Copper/BINOL-Catalyzed Enantioselective C-H Functionalization towards Planar Chiral Ferrocenes Under Mild Conditions

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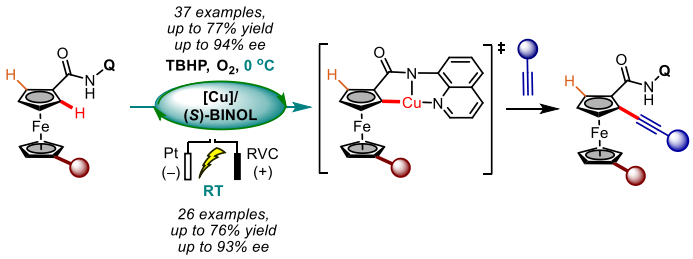
Abstract: Copper-catalyzed enantioselective C–H activation proceeds through inner-sphere mechanism remains a huge challenge. Herein, a copper-catalyzed enantioselective C−H alkynylation with terminal alkynes assisted by 8-aminoquinoline using readily available (*S*)-BINOL as chiral ligand was disclosed. The reaction proceeded under mild conditions with a catalytic amount of copper salt, providing a range of chiral ferrocenes in good yields and enantioselectivities (0 °C, up to 77% yield and 94% ee). The alteration of stoichiometric chemical oxidant with renewable electricity is also feasible at ambient temperature, demonstrating the robustness of this copper/BINOL catalysis. Notably, this is the first enantioselective cupraelectro-catalyzed C-H activation reaction. Gram-scale synthesis, versatile transformations, and application of the resulting oxazoline-olefin ligand in asymmetric synthesis also highlight the utility of the protocols.



Introduction

Over the past years, transition metal-catalyzed enantioselective C–H activation has emerged as a powerful and efficient tool for the construction of molecular chirality.[1] Significant progresses have been achieved on asymmetric C-H functionalization catalyzed by noble transition metals.[2] From a practical and sustainable viewpoint, it would be highly appealing and desirable to explore the use of earth-abundant 3d transition metals as inexpensive and biologically friendly alternatives with complementary or even better reactivity and enantiocontrol.[3] As an earth-abundant and inexpensive 3d transition metal, copper, was one of the prime contenders for this consideration.[4] More importantly, owning to the easily accessible oxidation states ranging from 0 to +3 through both radical pathway and two-electron transfer,[4] copper-complexes might offer unique reactivity that are unavailable for precious metals.[5-8] Significant advances have been achieved in Cu-catalyzed enantioselective C−H functionalization through outer-sphere mechanism, including asymmetric C(sp^3)–H insertion into copper carbenoid complexes with chiral Box ligand,[5] atroposelective dimerization of electron rich arenes to construct axial chirality via SET mechanism,[6] asymmetric Kharasch–Sosnovsky

reaction,[7] and hydrogen atom transfer radical relay mechanism involving the asymmetric reaction of the carbon-centered radical with a chiral Cu center (Figure 1A).[8] However, Cu-catalyzed asymmetric C−H activation by inner-sphere pathway, proceeding through the formation of an organometallic C−Cu intermediate, has scarcely been explored. In 2016, Ohmiya and Sawamura described the construction of quaternary stereogenic carbon centers through Cu-catalyzed enantioselective allylic alkylation of azoles.[9a] The reaction proceeded through a LiO*t*Bu-assisted cupration of acidic azole C-H bond, which doesn't involve the formation of chiral C-Cu species. Recently, Duan and coworkers disclosed the asymmetric C–H arylation with diaryliodonium salts enabled by Cu/bisoxazoline system.[9b] However, the scope was limited to specific electron-rich (hetero)arenes, since the reaction mechanically proceeded through the electrophilic cupration.

