Communication

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

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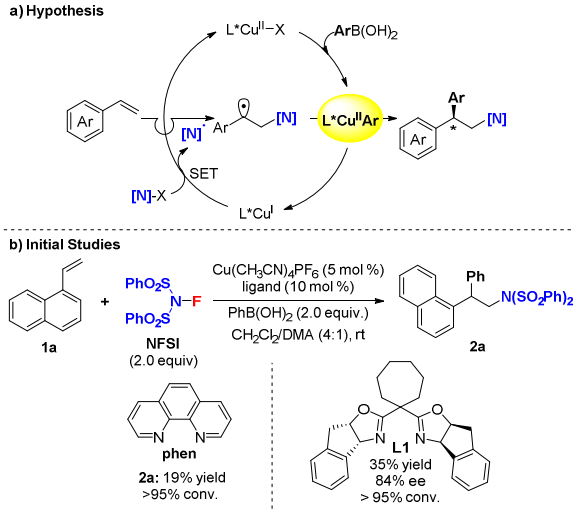
Supporting Information Placeholder

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 adding to styrene, the generated benzylic radical could couple with a chiral L*Cu^{II}Ar complex to achieve enantioselective arylation. Varieties of optical 2,2-diaryl-ethylamines 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] Compared with the above-mentioned reactions, enantioselective intermolecular aminoarylation reaction 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 the best of our knowledge, an intermolecular version of enantioselective aminoarylation reaction has not been reported.

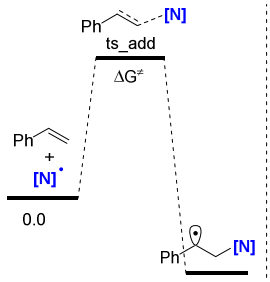
As we already know, addition of active amino radical species to styrenes often exhibits low energy barrier to generate benzylic radicals, and sequential functionalization of the benzylic radicals results in a variety of amination products.[7] However, due to the high reactivity of radical species, its enantioselective control is extremely challenging. Recently, Fu and co-workers disclosed that a benzylic radical can react with an (L*)Ni-Ar complex with high enantioselectivity.[8] In connection with our interest in the asymmetric radical transformation (ATR),[8,9,10] our group have revealed that enantioselective arylation of benzylic radicals can be achieved by 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). Herein, we reported this study, in which novel *N*-fluoro-*N*-alkyl**s**ulfonamides (NFAS) were employed as the key amination reagents.



Scheme 1. Asymmetric Radical Transformation (ART) for the Synthesis of Chiral 2,2-diarylethylamines.

To test above hypothesis, the initial studies were focused on the reaction of **1a** with NFSI and PhB(OH)$_2$ with an achiral (phen)Cu(I) catalyst. As shown in Scheme 1b, we were delighted to find that 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 trifluoromethyl-arylation,[11] was employed, the reaction provided **2a** in a higher

yield (35%) with a very promising ee of 84%. However, the styrene substrate **1a** was completely consumed in these two reactions. Unfortunately, further optimizing the reaction condition did not improve the reaction yield. Our previous studies showed that the transmetallation 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 transmetallation was unable to trap excess amount of the benzylic radical, resulting in heavy side reactions.[14] With this speculation, we believed that lowering down the electrophility of amino radical may help to slow the radical addition



UB3LYP 6-31G(D) for C, H, N, O, S

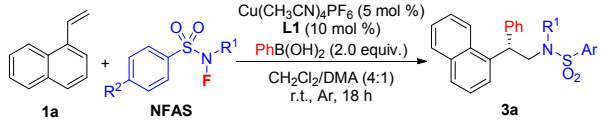
[N]• = *p*-R²C₆H₄SO₂N(R¹)•

	ΔG≠ (kcal/mol)
A (R^1 = $PhSO_2$, R^2 = H)	barrierless
B (R^1 = ^{t}Bu, R^2 = H)	21.8
C (R^1 = ^{i}Pr, R^2 = H)	20.4
D (R^1 = Et, R^2 = H)	15.3
E (R^1 = Et, R^2 = Me)	15.0
F (R^1 = Et, R^2 = OMe)	15.5
G (R^1 = Et, R^2 = CF_3)	14.5
H (R^1 = Me, R^2 = H)	14.6

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

process down, which possibly match the slow transmetallation step. In order to test this possibility, a series of amino radicals (**B-H**) were surveyed by DFT calculations (Figure 1) (see 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 steric bulky radical **H** (14.6 kcal/mol).

