanism. First, Stern-Volmer fluorescence quenching studies were performed to shed light on the potential species activated by the photocatalyst at the outset of the reaction[48]. The experiments were conducted using $[Ir[(dFCF_3)ppy]_2(dtbpy)]PF_6$ excited with light (430 nm) in the presence of the different reactants. In the case of *trans*-anethole, a decrease in fluorescence intensity was observed as a function of olefin concentration (Figure 2, top left). In sharp contrast, (*E*)-*N*-(prop-1-en-1-yl)benzamide did not quench the excited photocatalyst, even at high concentrations (see Supplementary Figures 7-12). Cyclic voltammetry of this vinylamide ($E_{1/2}$ = +1.45 V *vs* SCE in MeCN) confirmed the mismatched redox potential with respect to that of the photocatalyst ($E_{1/2}$ = +1.26 V *vs* SCE in MeCN) (see Supplementary Figure 25) [40]. Interestingly, fluorescence quenching was not observed at low concentrations of arylsulfinylamide **1a** and potassium benzoate. Increasing the concentration of either arylsulfinylamide **1a** or both **1a** and base (see Supplementary Figures 13-18) led to oxidation of the reagent[49]. A more soluble tetrabutylammonium conjugated sulfinylamide salt **3** proved to be an efficient quencher of the iridium photocatalyst (Figure 2, top right), in line with the reduction potential measured by cyclic voltammetry ($E_{1/2}$ = +0.57 V *vs* SCE in MeCN) (See Supplementary Figure 26).

These results indicate that different mechanisms might be operating at the outset of the reaction depending on the olefinic partner. In the case of electron-rich styrenes, the formation of a radical cation via single-electron oxidation can be confidently proposed as initial step of the

photocatalytic cycle. In contrast, the single-electron oxidation of the deprotonated arylsulfinylamide by the excited iridium photocatalyst to form an N-centered radical seems to be a more likely first step in the case of poorly oxidizable olefins.

To gain additional insights in the stereochemical outcome of these transformations, several control experiments as well as DFT calculations were performed using anethole derivatives as benchmark substrates. First, the standard reaction conditions were applied in three independent experiments featuring *cis*-, *trans*- and a 1:1 mixture of *cis*- and *trans*-anethole. The formation of the corresponding products was analyzed by ^{1}H-NMR (for the experimental details, see Supplementary Figure 29). In all three cases, the aminoarylation adduct **2.1** was obtained in comparable yields, with almost identical diastereo- and enantiomeric ratio. Next, and this time in the absence of arylsulfinylamide **1a**, *cis*- and *trans*-anethole were separately subjected to the standard reaction conditions and their potential isomerization[50] was monitored by ^{1}H-NMR. A plot of temporal concentration over time revealed that, after only 10 minutes, both isomers converge to a ca. 1.7:1 *cis* to *trans* ratio (see Supplementary Figures 5-6). Such photostationary state, reached at much faster regime than the aminoarylation reaction itself, suggests that both isomers will be present at the outset of the reaction, regardless of the initial alkene geometry. Upon olefin oxidation to the corresponding radical cation **II**, addition of the arylsulfinylamide **I** will proceed at the *β*-carbon atom so that the absolute configuration of the first stereogenic center is thus defined by that of the chiral sulfinyl moiety. DFT calculations revealed a low-energy transition state $\mathbf{TS_{I\text{-}III}}$ (S_S,*R*) ($\Delta G^{‡}$ = +4.8 kcal·mol^{-1}) for this step which delivers the benzylic radical **III** in a net exothermic process (ΔG = –25.2 kcal·mol^{-1}). Intermediate **III**, undergoes a 1,4-aryl shift. No radical Meisenheimer intermediate could be located along the reaction energy profile[51]. Instead, a spirocyclic transition state $\mathbf{TS_{III\text{-}IV}}$ was found to precede the exothermic formation of SO-centered radical **IV** (ΔG = –38.5 kcal·mol^{-1}). $\mathbf{TS_{III\text{-}IV}}$ can be considered an early transition state in which the new C-C bond between the benzylic radical

and the migrating aromatic group is only marginally formed ($d_{Cbn–Csp2}$ = 2.11 Å in **TS$_{III-IV}$** *vs.* $d_{Cbn–Csp2}$ = 1.52 Å in **IV**) and the S(O)–C bond is scarcely elongated ($d_{S–Csp2}$ = 1.82 Å in **TS$_{III-IV}$** *vs.* $d_{S–Csp2}$ = 1.80 Å in **III**). Formation of the minor diastereoisomer can be traced back to the generation of intermediate **III'** prior to the aryl transposition. The conformational analysis of the two intermediates suggests that the aryl translocation preferentially takes place through a trajectory in which the steric interactions between the PMP group and the methyl substituent within the anethole are minimized ($\Delta\Delta G_{III/III'}$ = +5.8 kcal·mol^{-1}). DFT calculations support the notion of the aryl migration being the rate determining step (**TS$_{III-IV}$**, $\Delta G^{‡}$ = +12.2 kcal·mol^{-1}). As a result, and regardless of any potential kinetic preference for the formation and/or subsequent reactivity of either a *Z*- or an *E*-anethole derived radical cation, the fast interconversion of **III'** into **III** by rotation along the C_α–C_β bond supports the *syn* relative configuration observed in the aminoarylation products (For additional details, see Supplementary Figure 30). The photocatalytic cycle is closed thereafter by oxidation of **IV** to **V** by Ir(II) to recover the Ir(III) catalyst. The precise fate of the sulfur-based chiral linker is challenging to assess. However, having detected bisulfite (HSO_3^-) anion using commercially available colorimetric test strips, we can confirm that sulfur (IV) species account at least in part for the SO lost[52] (for additional details, see Supplementary Figure 27). Additionally, Figure 2 shows **TS$_{I-III}$** (S_S,*S*), the alternative transition state for the enantiodetermining step in which **I** adds to the alkene radical cation **II**. **TS$_{I-III}$** (S_S,*S*) is 1.3 kcal·mol^{-1} higher in energy compared to **TS$_{I-III}$** (S_S,*R*), which rationalizes the absolute configuration observed in the aminoarylation products.

