Chiral arylsulfinylamides: *all-in-one* reagents for visible light-mediated asymmetric alkene aminoarylations

Cédric Hervieu[1], Mariia S. Kirillova[1], Yawen Hu[1], Sergio Cuesta-Galisteo[1], Estíbaliz Merino[2,3]*, Cristina Nevado[1]*.

[1]Department of Chemistry, University of Zurich, Winterthurerstrasse 190, CH 8057 Zurich, Switzerland.

[2]Universidad de Alcalá, Departamento de Química Orgánica y Química Inorgánica, Instituto de Investigación Andrés M. del Río (IQAR), Facultad de Farmacia, 28805, Alcalá de Henares, Madrid, Spain.

[3]Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Ctra. de Colmenar Viejo, Km. 9.100, 28034, Madrid, Spain.

*E-mail: estibaliz.merino@uah.es, cristina.nevado@chem.uzh.ch

Abstract

Two- or one-electron mediated alkene aminoarylations represent straightforward approaches to assemble molecular complexity by the simultaneous formation of two contiguous Csp^3-Csp^2/Csp^3-N 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 the corresponding aminoarylation adducts in a single operation. The sulfinyl group acts here as a traceless chiral auxiliary and is eliminated *in situ* under the reaction conditions. Optically pure β,β-diarylethyl- and aryl-α,β-ethylenediamines, prominent motifs in pharmaceuticals and bioactive natural products, are obtained 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. Cyanogenic glucosides, glucosinolates, natural and non-natural peptides, alkaloids and amines are representative examples of relevant bioactive compounds featuring N-containing motifs. Non-symmetrical *β,β*-diarylethylamines represent a prominent pharmacophore commonly found in drug candidates including HIV inhibitors[1], opioids[2,3] and endogenous neurotransmitters[4] (Fig.1a). *R*-(+)-Dinapsoline, a selective and efficient D_1 dopamine agonist[4] was found to be 161-fold more potent than its *S*-(-)-enantiomer, highlighting why access to these motifs in enantiomerically pure form is crucial, not only for accurate target engagement studies, but also for the optimization of their pharmacological profiles.

Conventional strategies towards the asymmetric construction of *β,β*-diarylethylamines rely on multistep sequences including conjugate additions[5-8], enamine hydrogenations[9] or ring opening[10-11] reactions. Two- or one-electron mediated alkene aminoarylations represent a powerful, atom-economic alternative, as two new C-C and C-N bonds are forged in a single operation[12-16]. Despite the intrinsic potential to impart both, relative and absolute stereocontrol in the newly formed stereocenters[17], asymmetric variants of these transformations, especially in intermolecular settings, are extremely scarce. Among the reported polar[18-21] and radical[22-29] mediated processes, only a handful of examples capitalizing on styrene derivatives as starting materials enabled the synthesis of optically pure *β,β*-diarylethylamines. Seminal work by Hajra et al showcased a two-electron Cu-catalyzed olefin aziridination/intramolecular Friedel–Craft reaction to produce *trans*-2-aminoaryltetralins in up to 96:4 e.r.[30,31] (Fig. 1b, left).

Later, Liu's group devised 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 yielding *β,β*-diarylethylamines with excellent levels of absolute

stereocontrol (Fig. 1b, right)[32]. Notwithstanding their undisputable synthetic utility, limitations regarding both, the type of Nitrogen donors and the olefinic partners (reactions are exclusively applicable to 2-arylethylstyrene or terminal styrenes, respectively), have fostered the quest for alternative, more flexible strategies in this context.

