EDGE ARTICLE

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CoH-catalyzed asymmetric remote hydroalkylation of heterocyclic alkenes: a rapid approach to chiral five-membered S- and O-heterocycles†

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Saturated heterocycles, which incorporate S and O heteroatoms, serve as fundamental frameworks in a diverse array of natural products, bioactive compounds, and pharmaceuticals. Herein, we describe a unique cobalt-catalyzed approach integrated with a desymmetrization strategy, facilitating precise and enantioselective remote hydroalkylation of unactivated heterocyclic alkenes. This method delivers hydroalkylation products with high yields and excellent stereoselectivity, representing good efficiency in constructing alkyl chiral centers at remote C3-positions within five-membered S/O-heterocycles. Notably, the broad scope and good functional group tolerance of this asymmetric $C(sp^3)-C(sp^3)$ coupling enhance its applicability.

Introduction

Saturated heterocycles, which incorporate S and O heteroatoms, stand as ubiquitous structural scaffolds found in natural products, bioactive molecules, and synthetic intermediates[1] (Fig. 1a). These structurally valuable frameworks offer distinct advantages, including enhanced solubility, improved pharmacokinetics, and increased bioavailability,[2] capturing significant attention from both industry and academia. Despite their importance, the aromatic driving force directs the construction toward five-membered heterocyclic aromatic compounds like triazole, imidazole, thiazole, thiophene, and furan. Consequently, synthesizing saturated heterocyclic compounds with diverse structures, especially chiral saturated S- and O-heterocyclic compounds, remains a challenging frontier in asymmetric synthesis. Traditional methods for achieving these compounds typically involve hydrogenation of heteroarenes,[3] intramolecular cyclization,[4] and annulation reactions.[5] However, despite significant progress, these approaches frequently encounter limitations related to the accessibility of starting materials, substrate scope, or stereoselectivity. In light of these challenges, there is a significant demand for the development of more direct and highly stereoselective methods

to synthesize chiral saturated S- and O-heterocycles from inexpensive and abundant heterocyclic substrates.
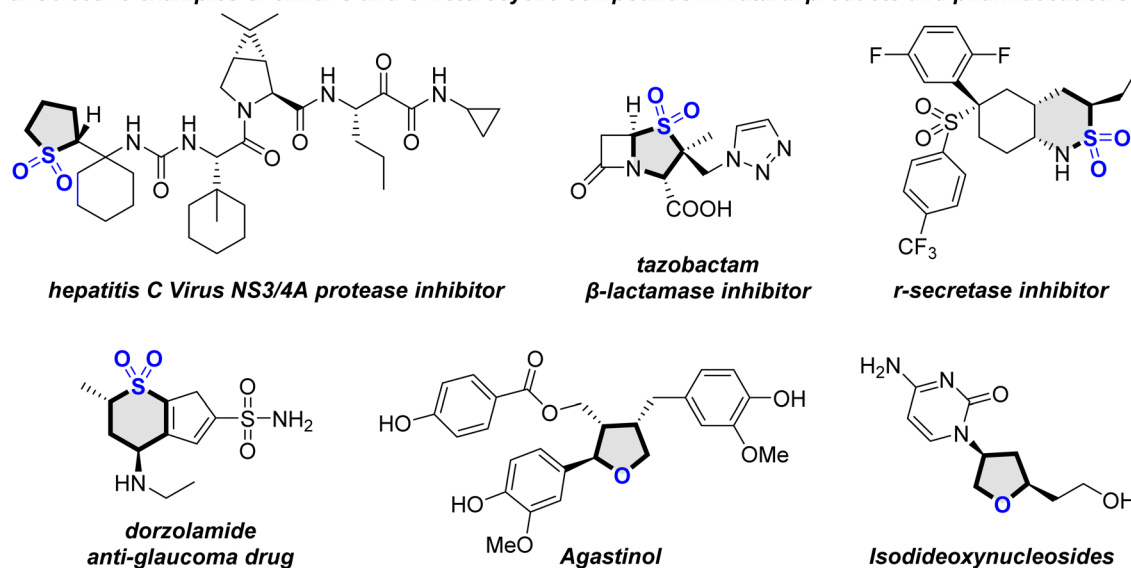
Recently, the enantioselective hydrofunctionalization of alkenes catalyzed by transition metals[6] has emerged as a central and extensively studied field. This method is particularly valued for its ability to efficiently construct intricate chiral functional molecules and heterocycles in organic synthesis. This approach significantly enhances precision in constructing chiral C–C bonds, offering a universal method to concurrently generate chiral carbon centers and regulate stereochemistry. This capability addresses a fundamental challenge in asymmetric synthesis, which is essential for shaping the core structures of a wide range of organic molecules. Recognizing the importance of chiral saturated heterocycles containing S and O heteroatoms, researchers have explored the feasibility of synthesizing these valuable compounds through a transition metal-catalyzed hydrofunctionalization of heterocyclic alkenes. In this innovative approach, readily available heterocyclic alkenes serve as pro-nucleophiles instead of highly active and unstable organometallic reagents[7] in the hydrofunctionalization process to establish a new C–C bond, ultimately realizing the construction of the chiral center on the five-membered saturated S- and O-heterocycles. However, constructing chiral centers on the remote C3 position of a five-membered heterocyclic ring poses a significant challenge. Addressing this challenge, Hayashi et al. recently presented a solution through their report on the rhodium-catalyzed asymmetric hydroarylation of 2,5-dihydrothiophene-1,1-dioxide under neutral conditions (Fig. 1b).[8] Despite the considerable advantage demonstrated by this methodology, existing studies predominantly focus on the asymmetric hydroarylation of alkenes, leading to the formation of chiral C3-arylated heterocycles.[9] In contrast, methods for

