

Asymmetric Copper-Catalyzed Intermolecular Aminoarylation of Styrenes: Efficient Access to Optical 2,2-Diarylethylamines

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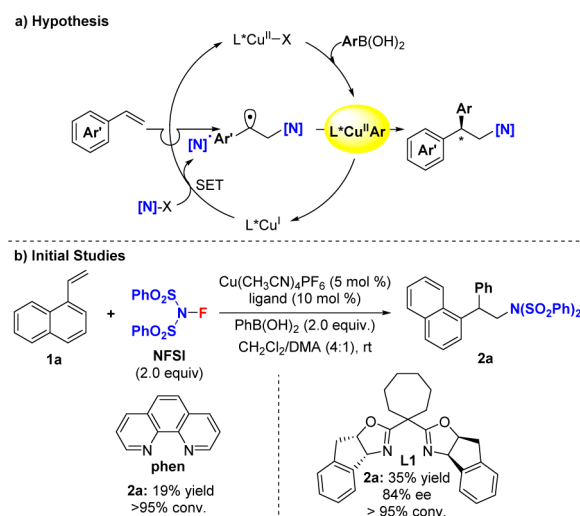
Supporting Information

ABSTRACT: We have developed a copper-catalyzed enantioselective intermolecular aminoarylation of alkenes using a novel *N*-fluoro-*N*-alkylsulfonamide as the amine reagent, which could react with the Cu(I) catalyst to release a related amino radical. After addition to styrene, the generated benzylic radical could couple with a chiral L*Cu^{II}Ar complex to achieve enantioselective arylation. Various optical 2,2-diarylethylamines were efficiently synthesized from simple styrenes with high enantioselectivity, and these products can serve as valuable synthons toward bioactive molecules' synthesis.

The optically pure 2,2-diarylethylamine scaffold serves as a pharmacologically important motif in dopamine receptor agonists, existing extensively in bioactive molecules and pharmaceuticals.¹ Thus, enantioselective construction of such a skeleton is highly demanded. However, only limited methods have been reported for its efficient synthesis, such as arylation of enantiopure 2-arylaziridines,² enantioselective arylation of β -nitroalkenes followed by reduction,³ and asymmetric hydrogenation of enamines.⁴ By comparison, enantioselective intermolecular aminoarylation represents one of the most efficient approaches to chiral 2,2-diarylethylamines from simple styrenes. In recent years, transition-metal-catalyzed enantioselective aminoarylation reactions of alkenes have received considerable attention. However, these reactions are limited to the intramolecular version,⁵ owing to the high entropic cost for intermolecular aminometallation of alkenes.⁶ So far, to our knowledge, no intermolecular version of an enantioselective aminoarylation reaction has been reported.

Addition of active amino radical species to styrenes often exhibits a low energy barrier to generate benzylic radicals, and sequential functionalization of the benzylic radicals results in a variety of amination products.⁷ However, due to the high reactivity of radical species, its enantioselective control is extremely challenging. Recently, Fu et al. disclosed that a benzylic radical can react with an (L*)Ni–Ar complex with high enantioselectivity.⁸ In connection with our interest in asymmetric radical transformation,^{8–10} our group has revealed that enantioselective arylation of benzylic radicals can be achieved by

Scheme 1. Asymmetric Radical Transformation for the Synthesis of Chiral 2,2-Diarylethylamines



using a copper catalyst in the case of enantioselective trifluoromethylarylation of styrenes.¹¹ Inspired by these studies, we hypothesized that if β -amino benzylic radicals, generated from amino radicals addition to styrenes,¹² could be enantioselectively coupled with L*Cu^{II}–Ar species, then asymmetric aminoarylation of styrenes should be expected to deliver enantiopure 2,2-diarylethylamines efficiently (Scheme 1a). Here we report this study, in which novel *N*-fluoro-*N*-alkylsulfonamides (NFAS) were employed as the key amination reagents.

