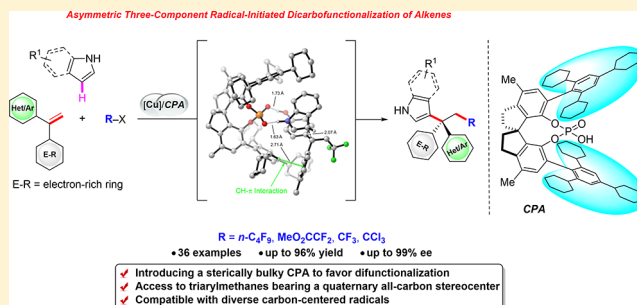


Cu/Chiral Phosphoric Acid-Catalyzed Asymmetric Three-Component Radical-Initiated 1,2-Dicarbofunctionalization of Alkenes

Jin-Shun Lin,^{†,§} Tao-Tao Li,^{†,§} Ji-Ren Liu,^{||,§} Guan-Yuan Jiao,[†] Qiang-Shuai Gu,[‡] Jiang-Tao Cheng,[†] Yu-Long Guo,[†] Xin Hong,^{*,||,§} and Xin-Yuan Liu^{*,†,§}[†]Department of Chemistry and Shenzhen Grubbs Institute, Southern University of Science and Technology, Shenzhen 518055, China[‡]SUSTech Academy for Advanced Interdisciplinary Studies, Southern University of Science and Technology, Shenzhen 518055, China^{||}Department of Chemistry, Zhejiang University, Hangzhou 310027, China

Supporting Information

ABSTRACT: An asymmetric intermolecular, three-component radical-initiated dicarbofunctionalization of 1,1-diarylalkenes with diverse carbon-centered radical precursors and electron-rich heteroarenes by a copper(I) and chiral phosphoric acid cooperative catalysis strategy has been developed, providing straightforward access to chiral triarylmethanes bearing quaternary all-carbon stereocenters with high efficiency as well as excellent chemo- and enantioselectivity. The key to success is not only the introduction of a sterically demanding chiral phosphoric acid to favor radical difunctionalization over the otherwise remarkable side reactions but also the in situ generation of carbocation intermediates from benzylic radical to realize asymmetric induction with the aid of a removable hydroxy directing group via cooperative interactions with chiral phosphate. Density functional theory calculations elucidated the critical chiral environment created by the hydrogen-bonding and ion-pair interactions between the chiral phosphoric acid catalyst and substrates, which leads to the enantioselective C–C bond formation.



INTRODUCTION

Dicarbofunctionalization of alkenes has recently attracted increasing attention given the rapid generation of molecular complexity from readily available alkene starting materials.¹ In regard to the booming radical chemistry, impressive advances have been achieved in the development of catalytic radical alkene difunctionalization initiated by intermolecular addition of carbon-centered radicals to alkenes catalyzed by transition-metal redox systems^{2,3} owing to the high innate reactivity and unique selectivity of radical intermediates.⁴ In contrast, catalytic radical asymmetric dicarbofunctionalization of olefins, especially for the intermolecular three-component version, is much less developed given the number of side reactions that highly reactive alkyl radical intermediates can undergo. In this aspect, Liu and co-workers recently adopted chiral metal species to trap reactive alkyl radical, a strategy pioneered by Fu and others (Scheme 1a),⁵ to elegantly develop state-of-the-art enantioselective intermolecular trifluoromethylarylation and cyanotrifluoromethylation (Scheme 1b).⁶ Although impressive results have been achieved with this approach, prefunctionalization of the carbon nucleophiles as boronic acid or trimethylsilane was mechanistically indispensable. On the other hand, there have been no general and practical solutions to allow for the efficient construction of chiral all-carbon

quaternary stereocenters,⁷ presumably because of the inherently unfavorable steric hindrance.⁵ From the viewpoint of high step-economy as well as versatility, a mechanistically distinct and alternative approach for reactions capable of not only generating all-carbon quaternary stereocenters but also accommodating direct intermolecular C–H functionalization is highly desirable.

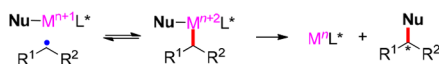
To this end, we wondered if our recently developed Cu(I)/chiral phosphoric acid (CPA) dual-catalysis for radical asymmetric intramolecular transformations⁸ could be translated into a general and practical solution toward this issue. It has been assumed that the in situ-generated electronically activated benzylic radical might readily undergo a single-electron oxidation process in the presence of Cu^{II} species to afford a carbocation intermediate. This carbocation might associate with chiral phosphate through electrostatic interactions, thereby resulting in a good chiral environment (Scheme 1c) for subsequent direct intermolecular C(sp²)–H functionalization on electron-rich heteroarene. Accordingly, it would provide the desired optically active dicarbofunctionalization product in a mode that is mechanistically distinct from

