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Stereoconvergent synthesis of chiral sulfonyl phthalide containing two chiral centers from *Z*/*E* mixed alkenes *via* copper catalysis

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ABSTRACT

Chiral phthalides are present in numerous natural products and bioactive molecules. Synthesizing phthalides from alkenes is an effective strategy. However, the challenges of facial-selectivity in the addition to *Z*/*E* mixed alkenes and diastereoselectivity at vicinal stereogenic centers have prevented the achievement of a highly selective stereoconvergent synthesis of chiral sulfonyl phthalides from *Z*/*E* alkene mixtures. Therefore, we have developed an efficient methodology for the stereoconvergent synthesis of chiral sulfonyl phthalides, using the Cu/PyBim catalytic system. This method enables the asymmetric construction of sulfonyl phthalides with multiple stereocenters for the first time. It exhibits broad applicability across various terminal and internal alkene substrates, and accommodates a diverse array of aryl, alkyl, and nitrogen radical precursors, all under exceptionally mild reaction conditions. The experimental results indicate that the reaction utilizes a Curtin-Hammett kinetic control strategy, leading to the stereoconvergent synthesis of *Z*/*E* internal alkene substrates with significant enantioselectivity and diastereoselectivity in the asymmetric construction of chiral sulfonyl phthalides.

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Chiral phthalides are prevalent as key structural motifs across a broad spectrum of pharmaceuticals, and natural products exhibiting diverse biological properties (Fig. 1A) [1–8]. Additionally, sulfonyl groups are significant pharmacophores capable of enhancing biological activity, modulating acid-base properties, and augmenting solubility [9–11]. Therefore, devising an asymmetric synthesis strategy to amalgamate these two divergent structures is of paramount research significance.

Starting from alkenes is a crucial approach for synthesizing phthalides [12–17], but classical methods for producing internal alkenes primarily yield *Z*/*E* mixtures that are challenging to separate [18]. Stereoconvergence strategy, on the other hand, can achieve the conversion of substrates with poor stereoselectivity into products with a single stereo configuration through precise control of reaction conditions and mechanisms, with a theoretical yield of 100% [19–22]. Therefore, the direct stereoconvergent transformation of *Z*/*E* alkene mixtures into optically pure products holds substantial practical importance. Recent advances in transition-metal-catalyzed, radical-initiated asymmetric alkene difunctionalization have significantly enhanced the asymmetric formation of carbon-carbon and carbon-heteroatom bonds [23–46]. Predominantly, these reactions have mainly been successful with terminal alkenes, as the radical addition to internal alkenes often encounters issues with facial-selectivity in the addition to *Z*/*E* mixed alkenes and diastereoselectivity at vicinal stereogenic centers. Consequently, there are limited studies that simultaneously generate two vicinal stereocenters using internal alkenes (Fig. 1B) [25,29,47].

Drawing inspiration from the research conducted by Liu [25] and Han [48], we propose employing *Z*/*E* internal alkene mixtures for the construction of chiral sulfonyl phthalides utilizing a stereoconvergent strategy (Fig. 1C). Recognizing that the addition of sulfonyl radicals to internal alkenes constitutes a rapid and reversible process [49–51], combined with the modularity and convenience advantages of sulfur dioxide insertion for the construction of diverse sulfonyl fragments [52–61], we envisaged that sulfonyl radicals, generating *via* sulfur dioxide insertion into radical precursors, were added to *Z*/*E* alkene mixtures, leveraging Curtin-Hammett kinetic control to yield diastereoisomers **A** and **B** (Fig. 1D). The disparity in the rates of subsequent cyclization processes ($k_A < k_B$) facilitates the swift conversion of intermediate **A** to intermediate **B**, facilitating stereoconvergence in the synthesis of chiral sulfonyl phthalides [62,63]. The key element of this strategy lies

