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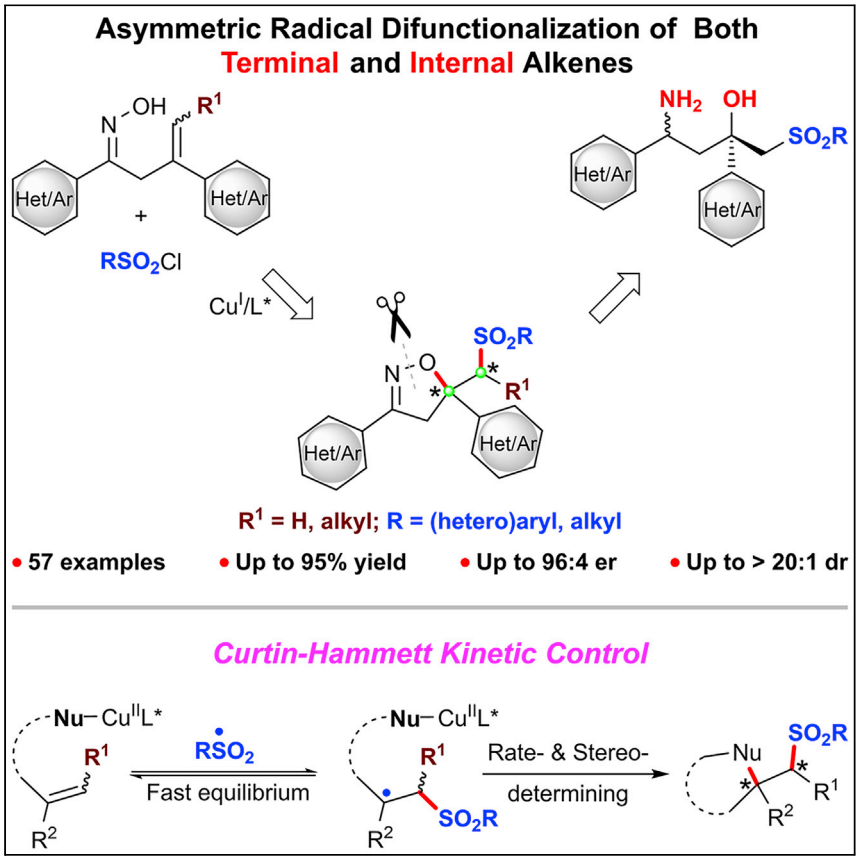

Liu and colleagues describe the first asymmetric radical oxysulfonylation of both terminal and internal alkenes in β,γ- unsaturated ketoximes using their developed copper(I)-cinchona alkaloid-derived sulfonamide ligand catalyst. Experimental and computational studies collectively suggest a Cu^{II}-Cu^{I} catalytic cycle involving fast and reversible sulfonyl radical addition and subsequent rate- and stereo-determining C–O bond formation, namely, a scenario under Curtin-Hammett kinetic control. The method provides a robust platform for the synthesis of a diverse array of valuable chiral sulfonyl-containing building blocks.

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HIGHLIGHTS

Asymmetric radical oxysulfonylation of both terminal and internal alkenes•

Copper(I)-cinchona alkaloid-derived sulfonamide ligand catalyst•

A radical stereodiscrimination process under Curtin-Hammett kinetic control•

Chiral sulfones with great potential for drug and agrochemical discoveries

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Diastereo- and Enantioselective Catalytic Radical Oxysulfonylation of Alkenes in β,γ-Unsaturated Ketoximes

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SUMMARY

The asymmetric radical-initiated difunctionalization of internal alkenes, which creates two vicinal stereocenters, has been a significant synthetic challenge despite the tremendous progress achieved for terminal alkenes. This is attributable to the common stepwise mechanism that involves an initial free radical addition to the alkene in a nonstereoselective fashion. We report here the first asymmetric radical 1,2-oxysulfonylation of both terminal and internal aryl alkenes in β,γ-unsaturated ketoximes in the presence of copper(I)-cinchona alkaloid-based sulfonamide catalyst. The experimental and computational mechanistic studies collectively support a Cu^{II}-Cu^{I} mechanism featuring fast, reversible addition of sulfonyl radicals to alkenes and subsequent rate- and stereo-determining C–O bond formation, namely, a scenario under Curtin-Hammett kinetic control. The method provides a robust platform for collective synthesis of a diverse array of valuable chiral sulfonyl-containing building blocks.

INTRODUCTION

Transition-metal-catalyzed asymmetric difunctionalization of alkenes enables the expedited construction of two vicinal carbon–carbon and/or carbon–heteroatom chemical bonds and stereogenic centers from readily available alkene starting materials. Thus, it has been established as a powerful technique for the sustainable preparation of chiral complex organic molecules.[1–6] Recently, very impressive advances have been achieved in the development of Cu-catalyzed radical-initiated asymmetric alkene difunctionalization. Such reactions usually involve the intermolecular addition of free carbon- or heteroatom-centered radicals to alkenes followed by asymmetric functionalization of the thus-generated alkyl radical intermediates with chiral metal species, a significant strategy pioneered by Fu, Reisman, Buchwald, Liu, and others (Scheme 1A).[7–19] In this aspect, Buchwald and Liu independently reported the use of a copper-chiral bis(oxazoline) system to elegantly realize a series of enantioselective alkene difunctionalization reactions.[20–30] At the same time, our group developed a copper-chiral anionic ligand system for several types of asymmetric transformations.[31–36] These methods, however, are generally limited to terminal alkenes, while the use of internal olefins for concomitant generation of two vicinal stereocenters across the C=C double bonds has proved very problematic. The difficulty lies on the stereocontrol in the first free radical (R•) addition step and nonstereoselective formation of **A** and **B** has been explicitly demonstrated in previous works (Scheme 1A, step 1).[20,24,25] Thus, a conceptually different strategy is urgently needed to achieve catalytic asymmetric

The Bigger Picture

Asymmetric catalysis with radical species has become a practical and robust tool for preparing chiral molecules, important in developing drugs, agrochemicals, and materials. In radical addition to alkene, however, the transient nature of radicals can greatly compromise the stereocontrol by any chiral catalyst and thus, catalytic asymmetric radical-initiated difunctionalization of internal alkenes has long remained underdeveloped. Here, we discovered a solution to this conundrum by capitalizing on an initial fast and reversible sulfonyl radical addition process, which renders the enantioselectivity in this step inconsequential to the overall stereoselectivity. Accordingly, both high enantioselectivity and high diastereoselectivity have been achieved in alkene oxysulfonylation. We envision that this strategy will elicit a surge of research efforts on asymmetric radical-initiated difunctionalization of internal alkenes, ultimately benefiting the drug, agrochemical, and material industries.

radical-initiated difunctionalization of internal alkenes with effective control of both the diastereoselectivity and the enantioselectivity.

