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

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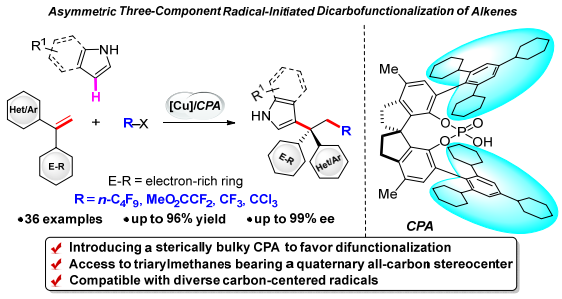
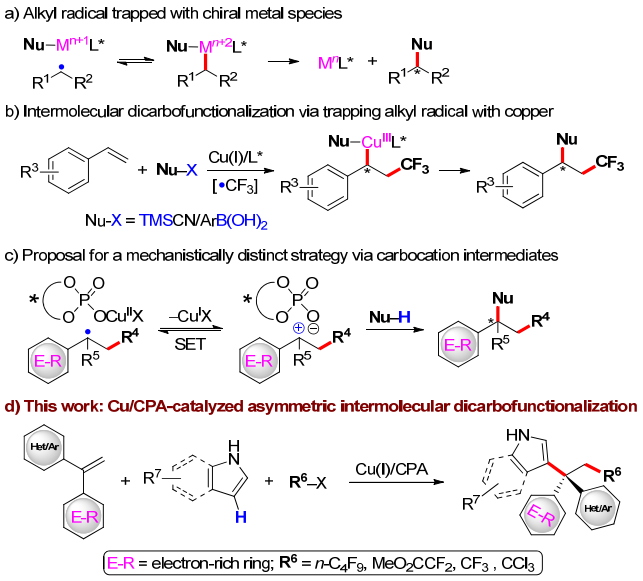
ABSTRACT: An asymmetric intermolecular, three-component radical-initiated dicarbofunctionalization of 1,1-diarylalkenes with diverse carbon-centered radical precursors and electron-rich heteroaromatics by a copper(I) and chiral phosphoric acid cooperative catalysis strategy has been developed, providing 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. DFT calculations elucidated the critical chiral environment created by the hydrogen-bonding and ion-pair interactions between 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, pre-functionalization 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 due to 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.

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



To this end, we wondered if our recently developed Cu(I)/chiral phosphoric acid (CPA) dual-catalysis for radical asymmetric intramolecular transformations[8] 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(sp^2)–H functionalization on electron-rich heteroarene (E-R). Accordingly, it would provide the desired optically active dicarbofunctionalization product in a mode that is mechanistically distinct from 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 of molecules in dye industry, medicinal chemistry, and material science as well as organic synthesis (Figure 1),[9] but their asymmetric construction remains a significant challenge and scare.[10] At the outset, we recognized that several challenges would need to be overcome to reduce this idea to practice, including securing good discrimination between the enantiotopic faces of this carbocation[11] 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-diarylalkenes with electron-rich heteroaromatics and a diverse array of carbon-centered radical precursors enabled by Cu(I)/CPA cooperative catalysis (Scheme 1d).[15]

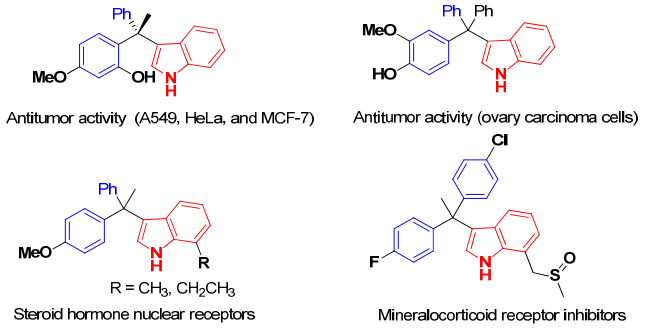


Figure 1. Representative biologically active indole-containing triarylmethanes bearing a quaternary carbon center.