To test the above hypothesis, we focused the initial studies on the reaction of 1a with NFSI and PhB(OH)₂ with an achiral (phen)Cu(I) catalyst. We were delighted to find that, as shown in Scheme 1b, the reaction indeed gave the desired product 2a, albeit in low yield (19%). When the chiral ligand L1, one of the best ligands found in our previous asymmetric trifluoromethylarylation,¹¹ was employed, the reaction provided 2a in a higher yield (35%) with a very promising enantiomeric excess (ee) of

Received: March 11, 2017

Published: May 4, 2017



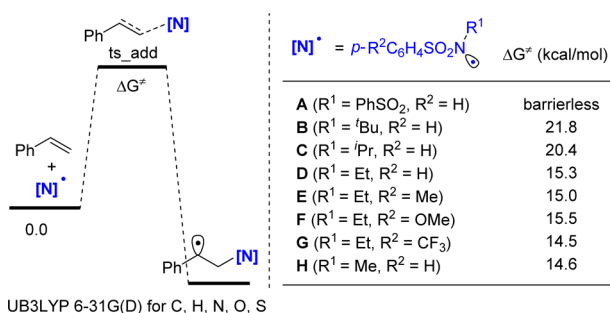


Figure 1. DFT calculated energy barriers for the radical addition processes with different electrophilic amino radicals.

84%. However, the styrene substrate **1a** was completely consumed in these two reactions. Unfortunately, further optimizing the reaction conditions did not improve the reaction yield. Our previous studies showed that the transmetalation reaction of arylboronic acid with Cu(II) intermediate is slow,¹³ while a highly electrophilic amino radical (e.g., **A** in Figure 1) generated from NFSI can react extremely fast with styrenes to generate benzylic radicals.^{9c} Thus, we speculated that the slowly formed ArCu(II) species derived from the transmetalation was unable to trap an excess amount of the benzylic radical, resulting in heavy side reactions.¹⁴ With this speculation, we believed that lowering the electrophility of the amino radical may help slow the radical addition process, to possibly match the slow transmetalation step. To test this possibility, a series of amino radicals (**B–H**) were surveyed by DFT calculations (Figure 1). (See Supporting Information (SI) for computational details. Note: the quality of the DFT calculations can only give a qualitative picture.) Compared with the radical **A**, which shows barrierless addition, the amino radicals **B–H** exhibit higher energy barriers toward radical addition to styrenes, which should lead to a relatively slow addition step. Among them, the sterically bulky radicals **B** and **C** (21.8 and 20.4 kcal/mol, respectively) showed appreciably higher barriers than the electron-poor radical **G** (14.5 kcal/mol) or the less sterically bulky radical **H** (14.6 kcal/mol).

Based on the above analysis, a series of *N*-F reagents NFAS^{B–H} were synthesized and employed in the asymmetric aminoarylation reaction. As shown in Table 1, due to the larger steric hindrance, both NFAS^B and NFAS^C showed poor reactivities and failed to provide the desired aminoarylation products, but resulted in a side product of 1,2-diphenylation of **1a** (entries 1 and 2).¹⁵ In contrast, the radical **D** was indeed proved to be efficient, and the reaction with NFAS^D provided the desired product **3a^D** in 77% yield with 85% ee (entry 3). Further modified *N*-F reagents NFAS^{E–G} were tested, and less electronic effect on the aryl ring was observed in the reaction yield and ee (entries 4–6). Compared to NFAS^D, NFAS^H with a smaller methyl group on the nitrogen exhibited a slightly higher enantioselectivity (87% ee) to give **3a^H** in 65% yield (entry 7). In consideration of methylamine as a popular motif in bioactive compounds and natural products, NFAS^H was chosen as the amino source for further optimizing reaction conditions.¹⁶ First, decreasing the reaction temperature was beneficial to enhance the enantiomeric excess (92% ee at 0 °C, 93% ee at –10 °C). However, the reaction conversion was significantly decreased to give a marked low yield (48% at 0 °C in entry 8, and 28% at –10 °C in entry 9), even over a prolonged time. Excitingly, addition of an extraneous base, LiOtBu, was beneficial to accelerate the transmetalation step, resulting in an obvious enhancement of the reaction yield from 28% to 77% without eroding the enantio-

