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A Counterion/Ligand-Tuned Chemo- and Enantioselective Copper-Catalyzed Intermolecular Radical 1,2-Carboamination of Alkenes

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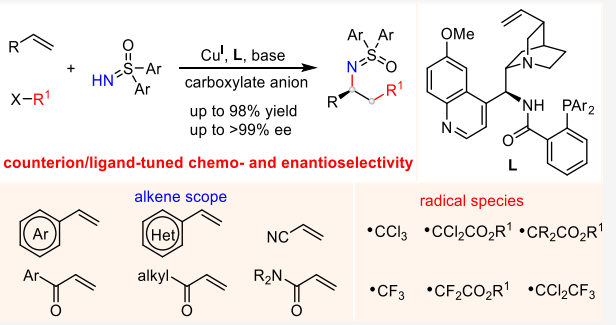
ABSTRACT: The copper-catalyzed enantioselective intermolecular radical 1,2-carboamination of alkenes with readily accessible alkyl halides is an appealing strategy for producing chiral amine scaffolds. The challenge arises from the easily occurring atom transfer radical addition between alkyl halides and alkenes and the issue of enantiocontrol. We herein describe a radical alkene 1,2-carboamination with sulfoximines in a highly chemo- and enantioselective manner. The key to the success of this process is the conceptual design of a counterion/highly sterically demanded ligand coeffect to promote the ligand exchange of copper(I) with sulfoximines and forge chiral C−N bonds between alkyl radicals and the chiral copper(II) complex. The reaction covers alkenes bearing distinct electronic properties, such as aryl-, heteroaryl-, carbonyl-, and aminocarbonyl-substituted ones, and various radical precursors, including alkyl chlorides, bromides, iodides, and the CF_3 source. Facile transformations deliver many chiral amine building blocks of interest in organic synthesis and related areas.



INTRODUCTION

Alkenes are ubiquitous feedstocks in all aspects of chemistry and are readily available starting materials for versatile transformations. The intermolecular enantioselective 1,2-difunctionalization of alkenes represents a powerful tool for upgrading the feedstocks into enantioenriched complex molecules since it allows simultaneous installation of two vicinal new bonds.[1] Given the significance of chiral amines in pharmaceuticals and organic synthesis,[2] the intermolecular enantioselective 1,2-carboamination of alkenes has attracted great interest (Scheme 1A). Particularly, the precious transition metal catalysis has been developed to achieve such transformations, where the reaction initiation and enantiocontrol are generally achieved via the alkene carbometallation, a strategy pioneered by Cramer, Rovis, and others.[3,4] In comparison, the radical-mediated intermolecular alkene 1,2-carboamination represents an important complementary approach because radicals have a high propensity to unsaturated bonds,[5] thus avoiding the utilization of precious transition metals for alkene activation.[6] Moreover, the abundance and easy availability of radical precursors further enriched the product diversity. As such, great progress has been made in developing the racemic intermolecular radical 1,2-carboamination of alkenes by harnessing the advantages of radical reactions.[6,7] Among them, three pathways account for the C−N bond formation after the addition of carbon-centered radical to alkenes: (i) the direct radical−radical cross-coupling or radical addition to unsaturated bonds;[7a−c] (ii) the radical−cation crossover followed by nucleophilic addition;[7d−i] and (iii) the 3d transition metal-mediated bond formation process (Scheme 1B).[7j−n] Notably, the lack of polar functional groups nearby the alkyl radical center renders the enantiocontrol over the radical extremely difficult through the first two pathways.[8,9] Although the last pathway provides a ready mechanism for enantiocontrol as pioneered by Fu and Peters,[10,11] it has been seldom used in the intermolecular enantioselective alkene carboamination.[12] Only until very recently, Bao and others have realized a unique class of asymmetric alkene 1,2-carboazidation with $TMSN_3$, where an aryl substituent on the alkenes is necessary to deliver high enantioselectivity.[13] Notably, the early-stage conversion of the chiral alkylazides to protected amines is generally required in a multiple-step transformation of the obtained chiral azide compounds.[13] Therefore, the development of an intermolecular enantioselective 1,2-carboamination of diverse alkenes bearing distinct electronic properties with readily accessible radical precursors