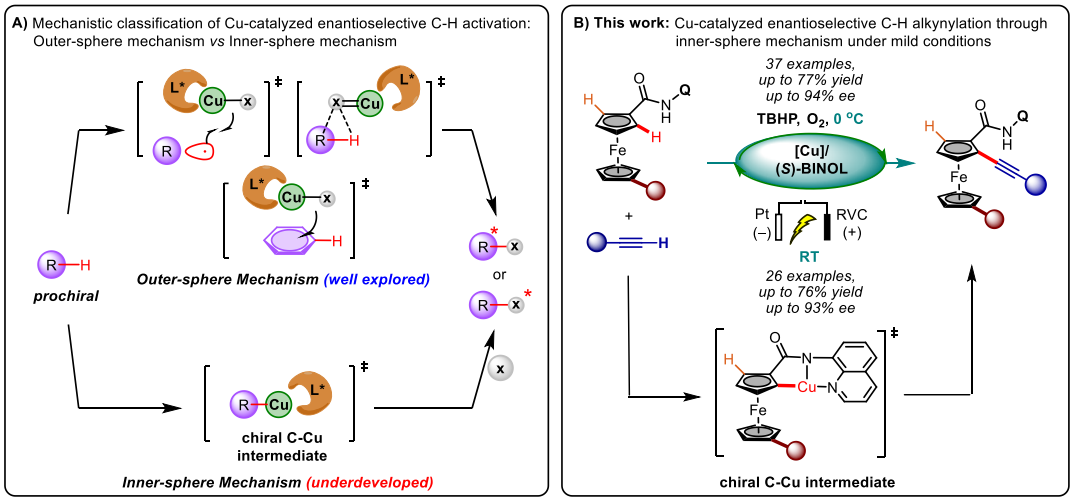


Figure 1. Copper-catalyzed/mediated enantioselective C-H activation.

Since the pioneering works by the Yu and Chatani groups in 2006,[10] copper-catalyzed/mediated C−H activation assisted by directing groups (DGs) is burgeoning, especially by the assistant of strongly coordinating bidentate DGs.[11,12] However, the enantioselective version is still underdeveloped. In 2018, Yu and Dai elegantly introduced a chiral oxazoline amide as directing group to achieve copper-mediated diastereoselective C−H thiolation reactions.[13a] Very recently, during the preparation of this manuscript, Yu and Wang disclosed the enantioselective C−H alkynylation using stoichiometric copper salts.[13b] This breakthrough highlighted the potential of copper catalysis, however, the reaction is limited to the use of stoichiometric amount of copper salts, and unsatisfactory selectivity (1.5:1 to 10:1 mono:di; 76%-86% ee). In continuation of our long-term interest in copper-catalyzed C-H activation[11c] and 3d metal-catalyzed enantioselective C-H activation,[14] we have long pursued to establish an efficient strategy that proceeded through the formation of a chiral C-Cu intermediate, which could be divergently transferred to various C-C and C-X bonds that is inaccessible through outer-sphere mechanism. However, the establishment of such a protocol is highly challenging due to several inherent properties of Cu-catalyzed/mediated C-H activation reactions:[11] 1) The coordination pattern and valence of copper intermediates during the whole reaction is unclear, because of the easily accessible oxidation states (from 0 to +3);[4] 2) Cu-catalyzed/mediated C-H activation reactions largely rely on the use of strongly coordinating directing groups, which could act as stoichiometric ligands to compete with catalytic chiral ligands, leading to strong background reaction; 3) The need of extremely high temperature (generally >130 °C) and selectivity between *mono-*