Table 1. Amine Reagents Screening and Condition Optimization^a

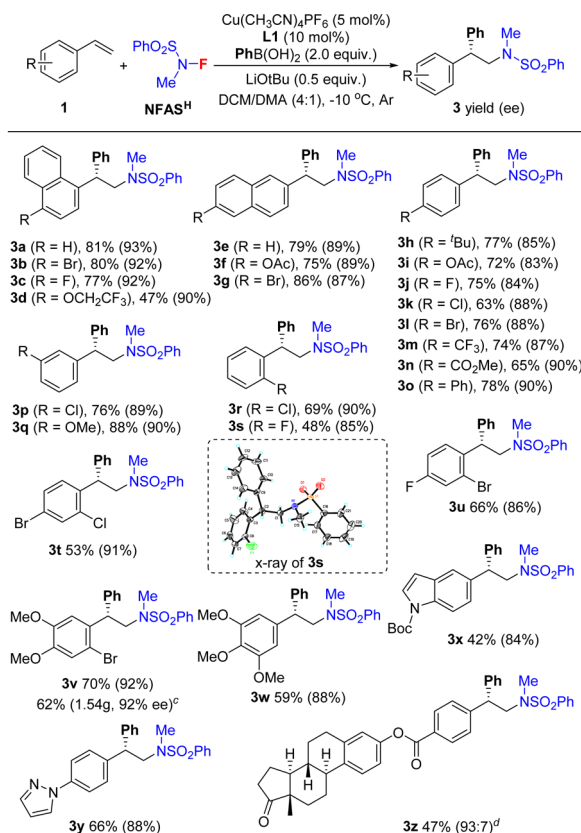
Entry	NFAS (R¹, R²)	Conversion	3a Yield ^b (ee) ^c
1	NFAS ^B (tBu, H)	42%	3a ^B : 0
2	NFAS ^C (iPr, H)	53%	3a ^C : trace
3	NFAS ^D (Et, H)	94%	3a ^D : 77% (85%)
4	NFAS ^E (Et, Me)	95%	3a ^E : 65% (83%)
5	NFAS ^F (Et, OMe)	96%	3a ^F : 54% (84%)
6	NFAS ^G (Et, CF₃)	98%	3a ^G : 73% (81%)
7	NFAS ^H (Me, H)	100%	3a ^H : 65% (87%)
8 ^d	NFAS ^H (Me, H)	80%	3a ^H : 48% (92%)
9 ^{e,f}	NFAS ^H (Me, H)	55%	3a ^H : 28% (93%)
10 ^{e,f,g}	NFAS ^H (Me, H)	92%	3a ^H : 77% (92%)
11 ^{e,g,h}	NFAS ^H (Me, H)	100%	3a ^H : 81% (93%)
12 ⁱ	NFAS ^H (Me, H)	100%	3a ^H : trace
13 ^j	NFAS ^H (Me, H)	60%	3a ^H : trace

^aAll reactions run on 0.2 mmol scale in 2 mL solvent. ^bYields determined by crude ¹H NMR with CH₂Br₂ as internal standard. ^cEnantiomeric excess (ee) values determined by HPLC on a chiral stationary phase. ^dAt 0 °C. ^eAt –10 °C. ^f4 d. ^gWith LiOtBu (0.5 equiv) as additive. ^h5 d. ⁱReaction of entry 12 in pure CH₂Cl₂ (2 mL). ^jReaction of entry 13 in pure DMA (2 mL).

selectivity (entry 10). Finally, the yield could be further improved with a longer reaction time (81% yield, entry 11). Notably, the solvent mixture of CH₂Cl₂/DMA was vital. The reactions in pure CH₂Cl₂ or DMA alone gave only a trace amount of the desired product **3a^H** (entries 12 and 13).

With the optimized reaction condition in hand, we first examined the substrate scope and functional group tolerance of the reaction. As shown in Table 2, for both electron-poor and electron-rich α -vinylnaphthalenes, the reactions provided the corresponding products **3a–3d** in good yields (around 80%, except for **3d** in 47%) with high enantioselectivities (90–93% ee). Meanwhile, β -vinylnaphthalenes were also proven to be suitable substrates, furnishing the products **3e–3g** in good yields and ee's (88–89%). A variety of vinylbenzenes were next surveyed. The *para*-substituted styrenes bearing both electron-poor and electron-rich arenes were effective for the reaction to give products **3h–3o** in good yields (65–78%) with good to excellent enantioselectivities (83–90% ee). In addition, *meta*- and *ortho*-substituted styrenes also exhibited good reactivities to give the desired products **3p–3s** in moderate to good yields with 85–90% ee. Beyond these, styrenes with di- and tri-substituents on the aryl ring were also compatible to give products **3t–3w** with similar yields and ee's. Notably, when the reaction of **1v** was scaled up to 5 mmol, the desired product **3v** was obtained with the same enantioselectivity (92% ee) in a satisfactory yield (62% yield, 1.54 g). Moreover, styrenes bearing heterocycles were suitable to give products **3x** and **3y** with 84% and 88% ee, respectively. Finally, a more complex substrate with an estrone moiety could be employed to generate product **3z** in 47% yield with a 93:7 diastereomeric ratio.