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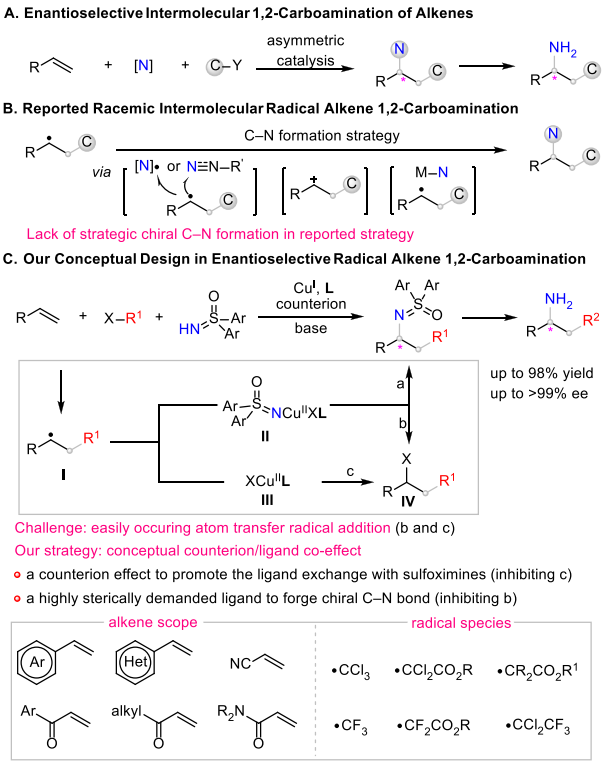
Scheme 1. Enantioselective Intermolecular Radical 1,2-Carboamiation of Alkenes



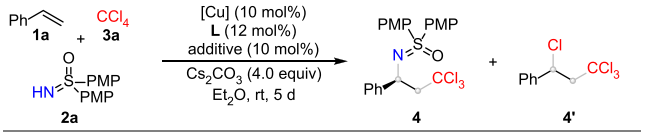
and new amine nucleophiles that tolerate multiple-step synthetic operations is highly desirable.

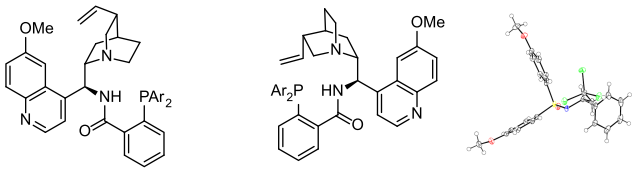
We have been investigating copper-catalyzed asymmetric radical reactions[14] and recently reported an enantioselective C(sp^3)–N cross-coupling of alkyl halides with sulfoximines through the interaction of alkyl radicals with L*Cu^{II}Nu.[15] Given the ready availability of alkyl halides, we wondered whether a three-component enantioselective alkene 1,2-carboamination can be achieved by merging our enantioselective C–N formation with the radical alkene addition process using sulfoximines as the amine sources.[16] However, the major challenge would be the inherently facile atom transfer radical addition (ATRA)[17] between alkyl halides and alkenes, which is one of the most prevailing strategies for alkene difunctionalization (Kharasch addition, the formation of ATRA product **IV** in Scheme 1C).[18] Our initial attempts with styrene, sulfoximine **2a**, and CCl_4 showed that CuI and the chiral *N,N,P*-ligand **L1**[15,19] could only afford the ATRA product (Scheme S1 in the Supporting Information). A further control experiment revealed that the ATRA product was also generated in a similar yield in the absence of sulfoximine **2a** (Scheme S1 in the Supporting Information). These results demonstrated that the ligand exchange with sulfoximine is so slow that the desired reaction pathway cannot compete with the ATRA process (Scheme 1C, pathway a versus c). To this end, we disclose a copper-catalyzed intermolecular radical 1,2-carboamination of alkenes with alkyl halides and sulfoximines with high chemo- and enantioselectivity. The key to the success of this process is the conceptual design of a combined counterion/chiral ligand effect to promote the desired process and suppress the easily occurring ATRA reaction: the counterion plays a pivotal role in accelerating the ligand exchange of sulfoximines with the copper catalyst; the highly sterically demanded chiral *N,N,P*-ligand forges the desired chiral C–N bond instead of the C–X bond in the last step (Scheme 1C, pathway a versus b). The reaction exhibits a remarkably broad substrate scope, covering aryl-, heteroaryl-, carbonyl-, and aminocarbonyl-substituted alkenes bearing distinct electronic properties as well as diverse radical precursors, such as alkyl chlorides, bromides, iodides, and the CF_3 source (Scheme 1C). Owing to the broad scope of alkenes and radical precursors, the straightforward transformation enables it to be a powerful tool in generating diverse chiral amine building blocks.