Table 1. Amine Reagents Screening and Condition Optimization[a]

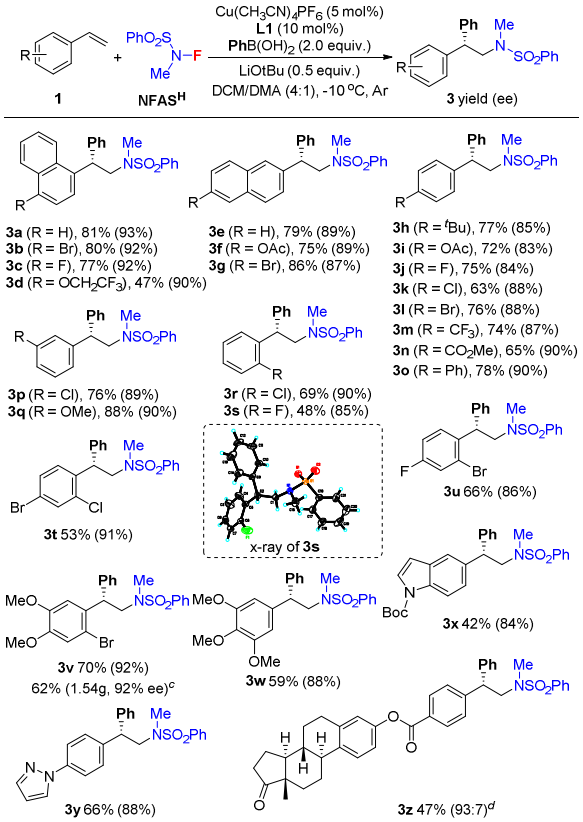


Entry	NFAS (R^1, R^2)	Conversion	**3a** Yield[b] (ee)[c]
1	**NFAS^B** (^{t}Bu, H)	42%	**3a^B**: 0
2	**NFAS^C** (^{i}Pr, H)	53%	**3a^C**: trace
3	**NFAS^D** (Et, H)	94%	**3a^D**: 77% (85%)
4	**NFAS^E** (Et, Me)	95%	**3a^E**: 65% (83%)
5	**NFAS^F** (Et, OMe)	96%	**3a^F**: 54% (84%)
6	**NFAS^G** (Et, CF_3)	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

[a] All reactions were run in 0.2 mmol scale in 2 mL solvent. [b] Yields were determined by crude ^{1}H NMR with CH_2Br_2 as internal standard. [c] Enantiomeric excess (ee) values were determined by HPLC on a chiral stationary phase. [d] at 0 °C. [e] at -10 °C. [f] 4 d. [g] with LiOtBu (0.5 equiv) as additive. [h] 5 d. [i] Reaction of entry 12 in pure CH_2Cl_2 (2 mL). [j] Reaction of entry 13 in pure DMA (2 mL).

On the basis of the above analysis, a series of N-F reagents **NFAS^B**-**NFAS^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 1-2).[15] In contrast, the radical **D** was indeed proved to be efficient, and the reaction with **NFSA^D** provided the desired product **3a^D** in 77% yield with 85% ee (entry 3). Further modified N-F reagents **NFSA^E**-**NFSA^G** were tested, and less electronic effect on the aryl ring was observed in the reaction yield and ee (entry 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 condition.[16] First, decreasing the reaction temperature was beneficial to enhance the enantioselective 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 in a prolonged time. Excitingly, addition of an

Table 2. Substrate Scope of Alkenes[a,b]