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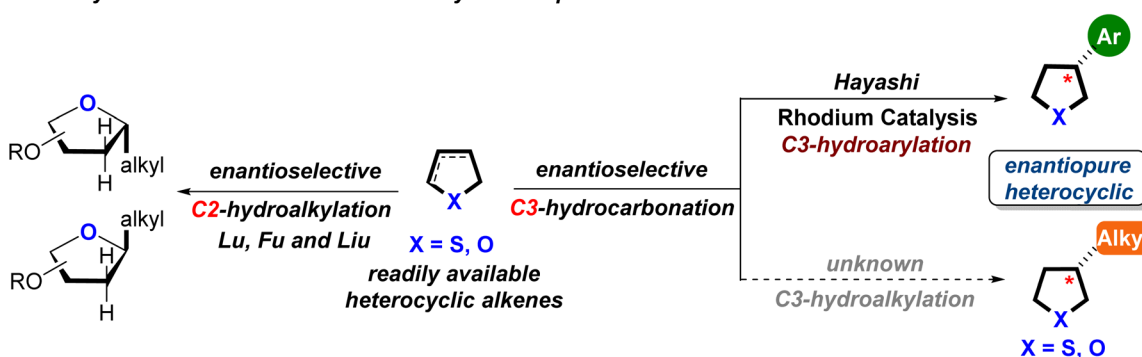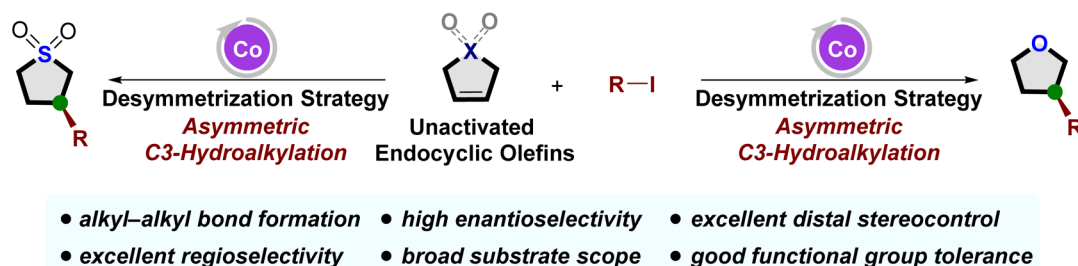
Fig. 1 Background for the development of the current work.