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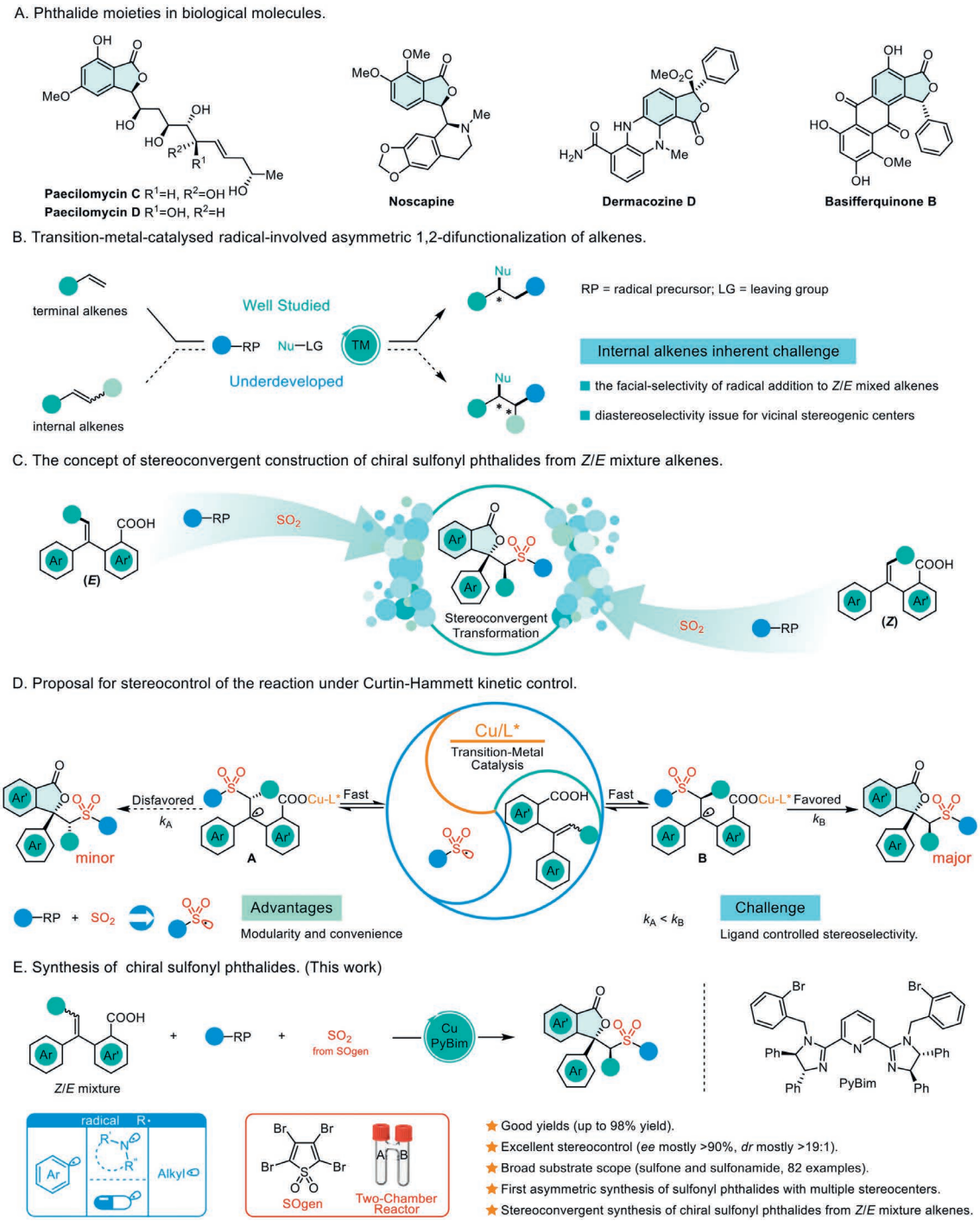
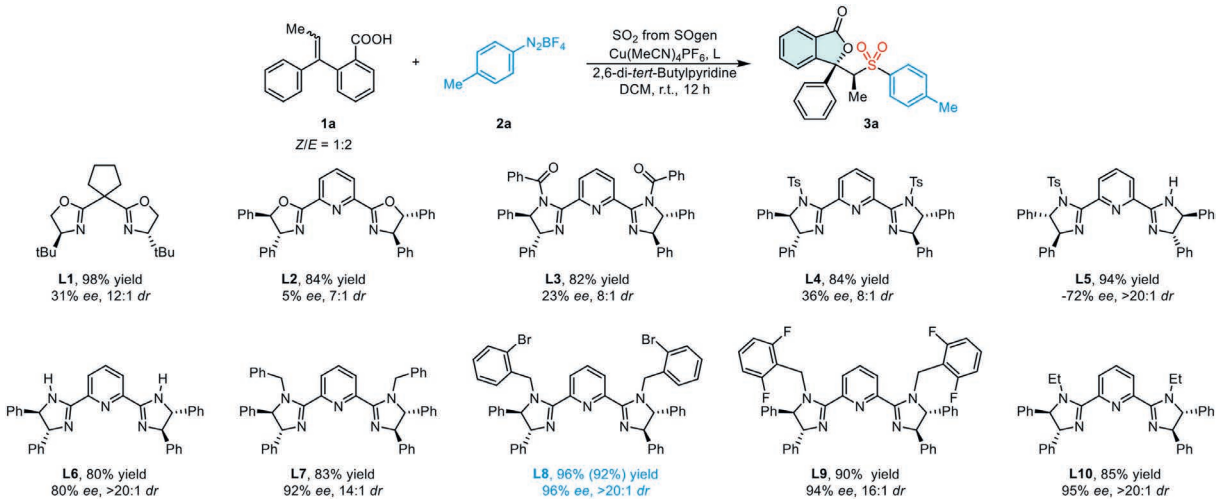


Fig. 1. Copper-catalyzed stereoconvergent transformation synthesis of chiral sulfonyl phthalide.

in the selection of suitable ligands, which not only enable enantioselective control but also modulate the cyclization rates of intermediates **A** and **B**, thereby facilitating diastereoselective control. The successful implementation of this strategy is expected to open new avenues for the stereoconvergence of *Z*/*E* mixed alkene substrates.

Recently, our group designed a cost-effective, solid, and benchstable external SO_2 surrogate (SOgen) in combination with two-chamber reactors for sulfur dioxide insertion reactions [43,64–66]. Herein, we present an efficient approach to synthesize chiral sulfonyl phthalides *via* SO_2 insertion enabled by SOgen and the Cu/PyBim catalytic system (Fig. 1). This approach exhibits high yield, exceptional stereoselectivity, and a broad substrate scope, enabling the stereoconvergent synthesis of chiral sulfonyl phthalides from *Z*/*E* alkene mixtures. Notably, it represents the first successful synthesis of a series of sulfonyl phthalide compounds with multiple stereocenters. The reaction achieves stereoconvergence of *Z*/*E* mixed alkenes through Curtin-Hammett kinetic control. The rapid and reversible addition of sulfonyl radicals to internal alkenes, combined with the strategic selection of appropriate ligands, is crucial for achieving high stereoselectivity in this reaction.

Table 1
Optimization of reaction conditions.[a]



