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Communication

Cu-Catalyzed Enantioselective Alkylarylation of Vinylarenes Enabled by Chiral Binaphthyl–BOX Hybrid Ligands

Shunya Sakurai, Akira Matsumoto, Taichi Kano, and Keiji Maruoka*

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ABSTRACT: Transition-metal-catalyzed radical relay coupling reactions have recently emerged as one of the most powerful methods to achieve difunctionalization of olefins. However, there has been limited success in applying this method to asymmetric catalysis using an effective chiral ligand. Herein we report the Cu-catalyzed enantioselective alkylarylation of vinylarenes using alkylsilyl peroxides as alkyl radical sources. This reaction proceeds under practical reaction conditions and affords chiral 1,1-diarylalkane structures that are found in a variety of bioactive molecules. Notably, a highly enantioselective reaction was accomplished by combining chiral bis(oxazoline) ligands with chiral binaphthyl scaffolds.

The difunctionalization of olefins is one of the most powerful methods to create complex organic molecules in a single step.[1] In recent years, a number of methods for the dicarbofunctionalization of olefins under transition-metal catalysis have been developed.[2] The alkylarylation of vinylarenes via radical relay coupling is practically attractive because it enables the facile and modular synthesis of 1,1-diarylalkanes,[3] which are found in a variety of pharmaceuticals and bioactive molecules (Figure 1).[4−6] Several attempts to achieve

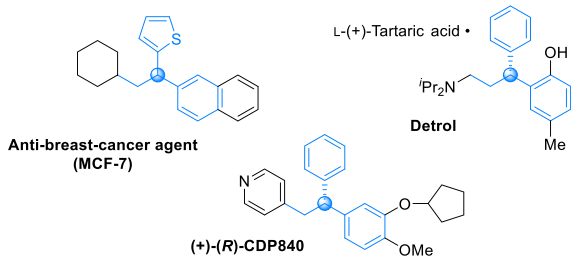

Figure 1. Pharmaceuticals and bioactive molecules with chiral 1,1-diarylalkane structures.

the asymmetric alkylarylation of vinylarenes using transition-metal catalysts and chiral ligands have already been reported. However, the number of successful examples with high enantioselectivity remains low, and these are limited to specific structures such as 2-trifluoromethylated 1,1-diarylethanes.[3b] To address this issue, we postulated that one of the most crucial reasons for the limited number of examples reported to date might be the lack of an effective chiral ligand scaffold for the construction of a variety of 1,1-diarylalkane structures with high enantioselectivity. Herein we report the design of novel chiral ligands that enable a highly regio- and enantioselective Cu-catalyzed synthesis of chiral 1,1-diarylalkanes.

We recently reported Cu-catalyzed C(sp^3)−C(sp^2) bond formations using alkylsilyl peroxides (ASPs),[7] which are bench-stable and easy-to-handle alkyl radical precursors, and arylboronic acids via a radical process.[7g] On the basis of that study, we hypothesized that the generation of alkyl radicals (**INT-1**) from ASPs and a Cu^I catalyst in the presence of vinylarenes could give the corresponding benzyl radicals (**INT-2**). The subsequent cross-coupling of **INT-2** with arylboronic acids under the influence of a Cu^{II} catalyst and a well-designed chiral ligand could furnish 1,1-diarylalkane structures in an enantioselective manner (Figure 2a).