■ RESULTS AND DISCUSSION

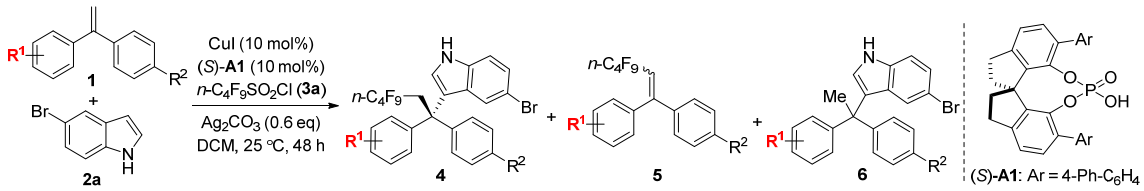
Given the increasing importance of fluoroalkyl-containing molecules in the development of pharmaceuticals and agrochemicals as well as materials,[16] we began our investigation using fluorine-containing carbon-centered radical precursors. To this end, we selected 1,1-diarylalkene **1aa** bearing one OMe-substituted electron-rich arene as the pilot alkene substrate, indole derivative **2a** as the carbon nucleophile, and perfluorobutanyl 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 Ag_2CO_3 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 NH_2 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 due to its significant steric bulkiness hindering nucleophilic indole from approaching toward the alkene. Noteworthy is 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 perfluoroalkylarylation of alkenes (Table 3). Various diversely functionalized 1,1-diarylethylenes, including those having aryl groups with electron-withdrawing (CF_3, F, Cl, NO_2, CO_2Me) or electron-donating groups (OMe, Me) at different positions (*ortho*, *meta*, or *para*) as well as a polyarene naphthalene ring were found to be suitable substrates to afford the expected products **4A**–**4P** in 56–97% yields with 91–98% ee. It is noteworthy that 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 (CF_2R) routinely serves as a core pharmacophore in drug discovery in recent years.[16] To our delight, the reaction of 1,1-diarylethylene substrate **1a** with $MeO_2CCF_2SO_2Cl$ (**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 pharmaceutical drugs,[19] and 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 CF_3-containing triarylmethanes, we identified the well-known Togni's reagent (**3d**)[2d] but not trifluoromethanesulfonyl chloride (CF_3SO_2Cl)[8b] as the appropriate CF_3 source to obtain **7A**–

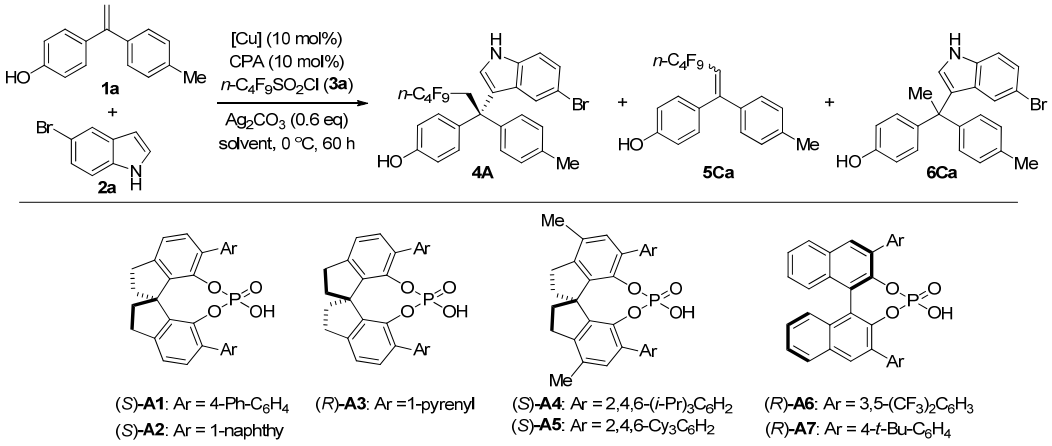
Table 1. Initial Exploration of Reaction Conditions[a]



Entry	1	R^1	R^2	4	y (%)[b]	ee (%)[c]	5	y (%)	6	y (%)
1	**1aa**	4-H	OMe	**4Aa**	20	7	**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

[a]Reaction conditions: **1** (0.1 mmol), **2a** (0.12 mmol), *n*-$C_4F_9SO_2Cl$ (0.12 mmol), CuI (10 mol%), Ag_2CO_3 (0.06 mmol), CPA (10 mol%), DCM (1.0 mL) under argon. [b]Isolated yield. [c]Ee value on HPLC.