RESULTS AND DISCUSSION

Reaction Development. With the preliminary reaction outcome in hand (Scheme S1 and Table 1, entries 1 and 2),

Table 1. Investigation of Counterions and Ligands for Model Reaction[a]





L1, Ar = 3,5-(3,5-$Me_2C_6H_3)_2C_6H_3$ **L5**, Ar = 3,5-(3,5-$Me_2C_6H_3)_2C_6H_3$ X-ray structure of **4**
L2, Ar = Ph
L3, Ar = 3,5-$Ph_2C_6H_3$
L4, Ar = 3,5-(3,5-^{t}Bu$_2C_6H_3)_2C_6H_3$

entry	[Cu]	L	additive	y. of **4** (%)	y. of **4′** (%)	ee of **4** (%)
1[b]	CuI	**L1**		trace	88	
2[c]	CuI	**L1**		0	88	
3	CuI	**L1**	AcOH	45	10	96
4	CuI	**L1**	PivOH	89	3	97
5	CuI	**L1**	BzOH	45	15	95
6	CuI	**L1**	TcH	40	10	96
7	CuOAc	**L1**		43	0	98
8	**CuTc**	**L1**		**90**	**0**	**96**
9[d]	CuTc	**L1**		85	0	96
10	CuTc	**L2**		2	24	59
11	CuTc	**L3**		10	35	82
12	CuTc	**L4**		11	0	96
13	CuTc	**L5**		94	0	−95

[a]Reaction conditions: **1a** (1.2 equiv), **2a** (0.05 mmol), **3a** (1.2 equiv), [Cu] (10 mol %), **L** (12 mol %), and Cs_2CO_3 (4.0 equiv) in Et_2O (0.5 mL) at room temperature for 5 days under argon; yields (y.) were based on ^{1}H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard; ee values were determined by HPLC analysis; all reactions were repeated twice. [b]The ee values of **4′** were less than 5% during the whole optimization process. [c]**2a** was removed. [d]Conducted at 40 °C for 1 day. PivOH, pivalic acid; Bz, benzoyl; and Tc, thiophene-2-carboxylate.

our endeavor toward the promotion of the desired pathway focused on accelerating the ligand exchange of sulfoximines with the copper catalyst. Inspired by the unique role of carboxylate anions in transition metal-catalyzed C–H activation via concerted metalation deprotonation (CMD),[20] we added carboxylic acid as an additive to assist the ligand exchange process. As such, several carboxylic acids were

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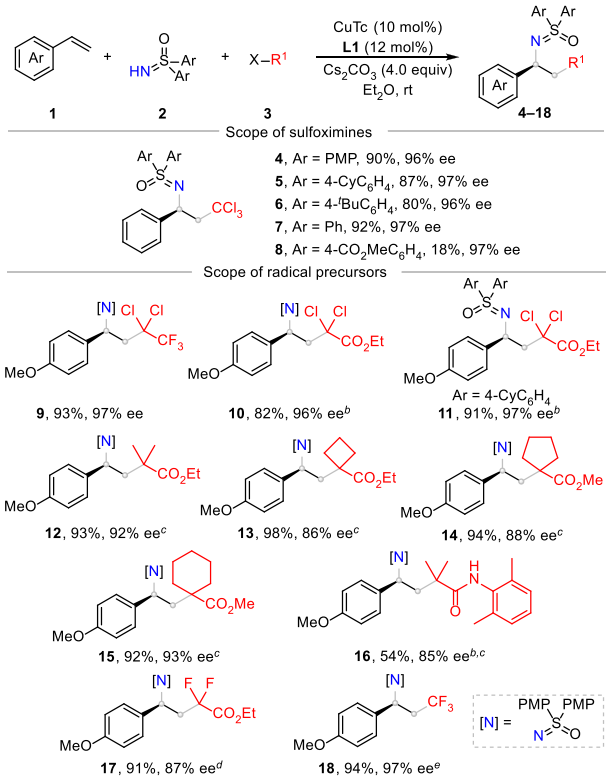
Table 2. Scope of Sulfoximines and Radical Precursors[a]