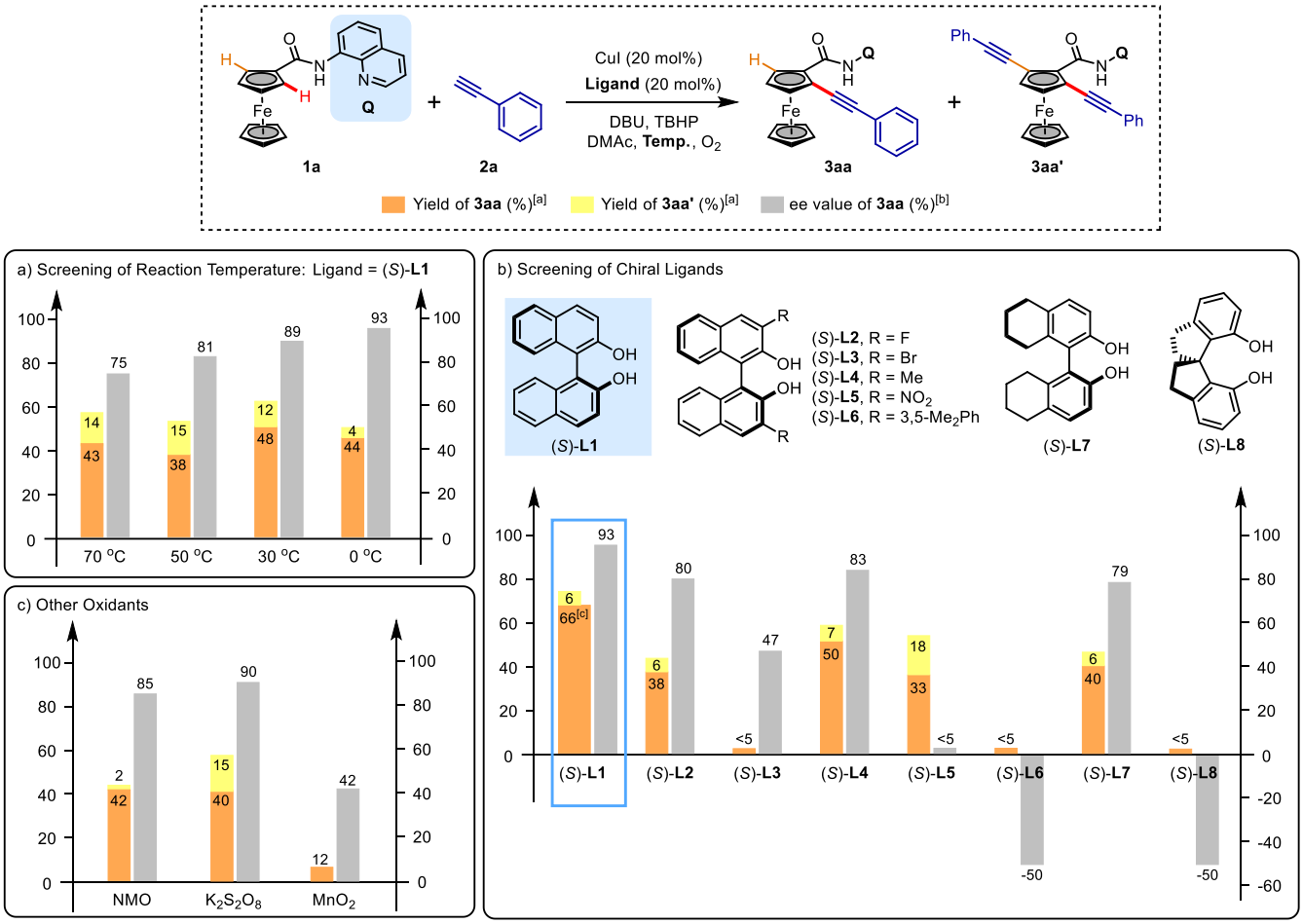
and *di*-functionalization are also long-term hurdles, which are detrimental to stereocontrol.[11] We reported herein a copper-catalyzed enantioselective C−H alkynylation with terminal alkynes assisted by 8-aminoquinoline DG using readily available (*S*)-1,1'-bi-2,2'-naphthol [(*S*)-BINOL] as chiral ligand (Figure 1B).[15] The reaction proceeded under mild conditions with catalytic amount of coper salt, providing a broad range of chiral ferrences in good yields and enantioselectivities (0 °C, 37 examples, up to 77% yield and 94% ee). The alteration of stoichiometric chemical oxidant with renewable electricity in an operationally simple undivided cell is also feasible (room temperature, up to 76% yield and 93% ee), demonstrating the robustness of this copper/BINOL catalysis. Gram-scale synthesis, versatile synthetic transformations, and application of the resulting oxazoline-olefin ligand in asymmetric synthesis also highlight the utility of the protocols.

Results and Discussion

Initial consideration and optimization studies

Planar chiral ferrocenes, are extensively utilized in material science, medicinal chemistry, and asymmetric synthesis. Therefore, extensive efforts have been devoted to their asymmetric synthesis.[16] Recently, transition metal-catalyzed enantioselective C−H activation has become an efficient strategy for the synthesis of planar chiral ferrocenes.[17] We initiated our investigation by testing the asymmetric synthesis of planar chiral ferrocenes by Cu-catalyzed enantioselective C-H alkynylation. Ferrocene carboxamides (**1a**), bearing a 8-aminoquinoline (**Q**) first developed by Daugulis was used as the standard substrate to survey our aforementioned design.[11,12]

At the outset of our studies, we investigated various chiral ligands on the reaction of **1a** with phenylacetylene **2a** in the presence of 20 mol% CuI (Table S1, see supporting information for details). To our delight, when (*S*)-BINOL (**L1**) was used as chiral ligand, the desired mono-alkylated product **3aa** was formed in 43% yield with 75% ee, along with the formation of achiral di-alkynylated product **3aa'** in 14% yield. Other chiral ligands including *N,N*-ligands (**SL1**, **SL2** and **SL5**), *N,P*-ligand (**SL3**), and *P,P*-ligand (**SL4**) were found to be ineffective. We reasoned that the hard nature of *O,O*-type chiral ligand would be more suitable for copper ions according to the classical HSAB (Hard-Soft-Acid-Base) principle. To improve the enanticontrol and diminish the undesired di-alkynylated product, we further evaluation the reaction temperature. Notably, the reaction maintained good reactivity even when the reaction temperature was decreased to 0 °C. The ee value of **3aa** was improved to 93% and the di-alkynylation reaction was significantly restrained (**3aa'**, 4%) (Scheme 1a). Several BINOL-derived *O,O*-bidentate ligands (**L2** to **L8**) were further screened under prolonged reaction time (24 h) and the simple (*S*)-BINOL (**L1**) led to the optimal results, giving **3aa** in 66% yield with 93 ee and only 6% yield of undesired **3aa'** (Scheme 1b). Interestingly, **L6** bearing bulky 3,5-di-Me-phenyl group at the 3,3'-positions and (*S*)-SPINOL (**L8**) exhibited poor reactivity and contrary stereocontrol. Moreover, other oxidants including 4-methylmorpholine-*N*-oxide (NMO), $K_2S_2O_8$, and MnO_2 were also investigated, and results indicated that TBHP is indispensable for this protocol. Finally, we identified the following optimal conditions (**Conditions A**): 20 mol% CuI, 20 mol% (**L1**), 1.5 equivalents of DBU, 2.0 equivalents of TBHP in 1.5 mL DMAc at 0 °C for 24 h under O_2 atmosphere.