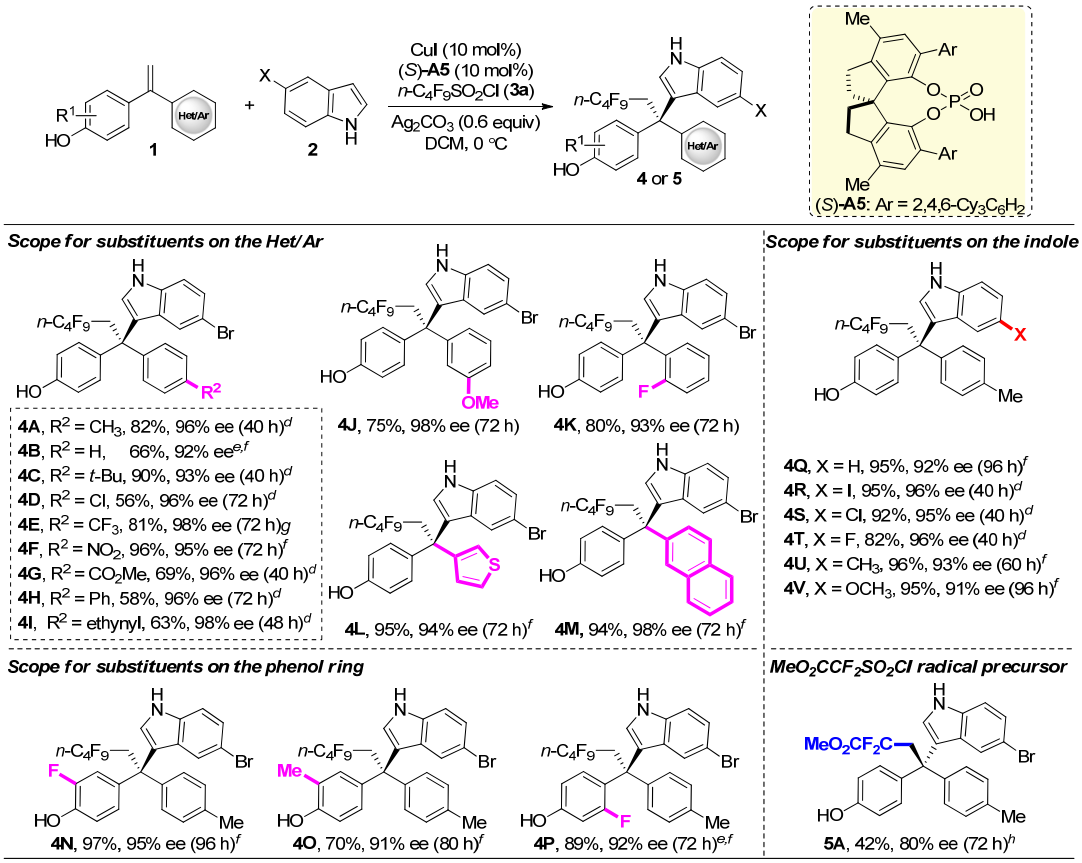
Table 2. Screening of Reaction Conditions[a]



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[e]	CuI	(*S*)-**A5**	DCM	88	0	11	-95

[a]Reaction conditions: **1a** (0.05 mmol), **2a** (0.06 mmol), *n*-$C_4F_9SO_2Cl$ (0.06 mmol), [Cu] (10 mol%), Ag_2CO_3 (0.03 mmol), CPA (10 mol%), dry solvent (0.5 mL), 0 °C, 60 h under argon. [b]Yield based on ^1H NMR analysis of the crude product using CH_2Br_2 as an internal standard. [c]Ee value on HPLC. [d] 20 °C. [e](*S*)-**A5** (7.5 mol%) was used at −3 °C.