Conclusion. Here we describe an asymmetric intermolecular aminoarylation of alkenes. A photoredox-mediated radical cascade capitalizes on a chiral *all-in-one* arylsulfinylamide reagent featuring a traceless chiral auxiliary to forge two vicinal Csp^3–Csp^2 and Csp^3–N bonds across the π-system in a stereocontrolled manner. Mechanistic investigations revealed the

likelihood of multiple reaction pathways operating in these transformations. In the case of electron-rich styrenes, the formation of a radical cation via single-electron oxidation can be confidently proposed at the outset of the reaction. In contrast, the single-electron oxidation of the deprotonated arylsulfinylamide by the excited iridium photocatalyst to form an N-centered radical seems favored in the case of poorly oxidizable olefins. The C–N bond formation is stereocontrolled by the chirality of the sulfoxide, whereas the subsequent transposition of the aromatic ring with concomitant elimination of the sulfinyl tether proceeds in a highly diastereoselective manner governed by steric factors. β,β-Diarylethylamines, aryl-α,β-ethylenediamines and α-aryl-β-aminoalcohols ubiquitous motifs in bioactive molecules as well as in bidentate transition metal ligands, are obtained herein with very high levels of regio- and both, relative and absolute stereocontrol, thus highlighting the synthetic utility of this methodology.

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Author contributions

C. H., M. S. K., Y. H. and S. C. G. performed the experiments. E. M. performed DFT calculations. C. H., M. S. K., E. M. and C. N. analyzed the data and co-wrote the manuscript. E. M. and C. N. conceptualized and supervised the project.

Competing interests

The authors declare no competing interests.

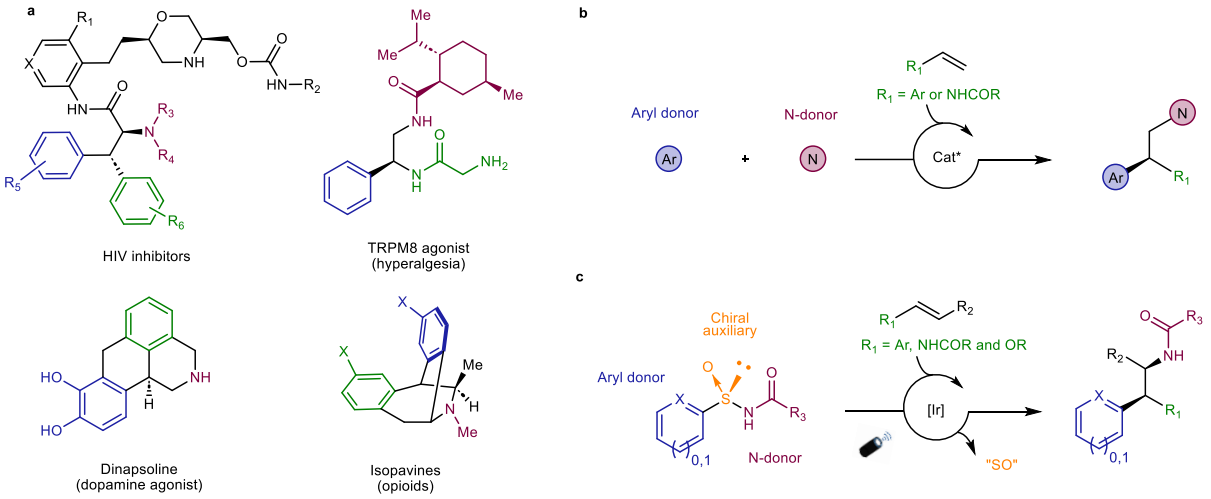
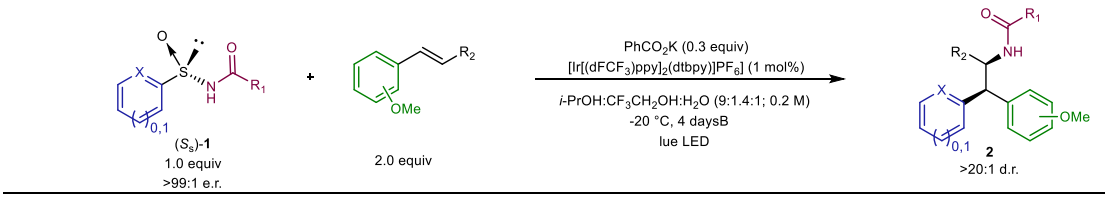
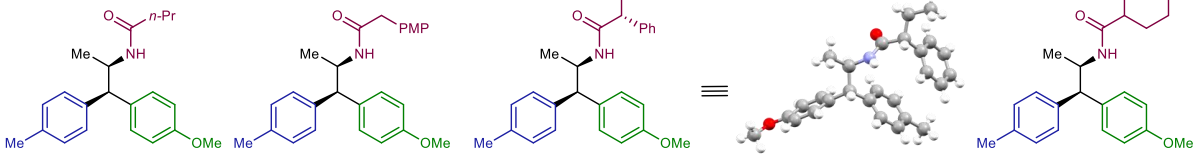


