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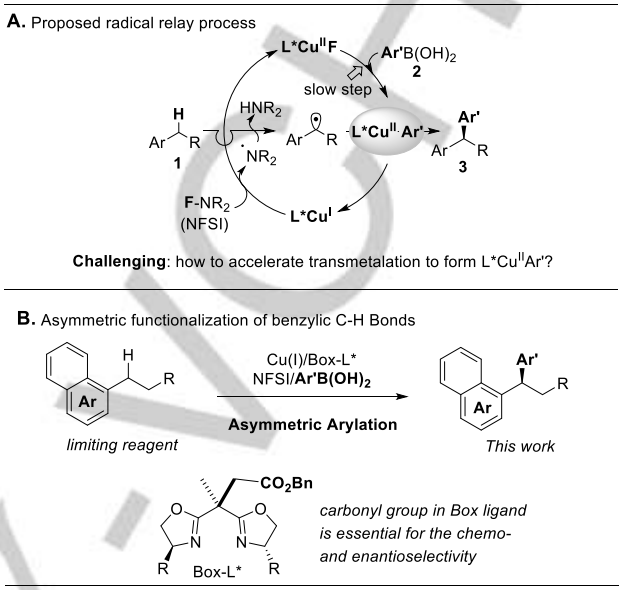
Enantioselective Arylation of Benzylic C-H bonds via Copper-Catalyzed Radical Relay

Wen Zhang, Lianqian Wu, Pinhong Chen, and Guosheng Liu*

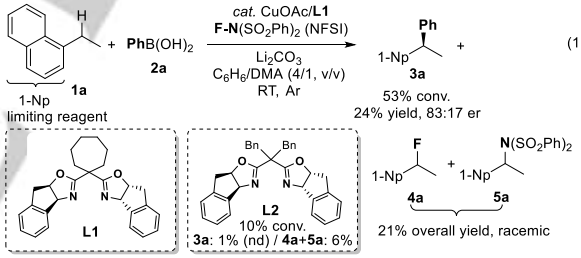
Abstract: A novel enantioselective Cu-catalyzed arylation of benzylic C-H bonds using alkylarenes as a limiting reagent has been developed, where a chiral bisoxazoline ligand bearing an acetate ester moiety plays a key role in both reactivity and enantioselectivity. The reaction provides an efficient access to various chiral 1,1-diarylalkanes in good yields with good to excellent enantioselectivities, and displays excellent functional group tolerance.

Asymmetric functionalization of sp^3 C-H bonds, which serves as a powerful tool for the straightforward synthesis of highly valuable chiral building blocks and drug candidates,[1] has received much attention in the last several decades.[2] Inspired by enzyme catalysis,[3] a series of direct oxidative functionalization of sp^3 C-H bonds under non-enzymatic systems has been developed, which was initiated by a hydrogen atom transfer (HAT) process.[4] However, the related asymmetric functionalization of sp^3 C-H bonds is still extremely difficult, due to the involvement of highly reactive carbon-centered radical intermediates.[5] Recently, several groups independently reported cooperative photoredox and nickel catalysis for the direct arylation of sp^3 C-H bonds using electrophilic aryl halides as arylation reagents, however, only moderate enantioselective control (54% *ee* at most) was achieved in sporadic examples.[6]

As our continuous efforts to develop asymmetric radical transformations (ARTs), a copper-catalyzed radical relay process for the asymmetric benzylic C-H cyanation using chiral bisoxazoline (Box) ligands and alkylarenes as a limited reagent has been demonstrated,[7] where a benzylic radical as a key intermediate generated through a HAT process could be enantioselectively trapped by chiral (Box)Cu(II) cyanides.[7,8] Meanwhile, we also disclosed the asymmetric copper-catalyzed arylation of styrenes, in which benzylic radicals generated by the addition of radicals to styrenes could also be efficiently trapped by chiral (Box)Cu^{II}Ar species, leading to enantiopure 1,1-diarylmethane derivatives.[9,10] By merging these studies, we thus envisioned that the asymmetric arylation of benzylic C-H bonds might be possible via a similar radical relay process (Scheme 1A),[11] providing an attractive protocol for the synthesis of enantiomerically enriched 1,1-diarylalkanes as important pharmacophores.[12] Herein, we communicate our study on the asymmetric benzylic C-H arylation (Scheme 1B), wherein introducing a carbonyl ester group into Box ligand is essential for the good chemo- and enantioselectivity.



Scheme 1. Asymmetric benzylic C-H arylation via radical relay.