[a]Reaction conditions: **1** (1.2 equiv), **2** (0.20 mmol), **3** (alkyl chloride, 1.2 equiv), CuTc (10 mol %), **L1** (12 mol %), and Cs_2CO_3 (4.0 equiv) in Et_2O (2.0 mL) at room temperature for 5 days under argon; yields were isolated ones; ee values were determined by HPLC analysis. [b]$Cu(HFac)_2$ was used. [c]Alkyl iodide was used. [d]1-Trifluoromethyl-1,2-benziodoxol-3(1*H*)-one (Togni reagent) was used. [e]HFac, hexafluoroacetylacetonate.

investigated in the reaction of styrene **1a**, sulfoximine **2a**, and CCl_4 **3a**. We are pleased to find a dramatic suppression of the ATRA product **4′** and the formation of the desired carboamination product **4** (Table 1, entries 3–6). The pivalic acid, performing an essential role in the CMD process,[20d] gave the best result with the formation of a trace amount of **4′** (Table 1, entry 4). We theorized that the low chemoselectivity of **4** with other carboxylic acids was possibly due to the equilibrium concentrations of copper iodide and carboxylate, which led to different reaction outcomes (Table 1, entries 3–6). Thus, we are encouraged to use pure copper(I) carboxylate as the catalyst to suppress the ATRA process. Gratifyingly, employing the commercially available CuOAc or CuTc salt significantly improved the chemoselectivity and the latter gave an excellent yield of **4** (Table 1, entries 7 and 8). Enhancing the reaction temperature to 40 °C could greatly increase the reaction rate to deliver **4** in a high yield without affecting the ee after 1 day (Table 1, entry 9). Further ligand investigation showed the steric effect on the *P*-aryl ring was also crucial for the chemoselectivity: while ligands with the less sterically hindered substituents (Dixon's ligand[19] **L2** and **L3**) afforded low chemoselectivity and efficiency, the one with a bulkier substituent (**L4**) delivered **4** in only 11% yield (Table 1, entries 10–12). We reasoned that the interaction of the prochiral alkyl radical intermediate **I** with the Cu^{II} complex **II** to forge the C–N and C–X bond was greatly affected by the ligand architecture (Scheme 1C, pathway a versus b). The small sterically hindered ligand was unfavorable for the C–N formation but preferred the C–X formation in the last step. The large sterically hindered ligand would prevent the interaction of intermediates **I** with **II** and be deleterious to the whole transformation. Considering the operational simplicity, we finally identified the optimal conditions as follows: **1a** (1.2 equiv), **2a** (1.0 equiv), **3a** (1.2 equiv), CuTc (10 mol %), **L1** (12 mol %), and Cs_2CO_3 (4.0 equiv) in Et_2O at room temperature, affording **4** in 90% NMR yield with 96% ee (Table 1, entry 8). The absolute configuration of **4** was determined to be *S* by X-ray analysis (Table 1 and Figure S1 in the Supporting Information) and those of other products were assigned by analogy. Replacing **L1** with its pseudoenantiomer **L5** afforded the enantiomer of **4** in 94% yield with 95% ee (Table 1, entry 13).

Substrate Scope. With the established optimal conditions in hand, we first evaluated the scope of sulfoximines (Table 2). The result showed that the reaction efficiency was influenced by the electronic effect on the aryl ring of sulfoximines: while the electron-donating or neutral substituents gave the desired carboamination products (**4**–**7**) with satisfactory yields and ee, the electron-withdrawing substituent was detrimental to the reaction efficiency (**8**). We next investigated the scope of radical precursors. Alkyl chlorides, such as trichlorotrifluoroethane and ethyl trichloroacetate, reacted well to result in **9**–**11** with excellent ee. A range of alkyl bromides that is α to ester or amide functional groups was amenable to the reactions, providing **12**–**16** with good ee. Furthermore, the fluoroalkyl iodide also proved to be suitable for the reaction to afford **17** in 91% yield with 87% ee. Most significantly, the Togni reagent reacted smoothly to furnish the pharmaceutically relevant β-trifluoromethylated amine **18** in 94% yield with 97% ee. However, the reaction could not be initiated with primary alkyl halides, such as ethyl chloroacetate and ethyl bromoacetate.