Figure 1 | Relevance of *β*–arylethylamine motifs and strategies towards their asymmetric assembly. a, Examples of bioactive compounds featuring *β*-arylethylamines. **b**, Previous examples of asymmetric three-component intermolecular alkene aminoarylations to attain *β*–arylethylamines (refs 38-39). Reactions are limited to the utilization of a single class of terminal olefins: either styrenes (R^1 = Ar) or vinyl amides (R^1 = NHCOR) and thus, to the generation of a single stereogenic center. *N*-fluoro-*N*-methylsulfonamides (NFAS) and *O*-acyl hydroxylmethylamine were used as N-atom donors providing access, exclusively, to *N*–Me tertiary amine products. **c**, This work describes an asymmetric intermolecular alkene aminoarylation using arylsulfinylamides as multifunctional *all-in-one* reagents featuring a traceless chiral auxiliary. The reaction tolerates a wide variety of N-atom donors and is compatible with both 1,2-disubstituted styrenes, vinyl amides and vinyl ethers thus providing access to valuable *β,β*-diarylethylamines, aryl-*α,β*-ethylenediamines and *α*-aryl-*β*-aminoalcohols. Excellent levels of both relative and absolute stereocontrol are achieved in the two newly forged stereogenic centers governed by the configuration of the chiral sulfoxide tether. Characterization of the reaction mechanism revealed an interesting dichotomy in the initiation of the photoredox catalytic cycle wherein either electron-rich alkenes or sulfinylamides are preferentially activated at the expense of the Ir photocatalyst.

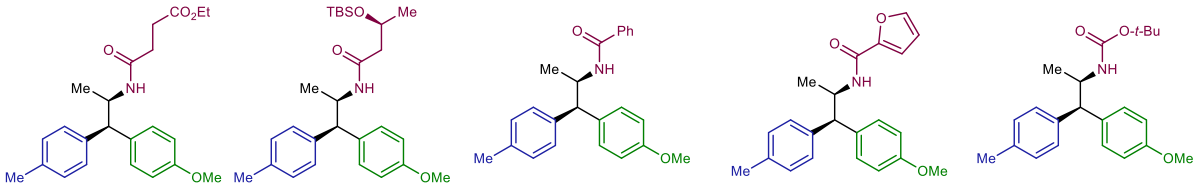
Table. 1 | Arylsulfinylamide scope of the intermolecular aminoarylation of styrenes.



N-donor

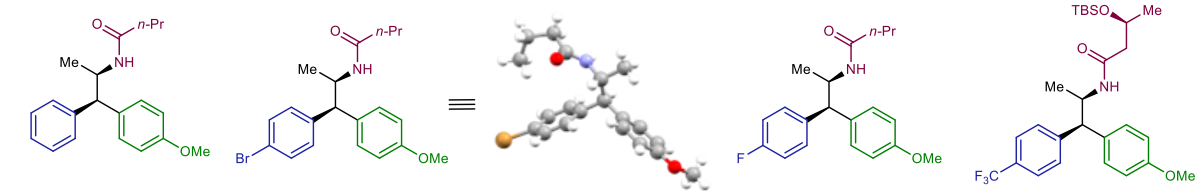


(1*R*,2*R*)-**2.1** 83%, >99:1 e.r. (1*R*,2*R*)-**2.2,** 81%, 97:3 e.r. (1*R*,2*R*)-**2.3,** 74%, 99:1 d.r. (1*R*,2*R*)-**2.4,** 77%, 92:8 e.r.

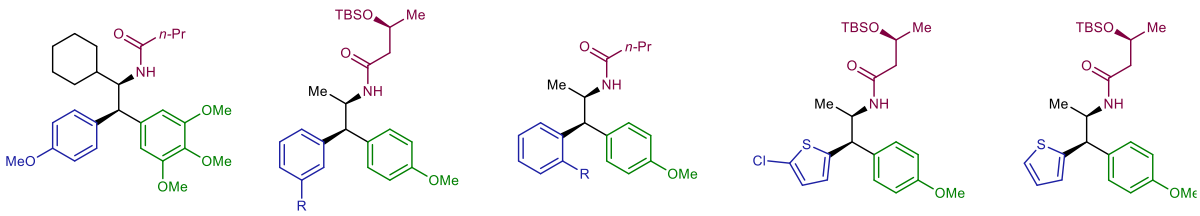


(1*R*,2*R*)-**2.5,** 80%, 99:1 e.r. (1*R*,2*R*)-**2.6,** 76%, 99:1 d.r. (1*R*,2*R*)-**2.7,** 87%, 99:1 e.r. (1*R*,2*R*)-**2.8,** 68%, 99:1 e.r. (1*R*,2*R*)-**2.9,** 76%, 94:6 e.r.