In 2018, Stephenson et al reported the use of arylsulfonylacetamides as bifunctional reagents in a light-mediated[33,34], non-asymmetric intermolecular radical aminoarylation of alkenes featuring an intramolecular 1,4-migration of the aromatic group[35]. Recently, our group described an asymmetric variant of a radical Truce-Smiles rearrangement exploiting the ability of chiral *N*-sulfinyl moieties to impart absolute stereocontrol in the challenging assembly of all-C quaternary centers[36]. Inspired by these results, we set out to develop a multifunctional reagent able to forge, regioselectively, two new Csp^3-Csp^2 and Csp^3-N bonds across the π-system controlling both relative and absolute stereochemistry by means of a traceless chiral auxiliary. Here, for the first time, enantioenriched arylsulfinylamides are applied as atom-economic, *all-in-one* reagents in the asymmetric intermolecular aminoarylation of alkenes. Nucleophilic addition of the nitrogen atom onto a photochemically generated styrene radical cation furnishes a benzylic C-radical intermediate which, upon translocation of the aromatic ring, delivers *β,β*–diarylethylamines with excellent levels of both regio- and stereocontrol. The protocol could be extended to vinyl amides as radical acceptors, thus providing access to enantiomerically enriched aryl-*α,β*-ethylenediamines. The excellent regio-, diastereo- and enantioselectivity, combined with mild reaction conditions and broad functional group tolerance, highlight both the generality and synthetic utility of these transformations.

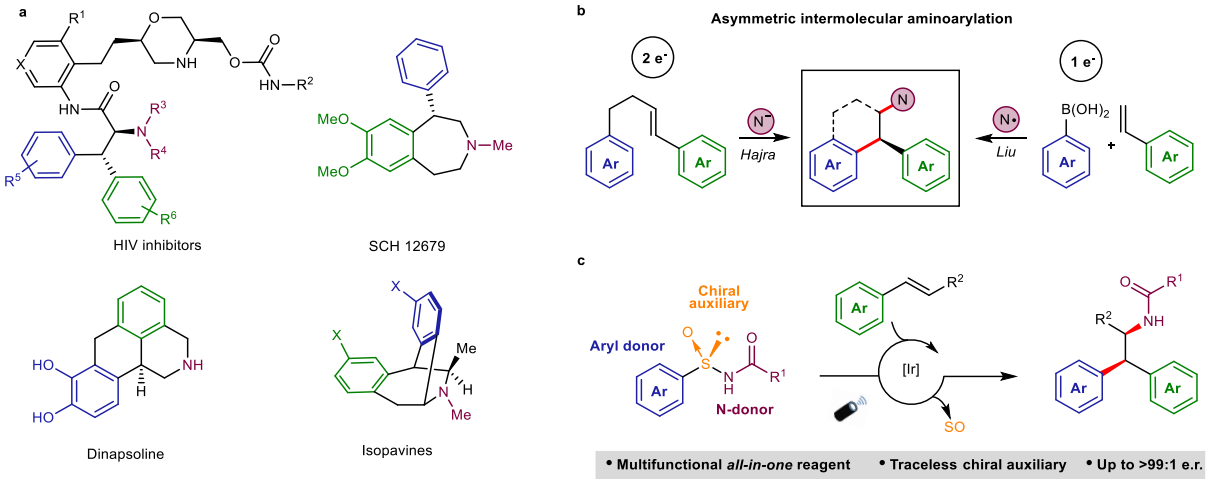


Fig. 1 | Strategies towards the synthesis of *β,β*-diarylethylamines. a, Examples of bioactive compounds featuring *β,β*-diarylethylamines. **b**, Two- and one-electron asymmetric intermolecular alkene aminoarylation strategies. **c**, This work: Asymmetric intermolecular aminoarylation of olefins using arylsulfinylamides as *all-in-one* reagents featuring a traceless chiral auxiliary.

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 **2a** 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 **2a** in an improved 83% yield with almost perfect levels of both relative and absolute stereocontrol (>20:1 d.r.; >99:1 e.r.). Additional control 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 structural diversity 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 an aromatic substituent at the *α*-carbon were efficiently transformed into the desired *β,β*-diarylethylamines **2b** and **2c** with excellent levels of regio-, and stereocontrol (Fig.2). Sterically demanding groups (e.g. cyclohexyl), as well as more reactive functionalities (e.g. esters, silylethers) were also compatible with the standard reaction conditions furnishing the corresponding adducts (Cy, **2d**; CO_2Et, **2e**; TBSO, **2f**) in good yields and with remarkable diastero- and enantioselectivities. Furthermore, successful incorporation of aromatic and heteroaromatic substituted amides and even *tert*-butyl carbamate derivatives (**2g**–**2i**) emphasizes the functional group compatibility of the method.