Sulfone moieties are prevalent in many biologically active molecules and pharmaceutical agents. Although great efforts have been devoted to establishing various racemic radical 1,2-sulfonyl functionalization reactions of alkenes,[37–46] the development of corresponding catalytic asymmetric methods for access to chiral sulfones has so far remained elusive.[21,47,48] Our group has recently developed a copper-cinchona alkaloid-based sulfonamide catalyst system for radical-initiated 1,2-oxytrifluoromethylation of alkenes under mild conditions.[35] Thus, we wondered whether such a copper catalyst system would meet the aforementioned challenges. The addition of sulfonyl radicals (RSO_2•) to alkenes is known to be fast and reversible.[49–53] Accordingly, we hypothesized that a scenario under Curtin-Hammett kinetic control[54,55] might be achieved via a rapid equilibrium between the initial addition diastereomers **C** and **D** (Scheme 1B). Subsequent rate-determining asymmetric functionalization of these alkyl radicals might deliver the desirable product (e.g., P_C) with excellent control of both enantioselectivity and diastereoselectivity. The successful implementation of this strategy will open a new door for precise stereocontrol on the challenging asymmetric radical-initiated difunctionalization of internal alkenes.

The aryl and alkyl sulfone groups, thanks to their unique physicochemical properties, are a kind of important pharmacophores in structure-based drug design and thus, are of great importance in the development of drugs and agrochemicals.[56–63] In addition, enantiomerically enriched β-hydroxysulfone represents a privileged scaffold found in many biologically relevant molecules, such as the anticancer drug bicalutamide and antifungal agents SSY726 and SCH42427.[64–72] Nonetheless, their asymmetric construction remains a significant challenge.[73–79] Herein, we describe our efforts toward the development of a general and efficient asymmetric radical oxysulfonylation of both terminal and internal alkenes using a Cu(I)-cinchona alkaloid-based sulfonamide catalyst. The reaction exhibits a broad scope across a range of alkenes and diverse (hetero)aryl- and alkyl-substituted sulfonyl chlorides (Scheme 1C). Experimental and computational studies[80] have been performed to suggest a stereodiscrimination process under Curtin-Hammett kinetic control.

RESULTS AND DISCUSSION

Optimization Study

We began our investigation by reacting β,γ-unsaturated ketoxime **1a** with *p*-toluenesulfonyl chloride (TsCl) **2a** in the presence of CuOAc and different cinchona alkaloid-based sulfonamide ligands (Table 1). In addition, Ag_2CO_3 was also added to quench the *in situ* generated HCl. A series of quinine-, cinchonidine-, and cinchonine-derived sulfonamide ligands readily provided the desired sulfonyl-containing isoxazoline **3aa** in good yields with moderate enantioselectivity (entries 1–8), and sulfonamide **L1** performed the best in terms of both yield and enantioselectivity (entry 1, 82% yield, 76:24 er). Subsequent screening of different Cu salts (entries 10–13) and solvents (entries 14–15) as well as an additive (entry 16) improved the er to 82:18 using $Cu(OAc)_2$ in the presence of 4 Å molecular sieves with $CHCl_3$ as the solvent (entry 16). Lowering the reaction temperature to −10°C obviously enhanced the enantioselectivity (entry 17). Further increasing the amount of Ag_2CO_3 and adding proton sponge slightly increased the er to 95:5, presumably by effectively and timely quenching the *in situ* generated acid during the reaction (entry 18).

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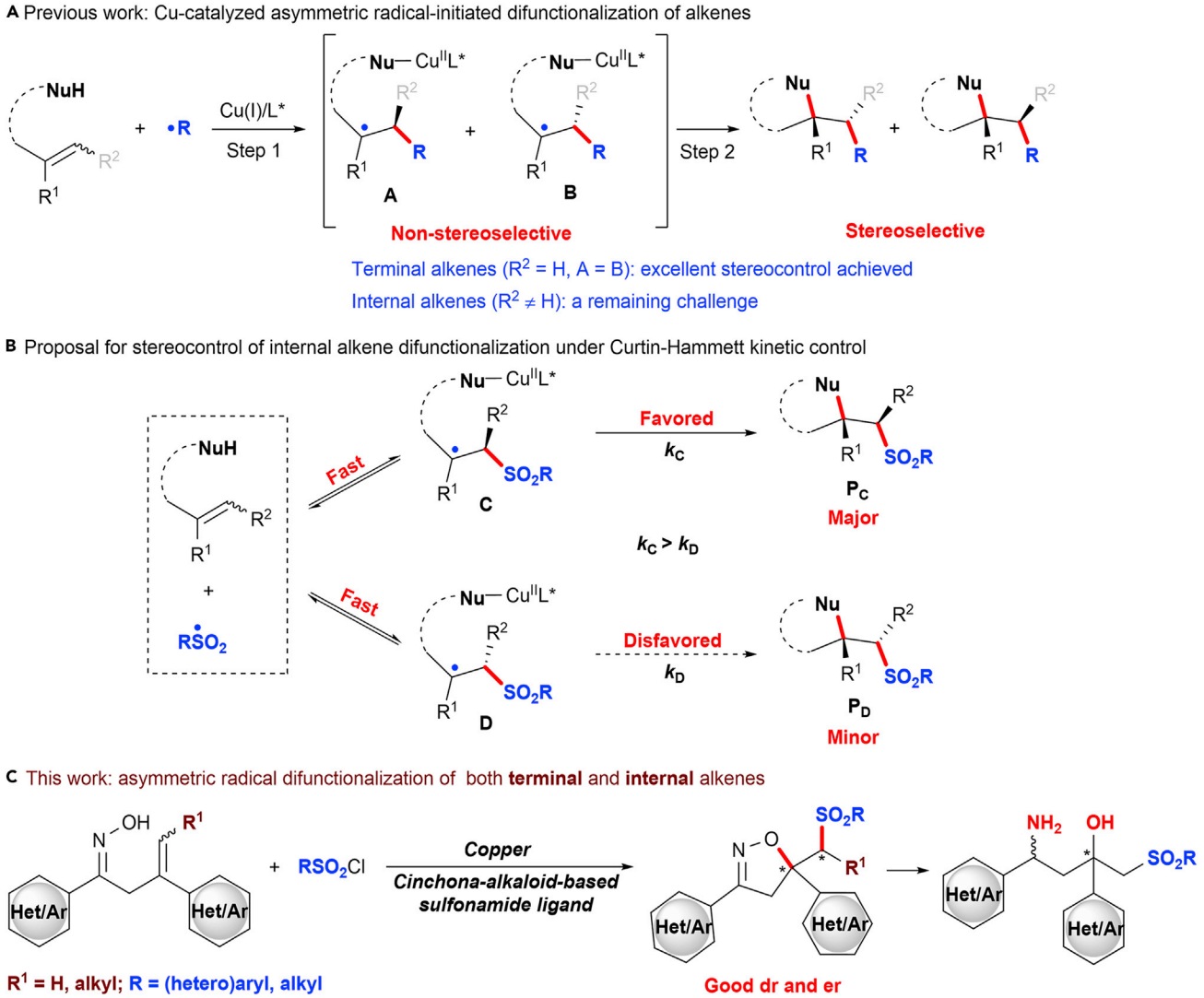