Aryl donor (Ar)



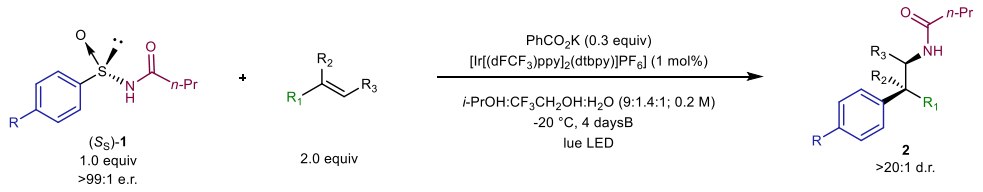
(1*R*,2*R*)-**2.10,** 80%, 95:5 e.r. (1*S*,2*R*)-**2.11,** 75%, 99:1 e.r. (1*S*,2*R*)-**2.12,** 61%, 97:3 e.r. (1*R*,2*R*)-**2.13,** 58%, 97:3 d.r



(1*R*,2*R*)-**2.14,** 57%, 99:1 e.r. (1*S*,2*R*)-**2.15,** (R = OMe), 69%, 92:8 d.r. (1*S*,2*R*)-**2.16,** (R = Br),59%, 91:9 d.r. (1*S*,2*R*)-**2.17,** (R = Me), 67%, >99:1 e.r. (1*S*,2*R*)-**2.18,** (R = Br), 68%, >99:1 e.r. (1*R*,2*R*)-**2.19,** 71%, 99:1 d.r. (1*R*,2*R*)-**2.20,** 58%, 99:1 d.r.

Notes: unless otherwise noted, reactions were carried out under the standard conditions; full conversion of the starting material was observed and yields are reported after purification by column chromatography in silica gel; all compounds were obtained with >20:1 d.r.; the d.r. and e.r. values were determined by ^{1}H-NMR of the crude reaction mixture and by chiral stationary high-performance liquid chromatography (HPLC) of the isolated products, respectively. *n*-Pr, *n*-propyl; PMP, *p*-methoxyphenyl; Ph, phenyl; TBS, *t*-butyldimethylsilyl; *t*-Bu, *t*-butyl; d.r., diastereomeric ratio; e.r., enantiomeric ratio.

Table. 2 | Scope of the alkene partner for the intermolecular aminoarylation with arylsulfinylamide (*Ss*)-1.

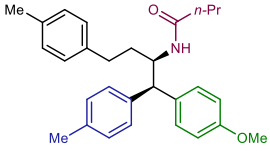


(S_S)-**1**
1.0 equiv
>99:1 e.r.

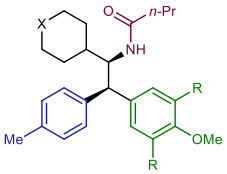
2.0 equiv

2
>20:1 d.r.

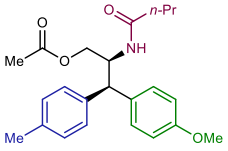
Styrene partners



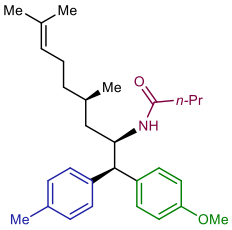
(1*R*,2*R*)-**2.21**, 65%, 95:5 e.r.



(1*R*,2*R*)-**2.22,** (X = C, R = H), 59%[a], 94:6 e.r.
(1*R*,2*R*)-**2.23,** (X = C, R = OMe),47%[a], 96:4 e.r.
(1*R*,2*R*)-**2.24,** (X = O, R = H),61%[a], 98:2 e.r.

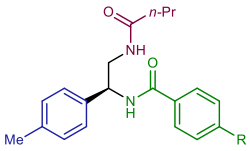


(2*S*,3*R*)-**2.25,** 52%, 96:4 e.r.

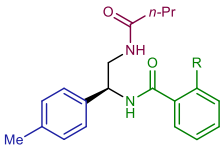


(2*S*,3*R*)-**2.26,** 44%, 99:1 d.r.

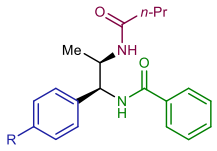
Vinyl amides partners



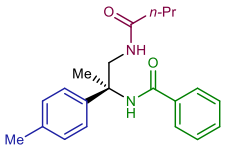
(*S*)-**2.27**, (R = OMe), 71%[a] 81:19 e.r.
(*S*)-**2.28,**(R = Me),65%[a], >99:1 e.r.



(*S*)-**2.29,** (R = OMe), 65%[a], 79:21 e.r.
(*S*)-**2.30,** (R = Me), 59%[a] 85:25 e.r.
(96:4 e.r. after recryst.)

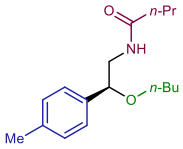


(1*S*,2*R*)-**2.31,** (R = H), 49%[a], 98:2 e.r.
(1*S*,2*R*)-**2.32,** (R = Me), 61%[a], 98:2 e.r.
(1*S*,2*R*)-**2.33,** (R = OMe), 76%[a], 94:6 e.r.