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 **2j** 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 (**2k**–**2n**) in good yields with outstanding levels of sterocontrol. *meta*-Methoxy and *meta*-bromo derivatives also delivered the desired products (*m*-OMe, **2o**; *m*-Br, **2p**) although with slightly lower enantiomeric excess. In contrast, more sterically hindered substrates bearing *ortho*-substituted aromatic rings (*o*-Me, **2q**; *o*-Br, **2r**) were obtained with excellent enantioselectivities.

X-ray crystallographic analysis of compounds **2c** and **2k** confirmed the *syn* addition of the N-atom and the arene across the π-system. Adduct **2k**, 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 though, that the substitution pattern in the aromatic ring affects the priority of the groups at the new

asymmetric carbon atom. As a result, the (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*)-**2a'** could be obtained in similar yield and enantiomeric ratio (for the experimental details, see Supplementary Fig. 12).

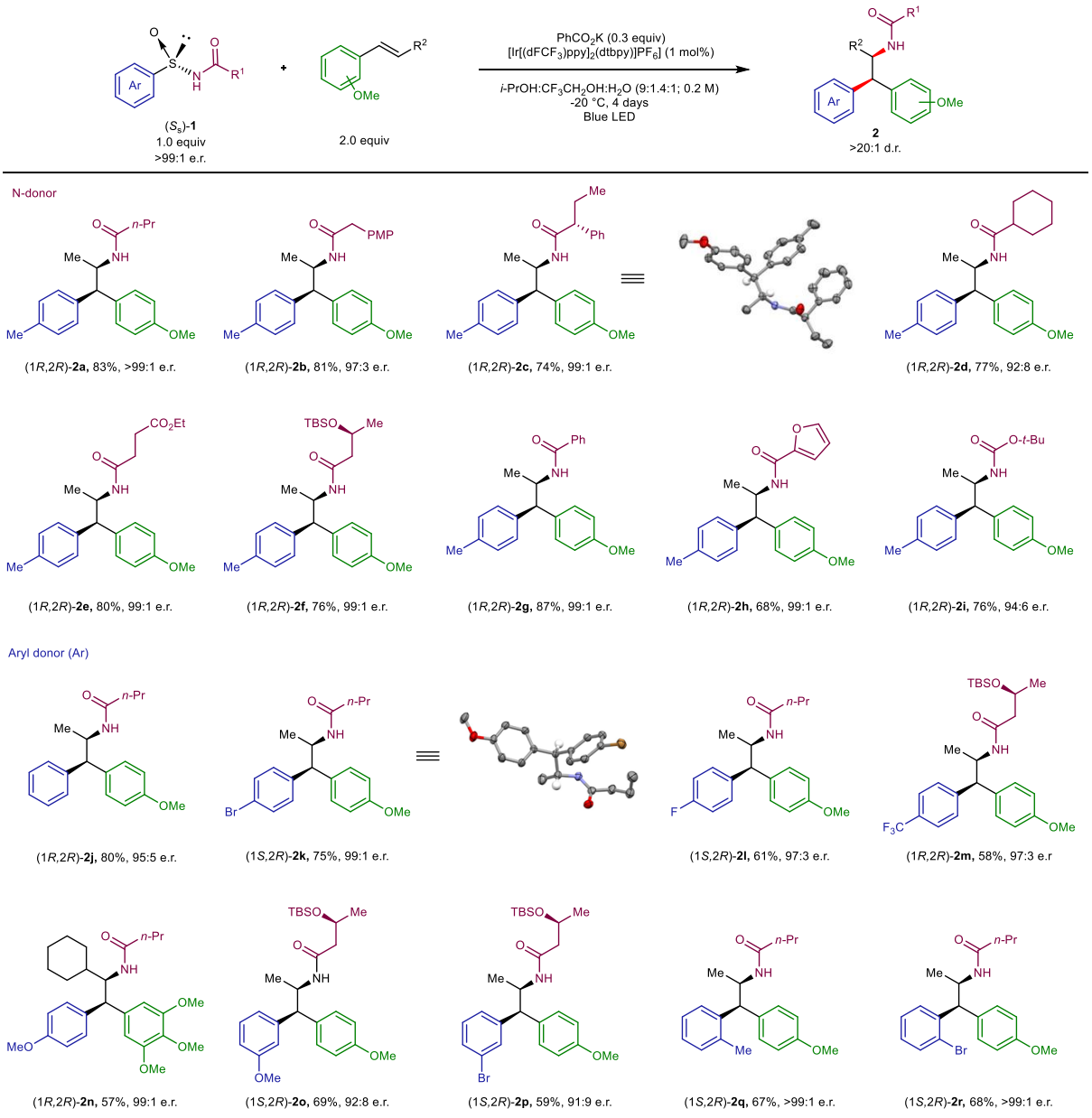


Fig. 2 | Arylsulfinylamide scope of the intermolecular aminoarylation. Notes: unless otherwise noted, reactions were carried out under the standard conditions; full conversion of the starting material was observed and yields are reported after purification by column chromatography in silica gel; all 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. *n*-Pr, *n*-propyl; PMP, *p*-

