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Concise Report

Copper catalysis, Arylcyanation, Asymmetric radical reactions, Styrene, Meerwein arylation

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Enantioselective Arylcyanation of Styrenes via Copper-Catalyzed Radical Relay†

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Summary of main observation and conclusion The first copper-catalyzed enantioselective arylcyanation of styrenes has been developed using readily available anilines as aryl radical precursors under mild conditions, which enables easy access to chiral 2,3-diaryl propionitriles with moderate to good enantioselectivities. This operationally straightforward reaction exhibits broad substrate scope and functional group tolerance. Notably, this method has been applied to the synthesis of chiral AIEgen as well as estrogen receptor-β agonist (R)-DPN.

Background and Originality Content

Optically pure organonitrile compounds are featured in natural products, pharmaceuticals, and agrochemicals.[1] Among them, chiral 2,3-diaryl propionitriles and their derivatives have received much attention (Figure 1). For instance, (R)-DPN is an estrogen receptor β-selective ligand, the other diaryl propionic acids and propionamides can be used in treatment of pulmonary embolism, or as an antiobesity agent.[2] In general, conventional synthesis of chiral 2,3-diaryl propionitriles relies on the dehydration of chiral amides, asymmetric arylation of α-halonitriles.[3] The Meerwein arylation of alkenes represents an effective strategy for the installation of an aryl group into alkenes,[4,5] where the alkyl radicals generated by aryl radical addition into alkenes would be trapped to form various C–C and C–heteroatom bonds. However, the variants of asymmetric Meerwein arylation of alkenes are rare, owing to the challenging asymmetric radical control. In 2015, Zhu and Buchwald developed an enantioselective copper-catalyzed intramolecular radical oxyfunctionalization of alkenes, including oxyarylation with aryl diazonium salts.[6] Liu and coworkers

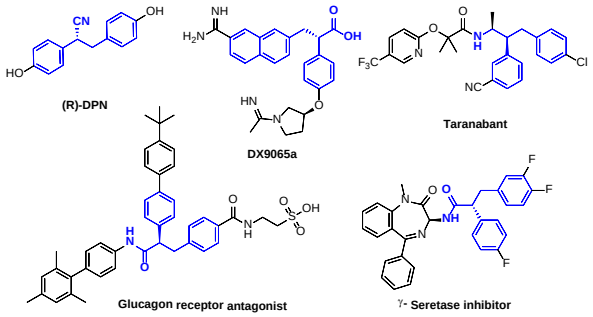
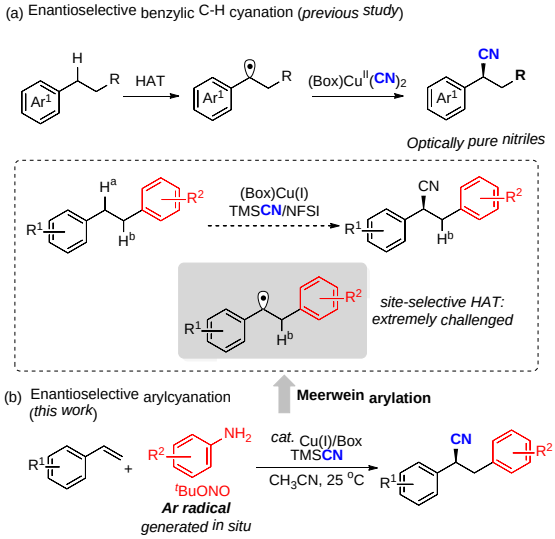


Figure 1 Representative bioactive molecules bearing chiral 2,3-diaryl propanitriles and related scaffolds

reported a Cu/CPA-catalyzed asymmetric aminoarylation of alkenes with aryldiazonium salts.[7] Recently, Zhang and coworkers disclosed a copper-catalyzed enantioselective arylalkynylation of alkenes with diaryliodonium salts.[8]

On the basis of our developed copper-catalyzed radical relay process,[9] we have recently realized the enantioselective cyanation,[10] arylation,[11] and alkynylation[12] reactions. For instance, the benzylic C-H cyanation has been developed, where the key benzylic radical generated from hydrogen atom transfer (HAT) could be trapped by a chiral (Box)$Cu^{II}(CN)_2$ complex with excellent enantioselectivity (Scheme 1a). For the efficient synthesis of chiral 2,3-diaryl propanitriles, the benzylic C-H cyanation of 1,2-