Very recently, we[13a] and Stahl[13b] group simultaneously reported copper-catalyzed arylation of benzylic C-H bonds via a radical relay process. Owing to the slow transmetalation (Scheme 1B), a less steric bulky ligand TMPhen (tetramethyl-phenanthroline) is essential for our reaction to give the desired arylation products **3** with excellent chemoselectivity.[13a] However, when the bulky chiral ligand **L1**, a privileged ligand used in our previous asymmetric arylation of styrenes,[10] was tested for the asymmetric benzylic C-H arylation, the reaction of **1a** exhibited a moderate reactivity (53% conversion) and poor selectivity to give the desired product **3a** in 24% yield, along with the side fluorination and amination products **4a** and **5a** in 21% overall yield. The chiral ligand **L2** with bulkier *gem*-dibenzylic groups showed worse reactivity and selectivity (eq 1). We reasoned that the larger steric hindrance of the chiral ligands **L1** and **L2** could make the transmetalation between **(L*)**Cu(II) species and PhB(OH)$_2$ more difficult,[14] thus leading to the low-concentrated **(L*)**Cu^{II}Ar species which is not enough to capture the active benzylic radicals efficiently (Scheme 1B).[15] Therefore, other side reactions of the benzylic radicals, such as radical fluorination[16] and radical oxidation/amination,[17] occurred to give the side products **4a** and **5a**. Although further optimization

[a] W. Zhang, L. Wu, Dr. P. Chen, Prof. Dr. G. Liu
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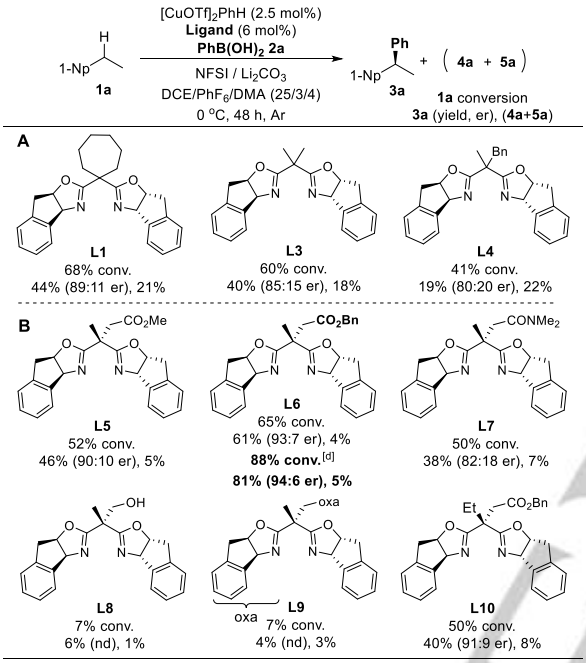
of the reaction conditions slightly increased a yield of the reaction, the chemo- and enantioselecivity could not be further improved (see Table 1A and SI). Similar results were obtained using other Box ligands (**L3**-**L4**).

In order to further survey the asymmetric benzylic C-H arylation, we assumed that enhancing the interaction between the (**L***)Cu(II) species and $ArB(OH)_2$ by introducing a functional group (FG) into the chiral ligands (**L***) might be a reasonable strategy to accelerate the transmetalation step, thus leading a higher concentration of (**L***)$Cu^{II}Ar$ and prohibiting side reactions.

Table1. Optimization of the reaction conditions.[a,b,c]



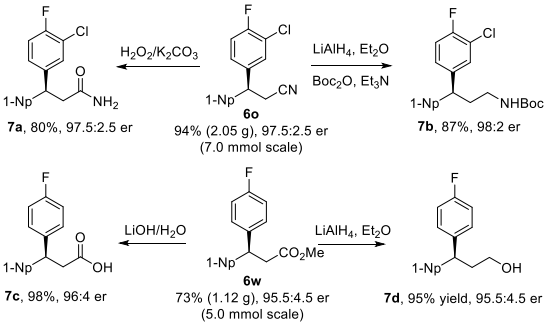
[a] All the reactions were conducted on a 0.1 mmol scale: [$(CuOTf)_2PhH$] (2.5 mol%), **L*** (6.0 mmol%), NFSI (4 equiv.), **2a** (4 equiv.) at 0 °C; [b] Conversion (**1a**) and yields of **3a** and **4a**+**5a** were determined by ^1H NMR using CH_3NO_2 as an internal standard. [c] Enantiomeric ratios were determined by HPLC on a chiral stationary phase. [d] Reactions were conducted with [$(CuOTf)_2PhH$] (1.0 mol%), **L6**(2.4 mmol%), NFSI (6 equiv.), **2a** (6 equiv.) at 0 °C.