Table 3. Substrate Scope for Perfluoroalkylarylation or Difluoroacetylarylation of 1[a,b,c]



[a]Reactions were conducted on 0.1 mmol scale. [b]Isolated yield based on **1** were given. [c]Ee was determined by HPLC analysis. [d]Run at −3 °C. [e]Run at 0 °C for 72 h, then 29 °C for 42 h. [f]15 mol% CuI. [g]20 mol% CuI. [h]The reaction was conducted on 0.025 mmol scale with Ag_2CO_3 (0.5 equiv.), (*R*)-3,3′-(3,5-$(Ph)_2C_6H_3)_2$-8H-BINOL-derived CPA at −30 °C for 72 h.

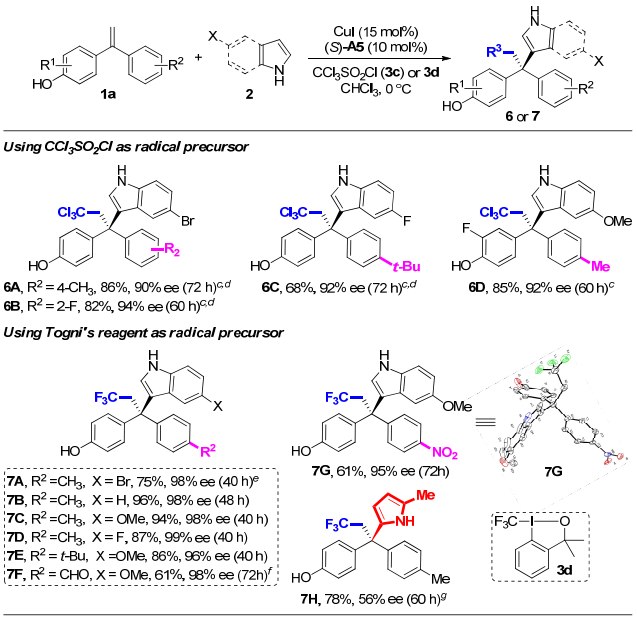
7G in good to excellent yields with excellent ee. Meanwhile, it was striking to note that 2-methyl-1*H*-pyrrole as a nucleophile also underwent the current reaction to deliver **7H** in 78% yield with promising enantioselectivity, which is currently under further optimization in our laboratory. The absolute configuration of **7G** has been determined to be *S* by X-ray crystallographic analysis (Figure S2 in SI 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 not only serve 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]

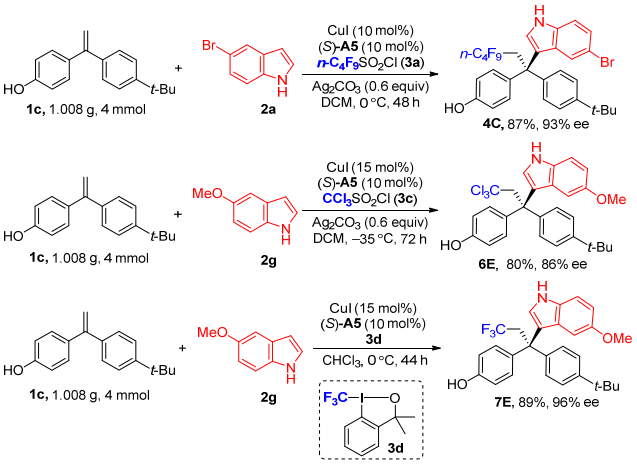
To gain some insight into the reaction mechanism, a series of control experiments were conducted. First, the present reaction was completely inhibited by the addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), and the radical trapping product *n*-C_4F_9–TEMPO was observed in ^{19}F NMR and detected by GC-MS, suggesting that the *n*-C_4F_9 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