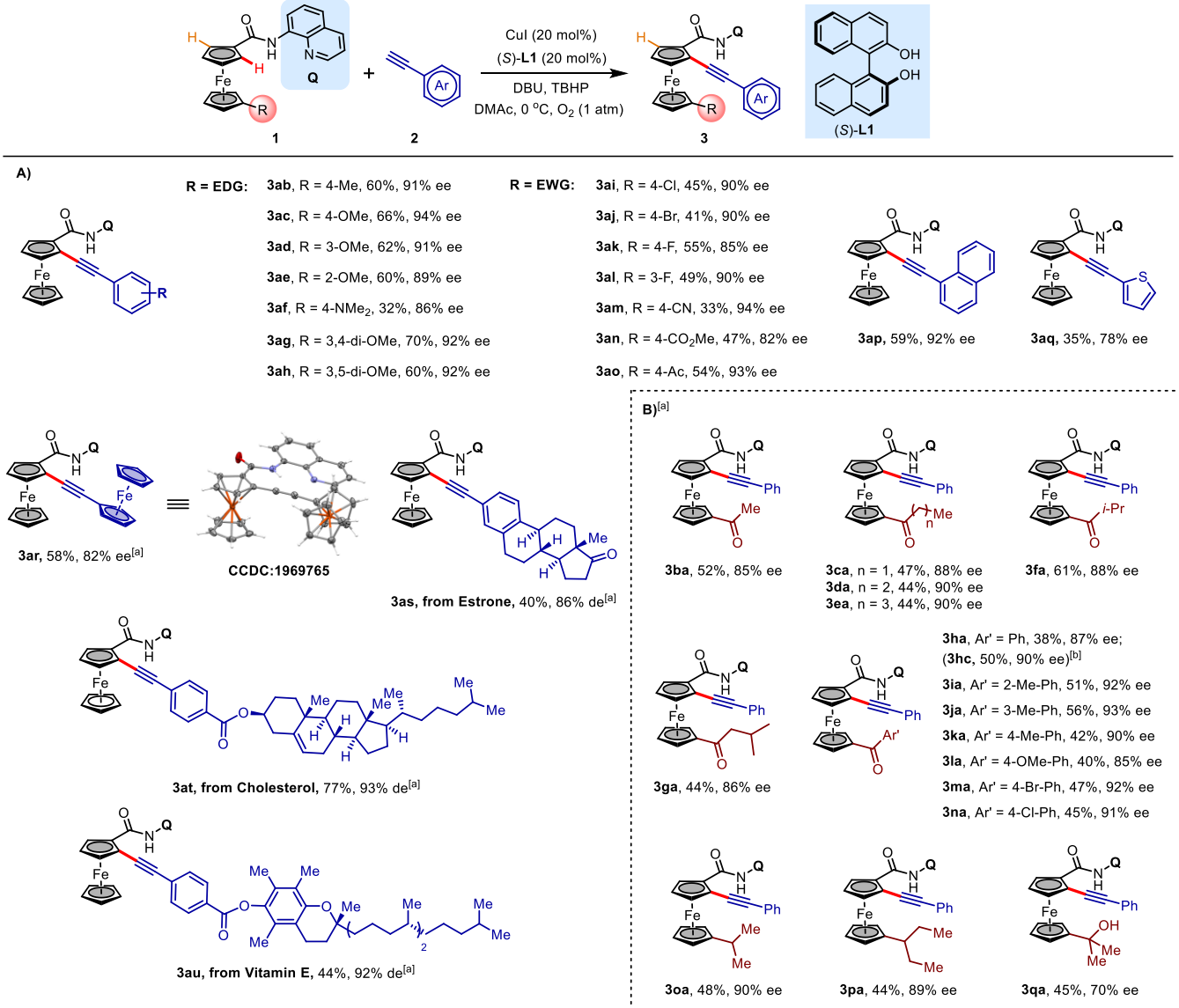


Scheme 1. Optimization of reaction conditions. Reaction conditions: **1a** (0.10 mmol), **2a** (1.2 equiv), CuI (20 mol%), **Ligand** (20 mol%), DBU (1.5 equiv), 70% TBHP in water (2 equiv) in 1.5 mL DMAc under O_2 atmosphere (1 atm). [a] Yields were determined by ^{1}H NMR using 1,3,5-Trimethoxybenzene as internal standard. [b] The ee value was determined by HPLC. [c] Isolated yield. DBU, 1,8-Diazabicyclo[5.4.0]undecane-7-ene. TBHP, butylhydroperoxid. DMAc, *N*,*N*-dimethylacetamide.

Versatility

With the optimized conditions in hand, we first evaluated the scope of the reaction with a broad range of alkynes (Scheme 2A). A series of aryl alkynes bearing electron-donating groups and electron withdrawing groups at different positions (*ortho*, *meta*, or *para*) of phenyl rings were well tolerated, delivering the alkynylated products **3ab**-**3ao** in moderate yield (32% to 66%) with good enantioselectivities (82% to 94% ee). Many valuable functional groups, such as *N*,*N*-dimethyl (**3af**), halogen (**3ai**–**3al**), cyano (**3am**), methyl ester (**3an**), and acetyl (**3ao**) were compatible. Naphthyl-substituted alkyne could also be employed, giving the desired product **3ap** in 59% yield with 92% ee. Thiphene acetylene **2q** was also found to be suitable, albeit with lower yield and enantioselectivity. Notably, ethynylferrocene was investigated to give the diferrocenyl alkynylation product **3ar** in 58% yield with 82% ee and the absolute configuration was confirmed by an X-ray crystallographic analysis.