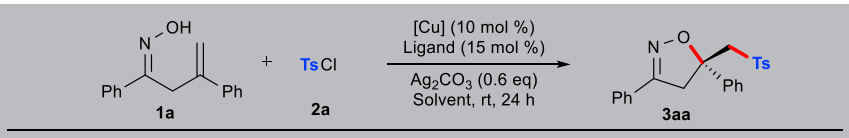
Scheme 1. Asymmetric Radical-Initiated 1,2-Difunctionalization of Terminal and Internal Alkenes

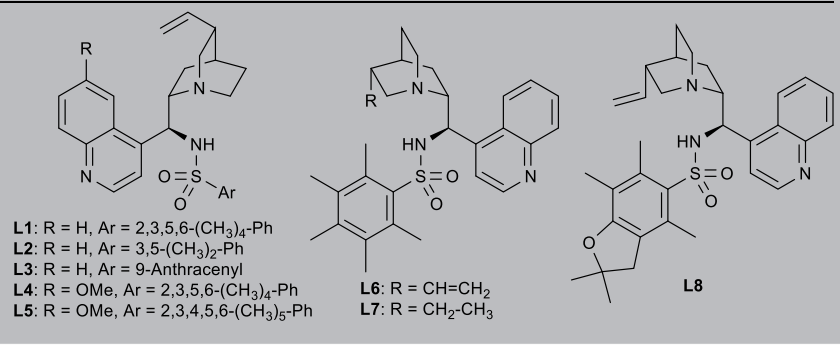
Substrate Scope with Terminal Alkenes

With the optimal conditions being established, we next investigated the substrate scope of the alkenyl ketoximes (Figure 1A). A variety of R^1 groups containing electron-neutral (H), -donating (Me, Et, ^{t}Bu, and OMe), or -withdrawing (F, Br, I, and CF_3) substituents at the *para*- or *meta*-positions of the phenyl ring were compatible with the reaction, giving **3aa–3ka** in 54%–85% yields with 93:7–96:4 er. In addition, a bicyclic naphthalyl and a heterocyclic thiophenyl R^1 groups were also tolerated to deliver **3la** and **3ma**, respectively, in good yields and excellent stereoselectivities. In regard to the R^2 on the alkene moieties, a broad series of phenyl rings with common electron-donating or -withdrawing functional groups at different positions (*meta* or *para*) were applicable to the reaction, affording **3na–3ta** in 55%–95% yields with 91:9–95:5 er. Heterocyclic furanyl- and thiophenyl-substituted alkenes could also be employed in the reaction to give **3ua** and **3va** with good results, respectively.

In the following study, we switched our attention to evaluate the scope of sulfonyl chlorides. We were pleased to observe that a series of arylsulfonyl chlorides bearing

Table 1. Optimization of Reaction Conditions for Terminal Alkenes





Entry[a]	[Cu]	Ligand	Solvent	Yield (%)[b]	Er[c]
1	CuOAc	L1	DCM	82	76:24
2	CuOAc	L2	DCM	77	61:39
3	CuOAc	L3	DCM	78	74:26
4	CuOAc	L4	DCM	79	74:26
5	CuOAc	L5	DCM	73	75:25
6	CuOAc	L6	DCM	79	24:76
7	CuOAc	L7	DCM	80	28:72
8	CuOAc	L8	DCM	68	33:67
9[d]	––	L1	DCM	0	––
10	CuBr	L1	DCM	60	60:40
11	CuI	L1	DCM	66	63:37
12	CuTc	L1	DCM	82	74:26
13	$Cu(OAc)_2$	L1	DCM	78	77:23
14	$Cu(OAc)_2$	L1	EtOAc	76	68:32
15	$Cu(OAc)_2$	L1	$CHCl_3$	80	78:22
16[e]	$Cu(OAc)_2$	L1	$CHCl_3$	80	82:18
17[e,f]	$Cu(OAc)_2$	L1	$CHCl_3$	81	94:6
18[e,f,g]	$Cu(OAc)_2$	L1	$CHCl_3$	79	95:5

[a]Reaction conditions: **1a** (0.05 mmol), **2a** (0.055 mmol), [Cu] (0.005 mmol), ligand (0.0075 mmol), and Ag_2CO_3 (0.03 mmol) in solvent (1 mL) under argon.
[b]Yield based on ^1H NMR analysis of the crude product using CH_2Br_2 as an internal standard.
[c]Determined by chiral HPLC analysis.
[d]No copper.
[e]4 Å molecular sieves (MS) (50 mg) were added.
[f]Run at −10°C for 96 h.
[g]Ag_2CO_3 (2.0 equiv), proton sponge (0.5 equiv), and $CHCl_3$ (2 mL) were used.

substituents ranging from electron-rich (Et, ^{t}Bu, OMe, and Ph) to electron-deficient groups (Br, F, and CF_3) and a polyarene naphthalene-derived sulfonyl chloride delivered the corresponding products **3ab–3ak** in 53%–84% yields with 90:10–96:4 er. The absolute configuration of **3aj** has been determined to be *S* by X-ray structural analysis (Figure S1). The heterocyclic thiophene-derived sulfonyl chloride also provided the product **3al** in 75% yield with a 95:5 er. The substrate scope is not limited to (hetero)aryl-substituted sulfonyl chlorides. For example, a series of acyclic alkyl sulfonyl chlorides, including simple unfunctionalized linear and branched alkyl