asymmetric hydroalkylation reactions, offering a promising pathway to generate diversified chiral alkylated heterocycles by introducing a chiral alkyl center at the remote C3 position after the association with the transition metal. Moreover, the rarity can be ascribed to the inherent challenges linked with establishing chiral C(sp^3)–C(sp^3) bonds in these reactions.[10] To this end, CoH-catalyzed enantioselective reductive hydrocarbonation of alkenes[11] has proven to be a feasible and promising method for enantioselective C–C bond formation compared to other transition metals, despite the remaining challenges in the enantioselectivity control. In 2021, Lu and Fu's

research group achieved a significant breakthrough in the field of cobalt-catalyzed hydroalkylation reactions, enabling the highly efficient synthesis of chiral alkylated fluoroalkanes.[12] Inspired by this work and based on our previous research,[13] we wondered if asymmetric hydroalkylation catalyzed by cobalt could be used in the rapid construction of chiral five-membered O/S-heterocyclic rings. Although very recently, Lu, Fu, Liu and coworkers developed the CoH-catalyzed stereoselective reductive hydroalkylation reaction of five-membered glycals for the synthesis of biologically important ribofuranosyl 2-deoxy-C-glycosides constructed alkyl chiral centers at the C2 position

(Fig. 1b),[14a] the asymmetric remote C3-hydroalkylation of five-membered O/S-heterocyclic alkenes still remains a challenge. Herein, we describe the development of new catalytic systems for the regio- and enantioselective hydroalkylation of O/S-endocyclic olefins to synthesize 3-alkylated heterocycles by a cobalt catalyst. The use of Co–H in the presence of different bisoxazoline (BOX) anchoring ligands enables precise stereoselectivity of hydroalkylation, allowing enantioselective access to different saturated heterocycles incorporating S and O heteroatoms. This approach offers precise control over regio- and enantioselectivity under mild reaction conditions (Fig. 1c).

Results and discussion

In our initial investigation, we employed 1-(2-iodoethyl)naphthalene **2a** as the alkylation reagent to explore the asymmetric remote hydroalkylation of 2,5-dihydrothiophene-1,1-dioxide **1**. Ligand screening experiments highlighted the crucial role of ligands in influencing the activity and stereoselectivity of the reaction (Table 1). The use of the chiral BOX ligand **L1** resulted in the desired product in a trace yield. Interestingly, the isopropyl-substituted chiral IndaBox ligand **L2** demonstrated promising results, providing the desired product in a 39% yield with 83% ee. However, further screening of modified chiral IndaBox ligands (**L3–L6**) resulted in significantly reduced yields and enantioselectivities. Similarly, the utilization of chiral Bn-Box ligand **L7**, chiral Ph-Box ligand **L8**, and ligand **L9** yielded inferior outcomes in terms of both yield and enantioselectivity. To explore the influence of additional reaction parameters on both coupling efficiency and stereoselectivity, various silanes were then investigated, and the results indicated that (MeO)$_2$-MeSiH still provided the best outcomes (Table 1, entries 1–3). Evaluation of bases revealed that other bases such as KF, K$_3$PO$_4$, K$_3$PO$_4$·H$_2$O, and Cs$_2$CO$_3$ were less effective than CsF (entries 4–7). The use of alternative cobalt precursors, including CoBr$_2$·glyme, CoCl$_2$, CoCl$_2$(PPh$_3$)$_2$, and CoI$_2$, instead of CoBr$_2$, resulted in a substantial reduction in reactivity and enantioselectivity (entries 8–11). Solvent assessment showed that other ether solvents, such as isopropyl ether and cyclopentyl methyl ether, are unsuitable for this asymmetric hydroalkylation reaction (entries 12 and 13). Interestingly, 1,4-dioxane also yielded comparable results to dimethoxyethane (DME) (entry 14). Considering the importance of reaction temperature, we then explored the effect of different reaction temperatures. The reaction achieved a satisfying level of yield (73%) and enantioselectivity (94%) when conducted at −20 °C (entry 16). Subsequent attempts to refine the experimental conditions did not lead to noteworthy enhancements (further details can be found in the ESI†).