[18] Several bioactive derivatives, such as estrone, cholesterol, and tocopherol, were well applicable to this transformation, delivering the alkynylation products **3as**, **3at** and **3au** in good yields and enantioselectivities (40%–77% yield, 86–93% ee).

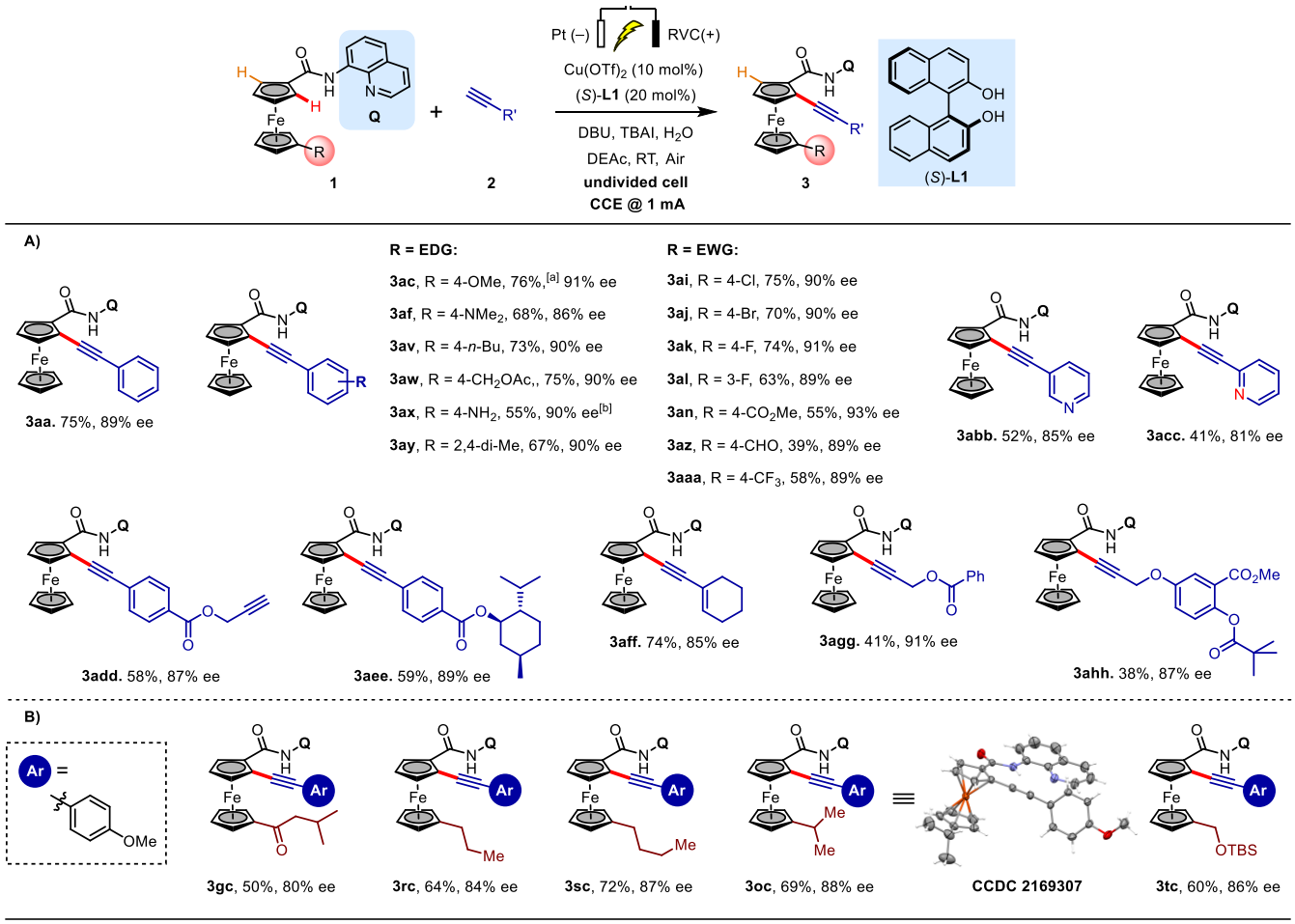
Subsequently, the scope of ferrocenyl amides was examined by prolonging the reaction time to 48 h (Scheme 2B). Ferrocene amides with various linear, branched acyl substituents at the other Cp ring worked well to give alkynylated products **3ba**–**3ga** with moderate yields and high enantioselectivities (44%–61% yield, 85–90% ee). Gratifyingly, benzoylferrocene amides, bearing different substituents (such as methyl-, methoxy-, bromo-, and chloro- on phenyl rings) were all compatible (**3ha**, **3hc**, **3ia-3na**, 38−50% yield, 85%−92% ee). The substrates bearing an isopropyl (**1o**) or pentan-3-yl (**1p**) group were found to give the desired products in good enantioselectivities (**3oa**, 90% ee; **3pa**, 89% ee). It is noteworthy that the undesired dialkynylation was suppressed at 0 °C and only trace amounts of dialkynylated products could be observed.