methoxyphenyl; TBS, *t*-butyldimethylsilyl; *t*-Bu, *t*-butyl; d.r., diastereomeric ratio; e.r., enantiomeric ratio.

The compatibility of the reaction between (S_S)-*N*-(*p*-tolylsulfinyl)butyramide **1a** with different styrene partners was also explored (Fig.3). While simple styrenes (R^3 = H) were not competent substrates, phenethyl, cyclohexyl, 4-tetrahydropyrane and carbinyl acetate groups at the terminal position of the double bond were effectively accommodated in the aminoarylation process. The corresponding β,β-diarylethylamines (**2s-2w**) were obtained in moderate to good yields with high enantioselectivity.

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[37] but have also been prominently used as bidentate ligands in transition metal complexes[38,39]. Unlike terminal styrenes, unsubstituted vinyl amides bearing electron-donating groups at the *para* and *ortho* positions of the aromatic ring smoothly underwent the corresponding difunctionalization reaction, delivering the desired α,β-diamine derivatives (*p*-OMe, **2x;** *p*-Me, **2y;** *o*-OMe, **2z;** *o*-Me, **2aa**) in good yields and with moderate to excellent enantioselectivities. Finally, α- and β-methyl-substituted vinyl benzamides were efficiently transformed into the corresponding adducts (β-Me, **2ab**, α-Me, **2ac**) featuring an even more sterically demanding quaternary stereocenter with perfect stereochemical information transfer.