On the basis of the above-mentioned hypothesis, a series of functional groups were introduced into Box ligands. The screening results revealed that the ligands **L5**-**L7** bearing a carbonyl group exhibited much better chemoselectivity (Table 1B). The reaction using the ligand **L5** provided the desired product **3a** in 46% yield (52% conversion) with an enantiomeric ratio (er) of 90:10. The ligand **L6** exhibited a better selectivity to give **3a** in 61% yield (65% conversion) with 93:7 er, along with trace side products. Notably, the selectivity for the reaction with **L7** bearing an acetamidyl group was slightly lower, and the ligand **L8** bearing a hydroxyl group also exhibited excellent chemoselectivity, but low conversion of **1a** was observed. When a strongly coordinating oxazoline moiety was introduced into the ligand **L9**, low conversion of **1a** was also observed, presumably due to the increased steric hindrance in copper catalysts by a side-arm effect.[18] In addition, increasing a little steric hinderance of alkyl groups in the Box ligand (**L10**) led to slightly lower reactivity and selectivity. Finally, with further optimizing reaction condition, the reaction of **1a** in the presence of Cu(I) (1 mol%) and **L6** (2.4 mol%) delivered the desired product **3a** in 81% yield with 94:6 er (Table 1B).

With the optimized reaction conditions in hand, the substrate scope of this asymmetric benzylic C-H arylation was then investigated. As shown in Table 2, 1-alkyl naphthalenes bearing different alkyl groups and various functional groups on the alkyl chain could be employed as substrate, affording the corresponding products **3b**-**3l** in moderate to good yields with excellent enantioselectivities (up to 98.5:1.5 er). Meanwhile, substrates bearing electron-donating or withdrawing groups on the naphthyl ring were also suitable for the reaction to give the desired products **3m**-**3x** with good to excellent enantioselectivities (up to 96:4 er). Notably, various functional groups, such as halide, phthalimide, HCF_2O, ether, cyano, ketone, silyl, ketone, and ester, were compatible with the reaction conditions. For 1,5-diethylnaphthylene **1t** bearing two benzylic positions, the reaction provided the major monoarylation product **3t** in 56% yield with 92.5:7.5 er, along with α,α'-diarylation product **3t'** in 22% yield (dr 9/1). In addition, 3-ethylbenzanthrone **1y** yielded the desired product **3y** in 43% yield with good enantioselectivity. Furthermore, the reactions of substrates bearing heteroarenes, such as benzothiophene (**3z**) and indazole (**6a**), also worked nicely to deliver the arylation products with good to excellent enantioselectivity, *albeit* in low yields. Compared to alkyl naphthalenes, alkyl benzenes as substrate generally exhibited worse reactivities to give the desired arylation products **6b**-**6c** with lower enantioselectivities (~85:15 er). The absolute configuration of the products was unambiguously determined by the X-ray crystal structure of **3o**.