With the established optimized reaction conditions, we systematically explored the universality of the reaction, investigating the versatility of alkyl halides as depicted in Scheme 1. Terminal-substituted alkyl halides, featuring electron-rich and electron-withdrawing groups at the *ortho*-, *meta*-, and *para*-positions of the benzene ring, exhibited competency in this enantioselective reductive C(sp^3)–C(sp^3) bond formation reaction. This led to the synthesis of the corresponding chiral C3-
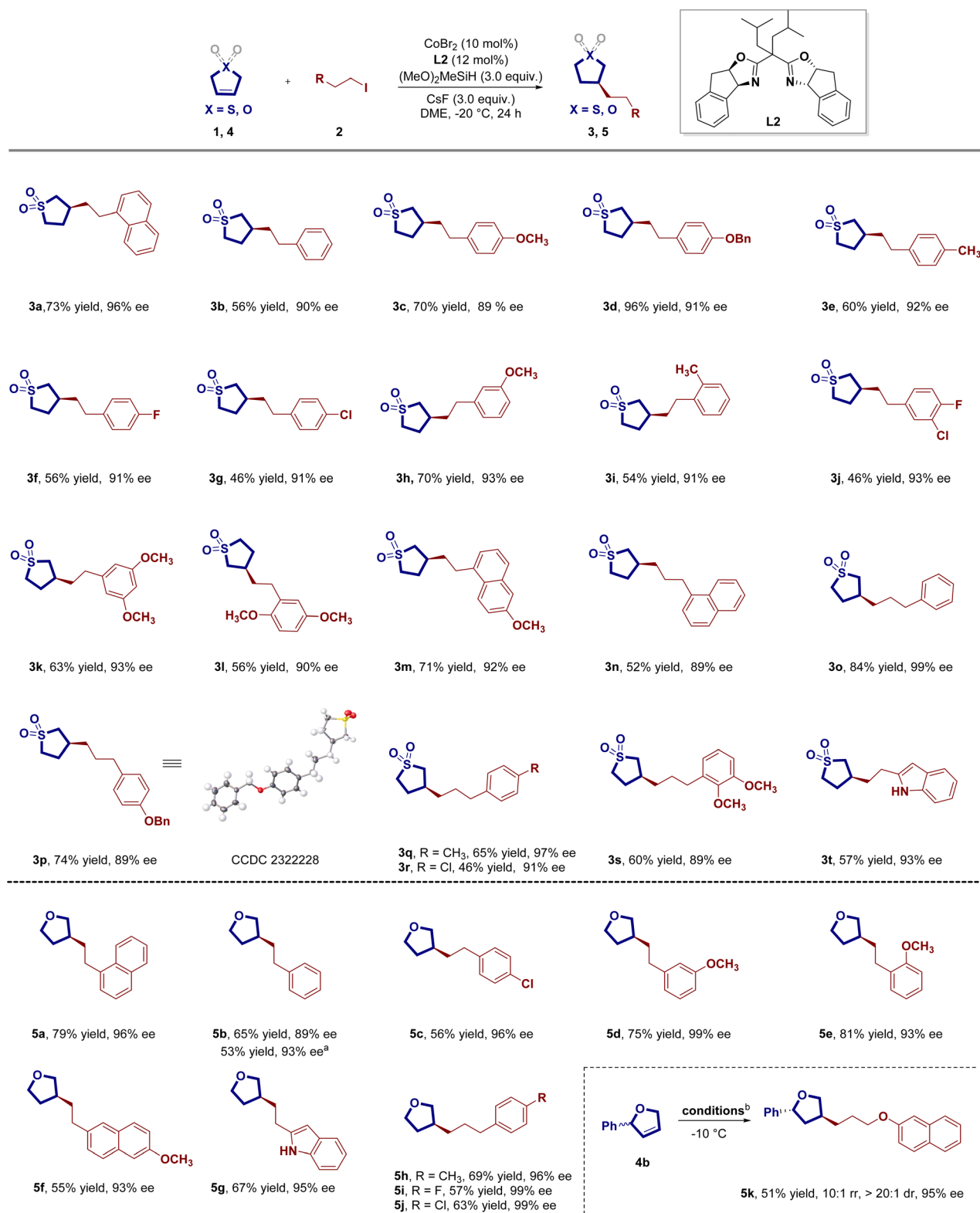
Table 1 Variation of reaction parameters[a]