Table 4. Substrate Scope for Trichloromethylarylation and Trifluoromethylarylation of 1[a,b]



[a]All the reactions were conducted on 0.1 mmol scale. [b]Ee was determined by HPLC analysis. [c]Ag_2CO_3 (0.6 equiv.), −35 °C, DCM. [d]20 mol% CuI. [e]Run at −2 °C. [f]Run at 0 °C for 12 h, then 28 °C for 48 h. [g](*S*)-3,3′-(3,5-(*t*-Bu)$_2$C$_6$H$_3$)$_2$-SPINOL-derived CPA, −15 °C for 72 h.

Scheme 2. Gram-Scale Reaction with Diverse Radical Precursors



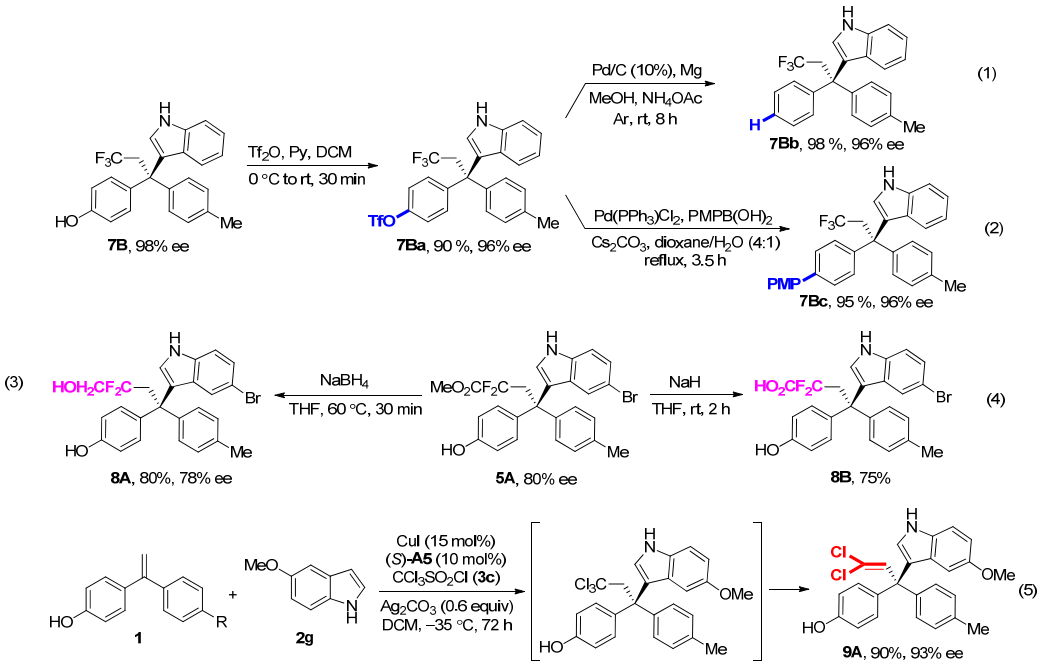
Cu(I) salt and CPA are essential for this reaction, and CPA might have played an important role in the activation of sulfonyl chloride.

Besides, either the *N*-protected indole **2i** (Scheme 4, eq. 2) or methyl-protected 1,1-diarylalkene **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. Noteworthy is 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-diarylalkene with CPA.[10b] In our reactions, a small amount of internal alkene product **5Ca** was formed via radical alkylation of 1,1-diarylethylene 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 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 as well as versatile functionalization of the products, thus constituting a more appealing alternative to the previous approach.[10,12]