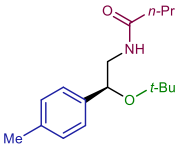


(*S*)-**2.34,** 69%[a], 99:1 e.r.

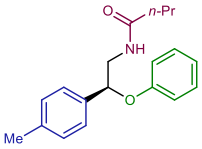
Vinyl ethers partners



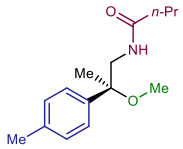
(*S*)-**2.35,** 63%[a], 88:12 e.r.



(*S*)-**2.36,** 57%[a], 90:10 e.r.



(*S*)-**2.37,** 76%[a], 79:21 e.r.



(*S*)-**2.38,** 69%[a], 98:2 e.r.

Notes: unless otherwise noted, reactions were carried out under the standard conditions; full conversion of the starting material was observed and yields are reported after purification by column chromatography in silica gel; all compounds were obtained with >20:1 d.r.; the d.r. and e.r. values were determined by ^{1}H-NMR of the crude reaction mixture and by chiral stationary high-performance liquid chromatography (HPLC) of the isolated products, respectively. [a] 5 mol% of [Ir[(dFCF$_3$)ppy]$_2$(dtbpy)]PF$_6$] at 0 °C. *n*-Pr, *n*-propyl; *n*-Bu, *n*-butyl; *t*-Bu, *tert*-butyl; d.r., diastereomeric ratio; e.r., enantiomeric ratio.