Entry[b]	Variation from standard conditions	Yield [%]	ee [%]
1	(EtO)$_2$MeSiH instead of (MeO)$_2$MeSiH	34	80
2	(MeO)$_3$SiH instead of (MeO)$_2$MeSiH	23	81
3	(EtO)$_3$SiH instead of (MeO)$_2$MeSiH	Trace	—
4	KF instead of CsF	32	66
5	K$_3$PO$_4$ instead of CsF	19	38
6	K$_3$PO$_4$·H$_2$O instead of CsF	19	38
7	Cs$_2$CO$_3$ instead of CsF	28	69
8	CoBr$_2$·glyme instead of CoBr$_2$	27	56
9	CoCl$_2$ instead of CoBr$_2$	19	27
10	CoCl$_2$(PPh$_3$)$_2$ instead of CoBr$_2$	7	17
11	CoI$_2$ instead of CoBr$_2$	33	65
12	Isopropyl ether instead of DME	Trace	—
13	Cyclopentyl methyl ether instead of DME	Trace	—
14	1,4-Dioxane instead of DME	33	80
15	0 °C instead of r.t.	32	91
16	**−20 °C instead of r.t.**	**73**	**96**
17	−40 °C instead of r.t.	49	90

[a] Summary of selected optimization of reaction conditions: conditions: **1** (0.1 mmol, 1.0 equiv.), **2a** (0.2 mmol, 2.0 equiv.), catalyst (10 mol%), ligand (12 mol%), DMMS (0.3 mmol, 3.0 equiv.), CsF (0.3 mmol, 3.0 equiv.), DME (2.0 mL, 0.05 M), 24 h, isolated yields. [b] **L2** as the ligand. The enantiomeric ratio was determined by HPLC analysis using a chiral stationary phase. Abbreviations: DME, 1,2-dimethoxyethane. DMMS, dimethoxymethylsilane.

alkylated sulfolanes **3a–3t**, yielding consistently excellent enantiomeric excess values (89–99%) with yields ranging from 46% to 96%. The mild reaction conditions facilitated the incorporation of various synthetically valuable functional groups, including ether (**3d**), aryl fluoride (**3f**), and aryl chloride (**3g**). In addition to the previously mentioned alkyl iodides, a series of longer alkyl chain substituted alkyl iodides (**3n–3s**) were found to be suitable for this transformation, producing moderate to good yields with high enantioselectivity in the cobalt catalytic system. The relative and absolute configuration of **3p** was unequivocally determined through single crystal X-ray analysis, while those of other products were assigned by analogy. Remarkably, the hydroalkylation process accommodated heterocyclic compounds, such as indole-substituted alkyl iodide, leading to smooth reactions with good yields and excellent enantioselectivity (**3t**).
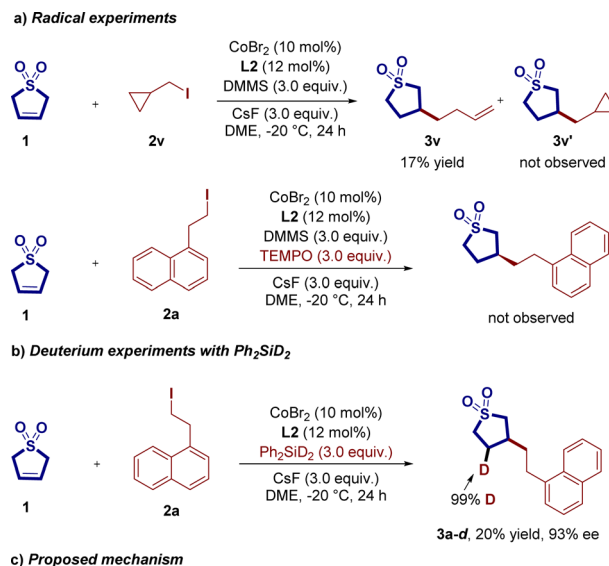
3a, 73% yield, 96% ee