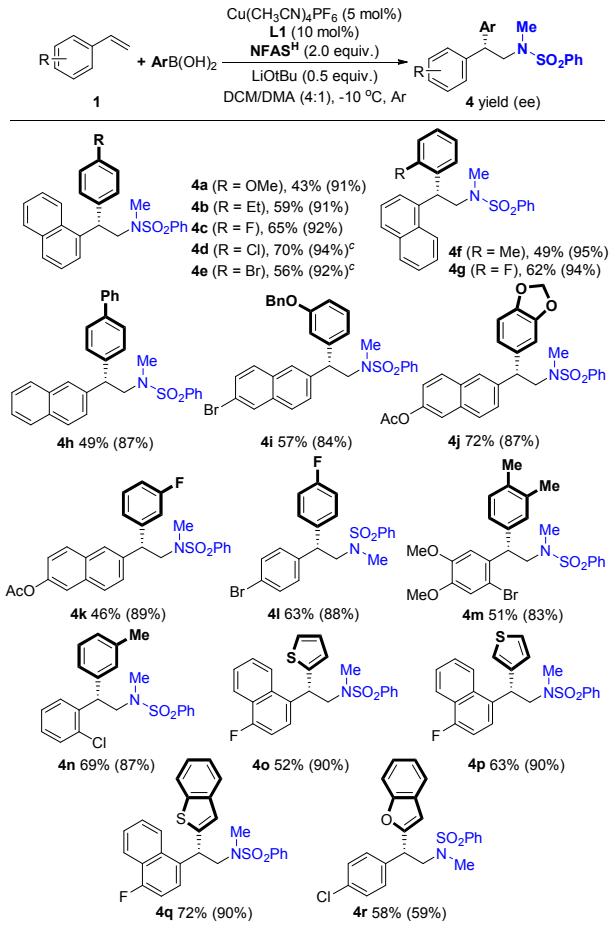


[a] All reactions were run in 0.2 mmol scale in 2 mL solvent for 3-7 d. [b] Isolated yields, and the enantiomeric excess (ee) values were determined by HPLC on a chiral stationary phase. [c] 5 mmol scale. [d] diastereomeric ratio.

extraneous base LiO^{t}Bu was beneficial to accelerate the transmetallation step, resulted in an obvious enhancement of the reaction yield from 28% to 77% without eroding the entantioselectivity (entry 10). Finally, the yield could be further improved with a longer reaction time (81% yield, entry 11). Notably, the mixture solvent of CH_2Cl_2/DMA was vital. The reactions in pure CH_2Cl_2 or DMA alone only gave a trace amount of the desired product **3a^H** (entries 12-13).

With the optimized reaction condition in hand, we firstly 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 **3d** in 47%) with high enantioselectivity (90-93% ee). Meanwhile, *β*-vinyl-naphthalenes were also proven to be suitable substrates, furnishing the products **3e-3g** in good yields and ee's (88-90%). A variety of vinyl benzenes 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 (83-92% 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*-substitutents 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-3y** with 84% ee 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.

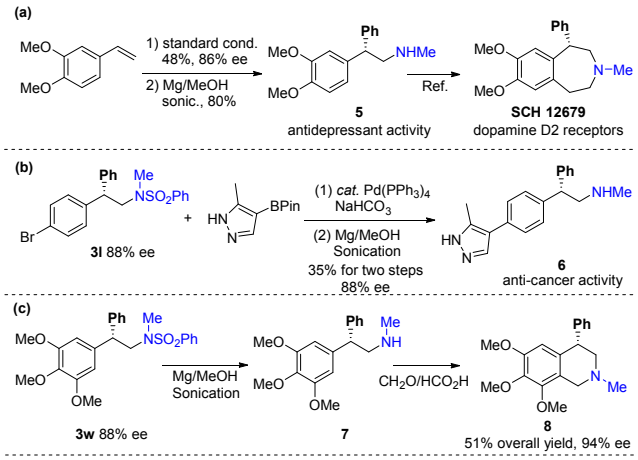
Table 3. Scope of Aryl Boronic Acids.[a,b]



[a]All reactions were run in 0.2 mmol scale in 2 mL solvent for 5-7 d. [b]Isolated yield, and the enantiom-eric excess (ee) values were determined by HPLC on a chiral stationary phase. [c] Catalyst loading: $Cu(CH_3CN)_4PF_6$ (10 mol%)/**L1** (20 mol%).