The substrate scope of arylboronic acids was then investigated. As shown in Table 3, again, both electron-rich and electron-poor *p*-arylboronic acids could react with 1-vinylnaphthalene to give the target products **4a–4e** with excellent enantioselectivities. Reactions of *ortho*-substituted arylboronic acids also proceeded to yield **4f** and **4g** in excellent enantioselectivities (94–95% ee). Moreover, for the reactions of 2-vinylnaphthalenes and vinyl-

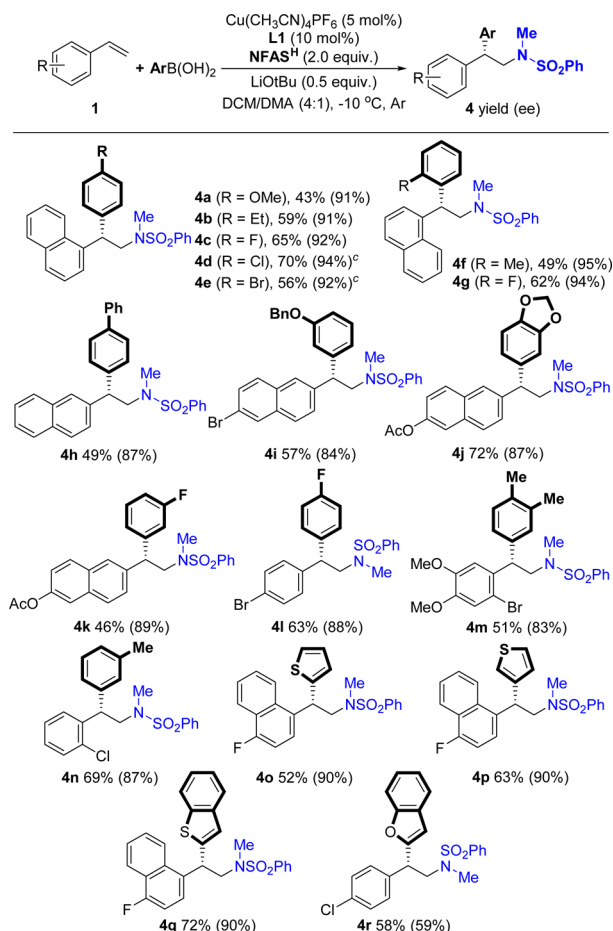
Table 2. Substrate Scope of Alkenes^{a,b}

^aAll reactions run on 0.2 mmol scale in 2 mL solvent for 3–7 d.
^bIsolated yields; ee values determined by HPLC on a chiral stationary phase. ^c5 mmol scale. ^dDiastereomeric ratio.

benzenes, a variety of arylboronic acids were effective to yield **4h–4n** in good enantioselectivities (83–89% ee). Excitingly, thiophenyl- and benzothiophenylboronic acids also showed good reactivities to deliver the target products **4o–4q** in excellent enantioselectivities (90% ee). In contrast, 2-benzofurylboronic acid was also active, but with only moderate enantioselectivity (59% ee).