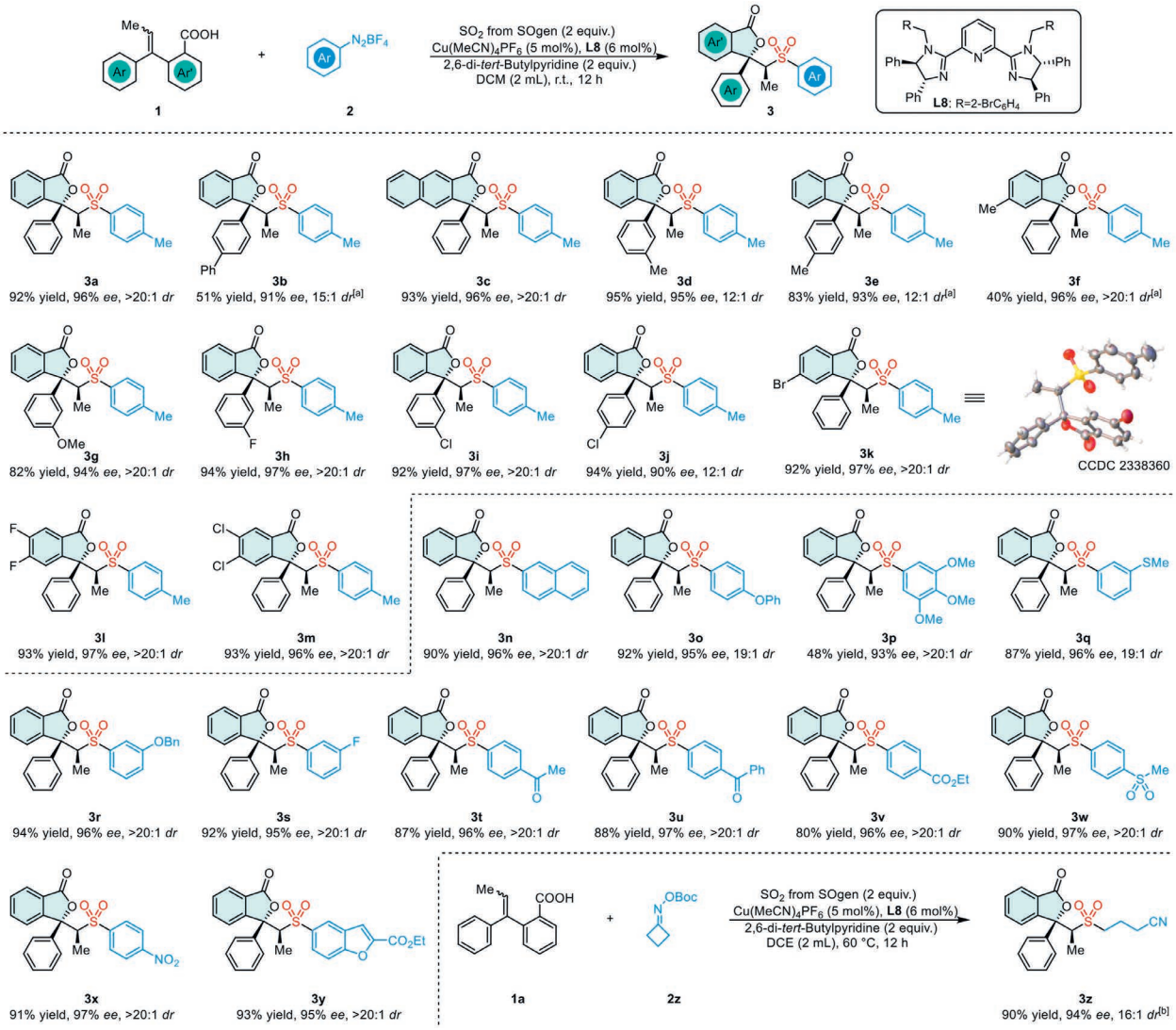
Entry	Deviation from standard conditions	Yield (%)[b]	*ee* (%)[c]	*dr*[d]
1	None	96 (92)	96	>20:1
2	MeCN instead of DCM	67	83	>20:1
3	1,4-Dioxane instead of DCM	trace	–	–
4	2-Me-THF instead of DCM	5	96	>20:1
5	DCE instead of DCM	97	92	19:1
6	2,6-Di-Me-pyridine instead of 2,6-di–*tert*-butylpyridine	21	85	17:1
7	Na_2CO_3 instead of 2,6-di–*tert*-butylpyridine	32	94	14:1
8	K_2CO_3 instead of 2,6-di–*tert*-butylpyridine	74	94	>20:1
9	*Z*/*E* = 8:1 of **1a** as the substrate	95	96	>20:1
10[e]	DABSO as SO_2 source	83	92	16:1
11[e]	$Na_2S_2O_5$ as SO_2 source	58	92	14:1
12[e]	$K_2S_2O_5$ as SO_2 source	60	90	10:1
13[e]	TsCl as sulfonyl precursor	8	96	>20:1

[a] Reaction conditions: Chamber A (SO_2 generation): SOgen (0.41 mmol), 1-methyl-4-vinylbenzene (0.40 mmol), tetradecane (1.0 mL), at 100 °C for 10 min. Chamber B: **1a** (0.20 mmol), **2a** (0.40 mmol, 2 equiv.), $Cu(MeCN)_4PF_6$ (0.01 mmol, 5 mol%), **L** (0.012 mmol, 6 mol%), Base (0.40 mmol, 2 equiv.), DCM (2.0 mL) at room temperature for 12 h under argon atmosphere.
[b] Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard.
[c] The *ee* value of **3a** was determined by HPLC analysis on a chiral stationary phase.
[d] The *dr* value of **3a** was determined by ^{1}H NMR.
[e] The reaction was set up in an 8 mL vial.

To assess the effectiveness of a stereoconvergent transformation strategy, we selected a 1:2 *Z*/*E* ratio mixture of 2-(1-phenylprop-1-en-1-yl)benzoic acid (**1a**) as the model substrate. This substrate was then reacted with 4-Me-PhN_2BF_4 (**2a**) and SO_2 (from SOgen), to evaluate the reaction outcomes (Table 1). In our initial experiments, we investigated various chiral ligands including Box (**L1**), PyBox (**L2**), and PyBim (**L3**–**L10**). The findings demonstrated that the 2-bromobenzyl substituent in ligand **L8** substantially enhances both enantioselectivity and diastereoselectivity, making it the most effective for exceptional stereoselectivity. As reported in the literature, we hypothesize that although both PyBox and PyBim ligands share similar chiral environments, they exhibit differences in their electronic properties. In this reaction, the stereoselectivity is significantly influenced by the distinct electronic characteristics of the ligands [61]. Building on these results, we further explored additional parameters of the reaction. Initially, various solvents were evaluated, with dichloromethane (DCM) emerging as the optimal choice (entries 1–5). Regarding the choice of base, 2,6-di–*tert*-butylpyridine proved more effective than either 2,6-di-Me-pyridine, Na_2CO_3 or K_2CO_3 (entries 6–8). This efficacy may be attributed to the steric hindrance provided by the *tert*–butyl groups in 2,6-di–*tert*-butylpyridine, which effectively mitigates catalyst deactivation by pyridine. When the substrate **1a**, characterized by an 8:1 *Z*/*E* ratio, was employed, the reaction consistently yielded product retaining the same configuration, suggesting that the reaction is governed by Curtin-Hammett kinetic control and achieves high stereoselectivity through stereoconvergent transformation. The substitution of sulfur dioxide surrogates or TsCl for SOgen invariably led to diminished yield and stereoselectivity in the reaction (entries 10–13). These findings clearly underscore the indispensable role of SOgen in enabling this efficient transformation.