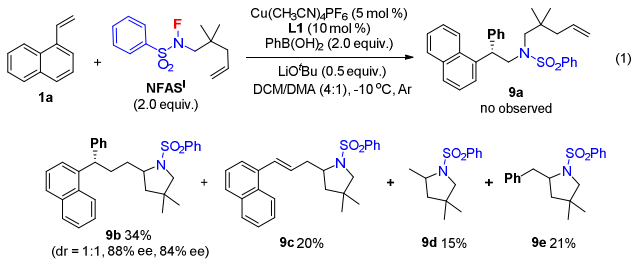
Then, the substrate scope of aryl boronic acids was investigated. As illustrated in Table 3, again, both electron-rich and electron-poor *para*-aryl boronic acids could react with 1-vinyl naphthalene to give the target products **4a-4e** with excellent enantio-selectivities. The reactions of *ortho*-substituted aryl boronic acids also proceeded to yield products **4f-4g** in excellent enantio-selectivities (94-95% ee). Moreover, for the reactions of 2-vinyl naphthalenes and vinyl benezenes, a variety of aryl boronic acids were effective to yield products **4h-4n** in good enantioselectivities (83-89% ee). Excitingly, thiophenyl and benzothiophenyl boronic acids also showed good reactivities to deliver the target products **4o-4q** in excellent enantioselectivities (90% ee). In contrast, 2-benzofuryl boronic acid was also active, but with only moderate enantioselectivity (59% ee).

Further synthesis of bioactive compounds was conducted by utilizing this current method. Reaction of 3,4-dimethoxystyrene provided the desired product in 48% yield with 86% ee, and the sequential desulfonylation under Mg/MeOH condition 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 on the basis of a previous report (Scheme 2a).[18] Moreover, compound **3l** underwent a sequential Suzuki coupling and desulfonylation to provide optically enriched anti-cancer agent **6** efficiently (Scheme 2b).[19] Finally, enantiopure tetrahydroisoquinoline as a privileged skeleton often existed in bioactive molecules and pharmaceuticals.[20] After removal of sulfonyl protecting group, **3w** was converted to the chiral methylamine **7**, which could conduct condensation with formaldehyde to generate chiral tetrahydro-isoquinoline derivates **8** in 51% overall yield with 94% ee (Scheme 2c).



Scheme 2. Synthetic Applications.

In order 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 condition. As shown in eq 1, the reaction failed to yield the aminoarylation product **9a**. Instead, the related alkylarylation product **9b** was obtained in 34% yield with 1:1 diastereomer ratio (88% ee and 84% ee respectively), companied with the Heck-type product **9c**. In addition, the side products **9d** and **9e** were also obtained in 15% and 21% yields, respectively. Meanwhile, the equal amount of diastereoisomers were obtained in the reactions of *E*-**1k**-2-d_1 and *Z*-**1k**-2-d_1 (see SI). Moreover, the reaction could be inhibited with addition of TEMPO. All these observations suggested that the reaction is more likely to involve a radical process.



In summary, we have developed an enantioselective amino-arylation of styrenes using the 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 transmetallation step, resulted in the successful chemo- and enantioselective reactions. This method provided an efficient approach to synthesize various enantiomerically enriched 2,2-diarylehthanylamine derivatives. These products could be easily converted to a series of valuable chiral bioactive molecules.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, characterization, Computational study data, and additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(14) When the reaction was conducted in CH_3CN, the related radical oxidation was occurred to result Ritter reaction. For details, see ref. 12a.
(15) The reaction provided the diphenylation product in 28% (for **NFAS^{B}**) and 24% yield (for **NFAS^{c}**), respectively. For more discussion, see the Supporting Information.
(16) In addition to the highly reactive **NFAS^{H}**, **NFSA^{D}** was also proven to be good reagent for the aminoarylation of styrenes to provide N-ethyl products efficiently. For the details , see the Supporting Information.
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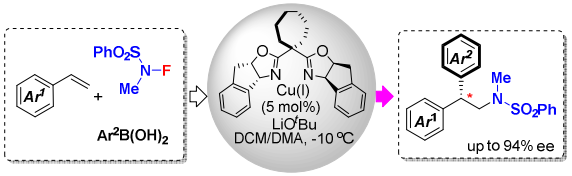

novel amination reagent
Highly enantioselective arylation of benzylic radical