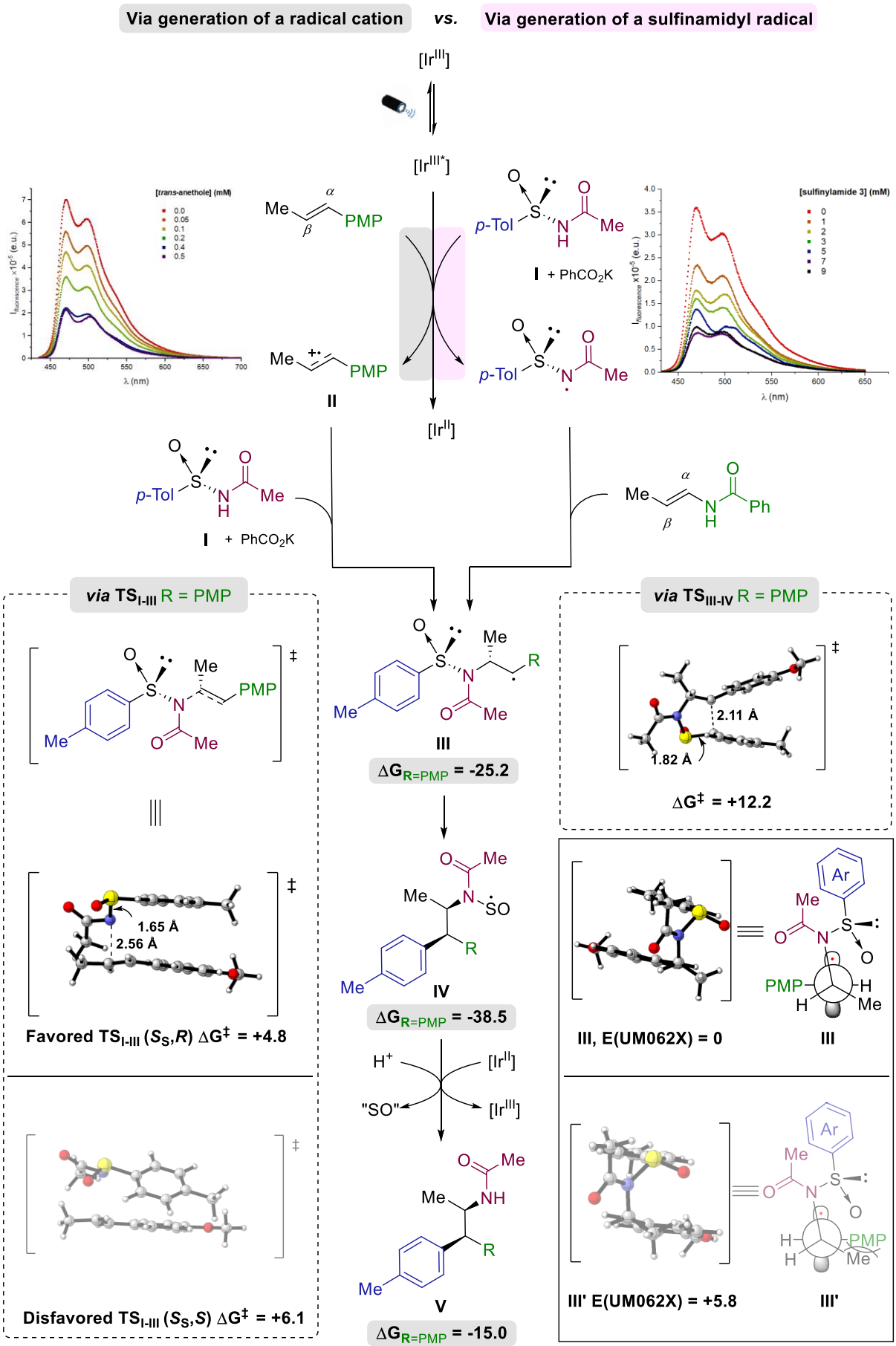


Figure 2 | Mechanistic studies and proposed reaction mechanism. Results of Stern−Volmer experiments using *trans*-anethole (top, left) and arylsulfinylamide **3** (top, right) as a quenchers. Proposed reaction mechanism featuring two different initiation pathways: formation of a radical cation for electron-rich olefins (grey) vs. formation of an amidyl radical in the case of vinylamide acceptors (pink). DFT calculations were performed on *trans*-anethole as benchmark substrate. Optimized transition states, relevant structural parameters, starting materials, products, reaction intermediates and transition states were computed at the M062X/6-31+G(d,p) level (IEFPCM: integral equation formalism with the polarizable continuum model), solvent = 2-propanol at −20 ºC (R = PMP). Energies are given in kcal·mol^{-1}. For further details, see Supplementary section 'DFT calculations'. **TS$_{\mathbf{I\text{-}III}}$** (S_S,*R*) visualizes the enantiodetermining step in which **I** adds to the alkene radical cation **II** in line with the absolute configuration observed in the aminoarylation products. The alternative **TS$_{\mathbf{I\text{-}III}}$** (S_S,*S*), is 1.3 kcal·mol^{-1} higher in energy compared to **TS$_{\mathbf{I\text{-}III}}$** (S_S,*R*). Conformations calculated for intermediate **III** and **III'**: conformer yielding the minor isomer is disfavored by steric factors: the PMP group adopts an unfavorable *syn*-periplanar disposition with the methyl group, unlike the case of the major diastereomer experimentally obtained, in which these groups exhibit a less sterically demanding *anti*-periplanar geometry. PMP, *p*-methoxyphenyl, *p*-Tol, *p*-methylphenyl.

References

1. McCauley, J. A. *et al.* HIV protease inhibitors. Wiscount, M. WO 2014043019 A1, (2014).
2. González-Muñiz, R., Bonache, M. A., Martín-Escura, C. & Gómez-Monterrey, I. Recent Progress in TRPM8 Modulation: An Update. *Int. J. Mol. Sci.* **20,** 2618 (2019).
3. Sverrisdóttir, E. *et al.* A review of morphine and morphine-6-glucuronide's pharmacokinetic–pharmacodynamic relationships in experimental and clinical pain. *Eur. J. Pharm. Sci*. **74**, 45–62 (2015).
4. Hanessian, S., Parthasarathy, S. & Mauduit, M. The power of visual imagery in drug design. Isopavines as a new class of morphinomimetics and their human opioid receptor binding activity. *J. Med. Chem.* **46**, 34–48 (2003).
5. Zhang, A., Neumeyer, J. L., & Baldessarini, R. J. Recent progress in development of dopamine receptor subtype-selective agents: potential therapeutics for neurological and psychiatric disorders. *Chem. Rev*. **107**, 274–302 (2007).
6. Wang, Z.-Q., Feng, C.-G., Zhang, S.-S., Xu, M.-H. & Lin, G.-Q. Rhodium-catalyzed asymmetric conjugate addition of organoboronic acids to nitroalkenes using chiral bicyclo[3.3.0] diene ligands. *Angew. Chem. Int. Ed*. **49**, 5780–5783 (2010).
7. He, F.-S. *et al.* Direct asymmetric synthesis of *β*-bis-aryl-*α*-amino acid esters via enantioselective copper-catalyzed addition of *p*-quinone methides. *ACS Catal.* **6**, 652−656 (2016).
8. Li, W. *et al.* Enantioselective organocatalytic 1,6-addition of azlactones to *para*-quinone methides: an access to *α,α*-disubstituted and *β,β*-diaryl-*α*-amino acid esters. *Org. Lett.* **20**, 1142−1145 (2018).
9. Nishino, S., Miura, M., & Hirano, K. An umpolung-enabled copper-catalysed regioselective hydroamination approach to *α*-amino acids. *Chem. Sci.* **12,** 11525–11537 (2021).
10. Röben, C., Souto, J. A., González, Y., Lishchynskyi, A. & Muñiz, K. Enantioselective metal-free diamination of styrenes. *Angew. Chem. Int. Ed.* **50**, 9478–9482 (2011).
11. Molinaro, C. *et al.* Catalytic, asymmetric, and stereodivergent synthesis of non-symmetric *β,β*-diaryl-*α*-amino acids. *J. Am. Chem. Soc.* **137**, 999−1006 (2015).
12. Gao, W. *et al.* Nickel-catalyzed asymmetric hydrogenation of *β*-acylamino nitroolefins: an efficient approach to chiral amines. *Chem. Sci.* **8,** 6419–6422 (2017).
13. Valdez, S. C. & Leighton, J. L. Tandem asymmetric aza-Darzens/ring-opening reactions: dual functionality from the silane Lewis acid. *J. Am. Chem. Soc*. **131**, 14638–14639 (2009).
14. Takeda, Y., Ikeda, Y., Kuroda, A., Tanaka, S. & Minakata, S. Pd/NHC-catalyzed enantiospecific and regioselective Suzuki-Miyaura arylation of 2-arylaziridines: synthesis of enantioenriched 2-arylphenethylamine derivatives. *J. Am. Chem. Soc*. **136**, 8544−8547 (2014).
15. Chai, Z. *et al.* Synthesis of chiral vicinal diamines by silver(I)-catalyzed enantioselective aminolysis of N-tosylaziridines. *Angew. Chem. Int. Ed.* **56,** 650–654 (2017).
16. Gómez-Arrayás, R. & Carretero, J. C. Catalytic asymmetric direct Mannich reaction: a powerful tool for the synthesis of α,β-diamino acids. *Chem. Soc. Rev.* **38,** 1940–1948 (2009).