Upon establishing the optimized reaction conditions, we then evaluated their general applicability. We initially explored the scope of the transformation with respect to *Z*/*E* mixture alkenes **1** (Scheme 1). These alkenes, characterized by electron-neutral substituents, yielded the corresponding products (**3a**–**3c**) with moderate to good yields and high stereoselectivities. Additionally, internal alkenes featuring both electron-donating and electron-withdrawing substituents were found to be compatible with this transformation, producing a series of products (**3d**–**3m**). The absolute configuration of **3k** was determined using X-ray crystallographic analysis.

Furthermore, we extended our investigation to a variety of substituted aryldiazonium salts in the transformation (Scheme 1). These salts, featuring electron-neutral, electron-donating, and electron-withdrawing substituents, demonstrated excellent stereoselectivity in this reaction (**3n**–**3x**). Additionally, the heterocyclic diazonium salt has demonstrated efficacy as a radical precursor, reliably producing the corresponding product (**3y**) with excellent



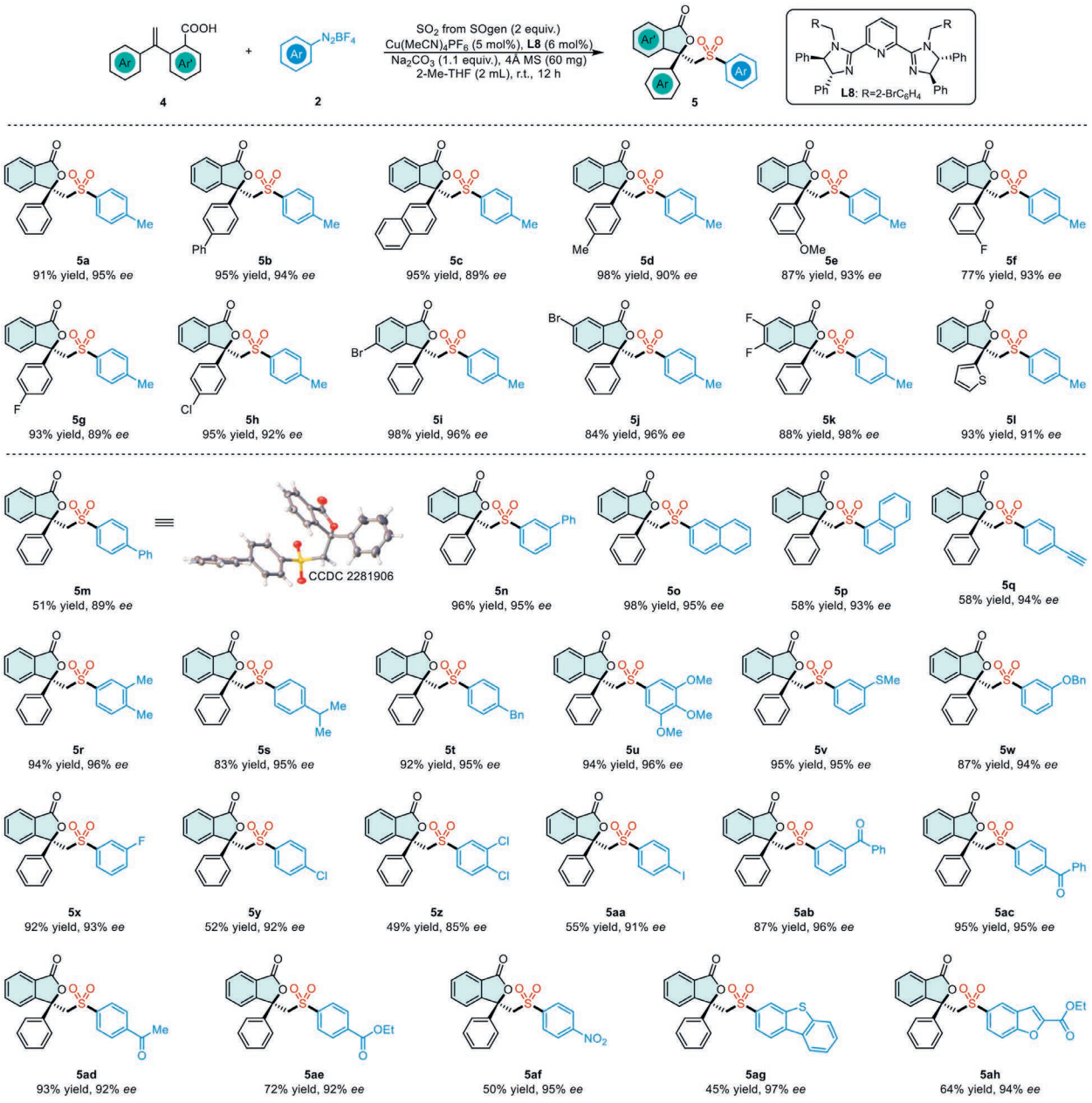
Scheme 1. Substrate scope. Reaction conditions: Chamber B: **1** (0.20 mmol), **2** (0.40 mmol, 2 equiv.), $Cu(MeCN)_4PF_6$ (0.01 mmol, 5 mol%), **L8** (0.012 mmol, 6 mol%), 2,6-di-*tert*-butylpyridine (0.40 mmol, 2 equiv.), DCM (2.0 mL) at room temperature for 12 h under argon atmosphere. [a] Na_2CO_3 (0.22 mmol, 1.1 equiv.) as base, 4 Å molecular sieve (60 mg) as additive, 2-Me-THF (2.0 mL) as solvent. [b] DCE (2.0 mL) as solvent, 60 °C for 12 h.

stereoselectivity. Moreover, with precise adjustments of the reaction conditions, cyclobutanone oxime ester can be effectively transformed, exhibiting notable control over stereoselectivity (**3z**).

Encouraged by these promising results, we explored the compatibility of terminal alkenes in our experiments. To our satisfaction, the reaction between terminal alkenes **4** and aryldiazonium salts **2** proceeded smoothly, consistently yielding the anticipated products (Scheme 2). The catalytic system exhibited remarkable tolerance to a variety of functional groups, efficiently converting various substituted terminal alkenes into products with moderate to high yields and excellent enantioselectivities (**5a**–**5l**). We further investigated a spectrum of aryl diazonium salts bearing a variety of substituents. These included electron-neutral groups such as naphthalene and biphenyl, electron-donating groups (Me, *i*-Pr, Bn, and OMe), and electron-withdrawing groups (*m*-SMe, *m*-OBn, halogens, acetylene, ketones, ester, and NO_2). All the investigated substituents were compatible with the reaction, producing the corresponding products (**5m**–**5af**) in 49 %–98 % yields with 85 %–96 % *ee*. The absolute configuration of **5m** was determined using X-ray crystallographic analysis. Heterocyclic compounds such as dibenzothiophene and benzofuran diazonium salts can also be utilized in this reaction, yielding products **5ag** and **5ah** with favorable outcomes, respectively.