3b, 56% yield, 90% ee

3c, 70% yield, 89 % ee

3d, 96% yield, 91% ee

3e, 60% yield, 92% ee

3f, 56% yield, 91% ee

3g, 46% yield, 91% ee

3h, 70% yield, 93% ee

3i, 54% yield, 91% ee

3j, 46% yield, 93% ee

3k, 63% yield, 93% ee

3l, 56% yield, 90% ee

3m, 71% yield, 92% ee

3n, 52% yield, 89% ee

3o, 84% yield, 99% ee

3p, 74% yield, 89% ee

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3q, R = CH₃, 65% yield, 97% ee
3r, R = Cl, 46% yield, 91% ee

3s, 60% yield, 89% ee

3t, 57% yield, 93% ee

5a, 79% yield, 96% ee

5b, 65% yield, 89% ee
53% yield, 93% ee[a]

5c, 56% yield, 96% ee

5d, 75% yield, 99% ee

5e, 81% yield, 93% ee

5f, 55% yield, 93% ee

5g, 67% yield, 95% ee

5h, R = CH₃, 69% yield, 96% ee
5i, R = F, 57% yield, 99% ee
5j, R = Cl, 63% yield, 99% ee

5k, 51% yield, 10:1 rr, > 20:1 dr, 95% ee

Scheme 1 Reaction scope. Standard conditions: **1** or **4** (0.2 mmol, 1.0 equiv.), **2** (0.4 mmol, 2.0 equiv.), **L2** (12 mol%), DMMS (0.6 mmol, 3.0 equiv.), CsF (0.6 mmol, 3.0 equiv.), DME (2.0 mL, 0.1 M), isolated yields. Conditions a: phenethyl bromide (2.0 equiv.) and sodium iodide (2.0 equiv.). Conditions b: Alkene (3.0 equiv.) and alkyl halide (1.0 equiv.). The enantiomeric ratio was determined by HPLC analysis using a chiral stationary phase. The dr and rr value was determined by NMR spectroscopy of the crude reaction mixture and GC analysis. DME = 1,2-dimethoxyethane, DMMS = dimethoxymethylsilane.

Efforts to obtain another enantioenriched class of important chiral organic skeletons, specifically C3-alkylated tetrahydrofurans, led us to explore the CoH-catalyzed asymmetric remote hydroalkylation of 2,5-dihydrofuran, with results summarized in Scheme 1. Encouragingly, using the established optimized reaction conditions, we successfully generated the desired hydroalkylation products in good yields with excellent enantiomeric excesses (ee). In the exploration of terminal-substituted alkyl halides, different substituents with varied electron properties at the *ortho*, *meta*, and *para* positions of the benzene ring were well-tolerated. This resulted in the formation of the desired chiral C3-alkylated tetrahydrofuran (**5a–5f**) with yields ranging from 60% to 82% and enantiomeric excess (ee) values between 96% and 99%. Notably, even reactions involving heterocycle-substituted alkyl halides proceeded efficiently, delivering the desired products **5g** with high efficiency. Furthermore, we extended the applicability of aryl ethyl iodines to longer chain aryl propyl iodines, yielding the corresponding chiral C3-alkylated tetrahydrofurans **5h–5j** with uniformly good yield and excellent stereoselectivity (57–69% yield, 96–99% ee). Notably, the cobalt-catalyzed hydroalkylation of racemic internal alkene **4b** has also demonstrated the ability to furnish C(sp^3)–C(sp^3) coupling product **5k** featuring 1,3-diastereocenters with remarkable levels of regio-, enantio-, and diastereoselectivity.