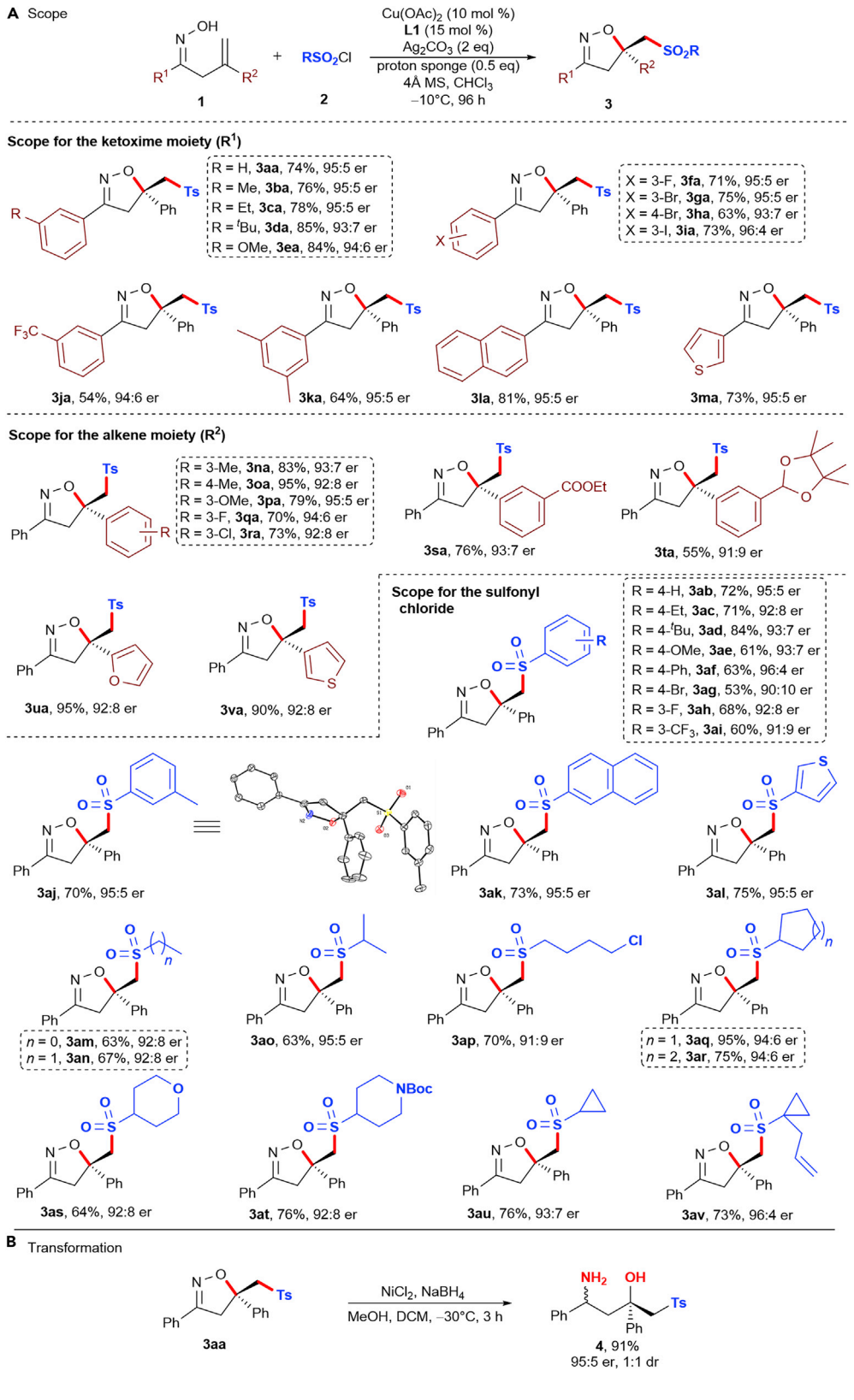

A Scope
Cu(OAc)2 (10 mol %)
L1 (15 mol %)
Ag2CO3 (2 eq)
proton sponge (0.5 eq)
4Å MS, CHCl3
–10°C, 96 h
1
2
3
Scope for the ketoxime moiety (R1)
R = H, 3aa, 74%, 95:5 er
R = Me, 3ba, 76%, 95:5 er
R = Et, 3ca, 78%, 95:5 er
R = tBu, 3da, 85%, 93:7 er
R = OMe, 3ea, 84%, 94:6 er
X = 3-F, 3fa, 71%, 95:5 er
X = 3-Br, 3ga, 75%, 95:5 er
X = 4-Br, 3ha, 63%, 93:7 er
X = 3-I, 3ia, 73%, 96:4 er
3ja, 54%, 94:6 er
3ka, 64%, 95:5 er
3la, 81%, 95:5 er
3ma, 73%, 95:5 er
Scope for the alkene moiety (R2)
R = 3-Me, 3na, 83%, 93:7 er
R = 4-Me, 3oa, 95%, 92:8 er
R = 3-OMe, 3pa, 79%, 95:5 er
R = 3-F, 3qa, 70%, 94:6 er
R = 3-Cl, 3ra, 73%, 92:8 er
3sa, 76%, 93:7 er
3ta, 55%, 91:9 er
3ua, 95%, 92:8 er
3va, 90%, 92:8 er
Scope for the sulfonyl chloride
R = 4-H, 3ab, 72%, 95:5 er
R = 4-Et, 3ac, 71%, 92:8 er
R = 4-tBu, 3ad, 84%, 93:7 er
R = 4-OMe, 3ae, 61%, 93:7 er
R = 4-Ph, 3af, 63%, 96:4 er
R = 4-Br, 3ag, 53%, 90:10 er
R = 3-F, 3ah, 68%, 92:8 er
R = 3-CF3, 3ai, 60%, 91:9 er
3aj, 70%, 95:5 er
3ak, 73%, 95:5 er
3al, 75%, 95:5 er
n = 0, 3am, 63%, 92:8 er
n = 1, 3an, 67%, 92:8 er
3ao, 63%, 95:5 er
3ap, 70%, 91:9 er
n = 1, 3aq, 95%, 94:6 er
n = 2, 3ar, 75%, 94:6 er
3as, 64%, 92:8 er
3at, 76%, 92:8 er
3au, 76%, 93:7 er
3av, 73%, 96:4 er
B Transformation
3aa
NiCl2, NaBH4
MeOH, DCM, –30°C, 3 h
4, 91%
95:5 er, 1:1 dr

Figure 1. Substrate Scope and Transformation

(A) Substrate scope for asymmetric oxysulfonylation of terminal alkenes. Reactions were conducted on 0.2 mmol scale, isolated yields were given, and er values were determined by HPLC analysis.

(B) Transformation of the oxysulfonylation product.

groups as well as a halogenated one, all worked well to give **3am**–**3ap** with good results. In addition, different cyclic and *O*- or *N*-containing heterocyclic alkyl sulfonyl chlorides were all well accommodated in this process to deliver **3aq**–**3at** in 64%–95% yield with 92:8–94:6 er. Notably, with this protocol, we were able to incorporate a cyclopropane ring (**3au** and **3av**), a versatile fragment frequently used in drug development,[81,82] into the chiral sulfonyl-containing isoxazolines. Nonetheless, benzyl and allyl sulfonyl chlorides and *o*-toluenesulfonyl chloride were found to be unsuitable for the reaction, possibly due to stability or steric issues associated with the corresponding sulfonyl radicals, respectively. As for the utility of this methodology, the isoxazoline unit in the products could be easily cleaved to afford amino alcohols (Figure 1B). For example, treatment of **3aa** under mild reductive conditions afforded **4** in excellent yield. It features three important functional groups, including amino, hydroxy, and sulfonyl moieties, and a conserved tertiary stereocenter, which are prevalent in numerous drugs and bioactive molecules.