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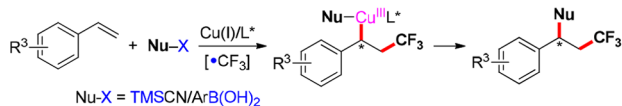
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Scheme 1. Asymmetric Three-Component Radical-Initiated 1,2-Dicarbofunctionalization of Alkenes

a) Alkyl radical trapped with chiral metal species



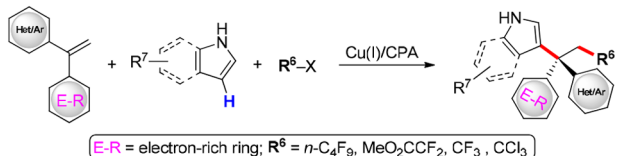
b) Intermolecular dicarbofunctionalization via trapping alkyl radical with copper



c) Proposal for a mechanistically distinct strategy via carbocation intermediates



d) This work: Cu/CPA-catalyzed asymmetric intermolecular dicarbofunctionalization



those in previous works invoking chiral Cu^{II} species to trap alkyl radical as a key step.^{6,8} If achieved, this type of radical redox-relay cooperative catalytic strategy would be synthetically significant because the resulting chiral triarylmethanes bearing quaternary all-carbon stereocenters represent key structural elements of a large number of molecules in the dye industry, medicinal chemistry, and material science as well as organic synthesis (Figure 1),⁹ but their asymmetric

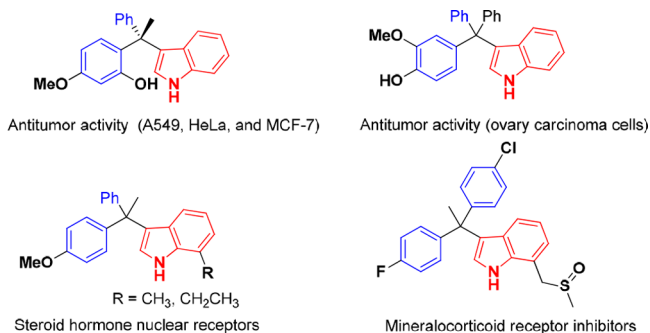


Figure 1. Representative biologically active indole-containing triaryl-methanes bearing a quaternary carbon center.

construction remains a significant challenge and scarce.¹⁰ At the outset, we recognized that several challenges would need to be overcome to put this idea into practice, including securing good discrimination between the enantiotopic faces of this carbocation¹¹ via electrostatic interactions that lack rigidity in their association and selectively controlling promiscuous reactivity, such as competitive β -elimination from the carbocation, a direct hydroarylation of alkene with electron-rich heteroaromatics,^{10b–e,12} Kharasch addition type reaction of alkene,^{8d,13} and direct radical fluoroalkylation of electron-rich heteroaromatics.¹⁴ Herein, we describe our efforts toward the development of the first general and efficient asymmetric intermolecular three-component radical-initiated dicarbofunctionalization of 1,1-diarylethenes with electron-rich heteroaromatics and a diverse array of carbon-centered radical

precursors enabled by Cu(I)/CPA cooperative catalysis (Scheme 1d).¹⁵

RESULTS AND DISCUSSION

Given the increasing importance of fluoroalkyl-containing molecules in the development of pharmaceuticals and agrochemicals as well as materials,¹⁶ we began our investigation using fluorine-containing carbon-centered radical precursors. To this end, we selected 1,1-diarylethene **1a** bearing one OMe-substituted electron-rich arene as the pilot alkene substrate, indole derivative **2a** as the carbon nucleophile, and perfluorobutyl sulfonyl chloride **3a** as the oxidative radical precursor (Table 1, entry 1). However, the three-component reaction in the presence of CuI and CPA (S)-**A1** (10 mol %) with Ag₂CO₃ as an additive provided the desired product **4Aa** in poor yield and enantioselectivity, along with side monofunctionalization product **5Aa** in good yield through a β -hydride elimination process and direct hydroarylation product **6Aa**, respectively. Given this, we surmised that the installation of a possibly removable hydroxy or amino directing group on one of the two aryl groups might impart effective stereocontrol, considering the fact that a chiral phosphate anion is able to interact with such groups via hydrogen bonding.¹⁷ Subsequently, we chose the substrates **1ba**, **1a**, and **1ca** bearing OH or NH₂ groups at different positions (*para* or *meta*) of one aryl ring based on our initial hypothesis (Table 1, entries 2–4), and we were pleased to observe a significant increase in enantioselectivity with the hydroxy directing group, albeit with low product yield and along with other side reactions, including perfluoroalkylation and direct hydroarylation with indole.

This proof-of-principle result encouraged us to carry out further systematic optimizations of different reaction parameters with use of **1a** as the model substrate (Table 2). To suppress the more common hydroarylation or perfluoroalkylation clearly observed in this reaction and improve the enantioselectivity, we screened different copper salts and various organic solvents as well as reaction temperature. Unfortunately, either enantioselectivity or chemoselectivity could not be significantly improved under these reaction conditions (Table 2, entries 1–6). Considering the reported significant steric effect of CPAs in the direct C-alkylation reaction,^{10e} we then screened various BINOL- and SPINOL-derived CPAs (Table 2, entries 7–12) and found that the use of a sterically bulky 6,6'-bis(2,4,6-triisopropylphenyl)-4,4'-dimethyl SPINOL-derived chiral phosphoric acid (S)-**A4**¹⁸ dramatically inhibited the hydroarylation process, presumably because of its significant steric bulkiness hindering nucleophilic indole from approaching toward the alkene. It is worth noting that CPA (S)-**A5** bearing sterically more bulky tricyclohexylphenyl groups at the 6,6'-positions totally abolished the perfluoroalkylation side reaction while significant inhibiting hydroarylation and efficiently providing **4A** in superior yield (88%) and enantioselectivity (95% ee) with a reaction temperature at –3 °C (Table 2, entry 13).