Scheme 2. Investigation of substrates scope. Reaction conditions (**Conditions A**): **1** (0.10 mmol), **2** (0.12 mmol), CuI (20 mol%), (*S*)-**L1** (20 mol%), DBU (0.15 mmol), 70% TBHP in water (0.20 mmol), DMAc (1.5 mL), under O_2 (1 atm) atmosphere at 0 °C for 24 h. Isolated yield. The ee value was determined by HPLC. [a] 48 h. [b] 1-ethynyl-4-methoxybenzene (**2c**) instead of phenylacetylene (**2a**).

Enantioselective electrocatalysis

Organic electrosynthesis has emerged as a sustainable platform for molecular construction over the past decades, replacing costly and waste-intensive redox agents by prospectively renewable electricity.[19] Very recently, the merger of enantioselective transition metal-catalyzed C−H activation with electrochemistry has been realized.[20] Herein, we extend the Cu/BINOL-system to enantioselective electrosynthesis of planar chiral ferrocenes. Notably, this represents the first enantioselective cupraelectro-catalyzed C−H functionalization reaction.



Scheme 3. Cupraelectro-catalyzed enantioselective C–H alkynylation of ferrocenes. Reaction conditions (**Conditions B**): undivided cell, **1** (0.2 mmol, 1.0 equiv), **2** (2.0 equiv), $Cu(OTf)_2$ (10 mol%), (*S*)-**L1** (20 mol%), DBU (2.0 equiv), TBAI (2.0 equiv), H_2O (10 µL) in 5.0 mL DEAc at room temperature for 12 h under air. The reaction was conducted with constant-current electrolysis (CCE) at 1.0 mA. Isolated Yields. The ee values were determined by HPLC. [a] Dialkynylated product **3ac'** was obtained in 7% yield. [b] CuI (20 mol%), (*S*)-**L1** (40 mol%) in DMAc (5.0 mL). DEAc, *N*,*N*-diethylacetamide. DMAc, *N*,*N*-dimethylacetamide.