To test our hypothesis, we initially conducted reactions using ASP **1a**, methyl 4-vinylbenzoate (**2a**), and 4-fluorophenylboronic acid (**3a**) with a Cu/bipyridyl catalyst system. While the use of 1.0 equiv of **2a** provided **4a′**, the two-component C(sp^3)−C(sp^2) coupling product from **1a** and **3a**, as the major product, the use of 3.0 equiv of **2a** afforded the desired product **4a** in 61% yield with the formation of **4a′** sufficiently suppressed. We also confirmed that the unreacted vinylarene **2a** could be recovered (see the Supporting Information (SI) for details). Next, we examined some chiral ligands to realize an asymmetric catalytic system as shown in Figure 2b. Neither chiral ligand **L1**[8] nor **L2**[9] promoted a highly enantioselective reaction, and other bidentate or tridentate ligands furnished **4a** with less than 48% ee (see Table S2 for details). While low enantioselectivities were observed in the case of the indanyl-substituted bis(oxazoline) (BOX) ligands[9] **L3** (20% ee) and **L4** (32% ee), the structure of the cyclic backbone was found to affect the enantioselectivity. We then tested chiral BOX ligand **L5**,[3b] which contains a cycloheptyl moiety on the backbone, and discovered that it provided **4a** with moderate ee (56% ee). These results indicate that the introduction of a simple cyclic alkane structure onto the backbone of a chiral BOX ligand was still insufficient to achieve

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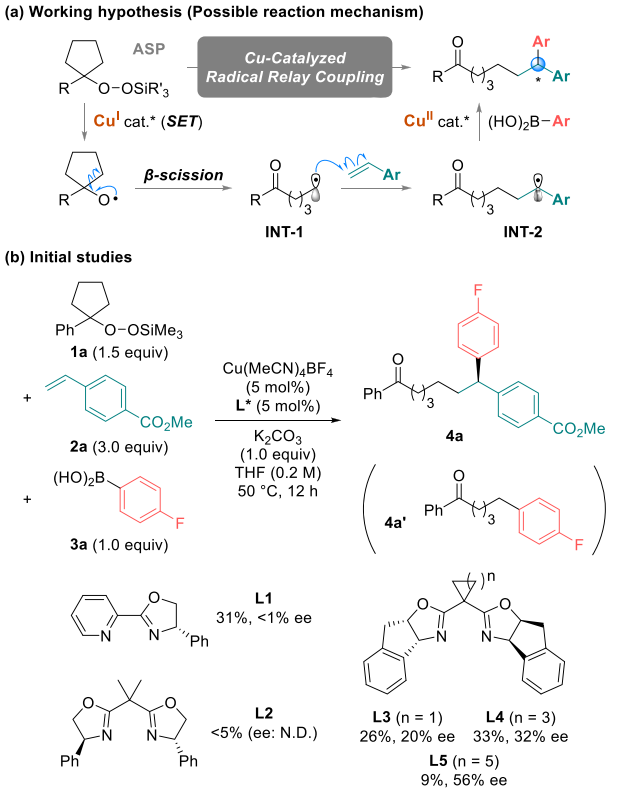


Figure 2. Working hypothesis and initial studies.

high enantioselectivity. Therefore, we envisioned that the introduction of another steric factor onto the cyclic backbone could change the asymmetric environment surrounding the reactive site, which would in turn provide the desired 1,1-diarylalkane structure in a more enantiomerically enriched form. In this context, we chose chiral 2,2′-dimethyl-1,1′-binaphthalene derivatives,[10] which are readily prepared from a variety of chiral BINOL derivatives, to form the new backbone and developed a series of novel chiral binaphthyl−BOX (BN−BOX) hybrid ligands (Figure 3a).[11] A notable feature of our ligand design is that the steric environment of the chiral backbone can be modified flexibly by the introduction of substituents at the 3- and 3′-positions of the binaphthyl moiety or partial reduction of the binaphthyl skeleton. To the best of our knowledge, such chiral BN−BOX hybrid ligands have not yet been studied in asymmetric cross-coupling reactions.[11]

To confirm what steric effects, if any, arise from the modulation of the substituents at the 3,3′-positions of the binaphthyl moiety, we synthesized the two novel chiral BN−BOX hybrid ligands **L6** and **L7**, and prepared their respective complexes with $CuBr_2$ (Figure 3b). Single-crystal X-ray diffraction analysis of $CuBr_2$·**L6** and $CuBr_2$·**L7** revealed that their steric environments differ significantly from each other and that of a previously reported crystal structure of a $CuBr_2$·chiral indanyl-substituted BOX ligand complex.[9b]