We subsequently investigated the feasibility of synthesizing chiral sulfonyl phthalides using radical species other than aryl diazonium salts (Scheme 3). Carboxylic acids with diverse functional groups on the phenyl ring or *O*-acyl-*N*-hydroxylamines consistently yielded the desired chiral sulfonylamide phthalides (**5ai**–**5at**). It is noteworthy that sulfur dioxide can act as a pharmaceutical linker, facilitating the one-step synthesis of compounds containing medicinal molecules, sulfonyl groups, and chiral phthalides (**5ap**–**5at**). We have established a reaction for vicinal sulfonyl-esterification of alkenes to construct chiral sulfonyl phthalides by using alkyl radicals derived from cycloketone oxime esters. A broad spectrum of carboxylic acids and cycloketone oxime esters was found to be compatible with the established reaction, resulting in the formation of products with moderate to high yields and high enantioselectivities (**5au**–**5aad**).

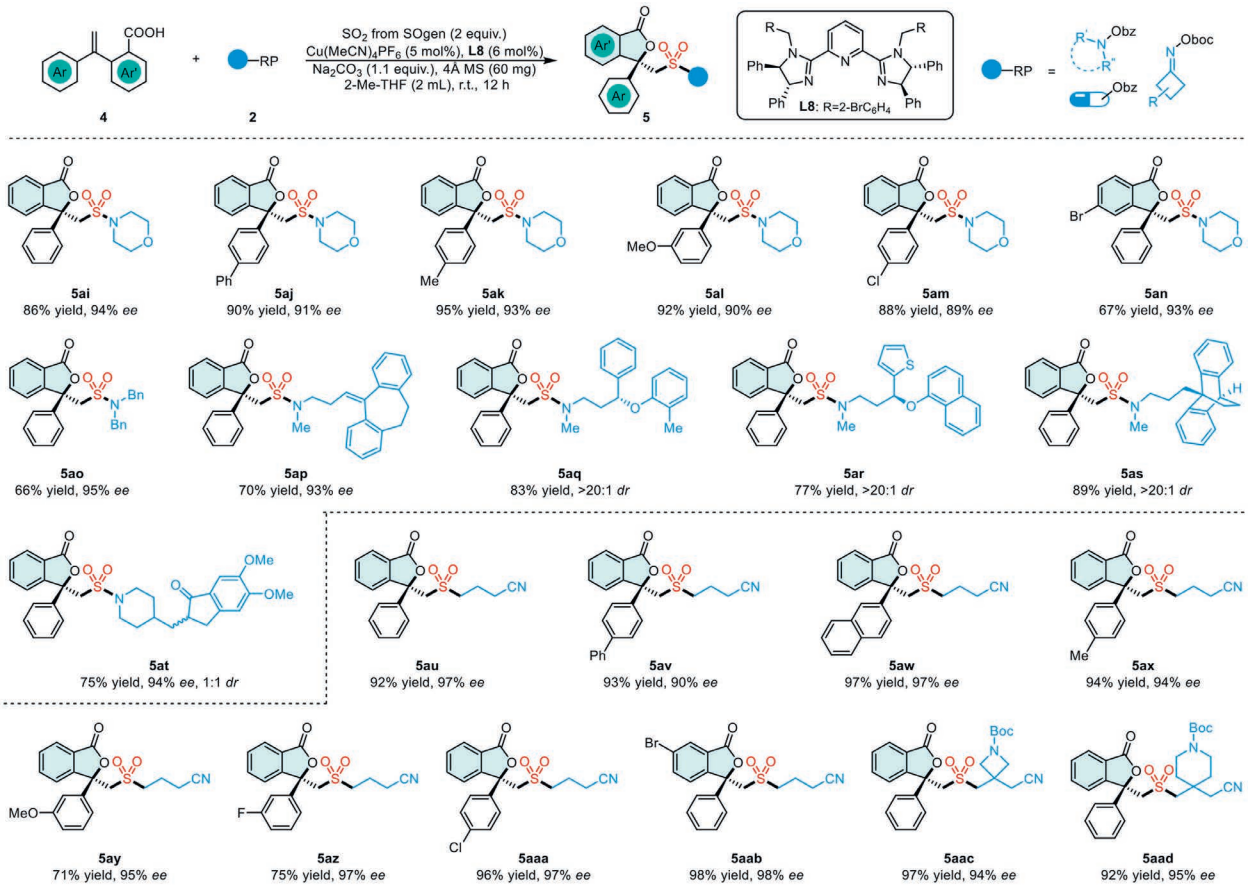
To demonstrate the practical applicability, we conducted a scaled-up reaction (1.0 mmol), which produced the target compound **5a** with a 92 % yield and 94 % *ee* (Scheme 4). Moreover, the chiral sulfonyl phthalides synthesized *via* this method can be eas-