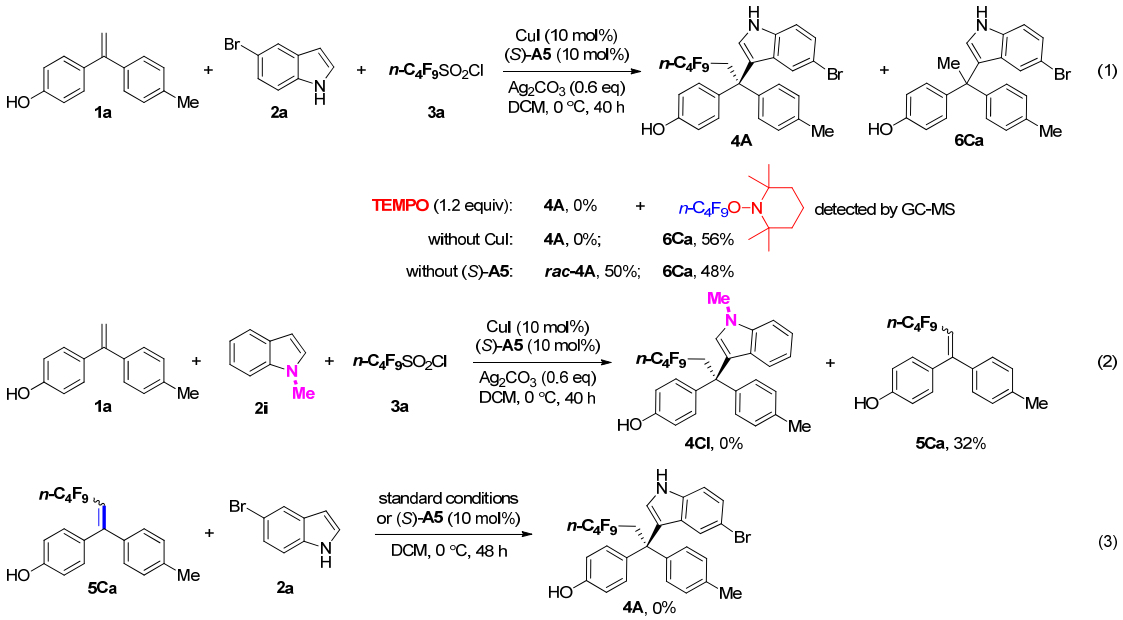
To further elaborate the mechanistic details, we studied the relationship between product enantiopurity and catalyst enantiopurity. The observed linear relationship indicates the involvement of one CPA catalyst in the enantioselectivity-determining transition states (Figure 2a). On the basis of above observations and previous reports,[6,8] we have proposed a working mechanism, as shown in Figure 2b. Cu(I) first reacts with CPA-activated RSO_2Cl 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 Ag_2CO_3 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 interactions[15] 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 since 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 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 (Figure S1–S4 in SI 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 SI 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 SI for Computations), while **TS10-R** does not possess this interaction due to the stereogenic configuration of forming C–C bond. The proposed CH-π interaction is also proved by IGM analysis;[25] the green oval represents the favorable interaction between the highlighted fragments

Scheme 3. Representative Product Transformations



Scheme 4. Mechanistic Study



(Figure 3). Therefore, our calculations indicate the importance of hydrogen bonding and ion-pair interactions in the chiral induction, as well as the non-covalent 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-diarylalkenes with a diverse array of carbon-centered radical precursors and electron-rich heteroaromatics, encompassing a direct intermolecular arene C(sp^2)–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 enanti-