We then investigated the scope of alkenes for the asymmetric 1,2-carboamination. As shown in Table 3, the styrene-type alkenes possessing diverse electron-donating and -withdrawing substituents at different (*ortho*, *meta*, or *para*) positions of the phenyl rings reacted smoothly to afford **19**–**35** in 70–98% yields with up to 99% ee. Importantly, a gamut of reactive functionalities, such as acetyl (**22**), thioether (**23**), halogen (**26**–**28**), nitrile (**30**), formyl (**31** and **32**), ketone (**33**), ester (**34**), and even nitro (**35**) groups, were well tolerated under the standard conditions. In addition, the phenyl ring having mono- and disubstituted conjugated groups (phenyl, terminal, and internal alkene, alkyne) was compatible with the reaction conditions to deliver **36**–**40** in moderate to good yields with high enantioselectivities. Alkenes bearing polycyclic aryl rings were also suitable for the reactions, giving rise to **41**–**47** in good yields with 87 to >99% ee. More importantly, alkenes containing many medically relevant heterocycles, such as pyridine, quinoline, thiophene, and benzo[*b*]thiophene, were viable substrates to furnish the desired products **48**–**51** with up to 99% ee.

Enantioenriched α-amino carbonyl compounds are a class of privileged motifs in many pharmaceutically active agents and valuable intermediates in organic synthesis.[21] To further strengthen the utility of the strategy, we next switched our attention to the scope of other carbonyl-substituted alkenes, which have not been utilized in the reported enantioselective radical alkene difunctionalization.[12b,13] We found that an array of carbonyl-substituted alkenes was suitable for the reaction to

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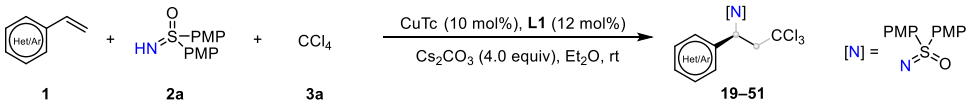
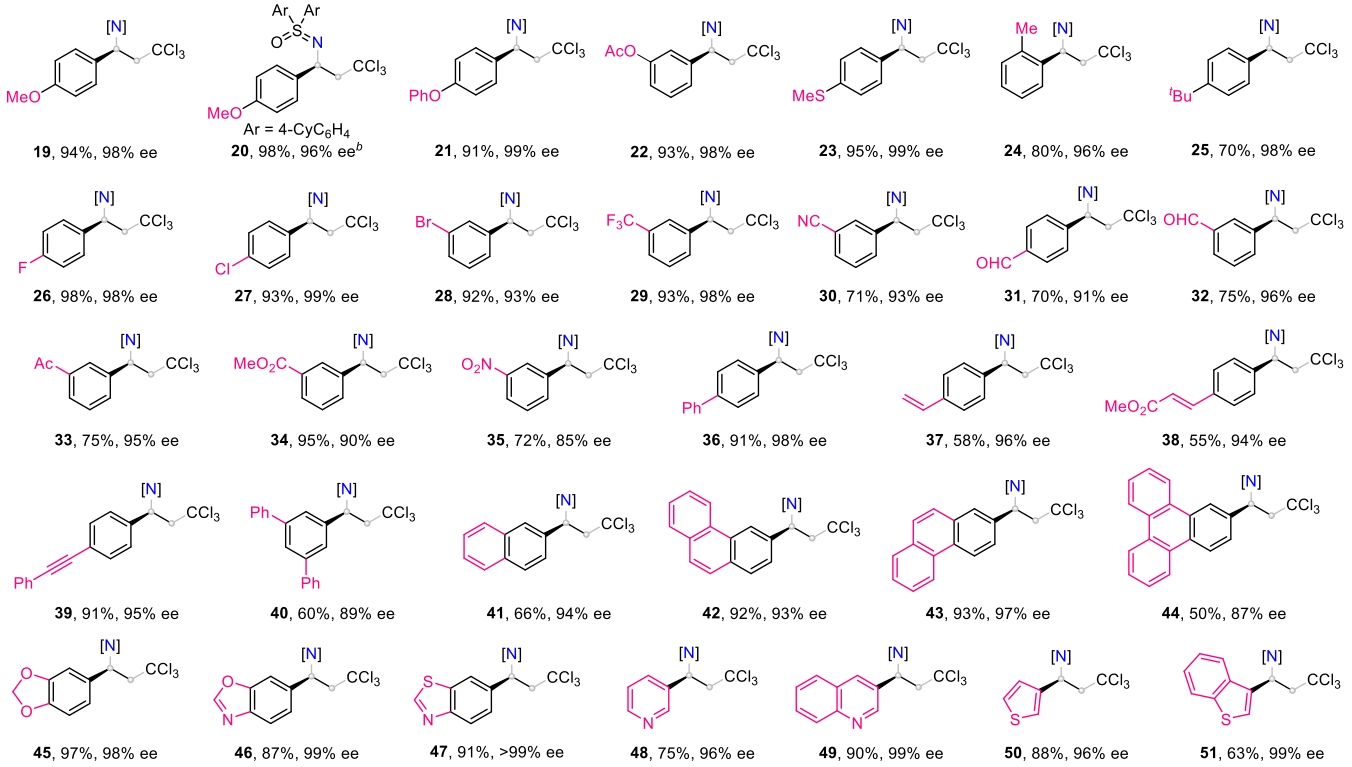
Table 3. Scope of Styrene-Type Alkenes[a]