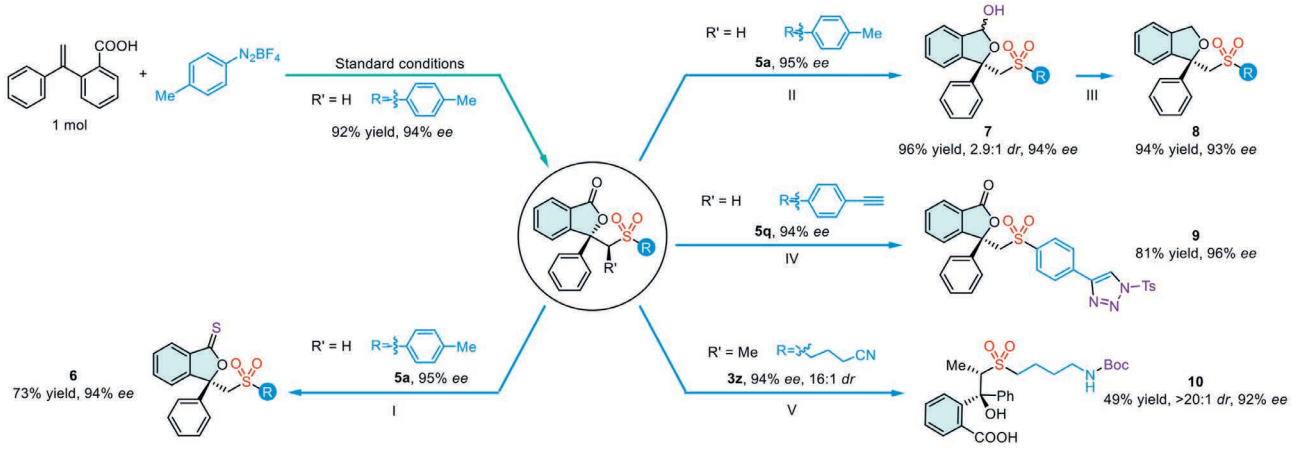
Scheme 2. Substrate scope. Reaction conditions: Chamber B: **4** (0.20 mmol), **2** (0.40 mmol, 2 equiv.), $Cu(MeCN)_4PF_6$ (0.01 mmol, 5 mol%), **L8** (0.012 mmol, 6 mol%), Na_2CO_3 (0.22 mmol, 1.1 equiv.), 4 Å molecular sieve (60 mg), 2-Me-THF (2.0 mL) at room temperature for 12 h under argon atmosphere.

ily converted into other valuable compounds that while preserving its enantioselectivity. For instance, the reaction of compound **5a** with Lawesson reagent resulted in the formation of the thiolated product **6**. Furthermore, phthalide in compound **5a** can be selectively reduced possess a variety of functional groups, using DIBAl-H to yield hemiacetal **7**. This intermediate is then further reduced by Et_3SiH to synthesize compound **8**. Similarly, compound **5q** was subjected to a copper-catalyzed click reaction, which introduced a crucial triazole moiety into the chiral sulfonyl phthalide, resulting in the generation of product **9** with excellent yield. Finally, compound **5au** was converted into the Boc-protected amino acid **10** *via* a nickel-catalyzed reduction process. Compound **10** contains several important functional groups, including an amino group, a carboxyl group, a hydroxyl group, and a sulfonyl group. Additionally, it features two conserved stereocenters, which are commonly found in various pharmaceutical agents and bioactive compounds [25].

To elucidate the mechanism more clearly, a series of experiments was conducted to achieve a comprehensive understanding of the process (Scheme 5). Initially, upon adding 3.0 equiv. of TEMPO under standard conditions, the desired product **5a** was not detected. Instead, the formation of TEMPO adducts **11** and **12** was observed (Scheme 5A). Secondly, upon introducing 1,1-diphenylethene into the reaction system, merely trace amount of the sulfonylated products were produced. Conversely, compounds **13** and **14**, originating from aryl radicals and sulfonyl radicals, were detected (Scheme 5B). The results suggest that the reaction may involve a radical process. Additionally, a linear correlation was observed between the enantiopurity of product **5a** and that of ligand **L8** (Scheme 5C). This suggests the involvement of a single chiral ligand and a copper complex in the enantiocontrol step [67]. Subsequently, we pre-synthesized the chiral catalyst **Cat1** and employed it to catalyze the reaction under standard conditions,



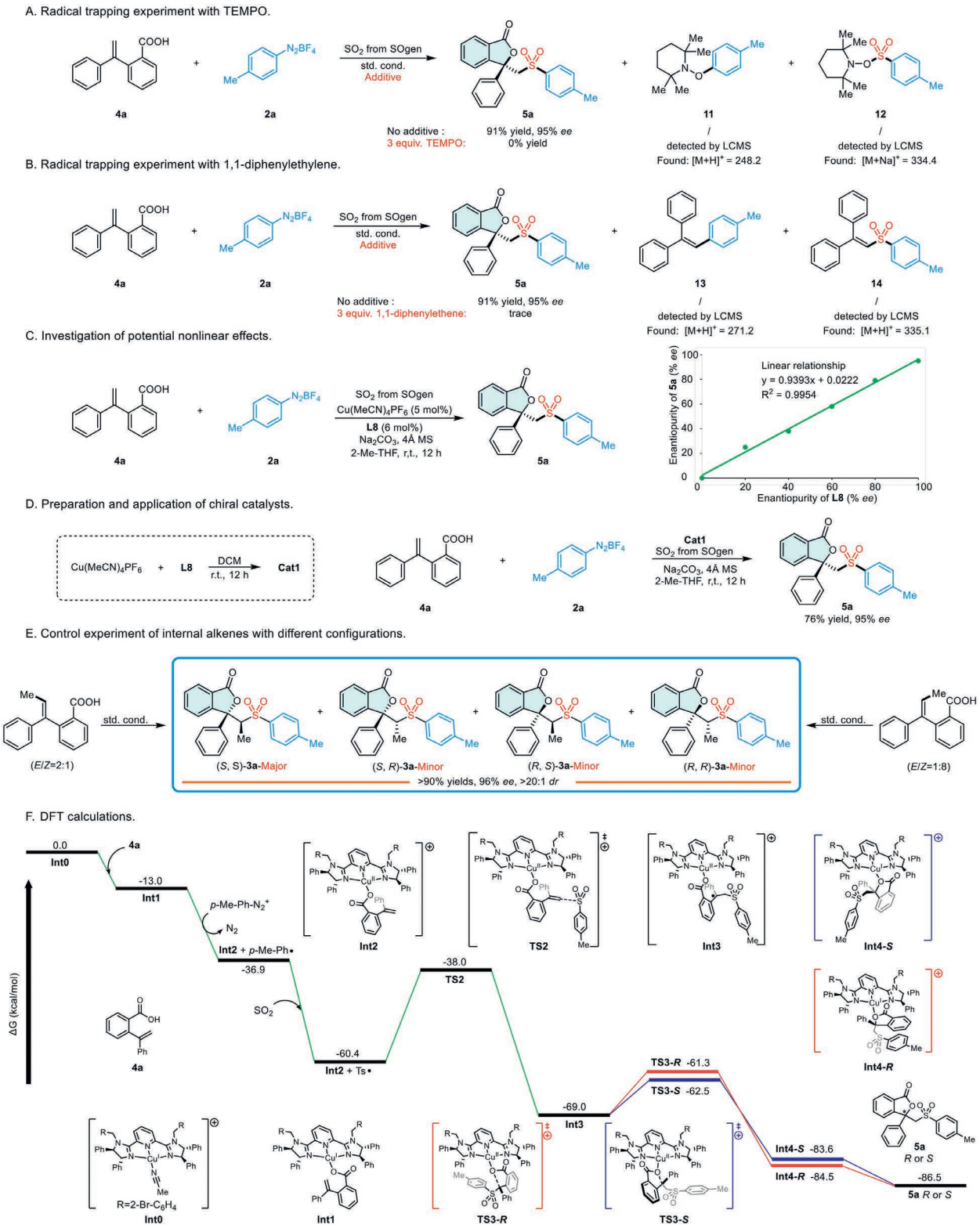
Scheme 3. Substrate scope. Reaction conditions: Chamber B: **4** (0.20 mmol), **2** (0.40 mmol, 2 equiv.), $Cu(MeCN)_4PF_6$ (0.01 mmol, 5 mol%), **L8** (0.012 mmol, 6 mol%), Na_2CO_3 (0.22 mmol, 1.1 equiv.), 4 Å molecular sieve (60 mg), 2-Me-THF (2.0 mL) at room temperature for 12 h under argon atmosphere.