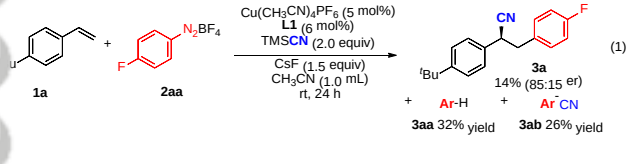
Scheme 1 Enantioselective Cu-catalyzed radical cyanation



diarylethanes presents an attractive method, but generally afforded the mixture of nitriles owing to the poor site-selective HAT in these cases. Therefore, we reasoned that if the diaryl benzylic radicals could be selectively generated from Meerwein arylation of styrenes, the enantioselective arylcyanation of styrenes could be expected to synthesize chiral 2,3-diaryl propanitriles (Scheme 1b). Herein, we communicate this study, where readily available anilines were used as aryl radical precursors under mild conditions. This method enables easy access to structurally diverse chiral 2,3-diaryl propionitriles with good to excellent enantioselectivities,[13] and could be applied to synthesize estrogen receptor-β agonist (R)-DPN (Scheme 1b).

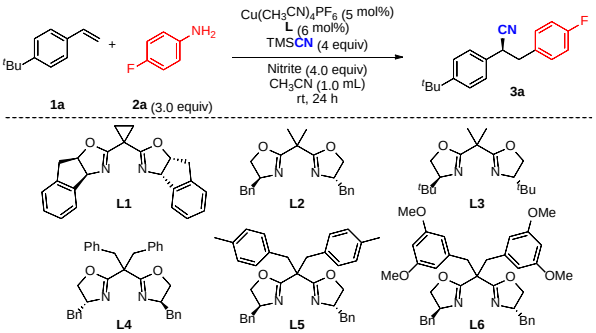
Results and Discussion

Our initial studies were commenced on the reaction of **1a** with 4-fluorobenzenediazonium salt **2aa** and TMSCN under chiral (**L1**)Cu(I) catalysis. We were delighted to find that, as shown in eq 1, the reaction indeed gave the desired product **3a** with good enantioselectivity, albeit in low yield (14%; 85:15 er). Unfortunately, further optimizing the reaction conditions did not improve the reaction yield. The arenediazonium salt predominately underwent the side reduction (**3aa**, 32% yield) and cyanation reaction (**3ab**, 26% yield), which is possibly resulted from



(1)

Table 1 Optimization of the Reaction Conditions[a,b]



Entry	Ligand	Nitrite	Yield (%)	Er
1	**L1**	t-BuONO	75	88.5:11.5
2	**L1**	BnONO	10	85.5:14.5
3	**L1**	PhCH(CH$_3$)ONO	44	85.5:14.5
4[c]	**L1**	t-BuONO	20	87.5:12.5
5	**L2**	t-BuONO	60	86:14
6	**L3**	t-BuONO	10	52.5:47.5
7	**L4**	t-BuONO	49	8:92
8	**L5**	t-BuONO	37	93.5:6.5
9	**L6**	t-BuONO	42	95:5
10[d]	**L1**	t-BuONO	75	88.5:11.5
11[d]	**L6**	t-BuONO	40	95:5