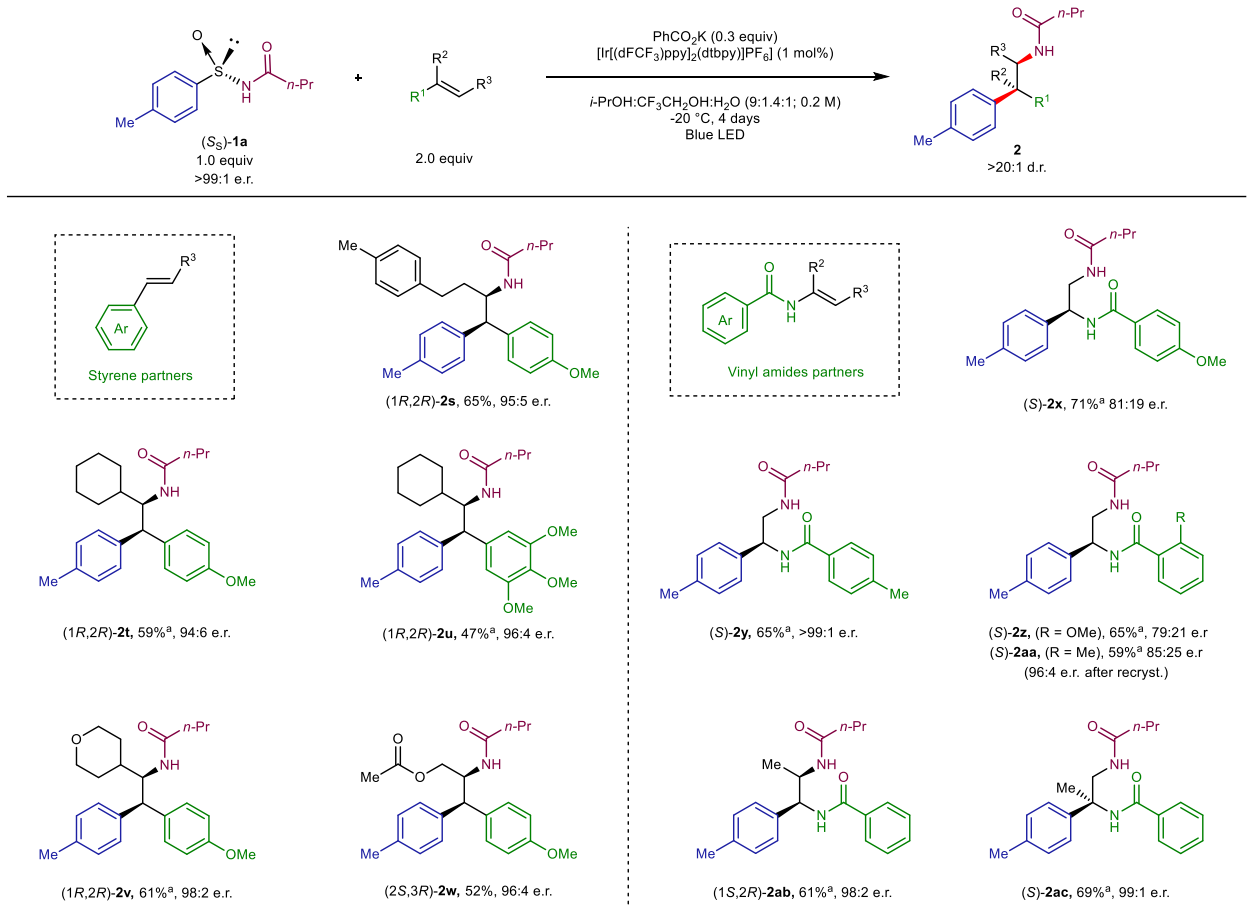


Fig. 3 | Scope of the alkene partner for the intermolecular aminoarylation with sulfinylacetamide (*Ss*)-1a. Notes: unless otherwise noted, reactions were carried out under the standard conditions; full conversion of the starting material was observed and yields are reported after purification by column 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. [a] 5 mol% of [Ir[(dFCF$_3$)ppy]$_2$(dtbpy)]PF$_6$] at 0 °C. *n*-Pr, *n*-propyl; d.r., diastereomeric ratio; e.r., enantiomeric ratio.

Mechanistic investigations.