Investigation on Internal Alkenes

With regard to the challenging internal alkenes, we initially conducted time-course experiments on internal alkenyl ketoximes (*E*)- and (*Z*)-**5a** using **L7** (see Table 1 for its structure) as the ligand under the otherwise standard conditions (Figure 2; Tables S1 and S2). Obvious *E*-*Z* isomerization occurred as the reactions started, indicating fast, reversible addition of sulfonyl radicals to alkenes as reported in literature.[49–53] Most importantly, both (*E*)- and (*Z*)-**5a** afforded (5*R*,2′*S*)-**6aa** with the same absolute configuration as the major product. The results strongly support the involvement of the same rate- and stereo-determining C–O bond formation step for reactions on both (*E*)- and (*Z*)-**5a**. And thus, the envisioned Curtin-Hammett kinetic control was very likely operating under our reaction conditions.

This proof-of-principle result encouraged us to carry out further optimization of reaction conditions with (*E*)-**5a** as the model substrate (Table 2). A screening of a series of cinchona alkaloid-derived sulfonamide ligands (entries 1–8) revealed **L8** (see Table 1 for structures) as the optimal one. The corresponding product (5*R*,2′*S*)-**6aa** with two vicinal stereocenters was obtained in good yield with good stereoselectivity (entries 8 and 9). Interestingly, the use of a 1:1 mixture of (*E*)- and (*Z*)-**5a** as the substrate gave similar results to that with one pure isomer (entry 10). In addition, the reaction on internal alkenes also well tolerated a range of different substituents on the ketoxime, the alkene, and the sulfonyl moieties. The desired products **6ab**, **6ac**, and **6ba**–**6ia** were afforded in 57%–73% yields with good stereoselectivity (Scheme 2). The absolute configuration of (5*R*,2′*S*)-**6aa** has been determined by X-ray crystallographic analysis (Figure S2), and those of other products were assigned by analogy. Furthermore, cyclic internal alkenes were also viable substrates for the reaction. A series of chiral spiro-heterocycles **6ja**–**6la** with different skeletons (such as 5–5 and 5–6 spiro rings) and functionalities (such as carbocycles and a *N*-containing heterocycle) were efficiently constructed in good yields with excellent diastereoselectivities (> 20:1 dr) and good enantioselectivities (up to 92:8 er) (Scheme 2). The absolute configuration of **6ja** has been determined by X-ray crystallographic analysis (Figure S3), and those of other products were assigned by analogy.

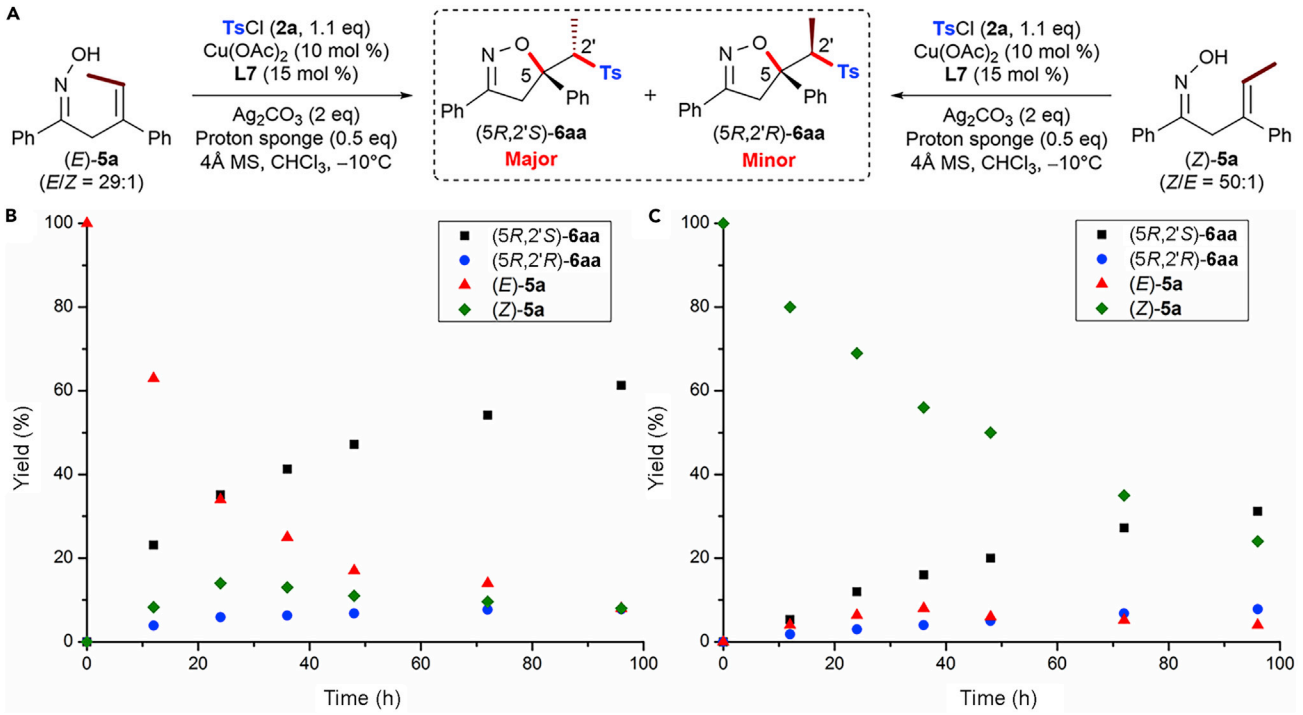


Figure 2. Time-Course Experiments

(A) Time-course experiments were conducted on (*E*)- and (*Z*)-**5a** using **L7** (see Table 1 for its structure) as the ligand under the otherwise standard conditions.

(B) Time-course experimental results on (*E*)-**5a**.

(C) Time-course experimental results on (*Z*)-**5a**.

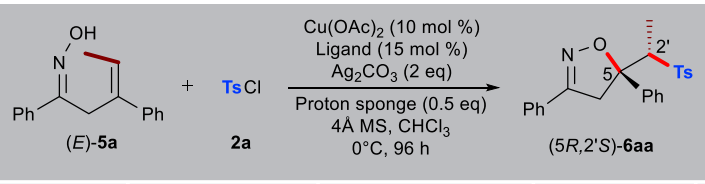
Mechanistic Study

Control experiments were conducted to gain further insights into the reaction mechanism. First, the addition of radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyl-oxy (TEMPO) significantly inhibited the desired reaction for the formation of **3aa** (Scheme 3A). Thus, our reaction likely involves a radical mechanism. Interestingly, the other product, **7**, was formed in 41% yield, presumably via the generation of an iminoxyl radical followed by *5-exo-trig* cyclization and trap by TEMPO. Such a mechanism has been consistently invoked for the formation of similar TEMPO-trapped products from β,γ-unsaturated ketoximes in literature.[83,84] Notably, **7** is racemic and thus, the presumed iminoxyl radical is likely not a common intermediate toward the formation of **3aa** and **7**. Radical clock probe **8** did not afford any desired oxysulfonylation product under the standard conditions. Instead, it provided **9** in 10% yield, possibly via tandem radical addition, cyclopropane ring opening, and hydroalkoxylation (Scheme 3B). All of these observations suggest that sulfonyl radicals are likely generated *in situ*, which upon further addition to alkenes and subsequent C–O bond formation, give rise to the desired oxysulfonylation products.