With the optimal reaction conditions established, we next investigated the substrate scope of the asymmetric intermolecular perfluoroalkylation of alkenes (Table 3). Various diversely functionalized 1,1-diarylethenes, including those having aryl groups with electron-withdrawing (CF₃, F, Cl, NO₂, and CO₂Me) or electron-donating groups (OMe and Me) at different positions (*ortho*, *meta*, or *para*) as well as a polyarene naphthalene ring were found to be suitable

Table 1. Initial Exploration of Reaction Conditions^a

entry	1	R ¹	R ²	4	y (%) ^b	ee (%) ^c	5	y (%)	6	y (%)
1	1aa	4-H	OMe	4Aa	20		5Aa	53	6Aa	24
2	1ba	3-OH	OMe	4Ba	54	43	5Ba	44	6Ba	0
3	1a	4-OH	Me	4A	10	68	5Ca	44	6Ca	43
4	1ca	4-NH ₂	H	4Ca	0		5Da	68	6Da	0

^aReaction conditions: **1** (0.1 mmol), **2a** (0.12 mmol), *n*-C₄F₉SO₂Cl (0.12 mmol), CuI (10 mol %), Ag₂CO₃ (0.06 mmol), CPA (10 mol %), DCM (1.0 mL) under argon. ^bIsolated yield. ^cee value on HPLC.

Table 2. Screening of Reaction Conditions^a

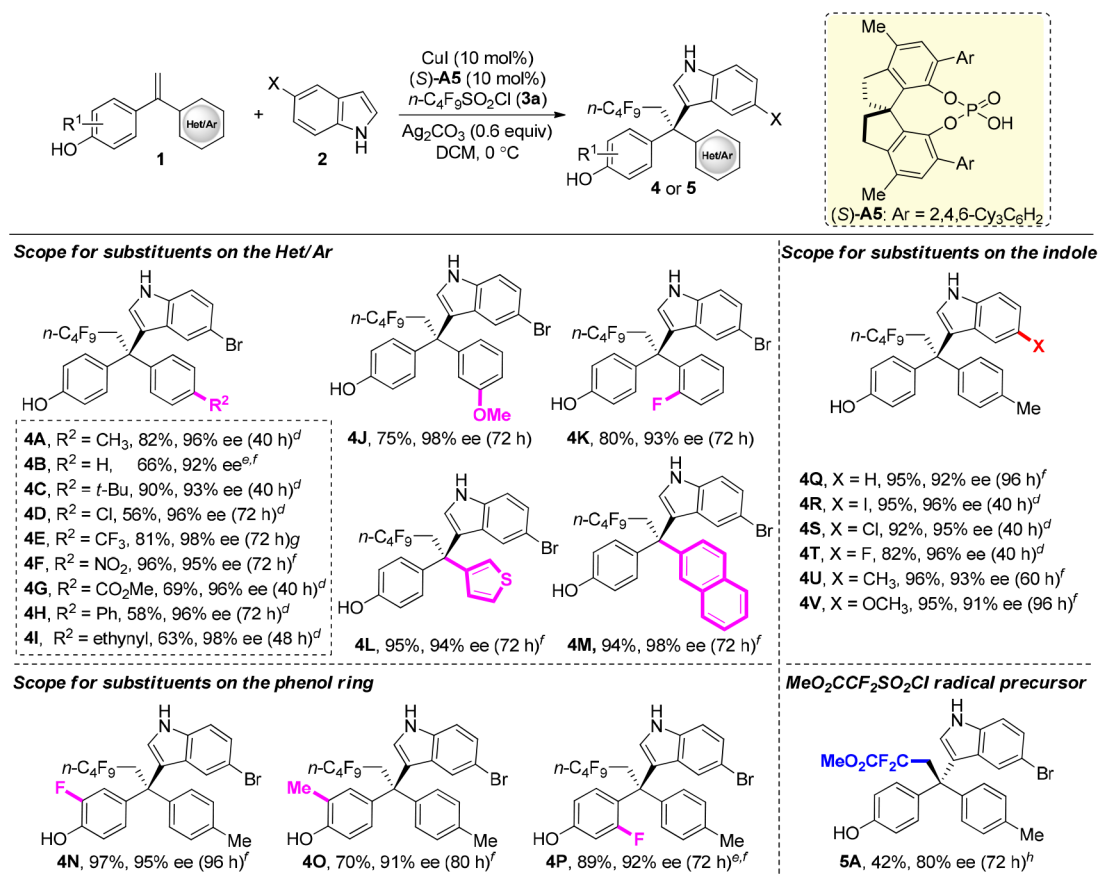
entry	[Cu]	CPA	solvent	yield (%)			ee (%) ^c
				4A ^b	5Ca ^b	6Ca ^b	
1 ^d	CuI	(S)-A1	DCM	6	45	47	73
2	CuI	(S)-A1	DCM	22	15	60	69
3	CuI	(S)-A1	EtOAc	0	86	13	
4	CuI	(S)-A1	PhCF ₃	20	0	79	62
5	CuBr	(S)-A1	DCM	8	10	80	71
6	CuOAc	(S)-A1	DCM	9	11	76	75
7	CuI	(S)-A2	DCM	28	34	33	38
8	CuI	(R)-A3	DCM	31	12	54	−72
9	CuI	(S)-A4	DCM	68	11	19	−75
10	CuI	(S)-A5	DCM	70	0	28	−95
11	CuI	(R)-A6	DCM	20	18	62	43
12	CuI	(R)-A7	DCM	44	36	20	48
13 ^c	CuI	(S)-A5	DCM	88	0	11	−95