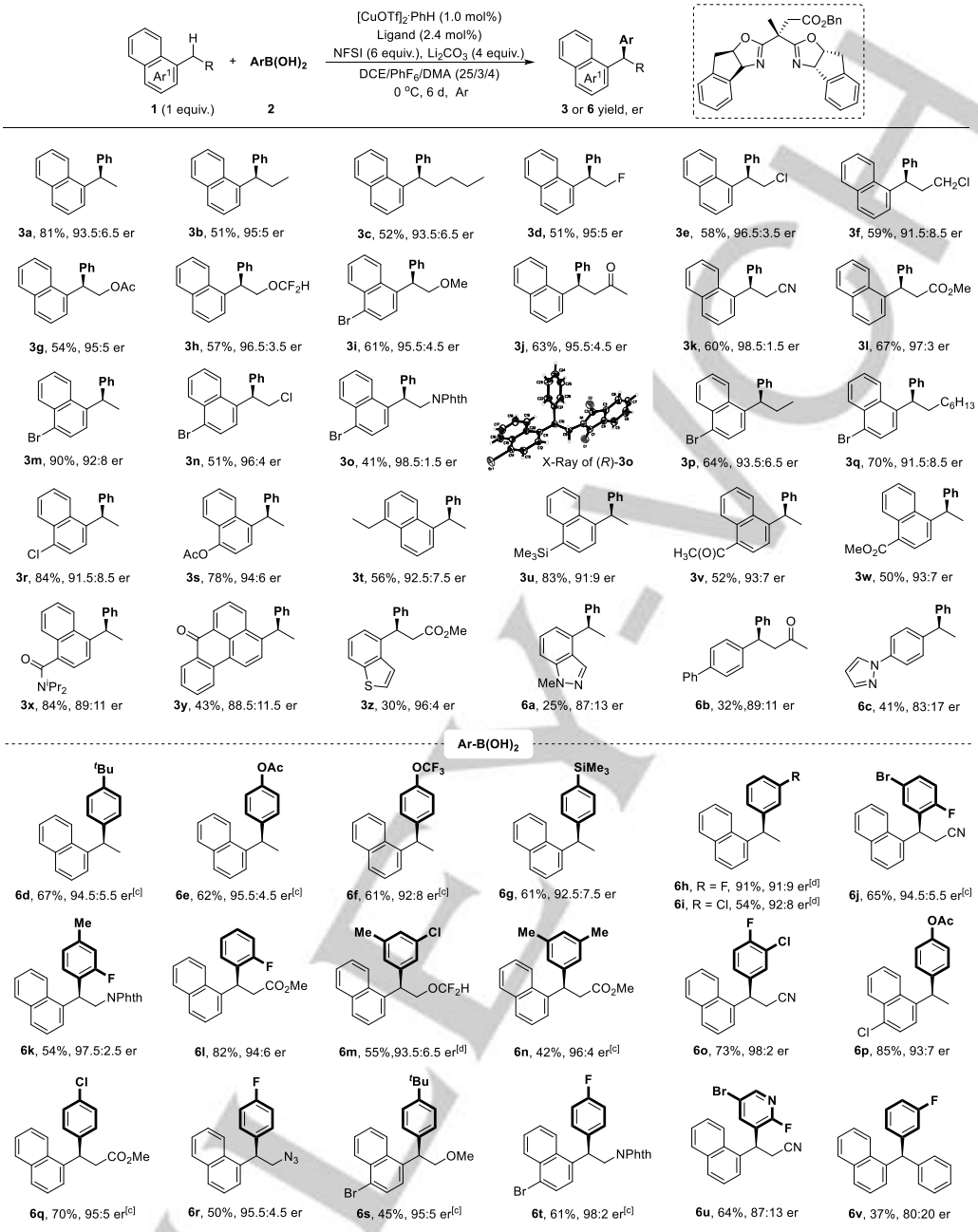
Then, we turn our attention to examining aryl boronic acids. As shown in table 2, a wide variety of aryl boronic acids bearing electron-donating or electron-withdrawing groups reacted smoothly with **1a** to give the corresponding products **6d**-**6i** in moderate to good yields (54-91%) with excellent enantio-selectivities (up to 95.5 : 4.5 er). In addition, these aryl boronic acids could also be coupled with various alkylnaphthylenes to afford the enantiomerically enriched 1,1-diaryl alkanes **6j**-**6t** in good yields with good to excellent enantioselectivities (93:7-98:2 er). Again, excellent functional group tolerance was observed, and pyridyl boronic acid was also suitable for the reaction to give the desired product **6u** in 64% yield with 87:13 er.

1,1,1-Triarylmethanes can be frequently found in pharmaceuticals and material science, but the synthesis of their enantiomers is quite challenging.[19] It is noteworthy that 1,1,1-triarylmethane **6v** was easily prepared by our methodology in acceptable yields with moderate enantioselectivity (80:20 er).



Scheme 2. Gram-scale reaction and further transformations.

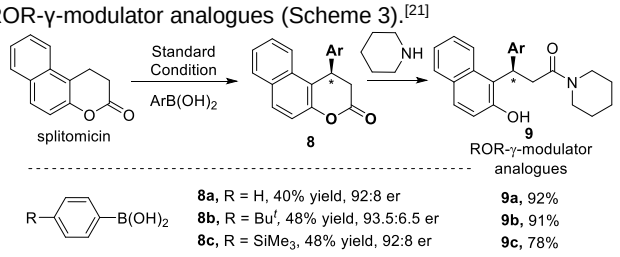
Table 2. Substrate scope of alkylarenes and aryl boronic acids.[a,b]



[a] All the reactions were conducted on a 0.2 mmol scale . [b] Isolated yields and er value was determined by HPLC on a chiral stationary phase. [c] $[CuOTf]_2$·PhH (2.5 mol%), ligand (6 mol%). [d] CuOAc (5 mol%), ligand (6 mol%).

To demonstrate the utility of our method, the asymmetric arylations were performed on a gram scale to provide the products **6a** (2.05 g, 91% yield, 97.5:2.5 *er*) and **6b** (1.12g, 73% yield, 95.5:4.5 *er*), which could be easily converted to the corresponding chiral 3,3-diarylpropionamide **7a**, acid **7c**, amine **7b** and alcohol **7d** in excellent yields without loss of enantioselectivity (Scheme 2).