To our delight, the reaction of **1a** with **2c** in an operationally simple undivided cell equipped with a reticulated vitreous carbon (RVC) anode and a platinum cathode at ambient temperature allowed us to provide the desired product **3ac** in good yield and enantioselectivity (76% yield, 91% ee) after slightly adjusting the reaction parameters (Table S8), and the undesired dialkynylated product was obtained in only 7% yield. Then, to compare with the results obtained through

chemical oxidation, representative substrates were explored under enantioselective electrochemical conditions (Scheme 3). Generally, the reaction proceeded efficiently to give the desired planar chiral products in good yields with high levels of enantiocontrol and only trace of dialkynylated products could be observed. Notably, alkynes bearing heteroaromatic (**2bb**, **2cc**) and alkyl (**2gg**, **2hh**) substituents were also compatible, giving the desired products in satisfactory results. In addition, ferrocenecarboxamides bearing diverse substituents, including acyl and alkyl, on the other Cp ring underwent C−H alkynylation smoothly, providing the planar chiral products (**3gc**, **3oc**, **3rc**, **3st**, **3ta**) in moderate yields (50% to 72%) with good enantioselectivities (80% to 87% ee). The absolute configuration of **3oc** was unanimously assigned by single-crystal X-ray diffraction analysis.[18]

Mechanistic insights

To gain further mechanistic insights, deuterium-labelling studies were performed. The *ortho* deuterated substrate **1a**-d_2 was subjected to the standard reaction conditions using chemical oxidant without **2a**, and notably, the **1a**-d_2 was recovered without any loss of deuterium, indicating that C–H activation in our method is irreversible (Figure 2a). Next, kinetic isotope effect (KIE) experiments were conducted, and the KIE value was determined to be 3.4, indicating that the C−H bond cleavage might be the rate-determining step (Figure 2b). Furthermore, the nonlinear effects of enantioselective C–H alkynylation was studied under the condition of electrolysis. A plot of ee_{3aa} as a function of ee_{L1} was found to be linear, suggesting the active catalytic species might be a monomeric copper-catalyst with a single bound BINOL ligand **L1** (Figure 2c).[21]

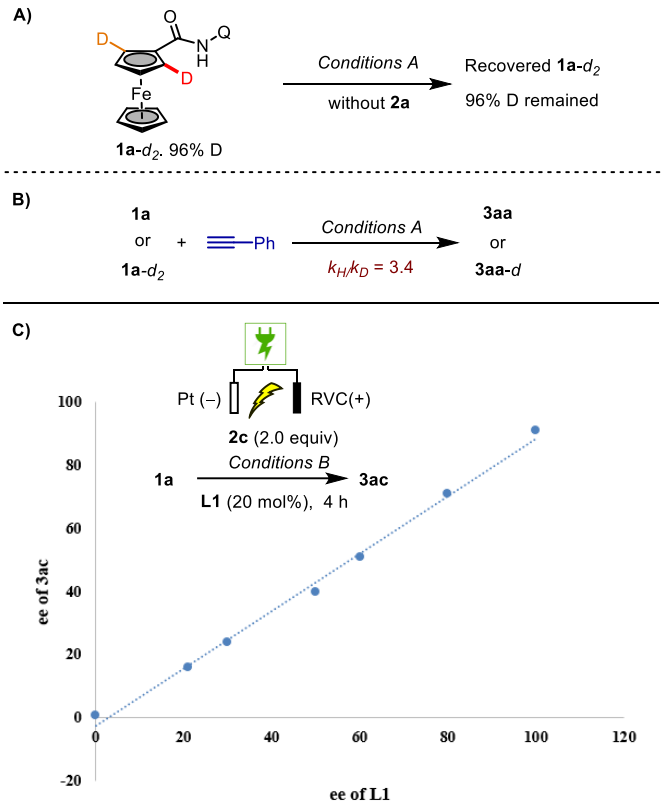
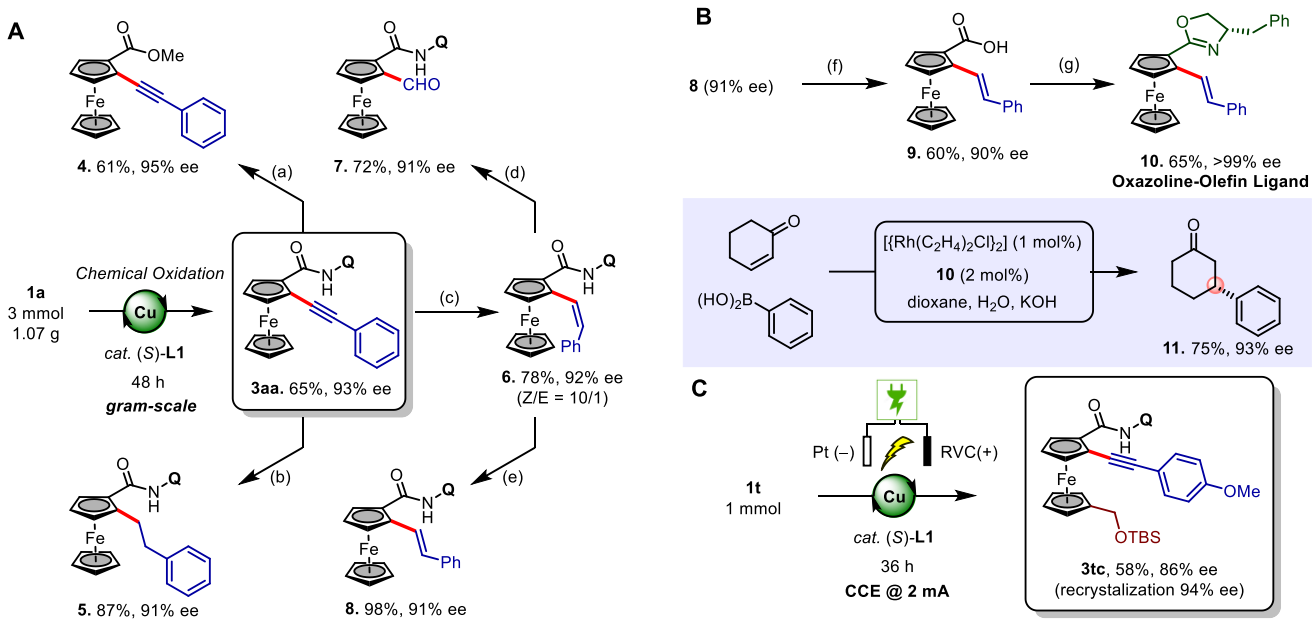