17. White, D. R., Hutt, J. T. & Wolfe, J. P. Asymmetric Pd-catalyzed alkene carboamination reactions for the synthesis of 2-aminoindane derivatives. *J. Am. Chem. Soc.* **137**, 11246–11249 (2015).

18. Ozols, K., Onodera, S., Woz´niak, L. & Cramer, N. Cobalt(III)-catalyzed enantioselective intermolecular carboamination by C-H functionalization. *Angew. Chem. Int. Ed.* **60**, 655–659 (2021).

19. Schultz, D. M. & Wolfe, J. P. Recent developments in Pd-catalyzed alkene aminoarylation reactions for the synthesis of nitrogen heterocycles. *Synthesis* **44**, 351–361 (2012).

20. Zhang, W., Chen, P. & Liu, G. Enantioselective palladium(II)-catalyzed intramolecular aminoarylation of alkenes by dual N-H and aryl C-H bond cleavage. *Angew. Chem. Int. Ed*. **56**, 5336–5340 (2017).

21. Jiang, H. & Studer, A. Intermolecular radical carboamination of alkenes. *Chem. Soc. Rev.* **49**, 1790–1811 (2020).

22. Moon, Y. *et al.* Visible light induced alkene aminopyridylation using N-aminopyridinium salts as bifunctional reagents. *Nat. Commun.* **10**, 4117 (2019).

23. Jiang, H., Yu, X., Daniliuc, C. G. & Studer A. Three-component aminoarylation of electron-rich alkenes by merging photoredox with nickel catalysis. *Angew. Chem. Int. Ed.* **60**, 14399–14404 (2021).

24. Muñoz-Molina, J. M., Belderrain, T. R. & Pérez, P. J. Copper-catalysed radical reactions of alkenes, alkynes and cyclopropanes with N–F reagents. *Org. Biomol. Chem*. **18**, 8757–8770 (2020).

25. Liu, Z. & Liu, Z.-Q. An intermolecular azidoheteroarylation of simple alkenes via free radical multicomponent cascade reactions. *Org. Lett*. **19**, 5649−5652 (2017).

26. Hari, D. P., Hering, T. & König, B. The photoredox-catalyzed Meerwein addition reaction: intermolecular amino-arylation of alkenes. *Angew. Chem. Int. Ed.* **53**, 725–728 (2014).

27. Fumagalli, G., Boyd, S. & Greaney, M. F. Oxyarylation and aminoarylation of styrenes using photoredox catalysis. *Org. Lett.* **15**, 4398–4401 (2013).

28. Brenzovich, W. E. *et al.* Gold-catalyzed intramolecular aminoarylation of alkenes: C-C bond formation through bimolecular reductive elimination. *Angew. Chem. Int. Ed.* **49**, 5519–5522 (2010).

29. Sahoo, B., Hopkinson, M. N. & Glorius, F. Combining gold and photoredox catalysis: visible light-mediated oxy- and aminoarylation of alkenes. *J. Am. Chem. Soc.* **135**, 5505–5508 (2013).

30. Tathe, A. G. *et al*. Gold-catalyzed 1,2-aminoarylation of alkenes with external amines. *ACS Catal.* **11**, 4576−4582 (2021).

31. Lee. S & Rovis. T. Rh(III)-catalyzed three-component *syn*-carboamination of alkenes using arylboronic acids and dioxazolones. *ACS Catal*. **11**, 8585−8590 (2021).

32. Liu, Z. *et al.* Catalytic intermolecular carboamination of unactivated alkenes via directed aminopalladation. *J. Am. Chem. Soc*. **139**, 11261−11270 (2017).

33. Hajra, S., Maji, B. & Mal, D. A catalytic and enantioselective synthesis of *trans*-2-amino-1-aryltetralins. *Adv. Synth. Catal.* **351**, 859–864 (2009).

34. Akhtar, S. M. S., Bar, S. & Hajra. S. Asymmetric aminoarylation for the synthesis of *trans*-3-amino-4-aryltetrahydroquinolines: an access to aza-analogue of dihydrexidine. *Tetrahedron* **103**, 132257 (2021).

35. Kwon, Y. & Wang, Q. Recent advances in 1,2-amino(hetero)arylation of alkenes. *Chem. Asian J.* **17,** e202200215 (2022).

36. Ye, B. & Cramer, N. Chiral cyclopentadienyl ligands as stereocontrolling element in asymmetric C–H functionalization. *Science* **338**, 504–506 (2012).