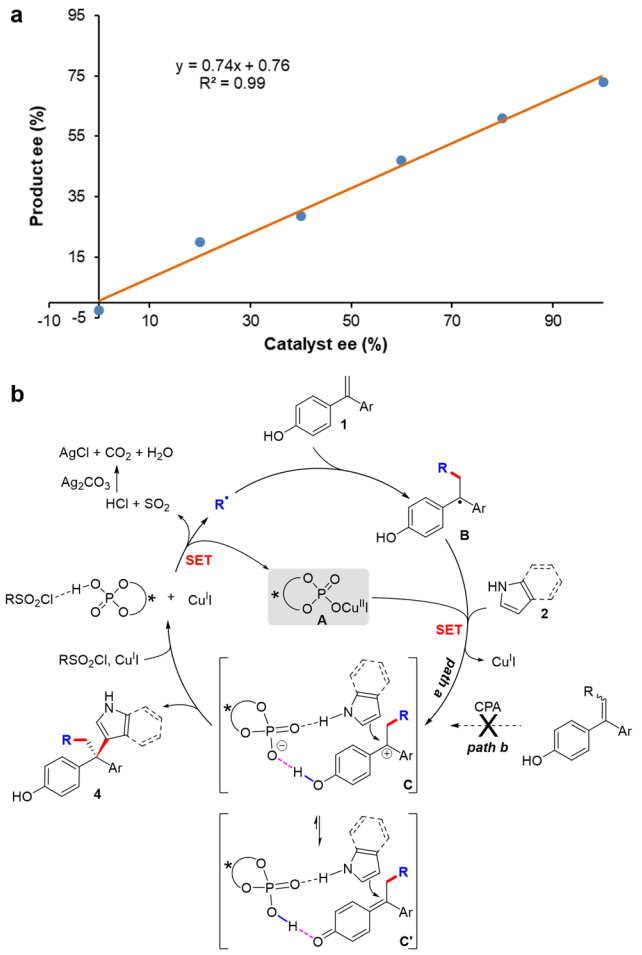


Figure 2. Absence of nonlinear effects and mechanistic proposal.

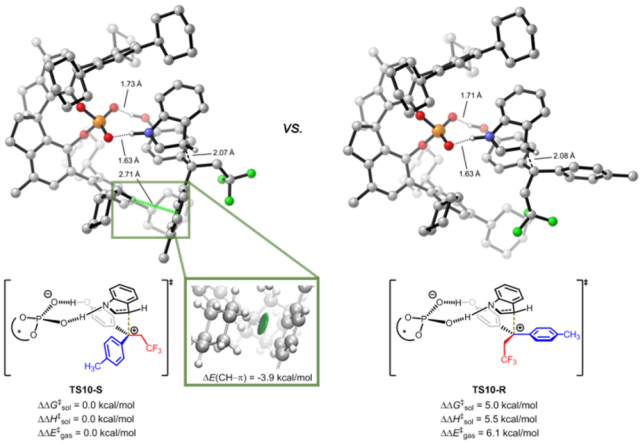


Figure 3. DFT-computed C–C bond formation transition states. Most hydrogens are omitted for clarity.

oselective 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.
Experimental procedures, characterization, and spectra data.
The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.
Figure S1, S2 and, experimental procedures and theory (DFT) calculations, characterization data (PDF)
Crystallographic data for **7G** (CIF)

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Notes

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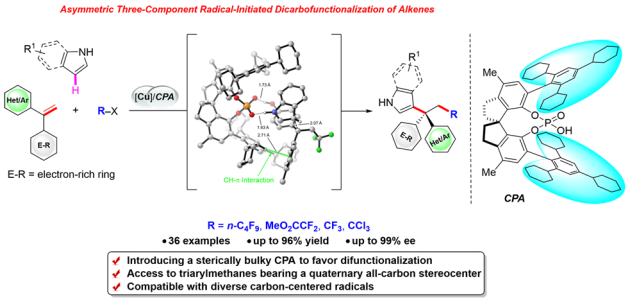
Asymmetric Three-Component Radical-Initiated Dicarbofunctionalization of Alkenes
Het/Ar
E-R
R–X
[Cu]/CPA
E-R = electron-rich ring
CH-π Interaction
HN
R
Me
OH
CPA
R = n-C4F9, MeO2CCF2, CF3, CCl3
• 36 examples • up to 96% yield • up to 99% ee
Introducing a sterically bulky CPA to favor difunctionalization
Access to triarylmethanes bearing a quaternary all-carbon stereocenter
Compatible with diverse carbon-centered radicals