Figure 2. Mechanistic insight.

Synthetic Transformation

To demonstrate the utility of our method, the asymmetric alkynylation of **1a** were performed on a gram-scale (3 mmol) to provide the product **3aa** in 65% yield with 93% ee (Scheme 4A). The directing group could be easily removed and the alkynylated planar chiral ferrocenyl ester **4** was obtained in 61% yield with 95% ee. The alkylated ferrocene **5** (87% yield, 91% ee) and *cis*-alkenylated ferrocenes **6** (78% yield, 92% ee) was obtained through hydrogenation of **3aa**. Oxidative cleavage of the double bond in **6** delivered the corresponding aldehyde **7** in 72% yield with 91% ee. *trans*-Alkenylated ferrocenes **8** could also be easily prepared in excellent yield via isomerization of *cis*-alkenylated ferrocenes **6**. To be noticed, an oxazoline-olefin chiral ligand **10** was synthesized efficiently in two-steps from **8** by the removal of and the formation of oxazoline (Scheme 4B). Then, the resulting oxazoline-olefin ligand **10** was subjected to a Rh-catalyzed1,4-addition of phenylboronic acid to α, β-unsaturated cyclohexanone.[22] The desired β-arylated ketone product **11** was obtained in 75% yield with a high-level of enantioselectivity (93% ee), which demonstrating that the high potential of the ferrocene products obtained in this work could act as a type of unique chiral ligands in asymmetric catalysis. Moreover, the enantioselective electrocatalysis reaction was also investigated for scalability, whereby efficiency and enantioselectivity could be maintained (Scheme 4C).



Scheme 4. Synthetic transformation. (a) Boc_2O, DMAP in THF at 80 °C for 24 h, then NaOH in MeOH/H_2O at 60 °C for 6 h, then K_2CO_3, MeI, acetone; (b) Pd/C, H_2 balloon in MeOH at r.t. for 24 h; (c) Pd/C, H_2 balloon in MeOH at r.t. for 40 min; (d) $K_2OsO_4 \cdot 2H_2O$, $NaIO_4$ in THF/H_2O at r.t. for 2 h; (e) I_2 in DCM at r.t. for 24 h; (f) Boc_2O, DMAP in THF at 80 °C for 24 h, then NaOH in MeOH/H_2O at 60 °C for 6 h; (g) $(COCl)_2$, DMF, in DCM at 0 °C to r.t., then (*L*)-Phenylglycinol, DMAP, TEA, in DCM at 0 °C, then, DMAP, MsCl, TEA, in DCM at 0 °C to r.t..

Conclusion

In summary, we developed a copper/BINOL catalytic system for enantioselective C–H activation through inner-sphere mechanism. A broad range of planar chiral ferrocenecarboxamides were obtained under mild conditions with good stereoselectivity (up to 94% ee). We also disclosed the first enantioselective organometallic C–H activation enabled by

copper with the merger of electrochemistry. We anticipate that this work will boost the study of copper-catalyzed enantioselective C-H activation.

Supporting Information

The data that support the findings of this study are available in the supplementary material of this article.

Acknowledgements

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Keywords: C-H activation • copper • electrochemistry • enantioselectivity • ferrocenes

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