^aReaction conditions: **1a** (0.05 mmol), **2a** (0.06 mmol), *n*-C₄F₉SO₂Cl (0.06 mmol), [Cu] (10 mol %), Ag₂CO₃ (0.03 mmol), CPA (10 mol %), dry solvent (0.5 mL), 0 °C, 60 h under argon. ^bYield based on ¹H NMR analysis of the crude product using CH₂Br₂ as an internal standard. ^cee value on HPLC. ^d20 °C. ^e(S)-A5 (7.5 mol %) was used at −3 °C.

substrates to afford the expected products **4A–4P** in 56–97% yields with 91–98% ee. It is noteworthy that a substrate containing the other reactive and useful ethynyl group also afforded the corresponding product **4I** with the additional triple bond intact. In addition, thiophene-substituted olefin was tolerated to give **4L** in 95% yield and 97% ee. Furthermore, a range of substituted indoles all underwent the current perfluoroalkylarylation reaction smoothly to deliver the corresponding products **4Q–4V** in excellent yields with excellent enantioselectivity. Encouraged by the above success,

we thus switched our synthetic target to chiral difluoroacetyl-triarylmethane, as the difluoromethyl group (CF₂R) has routinely served as a core pharmacophore in drug discovery in recent years.¹⁶ To our delight, the reaction of 1,1-diarylethylene substrate **1a** with MeO₂CCF₂SO₂Cl (**3b**) under the otherwise identical reaction conditions delivered difluoroacetyl-containing product **5A** in moderate yield with 80% ee.

The trihalomethyl unit has emerged as a key moiety presented in numerous bioactive natural products and

Table 3. Substrate Scope for Perfluoroalkylarylation or Difluoroacetylation of **1**^{a,b,c}

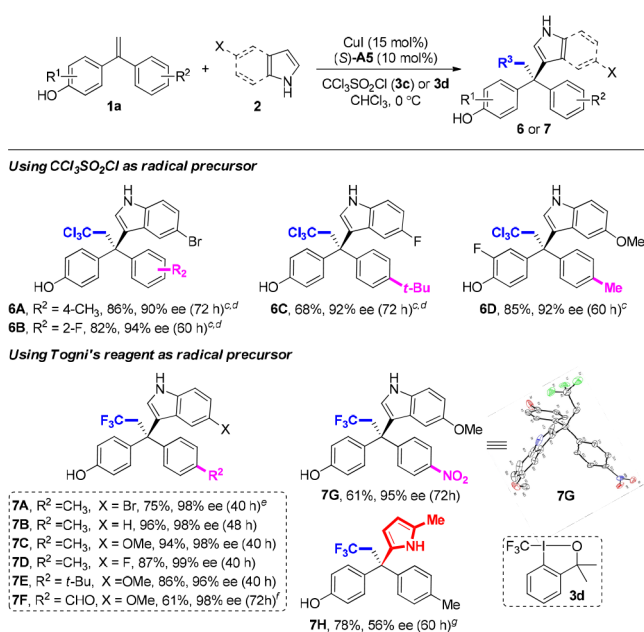
^aReactions were conducted on 0.1 mmol scale. ^bIsolated yield based on **1** is given. ^cee was determined by HPLC analysis. ^dRun at −3 °C. ^eRun at 0 °C for 72 h, then 29 °C for 42 h. ^f15 mol % CuI. ^g20 mol % CuI. ^hThe reaction was conducted on 0.025 mmol scale with Ag₂CO₃ (0.5 equiv), (R)-3,3'-(3,5-(Ph)₂C₆H₃)₂-8H-BINOL-derived CPA at −30 °C for 72 h.