1 2a 3a 19–51



[a]Reaction conditions: **1** (1.2 equiv), **2a** (0.20 mmol), **3a** (1.2 equiv), CuTc (10 mol %), **L1** (12 mol %), and Cs_2CO_3 (4.0 equiv) in Et_2O (2.0 mL) at room temperature for 5 days. [b]4-Cyclohexyl-substituted diaryl sulfoximine (**2b**) was used; yields were isolated ones; ee values were determined by HPLC analysis.

provide enantioenriched α-amino ketones **52**–**56** in moderate to good yields with 81–96% ee under slightly modified conditions (Table 4). Both aryl and alkyl ketones were compatible with the reaction conditions. Notably, the nitrile-substituted alkene was also a viable substrate, resulting in the chiral α-amino nitrile **57**, albeit with a moderate ee. More significantly, a panel of amide-substituted alkenes was well accommodated, leading to enantioenriched α-amino amides **58**–**61** with 81–92% ee. As for the carbonyl-substituted alkenes, the high reaction efficiency and enantioselectivity might be attributed to the coordination of the copper catalyst with the substrates.[22] Collectively, this strategy not only achieved the enantioselective radical 1,2-difunctionalization of carbonyl-substituted alkenes for the first time but also provided diverse enantioenriched γ-functionalized α-amino carbonyl compounds.

Synthetic Utility. To show the preparative utility of this method, a gram-scale reaction was first carried out to furnish the desired product **20** without a decrease in efficiency (Scheme 2A). The most important application is that it provides a versatile platform for expedient synthesis of diverse chiral amine building blocks. To showcase this potential, the enantioenriched sulfoximine **18** was successfully converted to the chiral β-trifluoromethylated amine derivative **62** using a sequential Na/naphthalene reduction/acidic hydrolysis/protection protocol (Scheme 2B). The facile functionality transformation/reduction of trichloromethylated product **20** afforded an γ-amino aldehyde **63** and further delivered **64** via a Wittig reaction, which was converted to an enantioenriched δ-alkenyl amine building block **65** (Scheme 2C). Moreover, the dichloromethylated product **11** also underwent a reduction process to furnish a γ-amino acid derivative **66**. The direct deprotection or reduction/deprotection of **66** resulted in the enantioenriched γ-lactam (**67**) and 1,4-amino alcohol (**68**) building blocks. Notably, no apparent loss of enantiopurity was observed during all these transformations. Notably, the sulfoximine moieties are proved to be stable protecting amine functionalities and could tolerate multistep synthesis, as demonstrated in the synthesis of **65**–**68**.

Mechanistic Consideration. To gain insights into the reaction mechanism, several control experiments were conducted. A radical trap experiment with butylhydroxytoluene (BHT) showed that the reaction was completely inhibited and the BHT-trapped product **69** was detected (Scheme 3A). The radical clock reaction with **70** bearing an α cyclopropyl substituent delivered the radical addition/ring-opening/C–N formation product **71** in 12% yield under the standard reaction conditions. The combined experiments indicated the involvement of a radical process (Scheme 3B). Notably, no coupling product between **4′** and **2a** was formed when the ATRA side product **4′** was exposed to the reaction of **1b** and only **19** was afforded. In comparison, both **4** and **19** were obtained when the corresponding alkenes **1a** and **1b** were simultaneously exposed to the standard reaction conditions