Computational Study

In order to gain more insight into the reaction mechanism, we resorted to theoretical calculations. Two plausible reaction mechanisms, i.e., Cu^{II}-Cu^{III}-Cu^{I} and Cu^{II}-Cu^{I} mechanisms[22,23,85–92] (paths A and B in Figure 3 and Figure S4) were proposed based on the experimental observations and calculated with the density functional theory (DFT) method. Both pathways start with the deprotonation of β,γ-unsaturated

Table 2. Optimization of Reaction Conditions for Internal Alkenes

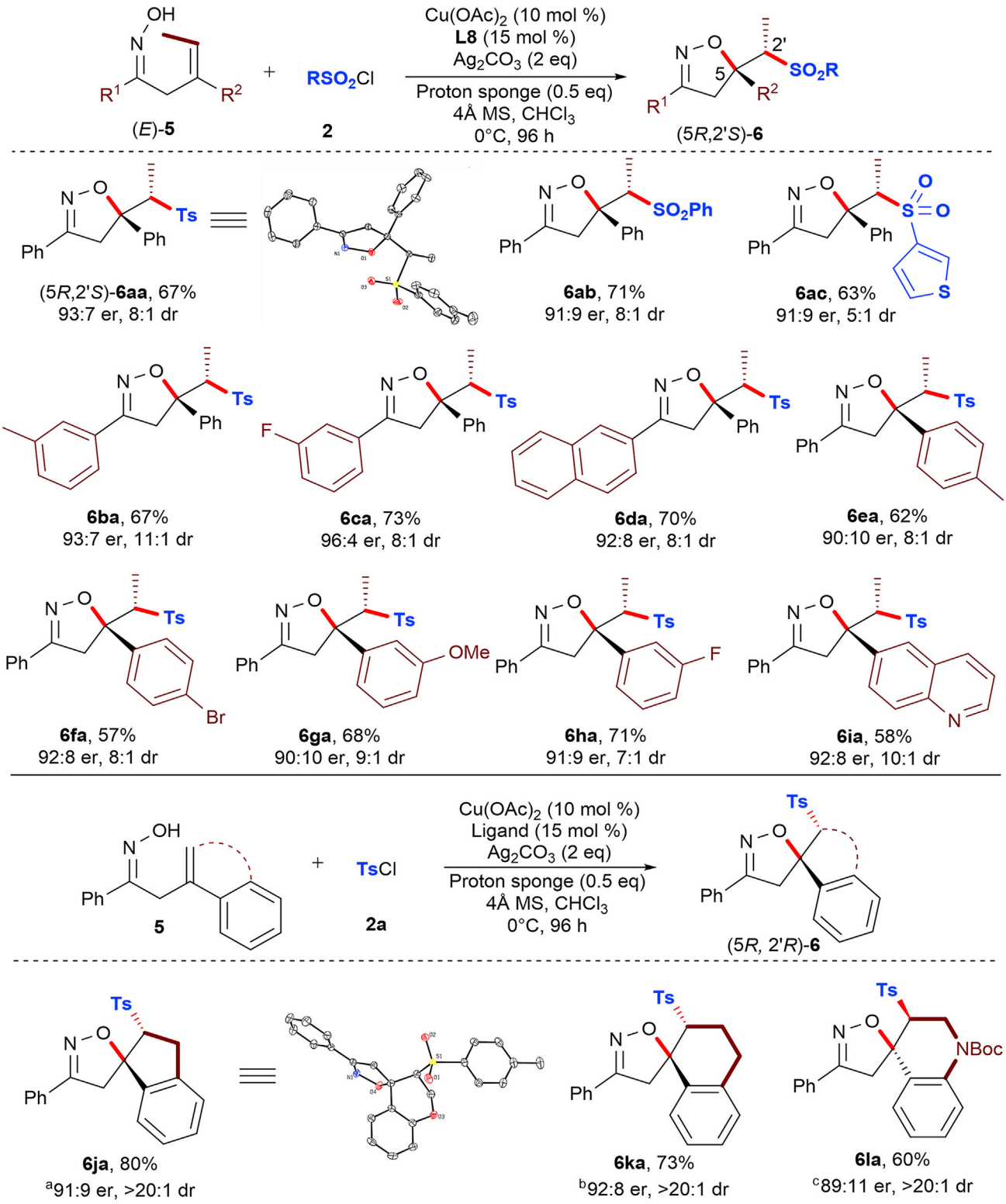


Entry[a]	Ligand	Yield (%)[b]	Dr[b]	Er[c]
1	L1	64	7:1	11:89
2	L2	52	5:1	25:75
3	L3	60	6:1	13:87
4	L4	61	7:1	11:89
5	L5	64	6:1	12:88
6	L6	66	7:1	89:11
7	L7	68	8:1	91:9
8	L8	67	8:1	93:7
9[d]	L8	40	4:1	93:7
10[e]	L8	53	6:1	93:7

[a]Reaction conditions: (*E*)-**5a** (*E*/*Z* = 29:1) (0.1 mmol), **2a** (0.11 mmol), $Cu(OAc)_2$ (0.01 mmol), ligand (0.015 mmol) (see Table 1 for structures), Ag_2CO_3 (0.2 mmol), proton sponge (0.05 mmol), and 4 Å MS (100 mg) in $CHCl_3$ (4 mL) under argon.
[b]Yield and dr were based on ^1H NMR analysis of the crude product using CH_2Br_2 as an internal standard.
[c]Determined by chiral HPLC analysis.
[d](*Z*)-**5a** (*Z*/*E* = 50:1) as the substrate.
[e](*E*)-**5a**:(*Z*)-**5a** = 1:1.

ketoxime **1a** by **CuOAc-L1** complex, affording the **Cu-L1**-alkene intermediate (**INT1**). Subsequently, the addition of sulfonyl radical to the alkene via triplet ^{t}**TSA1-*S*** or ^{t}**TSB1-*S*** generates the α-sulfonyl-alkyl radical (^{t}**INTA1-*S*** or ^{t}**INTB1-*S***). This radical may attach to the Cu^{II} center to form a Cu^{III} complex, which undergoes further reductive elimination to deliver the oxysulfonylation product and the **Cu-L1** catalyst (path A). Alternatively, it may directly attack the oxygen atom on the Cu^{II}–O bond to afford the product and **Cu-L1** (path B). The attempts to locate the transition states of the intramolecular addition of α-sulfonyl-alkyl radical to the Cu^{II} center or the O atom were unsuccessful. Instead, the minimum energy crossing points (MECPs),[93–96] **MECP_A-*S*** and **MECP_B-*S***, which connect the triplet α-sulfonyl-alkyl radical and singlet Cu^{III} complex (^{s}**INTA2-*S***, path A) or Cu^I species (^{s}**INTB2-*S***, path B), respectively, were located and calculated to be rate-determining. The latter (**MECP_B-*S***) has a lower electronic energy by 9.0 kcal/mol, which suggests that the Cu^{II}-Cu^I mechanism (path B) is likely more favorable.