To check their potential for asymmetric catalysis, we subsequently applied **L6** and **L7** to a Cu-catalyzed three-component radical relay coupling reaction of **1a**, **2a**, and **3a** (Table 1). We were pleased to see that the use of **L6** and **L7** afforded **4a** with better enantioselectivities (66% ee and 76% ee, respectively) than when **L5** was used (56% ee). We then extended the series of chiral BN−BOX hybrid ligands and tested them to identify the most suitable ligand structure. The

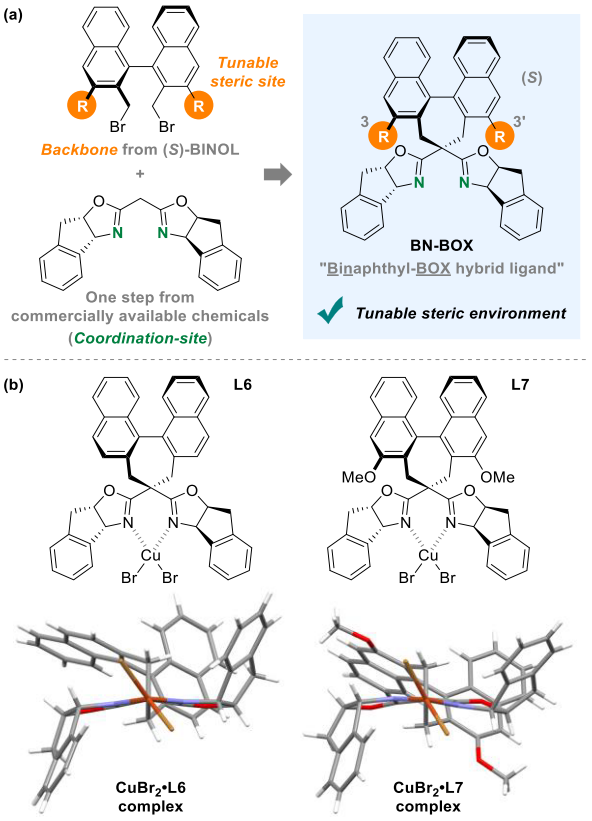
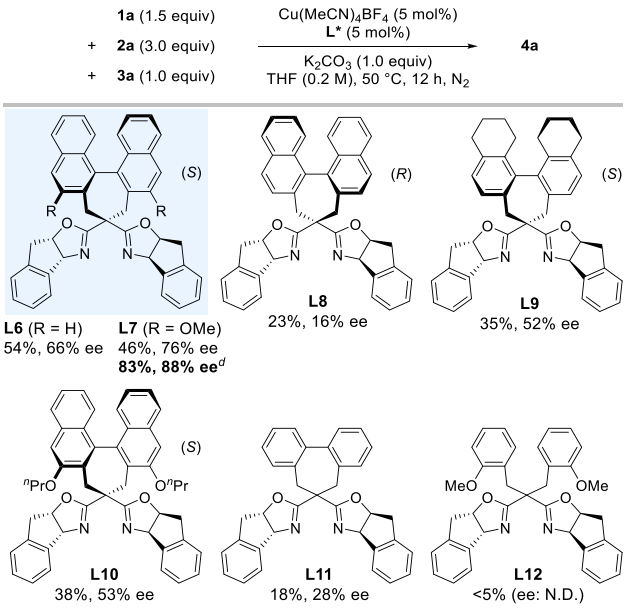


Figure 3. (a) Novel design of chiral binaphthyl−BOX hybrid ligands. (b) Single-crystal X-ray diffraction analysis of $CuBr_2$·**L6** and $CuBr_2$·**L7**.