To showcase the synthetic utility of the reaction, several transformations were then conducted (Scheme 2). Firstly, this method proved valuable for accessing C3-alkylated sulfolane/tetrahydrofurans of drug molecules and natural products with high efficiency, such as acemetacin (product **3u** and **5l**) and estrone (product **5m**). Additionally, the obtained chiral C3-alkylated sulfolane product **3b** could be easily reduced to yield the chiral C3-alkylated tetrahydrothiophene **6b** which is difficult to synthesize by traditional methods.
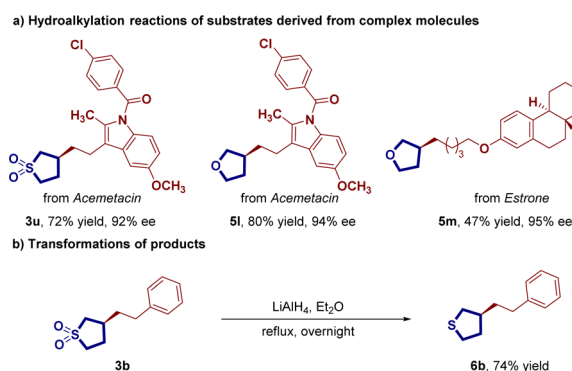
To gain insight into the reaction mechanism, we conducted a series of preliminary experiments. In Scheme 3a, alkene 2,5-dihydrothiophene-1,1-dioxide **1**, in the presence of 2.0 equivalent of the "radical-clock" (iodomethyl)cyclopropane **2v**, was subjected to the standard reaction conditions, yielding the ring-opening product **3v** in 17% yield. This result suggests that the C–I bond cleavage involves a radical pathway. Additionally, introducing a stoichiometric amount of the radical inhibitor 2,2,6,6-tetramethylpiperidinooxy (TEMPO) into the asymmetric

Scheme 3 Mechanistic investigations and proposed mechanism.

hydroalkylation reaction of **1** with **2a** significantly inhibited the reaction, strongly indicating the participation of a radical pathway in the reaction process. To delve deeper into the mechanism, we conducted isotopic labeling experiments using deuterated silane (PhSiD$_2$) as the hydride source, as depicted in Scheme 3b. These experiments revealed deuterium incorporation at the C4-position of **3a–d**, with 99% D, indicating that the migration insertion of Co–H with **1** might be irreversible.

Based on the conducted experiments and insights from previous literature reports,[14] we present the proposed catalytic cycles in Scheme 3c. The catalytic cycle begins with the ligated Co^{I}X precursor **A**, which can generate the cobalt hydride species Co^{I}H (**B**) in the presence of silane and base. The intermediate **B** then undergoes alkene hydrometallation with substrate **1** to generate the intermediate **C**. Subsequently, **C** participates in halogen-atom abstraction and radical addition processes, producing alkylcobalt(II) (**D**) and dialkylcobalt(III) (**E**). Finally, reductive elimination of **E** releases the desired C3-selective hydroalkylation product and regenerates **A**.

Scheme 2 Synthetic applications.

Conclusions

In conclusion, we have described a highly efficient cobalt-catalyzed regio- and enantioselective hydroalkylation of unactivated O/S-heterocyclic alkenes. This method provides a practical approach to generating alkyl chiral centers at remote positions within five-membered O/S-heterocycles, achieving excellent regio- and enantioselectivity through a desymmetrization strategy. Notably, the broad scope and excellent functional group tolerance of this asymmetric $C(sp^3)$–$C(sp^3)$ coupling enhance its applicability. Ongoing efforts in our laboratory are dedicated to exploring further applications and gaining a deeper understanding of the underlying mechanisms of this strategy.

Data availability

The data supporting this article have been uploaded as part of the ESI.†

Author contributions

Z. R. conceived the project. L. Z., F. L. and Y. Z. performed the experiments. L. Z., F. L. and Y. Z. analysed and interpreted the experimental data. L. Z., F. L. and Z. R. drafted the paper. Y. Z., M. S. and J. X. supervised the project. All the authors discussed the results and contributed to the preparation of the final manuscript.

Conflicts of interest

There are no conflicts to declare.

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