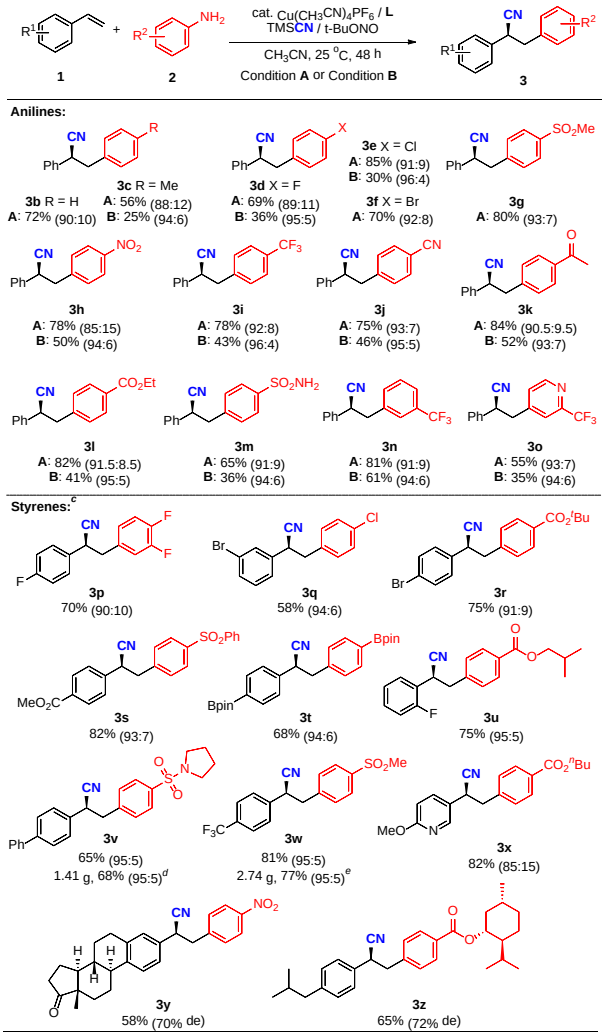
[a] Reaction Condition: Styrene **1a** (0.1 mmol), aniline **2a** (0.3 mmol), t-BuONO (0.4 mmol), TMSCN (0.4 mmol), Cu(MeCN)$_4$PF$_6$ (5.0 mol%), **L** (6.0 mol%) in CH$_3$CN (1.0 mL) at 25 °C for 24 h. [b] ^{1}H NMR yield using CH$_2$Br$_2$ as an internal standard, enantiomeric ratio (er) was determined by the HPLC on a chiral stationary phase. [c] At 0 °C. [d] The reaction was conducted on a 0.2 mmol scale, isolated yield.

its high concentration (eq. 1). With this speculation, we reasoned that, gradually generating arenediazonium salt from aniline *in situ* might be beneficial to lower its concentration, thereby suppressing these side reactions.

In order to monitor the reaction by ^{19}F NMR, 4-fluoroaniline **2a** was employed as the aryl radical source in the presence of *tert*-butyl nitrite, the reaction afforded the target product **3a** in 75% yield with slightly improved enantioselectivity (Table 1, entry 1). Other nitrite reagents (e.g., BnONO, PhCH(CH$_3$)ONO) were screened for tuning the rate of the arenediazonium salt formation, however, lower yields were observed in these reactions (entries 2 and 3). The enantioselectivity was not improved when the reaction was conducted at 0 °C (entry 4). Ligand screening indicated that Box-Bn **L2** gave the similar enantioselectivity (86:14 er), while Box-Bu^t **L3** gave worse result (52.5:47.5 er). Furthermore, introducing the steric bulky benzyl group into *gem*-carbon of Box ligands was essential to enhance the enantioselectivity (entries 7-9), and **L6** with a larger *gem*-3,5-dimethoxybenzyl group performed the best to give **3a** with 95:5 er, albeit in lower yield (entry 9). When the reactions were carried on a 0.2 mmol scale, similar results were

obtained (entries 10 and 11).

Table 2 Substrate scopes[a,b]

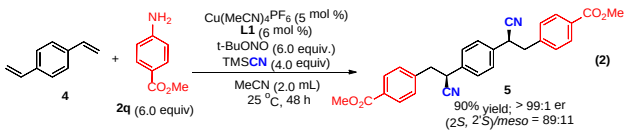


[a] Condition A: Styrene **1a** (0.2 mmol), aniline **2** (0.6 mmol), t-BuONO (0.6 mmol), TMSCN (0.4 mmol), $Cu(MeCN)_4PF_6$ (5.0 mol%), **L1** (6.0 mol%) in CH_3CN (2.0 mL) at 25 °C for 48 h; Condition B: **L6** was used instead of **L1**. [b] Isolated yield, enantiomeric ratio (er) was determined by the HPLC on a chiral stationary phase and showed in the parenthesis. [c] Under the condition A. [d] On a 5 mmol scale. [e] On a 10 mmol scale.

