Asymmetric Catalysis

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Asymmetric Desymmetrization of Oxetanes for the Synthesis of Chiral Tetrahydrothiophenes and Tetrahydroselenophenes

Renwei Zhang[+], Wengang Guo[+], Meng Duan[+], K. N. Houk, and Jianwei Sun**

Abstract: *Chiral tetrahydrothiophenes and tetrahydroselenophenes are highly useful structural units. Described here is a new catalytic asymmetric approach for their synthesis. With a suitable chiral Brønsted acid catalyst, an oxetane desymmetrization by a well-positioned internal sulfur or selenium nucleophile proceeded efficiently to generate all-carbon quaternary stereocenters with excellent enantioselectivities. Taming the sulfur and selenium nucleophile in the form of a thioester and selenoester, respectively, is crucial to the success of this work. This approach also allows the facile synthesis of chiral tetrahydrothiopyrans. Mechanistic studies, including DFT calculations, suggested an intramolecular acyl-transfer pathway. Utilities of the chiral products are also demonstrated.*

Introduction

Chiral organosulfur and organoselenium compounds play important roles in biological processes, organic synthesis, and medicinal chemistry.[1] In particular, chiral tetrahydrothiophenes and tetrahydroselenophenes are well-known subunits in a wide range of natural products and bioactive molecules that exhibit a broad spectrum of important biological activities (e.g., **I**–**V**, Figure 1).[2] Moreover, such chiral units embedded in a relatively rigid five-membered ring structure also impart special features, allowing them to serve as superior chiral ligands, organocatalysts, and synthetic building blocks (e.g., **VI**).[3,4] However, despite their wide applications, expedient strategies for the assembly of these chiral units are rather limited.[4–8]

Previous asymmetric syntheses of tetrahydrothiophenes and tetrahydroselenophenes have mainly relied on multistep sequences from chiral starting materials.[4–8] Direct synthesis by asymmetric catalysis has been scarce. The challenges may partly lie in the strong coordination ability of sulfur and selenium that can interfere in a metal-catalyzed approach. Nevertheless, Glorius and co-workers successfully achieved a pioneering example with metal catalysis by means of asymmetric hydrogenation of substituted thiophenes (Scheme 1 a).[6] However, unfortunately, this elegant process suffers from a limited scope: good enantioselectivity was only observed for a small number of thiophenes bearing specific aryl substituent at the 2-position.

Moreover, the nature of this approach excludes the possibility of generating a quaternary stereogenic center. Alternatively, through organocatalysis, Jørgensen and Wang pioneered the use of β-mercapto carbonyl compounds to participate in a domino process initiated by asymmetric sulfa-

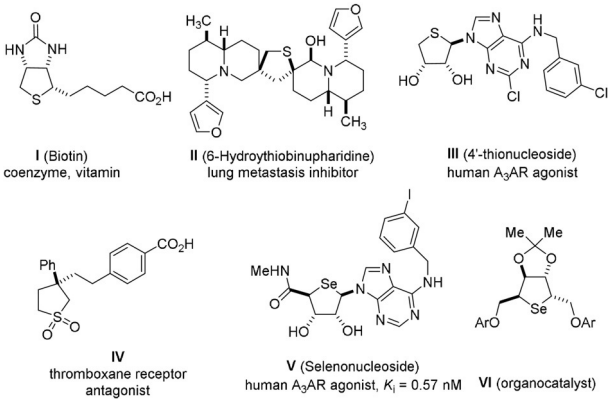
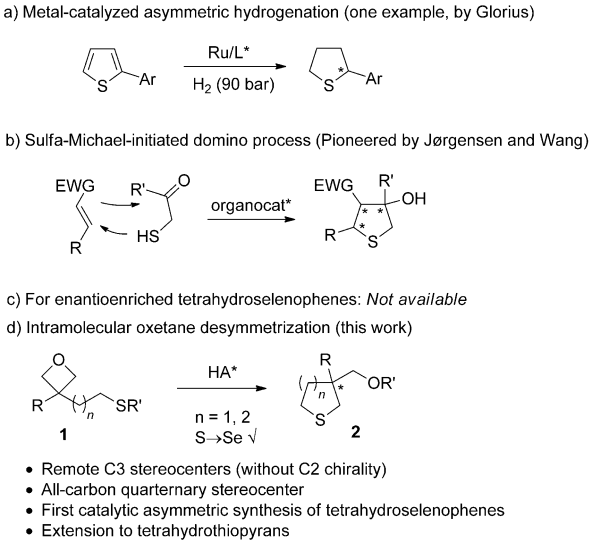


Figure 1. Useful compounds containing chiral tetrahydrothiophene and tetrahydroselenophene units.



Scheme 1. Catalytic asymmetric synthesis of chiral tetrahydrothiophenes and tetrahydroselenophenes. EWG = electron-withdrawing group.