pharmaceutical drugs;¹⁹ thus, its preparation has spurred the development of many new reagents and strategies.²⁰ To this end, we successfully prepared trichloromethyl-containing products **6A–6D** in good to excellent yields with 90–94% ee (Table 4) via reaction of 1,1-diarylethylene substrate **1** with trichloromethanesulfonyl chloride **3c** under the almost identical conditions. As for chiral CF₃-containing triarylmethanes, we identified the well-known Togni's reagent (**3d**)^{2d} but not trifluoromethanesulfonyl chloride (CF₃SO₂Cl)^{8b} as the appropriate CF₃ source to obtain **7A–7G** in good to excellent yields with excellent ee. Meanwhile, it was striking to note that 2-methyl-1H-pyrrole as a nucleophile also underwent the current reaction to deliver **7H** in 78% yield with promising enantioselectivity, which is currently under further optimization in our laboratory. The absolute configuration of **7G** has been determined to be *S* by X-ray crystallographic analysis (Figure S2 in the Supporting Information for Experiments), and those of other perfluoroalkyl-, trichloromethyl-, difluoroacetyl-, and trifluoromethyl-containing triarylmethanes were inferred accordingly.

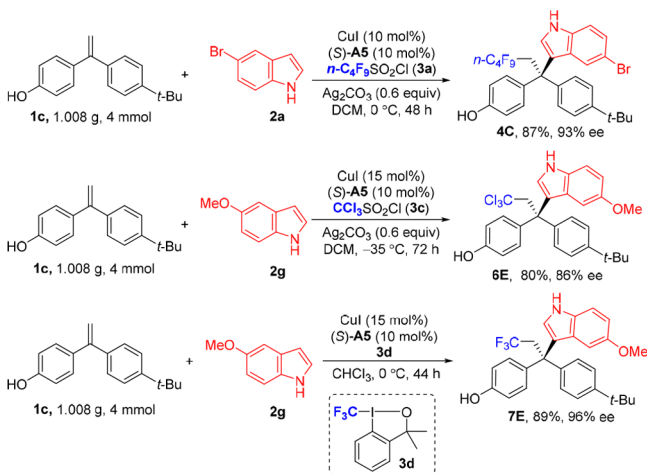
To further demonstrate the practicality of the current methodology in preparative organic synthesis, we carried out gram-scale synthesis of products **4C**, **6E**, and **7E**. As displayed in Scheme 2, the asymmetric 1,2-dicarbofunctionalization of **1c** with different radical precursors was performed on a 1.008 g scale under the standard reaction conditions, and high

efficiency and enantioselectivity were still maintained all the time.

An apparent drawback of our current transformation is the requirement for a hydroxy directing group. In fact, this hydroxy group was readily removed by straightforward triflation and subsequent reduction to afford **7Bb** with an unsubstituted phenyl ring (Scheme 3, eq 1). In addition, the triflated intermediate **7Ba** also provided extra synthetic potentials for further derivatization by cross-coupling reaction, as demonstrated by synthesizing **7Bc** with excellent efficiency (Scheme 3, eq 2). Besides, simple reduction or hydrolysis of the ester group in **5A** smoothly generated the corresponding difluoro-containing alcohol **8A** (Scheme 3, eq 3) and carboxylic acid **8B** in good yields (Scheme 3, eq 4). An important aspect of the transformations discussed above is that no significant enantiopurity erosion has ever occurred, establishing the utility of this method in practical synthetic chemistry. It is interesting to note that the chiral dichloroolefin-containing product **9A** was obtained in excellent yield and enantioselectivity through direct elimination of hydrogen chloride from corresponding trichloromethylated products in cases of electron-rich indole reactant (Scheme 3, eq 5). Such resultant dichloroolefin can serve not only as a potential synthetic platform for facile access to other valuable chiral triarylmethanes but also as a key structural element for potent activity in numerous bioactive compounds.²¹

Table 4. Substrate Scope for Trichloromethylarylation and Trifluoromethylarylation of 1^{a,b}

^aAll the reactions were conducted on 0.1 mmol scale. ^bee was determined by HPLC analysis. ^c Ag_2CO_3 (0.6 equiv), -35°C , DCM. ^d20 mol % CuI. ^eRun at -2°C . ^fRun at 0°C for 12 h, then 28°C for 48 h. ^g(S)-3,3'-(3,5-(*t*-Bu) $_2\text{C}_6\text{H}_3$) $_2$ -SPINOL-derived CPA, -15°C for 72 h.

Scheme 2. Gram-Scale Reaction with Diverse Radical Precursors

To gain some insight into the reaction mechanism, a series of control experiments were conducted. First, the present reaction was completely inhibited by the addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), and the radical trapping product *n*-C₄F₉-TEMPO was observed in ¹⁹F NMR and detected by GC-MS, suggesting that the *n*-C₄F₉ radical was likely generated in situ in the presence of Cu catalyst through a single electron-transfer process (Scheme 4, eq 1). In addition, no desired product **4A** was obtained in the absence of any copper catalysts. Furthermore, *rac*-**4A** was obtained in lower yield in the absence of phosphoric acid. These observations, together with the above-mentioned significant effects of different CPAs in the reaction condition