The substrate scopes were next surveyed under the standard conditions in entries 10 and 11 (Table 1). Aniline and p-toluidine were suitable aryl sources to give the desired products **3b** and **3c** in 72% and 56% yields with good enantiomeric ratios (Table 2). The reactions of various electron-deficient anilines provided the corresponding products **3d**–**3m** in good yields (65-85%) with good to excellent enantiomeric ratios (from 85:15 to 95:5 er). Compared to the condition A with **L1**, the condition B with **L6** provided higher er values, albeit in lower yields. For example, the reaction of styrene with 4-nitroaniline **2h** in the presence of **L1** afforded the product **3h** in 78% yield with 85:15 er, while the er value was improved to 94:6 in 50% yield. Various functional groups, such as halide, ester, nitro, cyano, ketone and sulfamide, were tolerated under the reaction conditions. Moreover, *meta*-(trifluoromethyl)-aniline also exhibited good reactivity to give the desired product **3n** in good yield and enantioselectivity. In addition, 2-CF_3-pyridinyl-2-amine were also compatible to give **3o** in moderate yield with 93:7~ 94:6 er. The absolute configuration of these products was determined by X-ray crystallography of product **3m** (see SI).

Then the scope of styrenes was also surveyed, and various substituents at *para*-, *meta*-, and *ortho*-positions on the benzene rings were suitable to generate the corresponding products **3p**-**3w** in good yields with up to 95:5 er. Moreover, aryl bromide and aryl borate are well tolerated, a meaningful feature with respect to further functional group manipulation. The reaction of 2-methoxy-5-vinylpyridine afforded **3x** in 82% yield with 85:15 er. We found that estrone-derived styrene as well as *L*-menthol-tethered aniline was amenable to this reaction and gave the corresponding arylcyanation products **3y** and **3z** in moderate yields with moderate diastereomeric excess. Notably, when the reactions of **1v** and **1w** were scaled up to 5 mmol and 10 mmol, respectively, the desired products **3v** and **3w** were obtained with the same enantiomeric ratio (95:5 er) in similar yields.

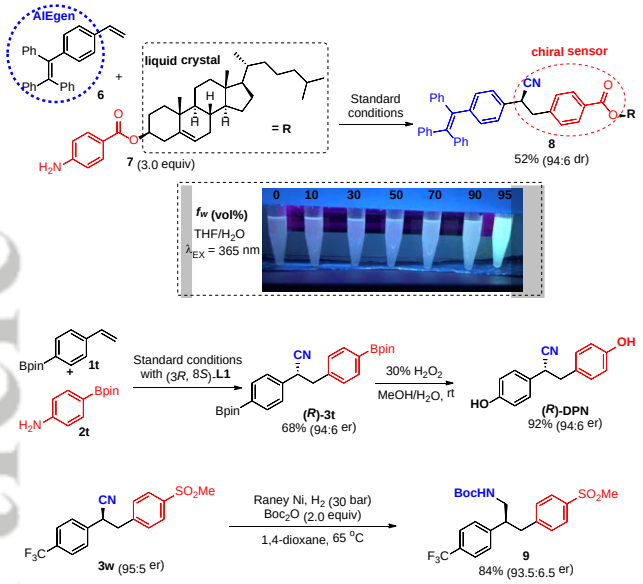
Furthermore, diene substrate **4** bearing two terminal double bonds also proved amenable to provide dinitrile **5** in 90% yield with good stereoselectivity (89:11) and excellent enantioselectivity (> 99:1 er, eq. 2).



The synthetic utility of the asymmetric arylcyanation was examined (Scheme 2). First, tetraphenylethylene (TPE) and its derivatives are a common class in aggregation-induced emission luminogen (AIEgen). When the AIEgens are endowed with chirality, the resultant chiral AIEgens can act as sensors to discriminate and analyze enantiomers of chiral compounds.[14] Cholesterol possessing a high level of liquid crystal property was attached with a tetraphenylethylene moiety through this method, providing the chiral AIEgen **8** in 52% yield with 94:6 dr, which might be a potential optical sensors for chiral compounds and chiral nematic liquid crystals.[15] The fluorescent photographs taken in tetrahydrofuran–water mixtures with different water fractions (f_w) under 365 nm UV irradiation indicated that product **8** indeed possessed AIE feature. Moreover, the estrogen receptor β-selective ligand (*R*)-DPN was quickly accessed by this method with (3*R*, 8*S*)-**L1** after the following oxidation reaction. Finally, product **4j** could be easily converted to amide **9** in 84% yield by hydrogenation.