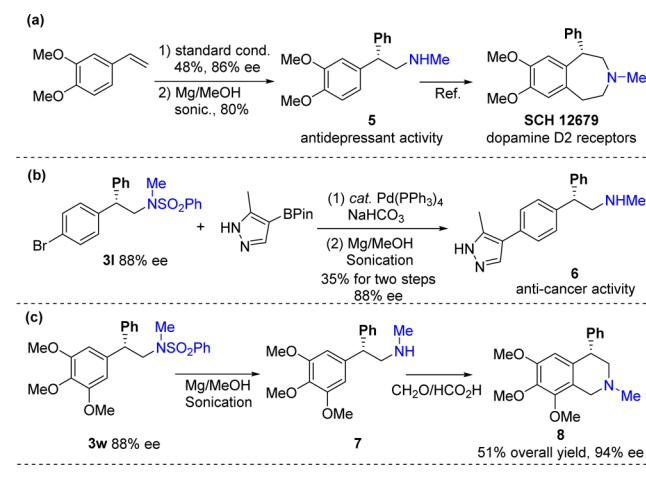
Further synthesis of bioactive compounds was conducted by utilizing this method. Reaction of 3,4-dimethoxystyrene provided the desired product in 48% yield with 86% ee, and sequential desulfonylation under Mg/MeOH conditions gave the related methylamine **5** in 80% yield with a retained ee, which was reported as an antidepressant agent.¹⁷ Meanwhile, compound **5** can be converted to bioactive SCH 12679 based on a previous report (Scheme 2a).¹⁸ Moreover, compound **3l** underwent sequential Suzuki coupling and desulfonylation to provide optically enriched anticancer agent **6** efficiently (Scheme 2b).¹⁹ Finally, enantiopure tetrahydroisoquinoline, as a privileged skeleton, often exists in bioactive molecules and pharmaceuticals.²⁰ After removal of the sulfonyl protecting group, **3w** was converted to the chiral methylamine **7**, which could undergo condensation with formaldehyde to generate chiral tetrahydroisoquinoline derivatives **8** in 51% overall yield with 94% ee (Scheme 2c).

To provide supporting evidence for the proposed radical process, a novel *N*-F reagent **NFAS^I** bearing an alkene moiety was treated under the standard aminoarylation reaction conditions. As shown in eq 1, the reaction failed to yield the aminoarylation product **9a**. Instead, the related alkylarylation

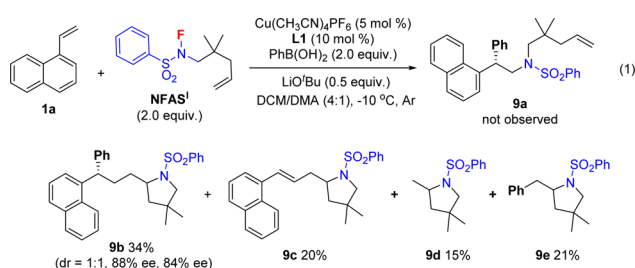
Table 3. Scope of Arylboronic Acids^{a,b}

^aAll reactions run on 0.2 mmol scale in 2 mL solvent for 5–7 d.
^bIsolated yields; ee values determined by HPLC on a chiral stationary phase. ^cCatalyst loading: Cu(CH₃CN)₄PF₆ (10 mol%)/L1 (20 mol%).

Scheme 2. Synthetic Applications



product **9b** was obtained in 34% yield with a 1:1 diastereomer ratio (88% and 84% ee, respectively), accompanied with the Heck-type product **9c**. The side products **9d** and **9e** were also obtained in 15% and 21% yield, respectively. Meanwhile, equal amounts of diastereoisomers were obtained in the reactions of *E*-1k-2-*d*₁ and *Z*-1k-2-*d*₁ (see SI). The reaction could be inhibited



by addition of TEMPO. All these observations suggest that the reaction is more likely to involve a radical process.

In summary, we have developed an enantioselective aminoarylation of styrenes using a Box/Cu(I) catalyst. A novel *N*-fluoro-*N*-methylsulfonamide was explored as an essential amino source to generate amino radical, which exhibited good reactivity toward benzylic radical formation to match the turnover-limiting transmetalation step, resulting in successful chemo- and enantioselective reactions. This method provided an efficient approach to synthesize various enantiomerically enriched 2,2-diarylethylamine derivatives. These products could be easily converted to a series of valuable chiral bioactive molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b02455.

Experimental details and characterization data (PDF)

NMR and HPLC spectra (PDF)

X-ray crystallographic data for 3s (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Basic Research Program of China (973-2015CB856600), the National Nature Science Foundation of China (Nos. 21532009, 21421091, and 21472219), and the Strategic Priority Research Program of the Chinese Academy of Sciences (No. XDB-20000000). This research was also partially supported by CAS Interdisciplinary Innovation Team. G.L. thanks the funding supported by Program of Shanghai Academic/Technology Research Leader.

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(14) When the reaction was conducted in CH₃CN, the related radical oxidation occurred, resulting in the Ritter reaction; see ref 12a.

(15) The reaction provided the diphenylation product in 28% (for NFAS^B) and 24% yield (for NFAS^C). For more discussion, see the SI.

(16) In addition to the highly reactive NFAS^H, NFSA^D was also proven to be a good reagent for the aminoarylation of styrenes to provide *N*-ethyl products efficiently. For details, see the SI.

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