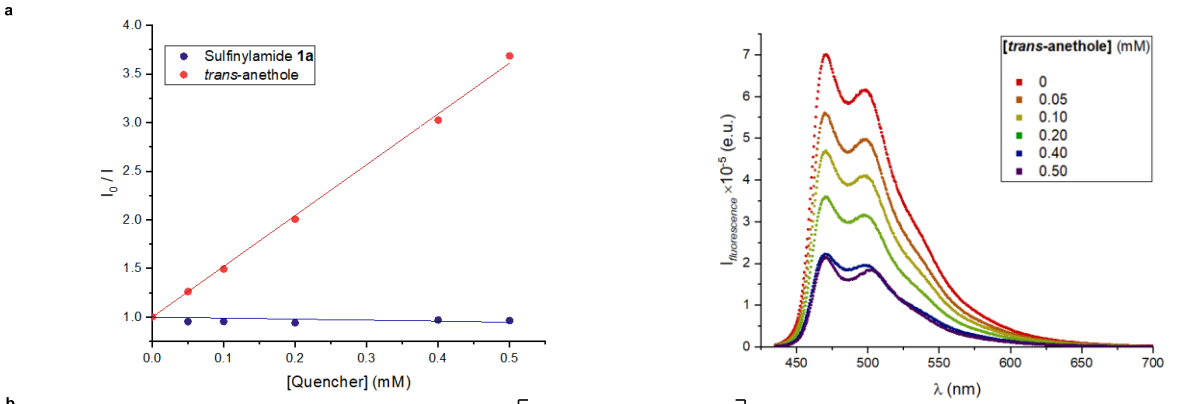
Having demonstrated the synthetic potential of this methodology, we focused on the investigation of the reaction mechanism underlying these transformations. Both, single electron oxidation of *trans*-anethole and oxidative proton-coupled electron transfer (PCET) at the arylsulfinylamide were considered as possible first steps of the photocatalytic cycle. Stern−Volmer experiments[40] were performed using [Ir[(dFCF$_3$)ppy]$_2$(dtbpy)]PF$_6$ excited with light (593 nm) in the presence of arylsulfinylamide **1a** and *trans*-anethole, respectively. No

fluorescence quenching was observed at any concentration of **1a** (Fig. 4a, left, blue). In contrast, in the case of *trans*-anethole, a decrease in fluorescence intensity was observed as a function of olefin concentration (Fig. 4a, right). These results support the notion of a radical cation being produced via single-electron oxidation of the olefin at the expense of the excited Ir photocatalyst.

A detailed analysis of the reaction energy profile was carried out using DFT calculations (Fig. 4b). At the outset, and in the presence of potassium benzoate, addition of the (S_S)-arylsulfinylamide **I** onto the olefin radical cation from *E*-anethole **II**[41] (generated by reduction of the photoactivated Ir(III) catalyst) proceeds through a low energy transition state **TS$_{I\text{-}III}$** (S_S,*R*) ($\Delta G^{‡}$ = +4.8 kcal·mol^{-1}) to give benzylic radical **III** in an overall exothermic process (ΔG = -25.2 kcal·mol^{-1}). In line with existing evidence for the formation of Meisenheimer intermediates in classical Smiles rearrangements proceeding via S_NAr mechanisms[42], we tried to localize the analogous radical intermediate, however to no avail. Instead, a spirocyclic transition state **TS$_{III\text{-}IV}$** was found preceding the exothermic formation of an SO-centered radical **IV** (ΔG = -38.5 kcal·mol^{-1}). The energy cost for the loss of the aromaticity is reflected in the activation barrier calculated for this step ($\Delta G^{‡}$ = +12.2 kcal·mol^{-1}). **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 ($d_{Cbn–Csp^2}$ = 2.11 Å in **TS$_{III\text{-}IV}$** *vs.* $d_{Cbn–Csp^2}$ = 1.53 Å in **VI**) and the S(O)–C bond is scarcely elongated ($d_{S–Csp^2}$ = 1.85 Å in **TS$_{III\text{-}IV}$** *vs.* $d_{S–Csp^2}$ = 1.82 Å in **I**) (Fig. 4b). The photocatalytic cycle is closed thereafter by oxidation of **IV** to **V** at the expense of Ir(II) to recover the Ir(III) catalyst. Additionally, Fig. 4b shows **TS$_{I\text{-}III}$** (S_S,*S*), the alternative transition state for the enantiodetermining step in which **I** adds onto the alkene radical cation **II**. **TS$_{I\text{-}III}$** (S_S,*S*) is 1.32 kcal·mol^{-1} higher in energy compared to **TS$_{I\text{-}III}$** (S_S,*R*), which is in agreement with the absolute configuration observed in the aminoarylation products.