Computational results suggested that the forward and backward reaction barriers for the radical addition step are indeed very low (path B: 0.1 kcal/mol, **INT1** → ^{t}**TSB1-*S***; 4.1 kcal/mol, ^{t}**INTB1-*S*** → ^{t}**TSB1-*S***), which, in agreement with our experimental observations, indicates a fast and reversible process. As a result, the C–O bond formation step should determine the enantioselectivity, which we analyzed next (Figure 4A). The located **MECP_B-*S*** (leading to *S* product) has a lower electronic energy than **MECP_B-*R*** (leading to *R* product) by 4.3 kcal/mol, which is consistent with the experimentally observed *S*-enantioselectivity with **L1** ligand (see Table 1 for its structure). A favorable hydrogen bonding interaction between the ligand and the substrate was identified in **MECP_B-*S***. Meanwhile, an unfavorable electrostatic repulsion between oxygen atoms of the sulfonamide ligand



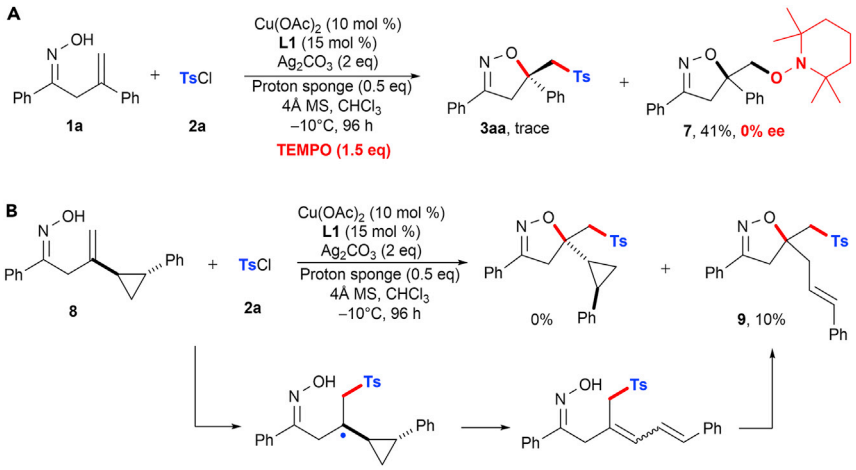
Scheme 2. Substrate Scope for Asymmetric Oxysulfonylation of Internal Alkenes

Reactions were conducted on 0.2 mmol scale, isolated yields were given, and er values were determined by HPLC analysis.

[a]L6 (see Table 1 for its structure) used as the ligand.

[b]L8 (see Table 1 for its structure) used as the ligand.

[c]L1 (see Table 1 for its structure) used as the ligand at RT.



Scheme 3. Mechanistic Study

and the sulfonyl radical was identified in MECP_B-*R* by the analysis of electrostatic potential (ESP) surface (Figure 4B). Computational results suggest that the enantioselectivity of this oxysulfonylation reaction on terminal alkenes originates from the hydrogen bonding interaction and electrostatic repulsion between the substrate and the ligand.

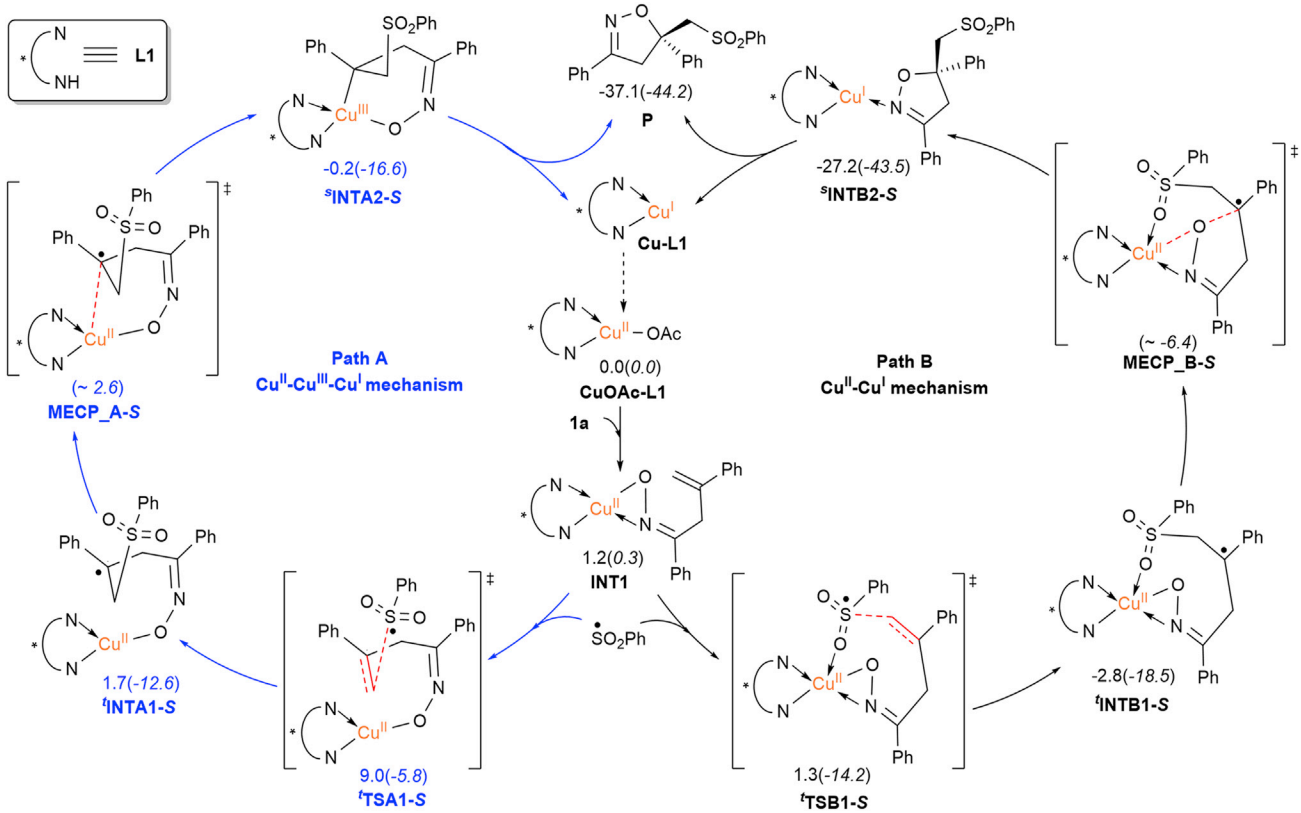


Figure 3. Calculated Catalytic Cycles for the Copper-Catalyzed Asymmetric 1,2-Oxylsulfonylation of Terminal Alkenes

Calculations were done on **1a** with $PhSO_2Cl$ as the radical precursor and **L1** (see Table 1 for its structure) as the ligand, respectively. Relative free energies (electronic energies) in kcal/mol are calculated with the DFT method in $CHCl_3$ solvent. The superscripts *s* and *t* refer to the singlet and triplet states, respectively.