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



[a]Reactions were performed on a 0.2 mmol scale based on **3a**. [b]Yields were determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [c]Enantiomeric excesses were determined by chiral HPLC. [d]Deviations: Cu(OTf)·$^1/_2$benzene (0.01 mmol) was used instead of $Cu(MeCN)_4BF_4$, and the reaction was performed in 1,4-dioxane (2.0 mL) for 3 h without K_2CO_3. Isolated yield. **4a′**: 6% NMR yield. N.D.: not determined.

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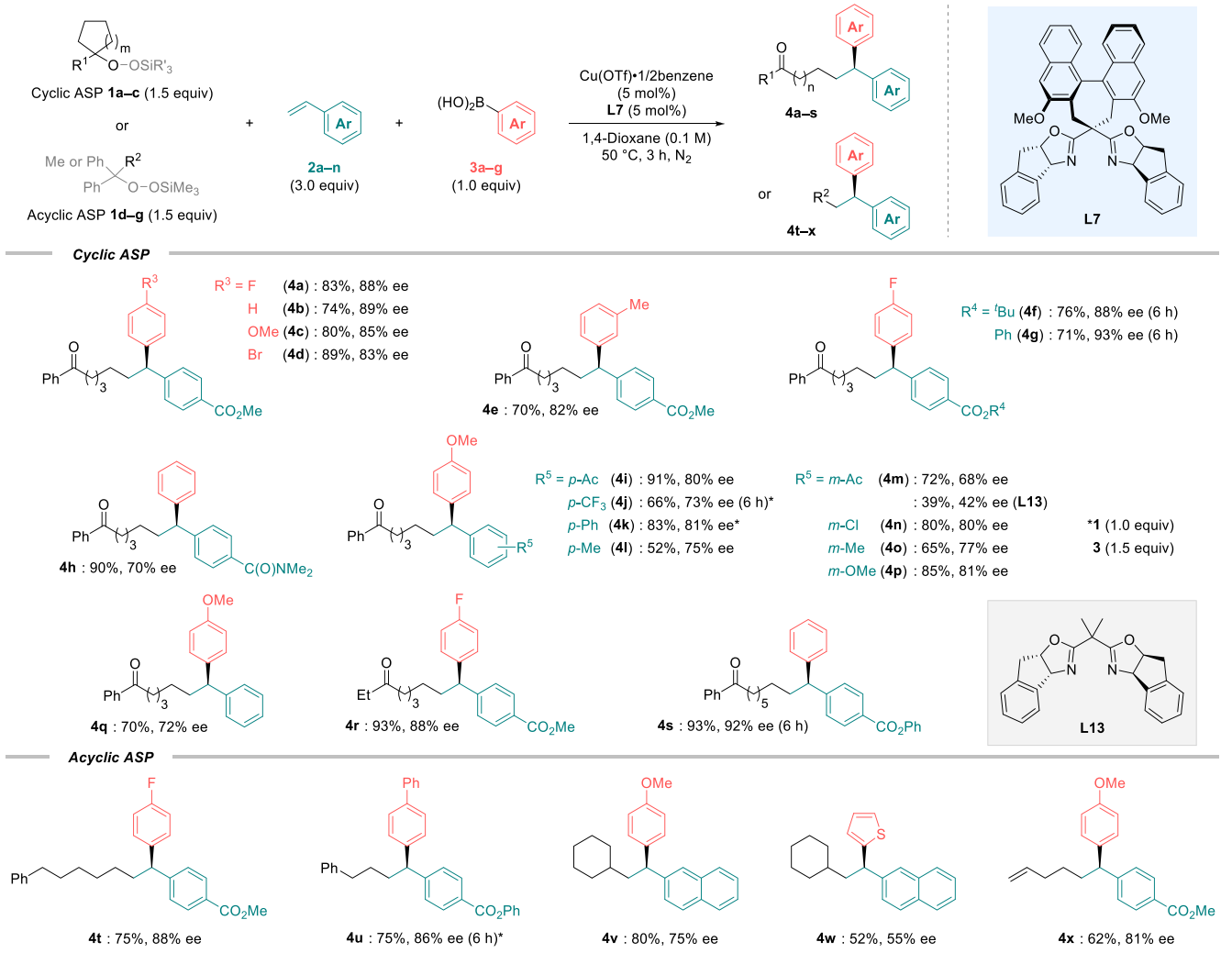
Table 2. Substrate Scope