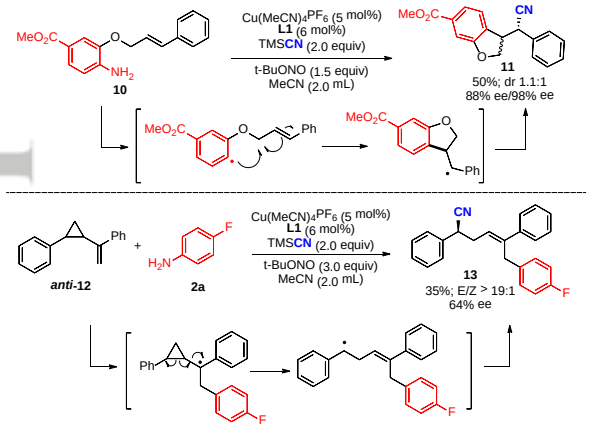
To provide supporting evidences for the proposed radical process, TEMPO and BHT were added to the standard reaction

Scheme 2. Synthetic applications



systems, and the formation of desired product **3a** was dramatically inhibited. Benzylic radical and aryl radical were captured with TEMPO and BHT, respectively (see SI). Radical clock experiments were also carried out under the standard conditions (Scheme 3). The intramolecular reaction of alkenes tethered aniline **10** afforded the cyclization cyanation product **11** in 50% yield with a 1.1:1 diastereomer ratio (88% and 98% ee, respectively). In addition, the reaction of cyclopropane containing substrate **12** afforded the ring-opened product **13** in 35% yield. These observations suggested that the reaction likely involves a benzylic radical.

Scheme 3 Radical clock experiments



Conclusions

In summary, we have developed a copper-catalyzed enantioselective arylcyanation reaction of styrenes with the readily available anilines as aryl radical precursors under mild conditions, affording a series of chiral 2,3-diaryl propionitriles with moderate to good enantioselectivities. Notably, this reaction has been applied to the synthesis of chiral AIEgen as well as estrogen receptor β agonist (R)-DPN.

Experimental

General experimental procedures for the asymmetric arylcyanation of alkenes

To a 10 mL sealed tube, **L1** (4.4 mg, 0.012 mmol, 6 mol%) or **L6** (7.8 mg, 0.012 mmol, 6 mol%) and $Cu(CH_3CN)_4PF_6$ (3.7 mg, 0.010 mmol, 5 mol%) were dissolved in anhydrous and oxygen-free CH_3CN (2.0 mL) under an atmosphere of argon. The solution was stirred at room temperature for 30 mins, and then alkene **1** (0.2 mmol, 1.0 equiv), aniline **2** (0.6 mmol, 3.0 equiv), t-BuONO (78 μL, 0.6 mmol, 3.0 equiv) and TMSCN (52 μL, 0.4 mmol, 2.0 equiv) were sequentially added, then the mixture was stirred for 48 h at 25 °C. After the reaction was completed, solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel with gradient of petroleum ether and ethyl acetate to afford product **3**.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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Enantioselective Arylcyanation of Styrenes via a Copper-Catalyzed Radical Relay

Weiwen Zhuang,[a] Pinhong Chen,[a] and Guosheng Liu*[a,b]

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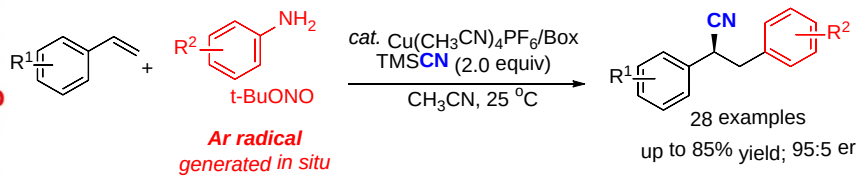

A copper-catalyzed enantioselective arylcyanation of styrenes was developed with the readily available anilines as aryl radical precursors under mild conditions, which allows the excess of chiral 2,3-diaryl propionitriles with moderate to good enantioselectivities. This reaction exhibits broad substrate scope and functional group tolerance.