37. Bizet, V., Borrajo-Calleja, G., Besnard, C. & Mazet, C. Direct access to furoindolines by palladium-catalyzed intermolecular carboamination. *ACS Catal.* **6**, 7183−7187 (2016).

38. Wang, D. *et al.* Asymmetric copper-catalyzed intermolecular aminoarylation of styrenes: efficient access to optical 2,2-diarylethylamines. *J. Am. Chem. Soc*. **139**, 6811−6814 (2017).

39. Zheng, D. & Studer, A. Asymmetric synthesis of heterocyclic γ-amino-acid and diamine derivatives by three-component radical cascade reactions. *Angew. Chem. Int. Ed.* **58**, 15803–15807 (2019).

40. Monos, T. M., McAtee, R. C. & Stephenson, C. R. J. Arylsulfonylacetamides as bifunctional reagents for alkene aminoarylation. *Science* **361**, 1369–1373 (2018).

41. Allen, A. R. *et al*. Mechanism of visible light-mediated alkene aminoarylation with arylsulfonylacetamides. *ACS Catal*. **12**, 8511-8526 (2022).

42. Noten, E., Ng, C., Wolesensky, R. & Stephenson, C. R. J. A general alkene aminoarylation enabled by N-centered radical reactivity of sulfinamides. ChemRxiv. Cambridge: Cambridge Open Engage (2022) This content is a preprint and has not been peer-reviewed.

43. Allen, A. R., Noten, E. A & Stephenson, C. R. J. Aryl transfer strategies mediated by photoinduced electron transfer. *Chem. Rev.* **122**, 2695–2751 (2022).

44. Hervieu, C. *et al.* Asymmetric, visible light-mediated radical sulfinyl-Smiles rearrangement to access all-carbon quaternary stereocentres. *Nat. Chem.* **13,** 327–334 (2021).

45. Desai, M. C., Lefkowitz, S. L., Bryce, D. K. & McLean, S. Articulating a pharmacophore driven synthetic strategy: discovery of a potent substance P antagonist. *Bioorg. Med. Chem. Lett.* **4**, 1865–1868 (1994).

46. Saito, B. & Fu, G. C. Enantioselective alkyl-alkyl Suzuki cross-couplings of unactivated homobenzylic halides. *J. Am. Chem. Soc*. **130**, 6694–6695 (2008).

47. Zhang, B., Wang, H., Lin, G.-Q. & Xu, M.-H. Ruthenium(II)-catalyzed asymmetric transfer hydrogenation using unsymmetrical vicinal diamine-based ligands: dramatic substituent effect on catalyst efficiency. *Eur. J. Org. Chem.* 4205–4211 (2011).

48. Gehlen, M. H. The centenary of the Stern-Volmer equation of fluorescence quenching: from the single line plot to the SV quenching map. *J. Photochem. Photobiol. C: Photochem. Rev.* **42**,100338 (2019).

49. Cismesia, M. A. & Yoon, T. P. Characterizing chain processes in visible light photoredox catalysis. *Chem. Sci.* **6,** 5426–5434 (2015).

50. Neveselý, T., Wienhold, M., Molloy, J. J. & Gilmour, R. Advances in the E → Z isomerization of alkenes using small molecule photocatalysts. *Chem. Rev.* **122,** 2650–2694 (2022).

51. Okada, K. & Sekiguchi, S. Aromatic nucleophilic substitution. 9. Kinetics of the formation and decomposition of anionic σ complexes in the Smiles rearrangements of *N*-acetyl-β-aminoethyl 2-X-4-nitro-1-phenyl or *N*-acetyl-β-aminoethyl 5-nitro-2-pyridyl ethers in aqueous dimethyl sulfoxide. *J. Org. Chem.* **43,** 441–447 (1978).

52. Herron, J. T. & Huie, R. E. Rate constants at 298 K for the reactions SO+SO+M→$(SO)_2$+M AND SO+$(SO)_2$→SO_2+S_2O. *Chem. Phys. Lett.* **76,** 322–324 (1980).

Methods

To an oven-dried Schlenk tube (5 mL) the corresponding arylsulfinylamide (0.1 mmol, 1 equiv), $PhCO_2K$ (4.8 mg, 0.03 mmol, 0.3 equiv), and $Ir[(dFCF_3)ppy]_2(dtbpy)]PF_6$ (1.1 mg, 0.001 mmol, 1 mol%) were sequentially added under a flow of nitrogen. The flask was evacuated and then backfilled with N_2 (three times). Trifluoroethanol (72 μL) and *i*-PrOH : H_2O (0.5 mL, 9:1 (v:v)) were then added to the reaction mixture followed by the olefin (0.2 mmol, 2.0 equiv). The reaction was sparged with argon for 15 min. The Schlenk tube was placed in the photo-reactor and stirred at 1400 rpm under blue light irradiation (EvoluChem 30W, HCK1012-01-008) at -20°C. After 4 days, the reaction mixture was diluted with ethyl acetate (10 mL) and transferred into a separatory funnel. The mixture was washed with a 5 wt% aqueous LiCl solution (3 x 10 mL). The organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography using a mixture of ethyl acetate and *n*-hexane.

Data availability

Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2270374 (**1s'**), 2212927 (**2.3**) and 2212932 (**2.11**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.