use of **L8** bearing an (*R*)-1,1′-binaphthyl moiety and **L9** bearing an (*S*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl moiety produced **4a** with lower enantioselectivities (16% ee and 52% ee, respectively) than when **L7** was used. The reaction using **L10**, which contains longer alkoxy groups at the 3- and 3′-positions of the binaphthyl moiety compared with **L7**, was found to be less enantioselective (53% ee). On the basis of these results, we chose **L7** as the optimal ligand structure for the present reaction. We also investigated the reactions using **L11** and **L12**, both of which do not contain a binaphthyl backbone. As expected, these ligands showed significantly lower enantioselectivities than **L7**, confirming the importance of the binaphthyl backbone for the creation of an efficient asymmetric environment. Using **L7** as chiral ligand, we optimized the other reaction conditions and found the use of Cu(OTf)·$^1/_2$benzene as the Cu source and 1,4-dioxane as the solvent in the absence of any additive to constitute the optimal conditions (83% yield, 88% ee; see the SI for details).[12]

With the optimized reaction conditions in hand, we investigated the substrate scope of the reaction using a variety of ASPs **1**, vinylarenes **2**, and arylboronic acids **3** (Table 2; a detailed list of the combinations of **1**−**3** and corresponding products **4** is shown in Table S8).[13] Initially, we examined the effect exerted by the substituents on the arylboronic acids using **1a** and **2a**. The use of phenylboronic acid (**3b**) and para-substituted arylboronic acids bearing an electron-donating methoxy group (**3c**) or an electron-withdrawing bromo group (**3d**) afforded the corresponding products **4b**−**d** in high yields (74−89%) with high enantioselectivities (83−89% ee). It was also possible to use *m*-tolylboronic acid (**3e**) in this reaction, which afforded **4e** in 70% yield with 82% ee. Then we attempted to expand the scope of the vinylarenes by using substrates substituted with esters or amide at the para position (**2b**−**d**). The introduction of a *tert*-butyl ester did not affect the enantioselectivity (**4f**, 88% ee), whereas the presence of a phenyl ester moiety improved the selectivity (**4g**, 93% ee). The reaction with a vinylarene having *N*,*N*-dimethylaminocarbonyl substitution at the para position also proceeded smoothly, albeit with a slightly lower enantioselectivity (**4h**, 70% ee). The use of other para-substituted vinylarenes **2e**−**h** with **3c** gave the desired products **4i**−**l** with good to high enantioselectivities (73−81% ee). We next applied meta-substituted vinylarenes **2i**−**l** to the reaction using **1a** and **3c** as coupling partners. In the case of 3-vinylacetophenone (**2i**), the reaction using BOX ligand **L13** without a binaphthyl backbone under the standard conditions provided the corresponding product **4m** with low enantioselectivity (42% ee). On the other hand, replacement of the chiral ligand with **L7** led to a significant increase in the enantioselectivity (68% ee). Although there is