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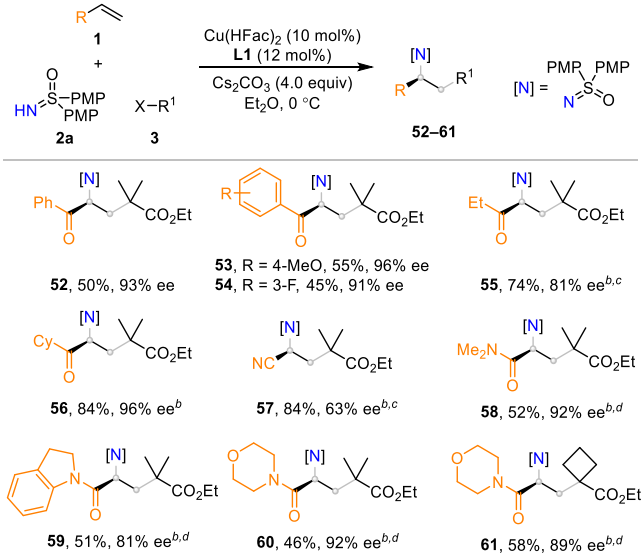
Table 4. Scope of Electron-Deficient Alkenes[a]



[a]Reaction conditions: **1** (2.0 equiv), **2** (0.20 mmol), **3** (alkyl bromides, 2.0 equiv), $Cu(HFac)_2$ (10 mol %), **L1** (12 mol %), and Cs_2CO_3 (4.0 equiv) in Et_2O (2 mL) at 0 °C for 5 days. [b]**1** (1.5 equiv), **2** (0.20 mmol), **3** (alkyl bromides, 1.5 equiv) were used. [c]**L4** (12 mol %) were used. [d]Conducted at room temperature; yields were isolated ones; ee values were determined by HPLC analysis.

(Schemes 3C and S2 in the Supporting Information). Meanwhile, the direct coupling of **4′** and **2a** did not occur under the standard conditions as well (Scheme S2 in the Supporting Information). Collectively, these experiments together with the formation of the carboamination product **18** excluded the possibility of a stepwise atom transfer radical addition/cross-coupling process (Scheme 3C and Table 2).

Based on the above experiments and literature reports,[14,15] we proposed a possible mechanism as depicted in Scheme 3D. First, the copper(I) salt reacted with ligand **L** and base to generate a complex **A**. Without the facilitation of the counterion, complex **A** would directly react with the radical precursors **3** to generate the ATRA side product **IV** via the interaction of **I** and **III** (the right-hand catalytic cycle). The addition of a carboxylate anion would switch the reaction pathway through the formation of a copper(I) carboxylate **B**, which underwent a fast ligand exchange with sulfoximines **2** to afford a copper(I)-sulfoximinato complex **C** (the left-hand catalytic cycle) via a CMD-type process.[20] This intermediate then reduced the radical precursors **3**, leading to the copper(II)-sulfoximinato complex **II** and an R^1 radical. The R^1 radical underwent a facile addition to alkenes **1** and provided the prochiral alkyl radical **I**. Next, radical **I** interacted with complex **II** to deliver the desired carboamination products **4**–**61** and regenerated the copper(I) species **A** in the presence of the highly sterically demanded ligand **L1**. As mentioned in the reaction development section, both the less and more sterically hindered ligands are harmful to the desired pathway by either forming the side product **IV** (pathway b in Scheme 1C) or retarding the interaction of **I** and **II**.

CONCLUSIONS

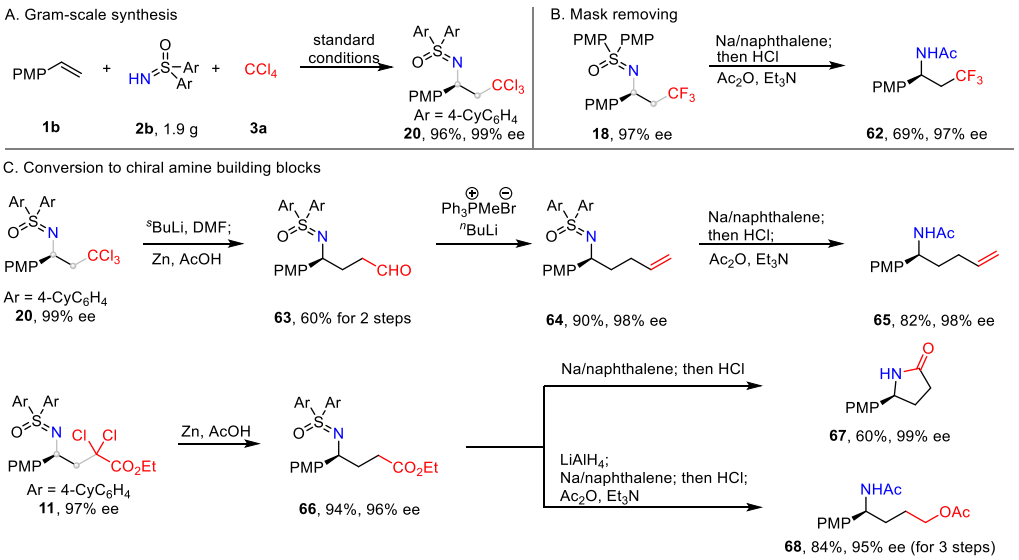
In summary, we have developed a copper-catalyzed intermolecular enantioselective radical 1,2-carboamination of alkenes from readily available alkyl halides and sulfoximines by successfully merging the radical addition to alkenes and enantioselective radical C–N formation. The employment of a carboxylate counterion and the highly sterically demanded *N,N,P*-ligand is vital for the high chemo- and enantioselectivity. More significantly, the alkene scope is very broad, covering not only aryl and heteroaryl alkenes but also carbonyl-substituted alkenes that have not been disclosed in reported asymmetric radical alkene 1,2-difunctionalization. A wide array of alkyl halide radical precursors is easily accommodated into alkenes under ambient conditions. This approach provides a versatile platform for the synthesis of chiral amines as well as other synthetically valuable chiral building blocks.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c08035.