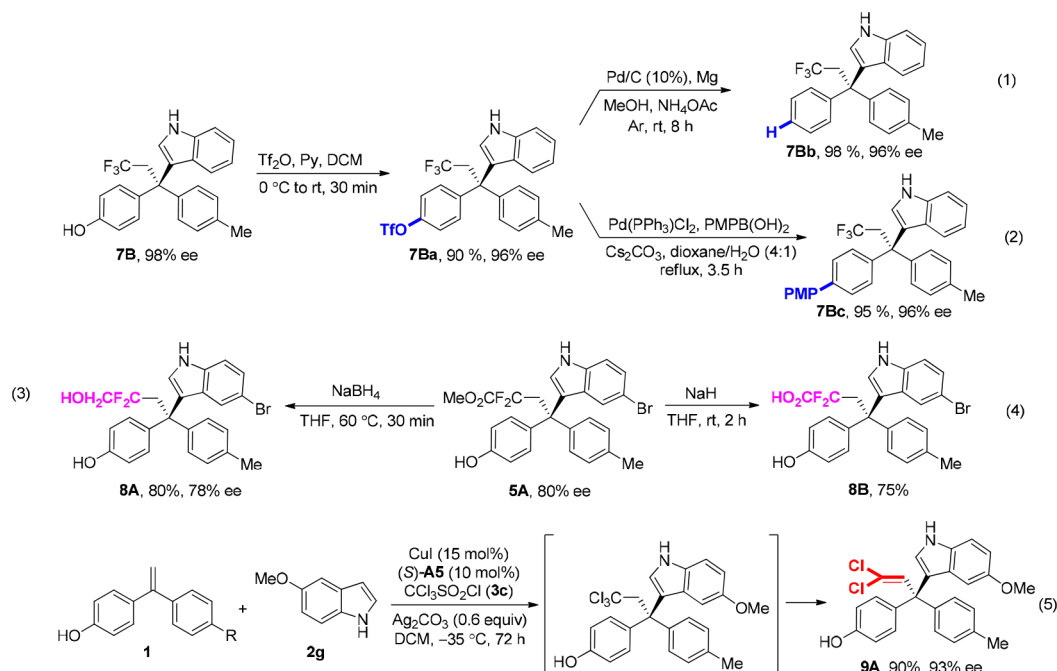
optimization study (Table 2), indicate that both the Cu(I) salt and CPA are essential for this reaction, and CPA might have played an important role in the activation of sulfonyl chloride.

In addition, either the *N*-protected indole **2i** (Scheme 4, eq 2) or methyl-protected 1,1-diaryllkene **1aa** (Table 1) is not an effective substrate to provide satisfactory enantioselectivity under similar reaction conditions. These facts indicate the important roles of the N–H and the O–H moieties in these substrates, presumably via formation of cooperative multiple hydrogen bonding with chiral phosphate. It is noteworthy that Sun and co-workers have elegantly developed direct C-alkylation reaction of indoles via formation of a tertiary carbocation intermediate by protonation of electron-rich terminal 1,1-diaryllkene with CPA.^{10b} In our reactions, a small amount of internal alkene product **5Ca** was formed via radical alkylation of 1,1-diaryllkene in some cases, but its participation in our desired reaction via either protonation with CPA^{10b} (path b in Figure 2b) or any other pathways was unlikely given that no reaction of **5Ca** was observed either under standard conditions or in the presence of CPA only, respectively (Scheme 4, eq 3). Thus, the in situ generated carbocation intermediate from benzylic radical might directly undergo attack by nucleophile (path a in Figure 2b), which would be mechanistically distinct from the previous work via the direct protonation of alkenes by CPA, i.e., path b.^{10b} Owing to not only the facile oxidation of electronically activated radical to a carbocation intermediate but also the straightforward installation of a diverse array of carbon-centered radicals to alkenes, the current synthetic protocol exhibits a number of clear advantages over the direct alkene protonation approach in terms of high reactivity, a broader substrate scope, and versatile functionalization of the products, thus constituting a more appealing alternative to the previous approach.^{10,12}