Splitomicin and its analogues **8** were identified as micromolar inhibitor of Sir2.[20] The late-stage asymmetric arylation of Splitomicin could be successfully achieved by our current method to provide various arylated products **8a**-**8c** in moderate yields with good enantioselectivities, which could be further converted into the ring-opening amination products **9** as ROR-γ-modulator analogues (Scheme 3).[21]



Scheme 3. Late-stage functionalization of Splitomicin.

In order to clarify the ligand effect on the arylation reaction, the same reaction using different ligands (**L6** *vs* **L1**) was analyzed at various times. As shown in Figure 1, both two reactions exhibited a remarkable induction period, and the reaction with **L6** had a shorter induction period than that using **L1**. Meanwhile, the different reaction rates were observed as follows: $k_{L6} > k_{L1}$, indicating that the ester moiety in **L6** had a significant effect on the reaction. We reasoned that a possible interaction between the ester group in **L6** and $ArB(OH)_2$ promoted the transmetalation step, thus leading to a relative higher concentration of (**L6**)$Cu^{II}Ar$ species, which could trap benzylic radicals efficiently. Therefore, a shorter induction period and faster rate were observed.[22]

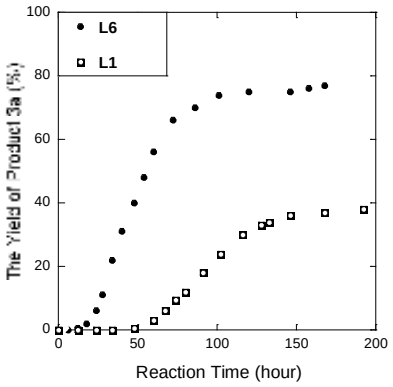


Figure 1. Ligand effect on the reaction of **1a**.

In conclusion, we have developed a copper-catalyzed enantioselective arylation of benzylic C-H bonds via radical relay using alkylarenes as limiting reagent, which provides an efficient and straightforward approach to various chiral 1,1-diarylalkanes with good to excellent enantioselectivities. The enhancement of chemo- and enantioselectivity for the arylation of benzylic C-H bonds depends on the introduction of a benzyl ester moiety into bisoxazoline (BOX) ligands. Owing to the limited substrate scope on alkyl naphthylene substrates of this arylation,[23] further improving catalytic systems and the mechanism study are still in progress in our laboratory.

Acknowledgements

We are grateful for financial support from the National Basic Research Program of China (973-2015CB856600), the National Nature Science Foundation of China (NFSC, Nos. 21532009, 21790330, 21821002 and 21761142010), the Science and Technology Commission of Shanghai Municipality (Nos. 17XD1404500, 17QA1405200 and 17JC1401200), and the strategic Priority Research Program (No. XDB20000000) and the Key Research Program of Frontier Science (QYZDJSSWSLH055) of the Chinese Academy of Sciences. This research was also partially supported by CAS Interdisciplinary Innovation Team.

Keywords: Asymmetric radical reaction • Copper-Catalyzed • Benzylic C-H • Arylation • hydrogen atom abstraction

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[22] Although details are unclear at the moment, we assumed a weak hydrogen bonding effect between the ester moiety in **L6** and aryl boronic acids might be possibly beneficial for the transmetalation step.

[23] When *p*-ethyl *tert*-butylbenzene was treated under standard condition, the reaction exhibited poor reactivity to give trace amount product, along with recovered substrate (>95%). It is possible that the hydrogen atom abstraction of benzylic C-H did not occur with unclear reason.

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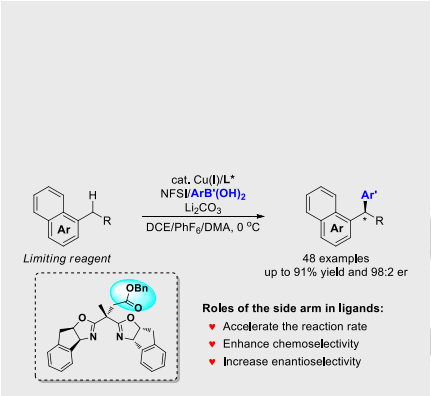
Asymmetric Cu-catalyzed arylation of benzylic C-H bonds using alkylarenes as a limiting reagent has been developed, providing an efficient access to various chiral 1,1-diarylalkanes in good yields with good to excellent enantioselectivities, and displays excellent functional group tolerance. A chiral bisoxazoline ligand bearing an acetate ester moiety plays a key role in both reactivity and enantioselectivity.



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