Scheme 4. Scale-up reaction and transformations of chiral sulfonyl phthalides. Reaction conditions: (I) Lawesson reagent (2.25 equiv.), toluene, reflux; (II) DIBAl-H (1.1 equiv.), CH_2Cl_2, −78 °C, 1 h; (IV) Et_3SiH (5 equiv.), $BF_3{\cdot}Et_2O$ (4 equiv.), CH_2Cl_2, r.t., 3 h; (IV) TsN_3 (1.1 equiv.), CuTc (10 mol%), toluene, r.t., 12 h; (V) $NiCl_2{\cdot}6H_2O$ (3.0 equiv.), $(Boc)_2O$ (3.0 equiv.), $NaBH_4$ (10 equiv.), MeOH, r.t., 12 h.

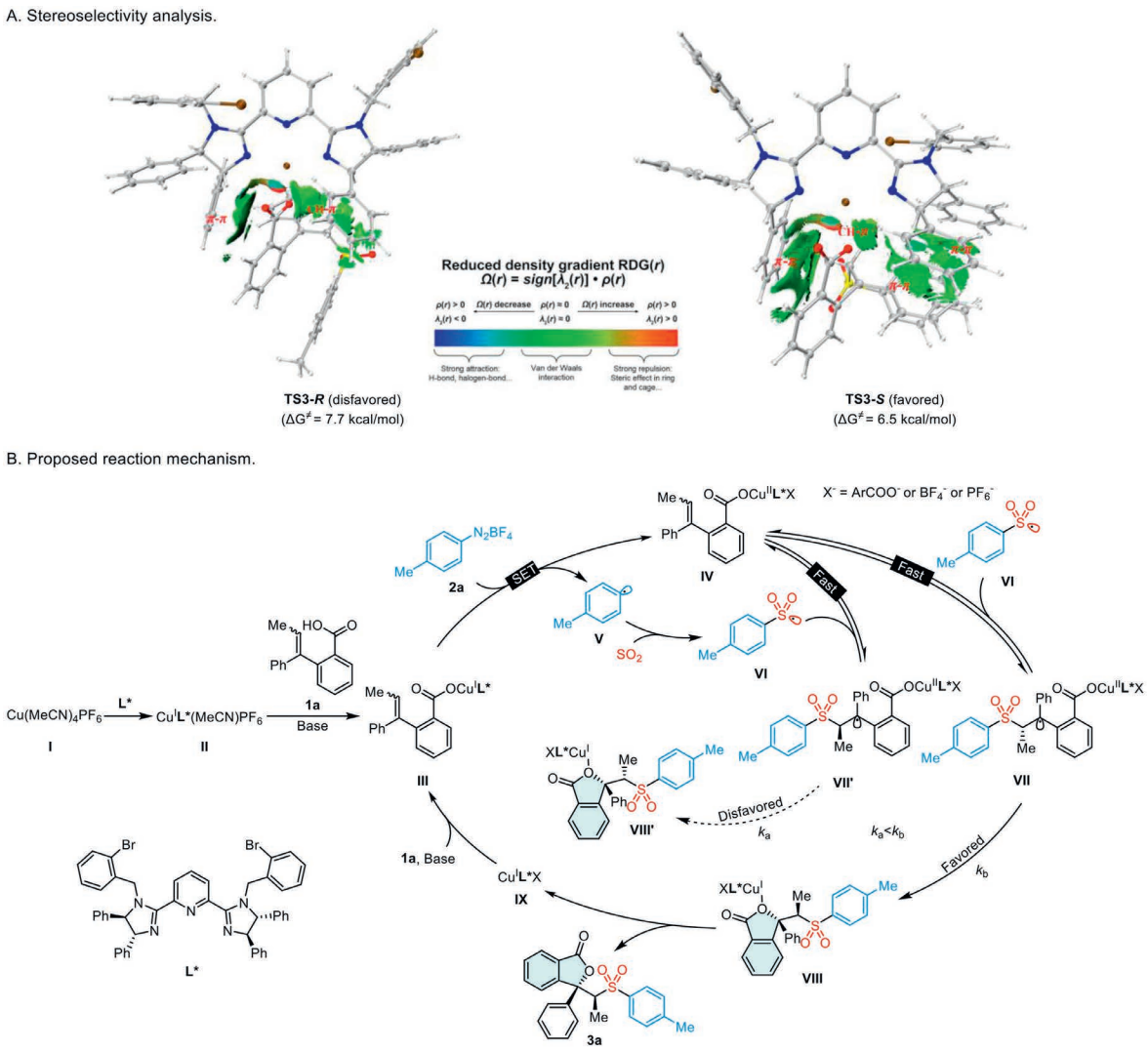
achieving the target product with a 76 % yield and 95 % *ee* (Scheme 5D). This outcome suggests that **Cat1** possesses the same catalytic active center as the originally synthesized catalyst. Finally, under standard conditions, substrates with *E*/*Z* ratios of 2:1 and 1:8 in alkenes consistently yield target product (*S*,*S*)-**3a**, which exhibits a dominant stereoconfiguration (Scheme 5E). This outcome demonstrates the reaction's capability for stereoconvergent synthesis of chiral sulfonyl phthalides from *Z*/*E* alkene mixtures. Drawing on previous literature, it is highly probable that the envisioned Curtin-Hammett kinetic control was operative under our experimental conditions [62,63].