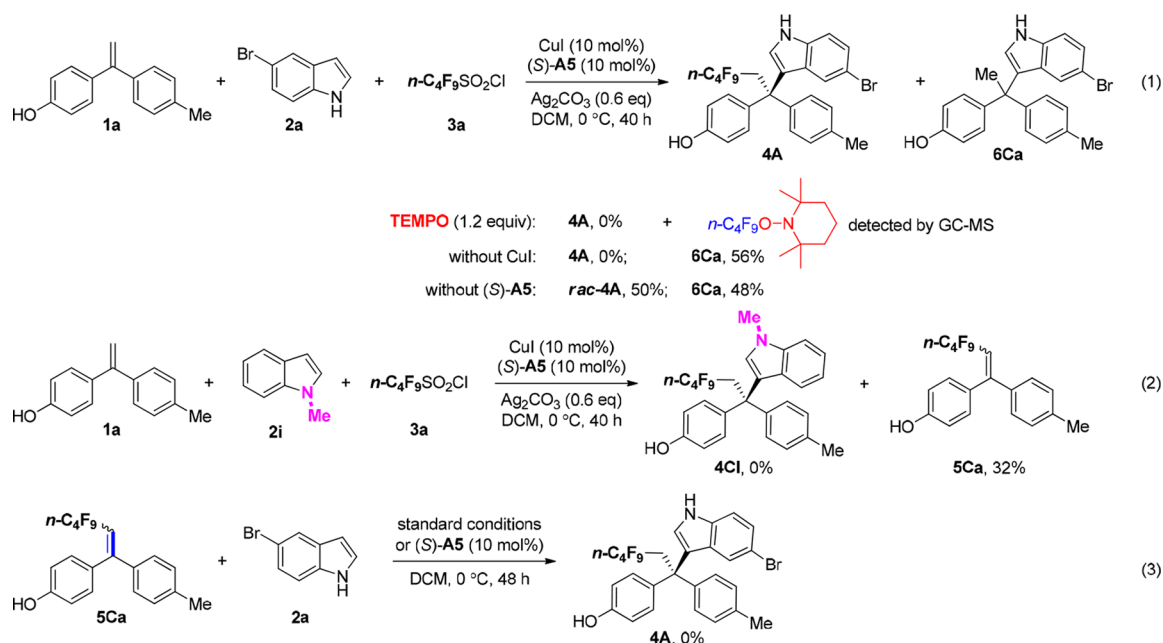
To further elaborate the mechanistic details, we studied the relationship between product enantiopurity and catalyst enantiopurity. The observed linear relationship indicates the involvement of one CPA catalyst in the enantioselectivity-determining transition states (Figure 2a). On the basis of above observations and previous reports,^{6,8} we have proposed a working mechanism, as shown in Figure 2b. Cu(I) first reacts with CPA-activated RSO₂Cl by hydrogen bonding^{8d} via single-electron transfer, giving the crucial chiral Cu(II) phosphate complex **A** accompanied by the generation of carbon-centered radical and a stoichiometric amount of sulfur dioxide and hydrogen chloride (HCl). The additive Ag₂CO₃ acts as a HCl scavenger via the formation of insoluble AgCl in organic solution. Subsequently, the addition of carbon-centered radical to alkene **1** gives alkyl radical **B**, which subsequently undergoes single-electron oxidation with the Cu(II) complex **A** to form the corresponding carbocation intermediate. This carbocation intermediate is next attacked by electron-rich heteroaromatics through intermediate **C** or its *p*-quinone methide resonance structure **C'**^{10,12} invoking both hydrogen-bonding interactions¹⁵ and ion-pair interactions in **C** or only hydrogen bonding interactions in **C'** to realize excellent stereocontrol.¹¹ In the case of the *meta*-phenol substrate **1ba** (**4Ba** up to 53% ee, Scheme S1), only intermediate **C** is reasonably involved because no quinone methide resonance structure can be invoked.

Our hypothesized enantioselective C–C bond formation through intermediate **C** is supported by density functional theory (DFT) calculations.²² Using (S)-A5 as the model CPA

Scheme 3. Representative Product Transformations



Scheme 4. Mechanistic Study



catalyst and **1a** and indole **2b** as the model substrates, we were able to locate the C–C bond formation transition states **TS10-S** and **TS10-R** that lead to enantiomeric product formation (Figure 3). Various complexation types between CPA catalyst and substrates, as well as careful conformational searches, are considered to ensure that the most favorable transition states are located (see Figures S1–S4 in the Supporting Information for Computations). Both transition states involve the proposed hydrogen bonding and ion-pair interactions between the CPA catalyst and substrates, which create the chiral environment for enantiodiscrimination.²³ **TS10-S** is 5.0 kcal/mol more favorable than **TS10-R** in terms of free energy (Figure 3), which is consistent with the observed enantioselectivity (Table

4). Calculations with additional functionals were performed to further validate the energy difference between the two transition states (Table S1 in Supporting Information for Computations). The leading factor that differentiates the two competing transition states is the CH- π interaction between the cyclohexyl group of CPA catalyst and the *para*-methylphenyl group of alkene.²⁴ This favorable CH- π interaction stabilizes **TS10-S** by 3.9 kcal/mol based on the calculations of interacting fragments (Figure S5 in Supporting Information for Computations), while **TS10-R** does not possess this interaction because of the stereogenic configuration of forming the C–C bond. The proposed CH- π interaction is also proved by IGM analysis;²⁵ the green oval