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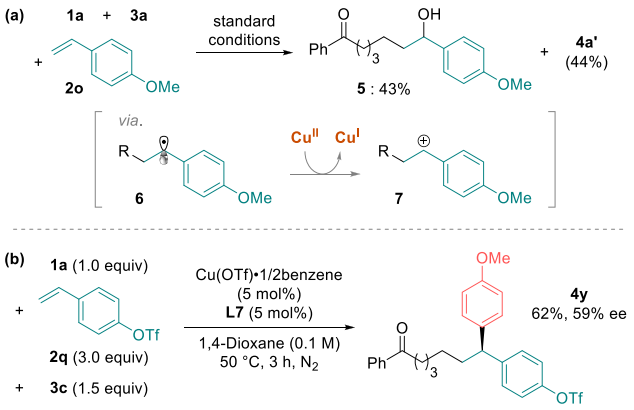
still room for improvement, these results further support the effectiveness of our designed BN−BOX hybrid ligand **L7**. An electron-withdrawing chloro group and a weak electron-donating methyl group were tolerated in the reaction, as was a strong electron-donating methoxy group at the meta position of the vinylarene (**4n−p**, 77−81% ee). Nonsubstituted styrene (**2m**) was also applicable under the reaction conditions (**4q**, 70% yield, 72% ee). Subsequently, we investigated the scope of ASPs and discovered that both cyclic and acyclic ASPs could be used. Cyclic ASPs (**1b** and **1c**) provided the corresponding products **4r** and **4s** with high enantioselectivities (88% ee and 92% ee, respectively). Moreover, the use of acyclic ASPs (**1d−f**) resulted in the formation of various primary and secondary alkyl radicals without a carbonyl moiety, affording 1,1-diarylalkanes **4t−v** with good to high enantioselectivities (75−88% ee). Notably, our method was also applicable to the enantioselective synthesis of **4w** (52% yield, 55% ee), which has anti-breast-cancer activity against MCF-7 breast cancer cells. The use of ASP **1g** containing a cyclopropylmethyl moiety furnished ring-opened product **4x** in 62% yield with 81% ee, indicating that this three-component coupling proceeded via a radical process.

During the investigation into the scope of vinylarenes, we observed that the use of electron-rich vinylarene **2o** under the standard conditions provided benzylic alcohol **5** along with **4a′**, whereas the desired 1,1-diarylalkane was not obtained (Scheme 1a). Considering that electron-rich benzylic radicals

Scheme 1. Reactions Using Vinylarene 2o or 2q



are readily oxidized to benzylic cations,[6] we suppose that single-electron oxidation of benzylic radical **6** by Cu^{II} and subsequent nucleophilic addition of the silanoxide derived from the ASP to the benzylic cation intermediate **7** gave benzylic alcohol **5** faster than the formation of the three-component radical coupling product. In addition, the formation of a considerable amount of **4a′** would be attributed to the relatively slow addition of the nucleophilic alkyl radical to electron-rich vinylarene **2o** (see the SI for details). As an alternative method, we applied 4-vinylphenyl trifluoromethanesulfonate (**2q**) as a *p*-oxygen-substituted vinylarene instead of **2o**.[14] The desired reaction using **2q** proceeded to give the product **4y**, albeit in moderate yield and enantioselectivity (Scheme 1b).

The synthetic utility of the obtained 1,1-diarylalkane products was successfully demonstrated for the transformations of **4a** and **4d** as shown in Figure 4. The benzoyl moiety of **4a** was reduced to a simple alkane in a one-pot deoxygenation,

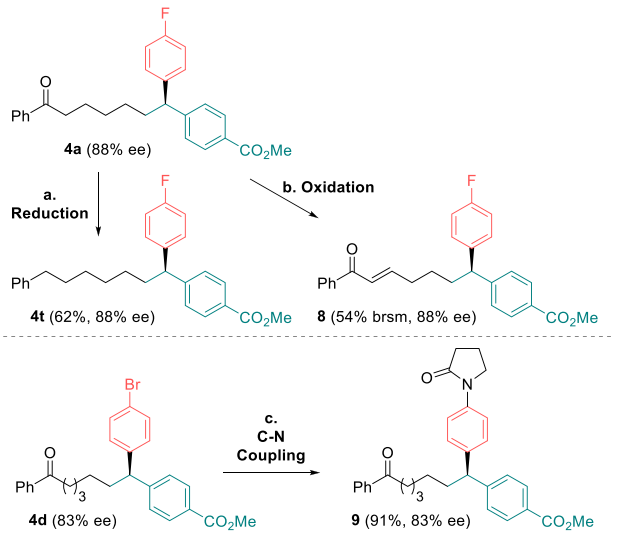
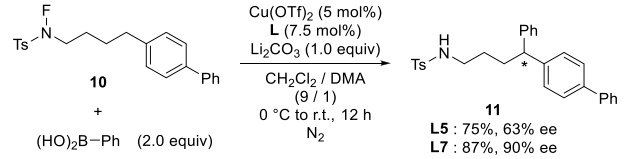