To gain additional insights in the stereochemical outcome of these transformations, several control experiments were performed. 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 Fig. 12). In all three cases, the aminoarylation adduct **2a** 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[43] 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 (Fig. 4c and Supplementary Fig. 4-5 in the SI). 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, attack of the arylsulfinylamide will proceed at the *β*-carbon atom and the absolute configuration of the first stereogenic center is thus defined by that of the chiral sulfinyl moiety. The obtained intermediate **III** (Fig. 4b and Supplementary Fig. 14), undergoes a 1,4-aryl shift yielding the observed major *syn*-addition product **VI**. 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 ($\Delta\Delta G_{\mathbf{III/III'}}$ = 5.8 kcal·mol^{-1}, Fig. 4d). DFT calculations support the notion of the aryl migration being the rate determining step ($\mathbf{TS_{III\text{-}IV}}$ = 12.2 kcal·mol^{-1} in Fig. 4b). 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 Fig. 14).


a
Sulfinylamide 1a
trans-anethole
I0 / I
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0
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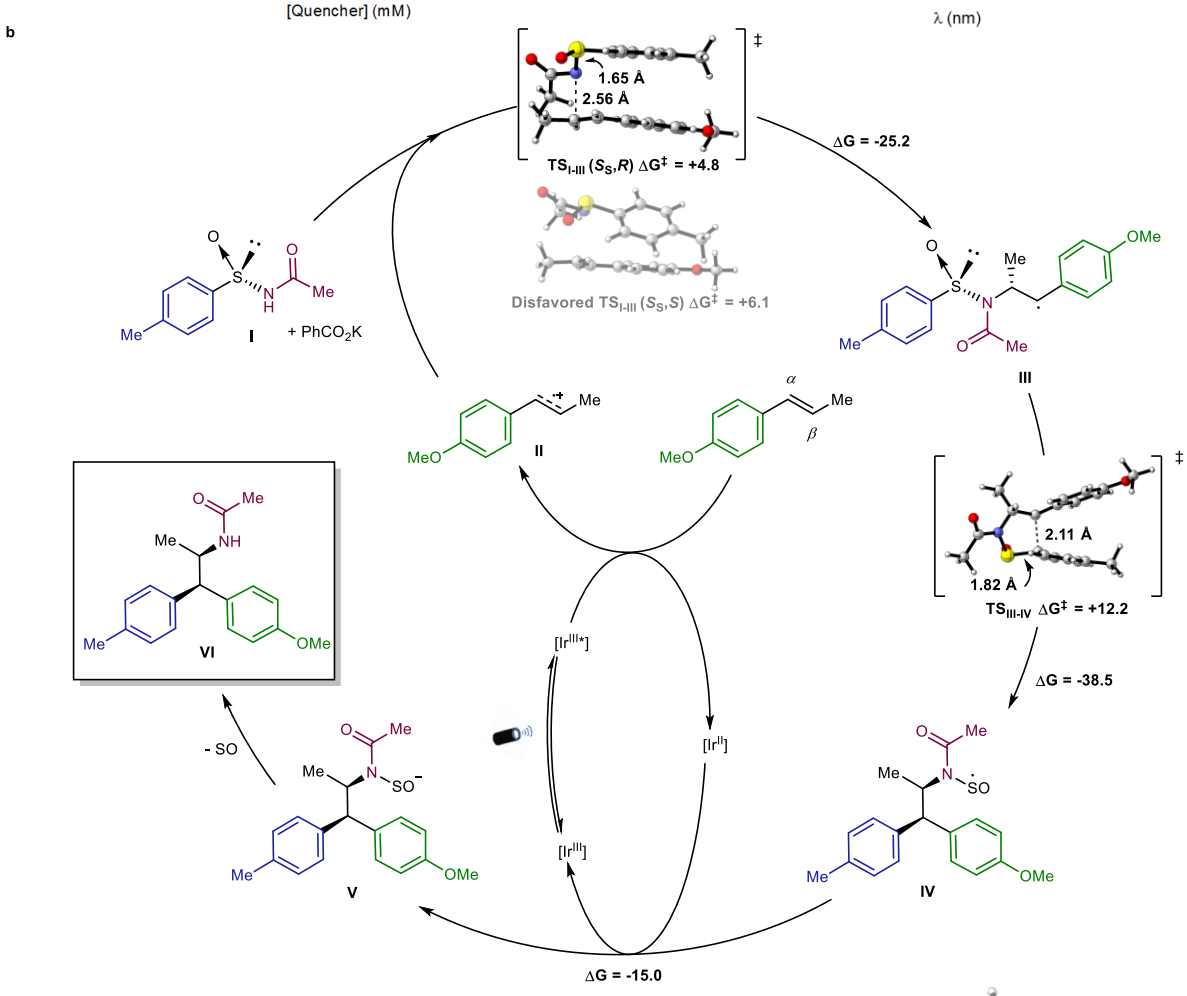
b
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2.56 Å
TSI-III (SS,R) ΔG‡ = +4.8
Disfavored TSI-III (SS,S) ΔG‡ = +6.1
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I
+ PhCO2K
II
III
2.11 Å
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TSIII-IV ΔG‡ = +12.2
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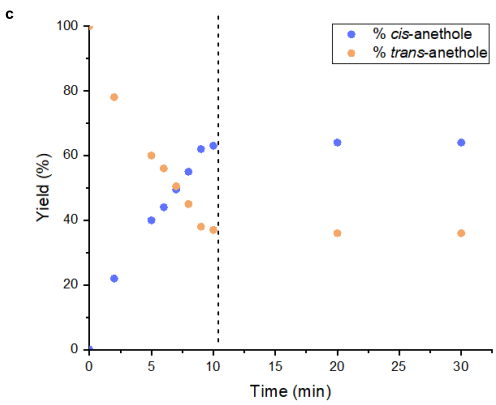