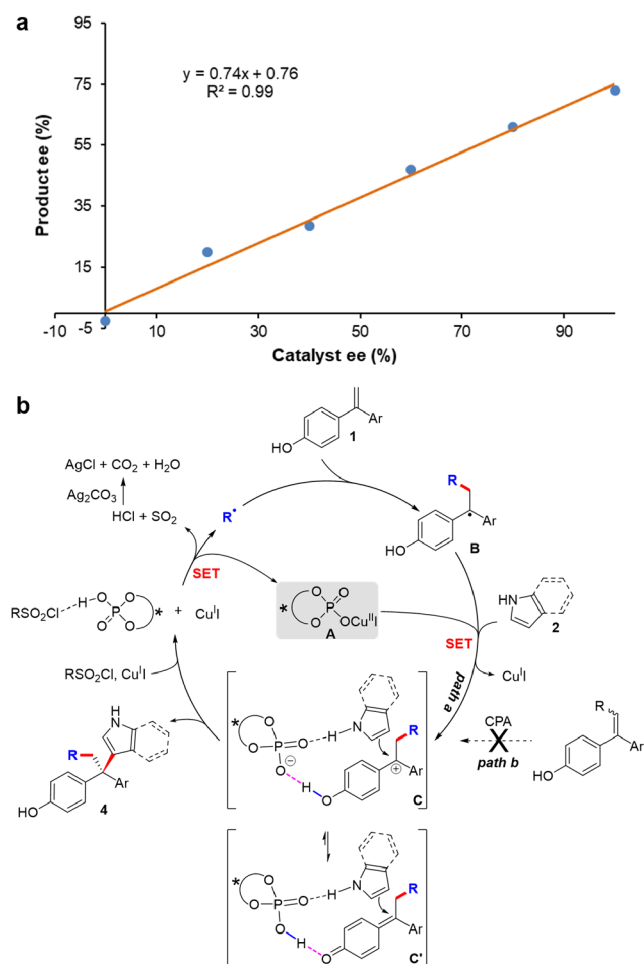


Figure 2. Absence of nonlinear effects and mechanistic proposal.

represents the favorable interaction between the highlighted fragments (Figure 3). Therefore, our calculations indicate the importance of hydrogen bonding and ion-pair interactions in the chiral induction, as well as the noncovalent CH- π

interaction that differentiates the enantiomeric C-C bond formations.

CONCLUSION

In summary, we have utilized copper(I) and chiral phosphoric acid cooperative catalysis to develop an asymmetric intermolecular three-component radical-initiated dicarbofunctionalization of 1,1-diaryllkenes with a diverse array of carbon-centered radical precursors and electron-rich heteroaromatics, encompassing a direct intermolecular arene C(sp²)-H functionalization. It provides straightforward access to chiral triarylmethanes bearing quaternary all-carbon stereocenters with high efficiency as well as excellent chemo- and enantioselectivity. Incorporating a removable/convertible hydroxy group as the directing group and introducing a sterically demanding chiral phosphoric acid jointly favor the desired radical difunctionalization over the otherwise remarkable side reactions. This method represents a mechanistically distinct approach to enable the rapid asymmetric difunctionalization of olefins via the intermediacy of a carbocation species through single-electron oxidation. The obtained products can serve as practical synthons toward valuable chiral molecular entities in the fields of pharmaceuticals, agrochemicals, and materials. Mechanistic investigations by combined experiments and computations elucidated the reaction mechanism and origins of enantioselectivity. The key enantioselective C-C bond formation process between a heteroaromatic compound and a carbocation intermediate occurs in a chiral environment, which is created by the hydrogen-bonding and ion-pair interactions with CPA catalyst. The controlling factor of enantioselectivity is the CH- π interaction between the cyclohexyl group of CPA catalyst and one of the aryl rings on the alkene substrates.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b11736.

Theory (DFT) calculations and characterization data (PDF)

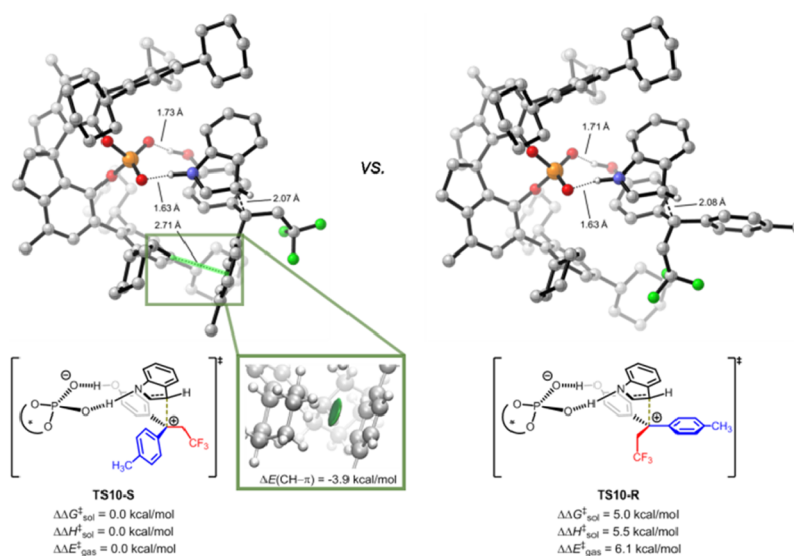


Figure 3. DFT-computed C-C bond formation transition states. Most hydrogens are omitted for clarity.

Figures S1 and S2 and experimental procedures (PDF)
Crystallographic data for 7G (CIF)

AUTHOR INFORMATION

Corresponding Authors

*liuxy3@sustc.edu.cn (X.-Y.L.)

*hxchem@zju.edu.cn (X.H.)

ORCID

Xin Hong: 0000-0003-4717-2814

Xin-Yuan Liu: 0000-0002-6978-6465

Author Contributions

[§]J.-S.L., T.-T.L., and J.-R.L. contributed equally.

Notes

The authors declare no competing financial interest.

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