Figure 4. Transformations of **4a** and **4d**: (a) (i) $NaBH_4$, MeOH, 0 °C; (ii) BF_3·OEt_2, $HSiEt_3$, CH_2Cl_2, 0 °C to r.t.; 62% yield (in total, one pot). (b) TsOH·H_2O, IBX, DMSO, 85 °C; 54% brsm. (c) $Pd_2(dba)_3$, Xantphos, pyrrolidone, Cs_2CO_3, 1,4-dioxane, 100 °C; 91% yield.

furnishing **4t** in 62% yield with 88% ee. In addition, desaturation of **4a** by 2-iodoxybenzoic acid (IBX) provided the corresponding α,β-unsaturated ketone **8** without decreasing the enantiomeric excess. Furthermore, we also conducted Pd/Xantphos-catalyzed amidation of the C(Ar)−Br bond using **4d** as a substrate.[15] As expected, the desired product **9** was obtained in 91% yield with 83% ee.

To show the applicability of chiral BN−BOX hybrid ligands to the Cu-catalyzed enantioselective synthesis of 1,1-diarylalkane structures, we conducted the enantioselective δ-C−H arylation of *N*-fluorotosylamide, in which benzyl radicals are generated via an intramolecular hydrogen atom transfer (HAT) process.[16] The desired enantioselective δ-C−H arylation of **10** proceeded smoothly to afford **11** in 87% yield with 90% ee when **L7** was used under slightly modified reaction conditions (Scheme 2). When **L5** was used instead,

Scheme 2. Application of BN−BOX Hybrid Ligands to Another Enantioselective Cu Catalysis



11 was obtained in 75% yield with 63% ee. These results demonstrate the versatility of BN−BOX hybrid ligands for the enantioselective cross-coupling reaction of benzyl radicals with arylboronic acids to construct chiral 1,1-diarylalkane structures.

In summary, we have developed a highly enantioselective three-component radical relay coupling of alkylsilyl peroxides, vinylarenes, and arylboronic acids. In this study, we designed a novel set of binaphthyl−bis(oxazoline) (BN−BOX) hybrid ligands and demonstrated their applications in a versatile fashion to Cu-catalyzed couplings for the asymmetric construction of 1,1-diarylalkane structures. We are convinced that these BN−BOX hybrid ligands will find applications in a broad range of asymmetric transition-metal-catalyzed reactions.

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Further investigations of applications of the Cu/BN−BOX hybrid ligand system are currently in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c09008.

Experimental procedures and spectral data (PDF)
Crystallographic data of $CuBr_2$·**L6** (CIF)
Crystallographic data of $CuBr_2$·**L7** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Keiji Maruoka − *Department of Chemistry, Graduate School of Science and Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto 606-8502, Japan; School of Chemical Engineering and Light Industry, Guangdong University of Technology, Guangzhou 510006, China;* orcid.org/0000-0002-0044-6411; Email: maruoka.keiji.4w@kyoto-u.ac.jp

Authors

Shunya Sakurai − *Department of Chemistry, Graduate School of Science, Kyoto University, Kyoto 606-8502, Japan*

Akira Matsumoto − *Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto 606-8501, Japan;* orcid.org/0000-0002-3719-8597

Taichi Kano − *Department of Chemistry, Graduate School of Science, Kyoto University, Kyoto 606-8502, Japan;* orcid.org/0000-0001-5730-3801

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c09008

Notes

The authors declare no competing financial interest.

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