Scheme 2. Synthetic Utility



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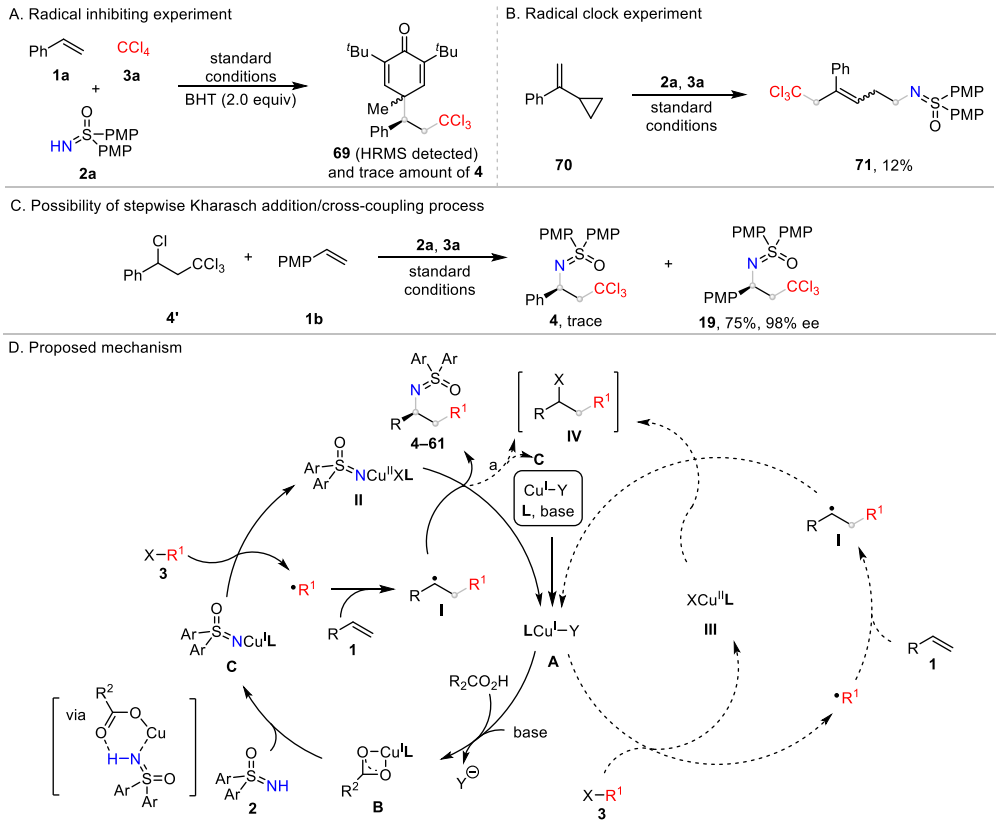
Scheme 3. Mechanistic Investigation



Experimental procedures, characterization of compounds, initial test on copper-catalyzed enantioselective 1,2-carboamination, control experiments to exclude the stepwise ATRA/cross-coupling process, and crystallographic data of **4** (PDF)

Accession Codes

CCDC 2192979 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

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Author Contributions

The manuscript was written through the contributions of all authors.

Notes

The authors declare no competing financial interest.

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