To gain a comprehensive understanding of the underlying mechanisms, we conducted extensive investigations utilizing density functional theory (DFT) calculations in this study. These calculations focused on the reaction pathway of the terminal alkene substrate **4a** in the asymmetric construction of the chiral sulfonyl phthalide **5a**. The precatalyst $[Cu(MeCN)_4]^{\oplus}$ engages in a ligand exchange with **L8**, leading to the formation of the com-



Scheme 5. Mechanistic studies.

plex [Cu^{I}MeCN-**L8**]$^{\oplus}$ (**Int0**) (Scheme 5F). First, the deprotonated terminal alkene substrate (**4a**) complexes with **Int0** to form the Cu^{I}-**L8**-aryl carboxylic acid complex (**Int1**), accompanied by a decrease in Gibbs free energy of 13.0 kcal/mol. Next, through a single electron transfer (SET) process, **Int1**, in conjunction with the *p*-methylphenyl diazonium compound, generates the [Cu^{II}-**L8**-aryl carboxylic acid]$^{\oplus}$ complex (**Int2**) and an aryl radical, resulting in a decrease in Gibbs free energy of 23.9 kcal/mol. Subsequently, the aryl radical captures sulfur dioxide, undergoing a barrierless process to generate an aryl sulfonyl radical (Gibbs free energy decrease by 23.5 kcal/mol). While aryl radicals are theoretically predisposed to engage in direct addition reactions with alkenes, DFT



Scheme 6. Stereoselectivity analysis and proposed reaction mechanism.

calculations conducted by the Lei group reveal the presence of an energy barrier in this addition process [68]. Therefore, under conditions where sulfur dioxide is present, aryl radicals are more inclined to capture sulfur dioxide to form sulfonyl radicals, rather than undergoing radical addition with alkenes. This calculation result is consistent with the observation that no by-products from the direct addition of aryl radicals to alkenes, in the absence of sulfur dioxide capture, were detected in the experiment. Then, the sulfonyl radical undergoes radical addition to the C=C bond of [Cu^{II}-**L8**-aryl carboxylic acid]$^{\oplus}$ (**Int2**) *via* the transition state **TS2**, leading to the formation of a new divalent copper complex (**Int3**) that contains a carbon radical. The process releases an energy of 8.6 kcal/mol, which aligns with the well-documented tendency of radicals to react with unsaturated bonds [69]. Following the radical addition, the oxygen atom coordinated to copper in **Int3** approaches the carbon radical and transitions through the **TS3** transition state to generate the new copper complex **Int4**. **Int3** undergoes distinct reaction intermediates **TS3-*R*** and **TS3-*S*** to produce the diastereoisomers **Int4-*R*** and **Int4-*S***. In this process, an intramolecular radical attack on the carboxylate oxygen results in the generation of a chiral carbon atom, which is influenced by the orientation of the approaching planar phenyl radical. This leads to the formation of **Int4-*R*** and **Int4-*S***, which release distinct enantiomers. Computational analysis demonstrates that **TS3-*S*** is lower in energy by 1.2 kcal/mol compared to **TS3-*R***, indicating a preference for the formation of the *S*-product.

To gain a more comprehensive understanding of the enantioselectivity of the reaction, we conducted a comparative analysis of the non-covalent interactions in the transition states **TS3-*R*** and **TS3-*S*** (Scheme 6A) [70]. The analysis revealed that the phenyl group on the ligand in **TS3-*S*** forms stronger $\pi-\pi$ interactions with the aryl group on the substrate compared to **TS3-*R***. Furthermore, **TS3-*S*** features additional $\pi-\pi$ interactions between the phenyl groups on the substrate and both the phenyl group on the ligand and the Ts group on the substrate. These interactions result in a larger RDG surface area in **TS3-*S*** relative to **TS3-*R***, thereby providing a more favorable environment for enantioselectivity. Overall, the analysis indicates that **TS3-*S*** demonstrates more favorable non-covalent interactions than **TS3-*R***, which likely contributes to its enhanced enantioselectivity.

Based on the combined evidence from experimental results and literature reports, we propose a potential mechanism for the reaction (Scheme 6B) [25,62,63]. In the presence of a base, species **II**, Cu^{I}-L*(MeCN)PF_6, reacts with reactant **1a**, ultimately forming species **III**, [Cu^{I}-L*O_2CAr]. Subsequently, species **III** undergoes a SET process with aryldiazonium salt **2a**, resulting in the formation of [Cu^{II}-L*O_2CArX] species **IV** and *p*-methylphenyl radical **V**. Then, the radical **V** captures sulfur dioxide to generate a sulfonyl radical **VI**.

Subsequently, the sulfonyl radical rapidly and reversibly adds to intermediate **IV**, resulting in the formation of alkyl radicals **VII** and **VII'**. Due to the significantly slower rate of intramolecular radical substitution reactions in intermediate **VII'** compared to intermediate **VII** ($k_a < k_b$), intermediate **VII'** rapidly and reversibly converts back to **VII**. Subsequently, species **VII** undergoes an intramolecular radical substitution, leading to the formation of the Cu^I complex **VIII**. This is followed by the dissociation of species **VIII**, resulting in the production of compound **3a** and [Cu^I-L*X] **IX**.

In summary, we have developed a method that allows for the stereoconvergent synthesis of chiral sulfonyl phthalides using *Z*/*E* alkene mixtures under a Cu/PyBim catalytic system. This method not only enables the successful synthesis of sulfonyl phthalides with multiple stereocenters for the first time, but also exhibits broad applicability across a range of terminal and internal alkene substrates, as well as diverse aryl, alkyl, and nitrogen radical precursors, under exceptionally mild reaction conditions. The Cu/PyBim catalytic system is crucial for controlling the stereoselectivity of this reaction. The experimental results suggest that the reaction utilizes a Curtin-Hammett kinetic control strategy to achieve stereoconvergent construction of compounds with high stereoselectivity. We anticipate that this strategy will have broad implications and practical applications in the field of organic synthesis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Zhiqian Chang: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Xiaochun He:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Xuemei Zhang:** Writing – review & editing, Writing – original draft, Project administration, Investigation, Funding acquisition, Conceptualization. **Zhong Lian:** Writing – review & editing, Supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2025.111405.

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