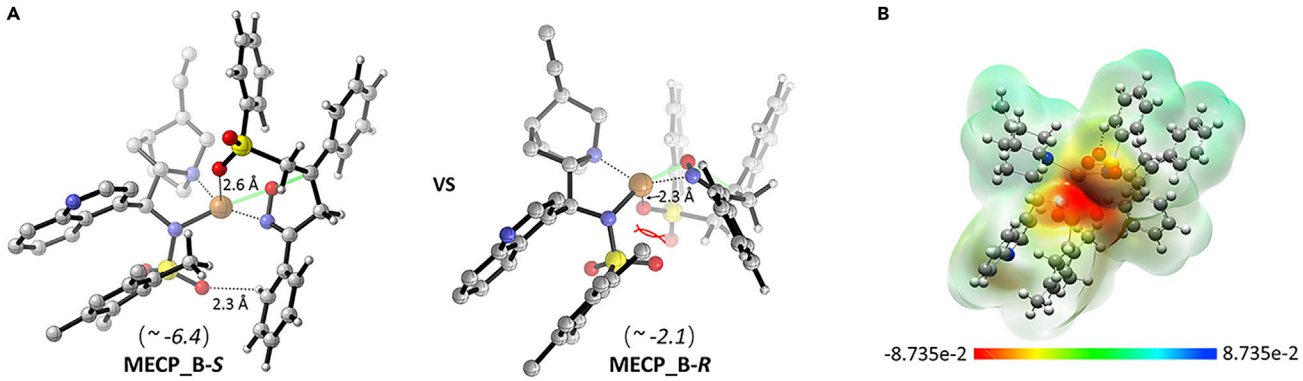


Figure 4. Stereoselectivity Analysis of Reactions on Terminal Alkenes

(A) 3D structures and relative electronic energies (kcal/mol) of MECP_B-*S* and MECP_B-*R*.

(B) The electrostatic potential surface of MECP_B-*R*.

On the basis of the above experimental and computational studies, a working mechanism for the asymmetric radical oxysulfonylation reaction was tentatively proposed, shown in Figure 5. The *in situ* formed bis-chelating Cu^{I} complex **A** with a strong reducing capability first undergoes single-electron transfer with sulfonyl chloride to afford Cu^{II} complex **B** and sulfonyl radical. Next, the Cu^{II} complex **B** reacts with substrate **1** or **5** via deprotonation, leading to intermediated **C**. This intermediate is then reversibly attacked by sulfonyl radical, giving rise to alkyl radical **D**. Its subsequent intramolecular radical substitution reaction delivers Cu^{I}-product complex **E**, which finally dissociates to give product **3** or **6** and regenerate the Cu^{I} complex **A**. The stoichiometric amounts of acid and chloride side products are scavenged by Ag_2CO_3.

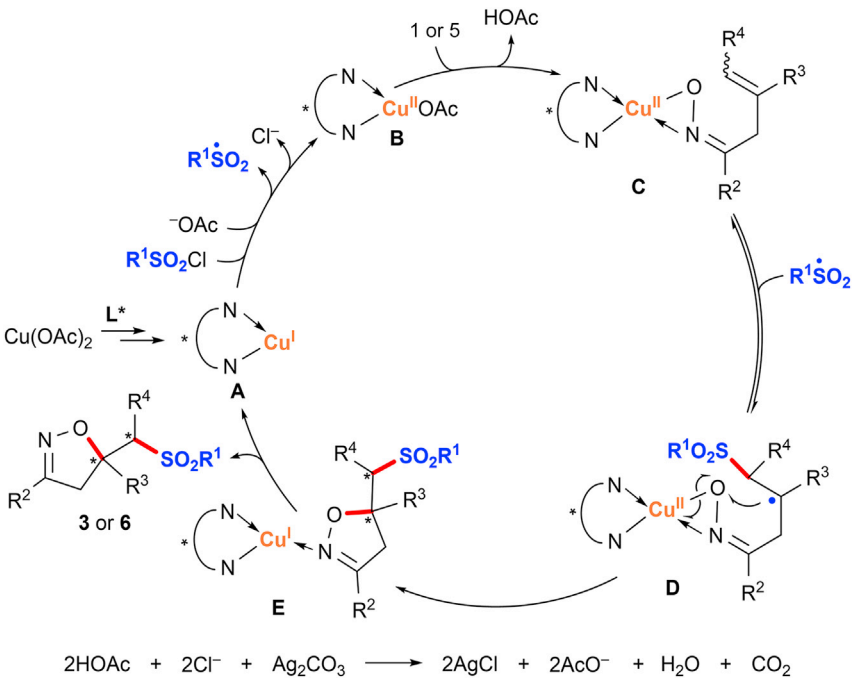


Figure 5. Mechanistic Proposal

Catalytic cycle for asymmetric radical 1,2-oxysulfonylation of both terminal and internal alkenes.

Conclusions

In summary, we have developed a general and efficient asymmetric radical oxysulfonylation of alkenes in β,γ-unsaturated ketoximes using copper(I)-cinchona alkaloid-based sulfonamide complex as a strong single-electron-reducing catalyst. This method exhibited a broad scope across a range of both terminal and internal alkenes as well as diverse (hetero)aryl- or alkyl-substituted sulfonyl chlorides under very mild conditions. Experimental and computational studies suggested a likely Cu^{II}-Cu^{I} catalytic cycle with efficient stereodiscrimination under Curtin-Hammett kinetic control. The sulfonyl-containing isoxazolines could undergo further transformations to provide valuable building blocks prevalent in numerous bioactive molecules. We anticipate that the present strategy would open a new door for the precise control of diastereo- and enantioselectivities in the challenging asymmetric radical-initiated difunctionalization of internal alkenes.

EXPERIMENTAL PROCEDURES

Full experimental procedures are provided in the Supplemental Information.

DATA AND CODE AVAILABILITY

The data for the X-ray crystallographic structures of **3aj**, (5*R*,2′*S*)-**6aa**, and **6ja** have been deposited in the Cambridge Crystallographic Data Center under accession numbers CCDC: 1957456, 1957457, and 1957458 and can be obtained free of charge from www.ccdc.cam.ac.uk/getstructures.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.chempr.2020.03.024.

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AUTHOR CONTRIBUTIONS

X.-T.L. performed the condition optimization, investigated the scope of the substrates, and conducted the experimental mechanistic studies. L.L., G.-X.X., Z.-L.L., and L.Y. synthesized the alkene substrates and performed the application. T.W. performed the computational study of the mechanism. Q.-S.G. participated in the design and discussion of the mechanistic experiments. G.-J.C. and X.Z. directed the computational study. X.-Y.L. directed the project and wrote the manuscript with input from all authors. All authors analyzed the results and commented on the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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