c
% cis-anethole
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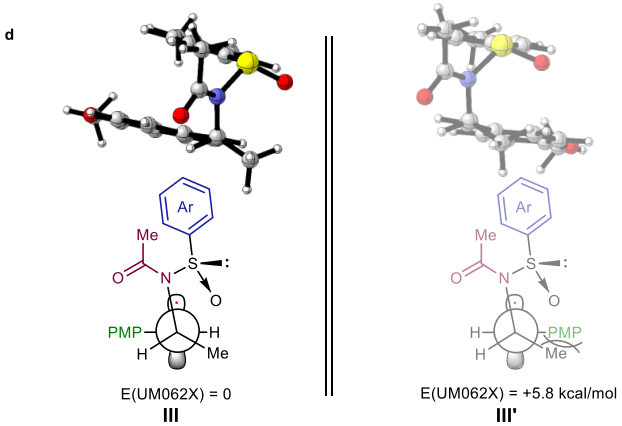
d
E(UM062X) = 0
III
E(UM062X) = +5.8 kcal/mol
III'

Fig. 4 | Mechanistic studies. a, Results of a Stern−Volmer experiment using arylsulfinylamide **1a** and *trans*-anethole as a quenchers. **b**, DFT calculations. Optimized transition states and 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. Energies are given in kcal·mol^{-1}. For further details, see Supplementary section 'DFT calculations'. **c**, Kinetics of isomerization of *trans*-anethole under the reaction conditions. **d**, Conformations calculated for intermediate **III** and **III'**. The 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.

Conclusion.

Here we describe a new asymmetric intermolecular aminoarylation of alkenes. This photoredox-mediated radical cascade capitalizes on an *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. Experimental and computational studies support a mechanism involving the Nitrogen addition onto an olefin radical cation followed by transposition of the aromatic ring with concomitant elimination of the sulfinyl tether. Both, *β,β*–diarylethylamines and aryl-*α,β*-ethylenediamines, ubiquitous motifs in bioactive molecules as well as in bidentate transition metal ligands, are obtained herein in enantiomerically enriched form, thus highlighting the synthetic utility of multifunctional arylsulfinylamides as traceless chiral auxiliars and *all-in-one* reagents.

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.

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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.