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Michael addition to electron-deficient olefins (Scheme 1 b).[7a–d] This strategy was later extended to various other olefin and thiol partners with different catalysts.[7e–h] While these reactions generally gave high enantioselectivities, they uniformly required the establishment of a C2 stereogenic center, which is presumably crucial to good asymmetric induction during the enantiodetermining sulfa-Michael addition step. Notably, no example has been demonstrated to generate chiral tetrahydrothiophenes bearing C3 chirality in the absence of a C2 stereocenter.

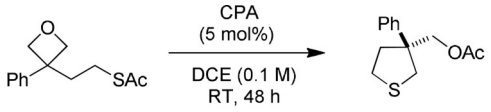
Though with limitations, the above two strategies represent important progress in catalytic asymmetric synthesis of chiral tetrahydrothiophenes. In awkward contrast, the counterparts for the synthesis of chiral tetrahydroselenophenes are not yet available.[5] Here we report a new unified organocatalytic approach for the efficient and mild asymmetric synthesis of both structures, and it also allows extension to the six-membered ring tetrahydrothiopyrans (Scheme 1 d). Moreover, this approach complements the above two strategies by generating a C3 all-carbon quaternary stereocenter in the absence of C2 chirality.

Results and Discussion

We envisioned that a prochiral oxetane tethered with a properly installed internal sulfur nucleophile (e.g., **1**), upon activation by a chiral Brønsted acid, would lead to the synthesis of chiral tetrahydrothiophenes by oxetane desymmetrization (Scheme 1 d).[9,10] To verify our hypothesis, we initially sought to synthesize such a substrate bearing a free thiol unit (R′ = H, Scheme 1 d). Unfortunately, this effort proved fruitless. Upon formation, this thiol undergoes spontaneous background oxetane opening to generate the racemic tetrahydrothiophene **2** in the absence of a catalyst, presumably as a result of the strong nucleophilicity of the well-positioned thiol unit.

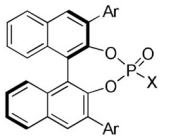
To tame the reactivity as well as stability of such compounds to be suitable for our study, we protected the free thiol in the form of a thioester (e.g., **1aa**, Table 1), which was prepared from the readily accessible known compound ethyl 2-(oxetan-3-ylidene)acetate in four simple steps, including conjugate addition, ester reduction, tosylation, and S_N2 subsitution by thioacid (see the Supporting Information for details). Next, we evaluated various chiral phosphoric acids as potential catalysts.[11] However, these phosphoric acids (X = OH), including the widely known TRIP (**A2**) and STRIP (**B1**), were found to exhibit no catalytic activity (entries 1, 2, and 4), presumably because of their low acidity. To our delight, the stronger acid *N*-triflyl phosphoramide **A3** led to the desired product tetrahydrothiophene **2aa** in 86% yield, albeit with low enantioselectivity (27% *ee*, entry 3). Notably, the acyl protective group was transferred to the alcohol motif in the form of acetate. Next, other *N*-triflyl phosphoramides with BINOL and SPINOL backbones bearing different 3,3′-subsitutents were evaluated. These efforts led us to identify **B3** as the best catalyst regarding enantioselectivity (72% *ee*, entry 6).[11f]

Table 1: Screening of catalysts

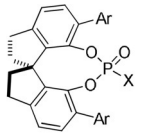


1aa **2aa**

Entry	Catalyst	*t* [h]	Yield [%][a]	*ee* [%][b]
1	(*S*)-**A1**	24	< 10	–
2	(*R*)-**A2**	24	< 10	–
3	(*R*)-**A3**	24	86	27
4	(*R*)-**B1**	24	< 10	–
5[c]	(*S*)-**B2**	16	86	6
6	(*R*)-**B3**	30	69	72



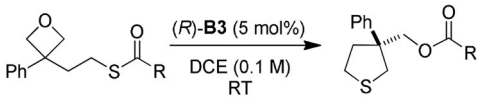
(*S*)-**A1**: Ar = 9-phenanthryl, X = OH
(*R*)-**A2**: Ar = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$, X = OH
(*R*)-**A3**: Ar = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$, X = NHTf



(*R*)-**B1**: Ar = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$, X= OH
(*S*)-**B2**: Ar = Ph, X = NHTf
(*R*)-**B3**: Ar = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$, X = NHTf

We next examined other acyl protective groups (Table 2). Indeed, increasing the size from acetyl to pivaloyl (R = ^{t}Bu) led to substantial increase in enantioselectivity to 91% *ee* (entries 1–3). However, further variation to 1-adamantanecarbonyl could not improve the selectivity (entry 4). The benzoyl group also proved inferior. Next, with the pivalate as the substrate, we examined other parameters. The reaction was very sensitive to solvents. The use of chloroform and toluene completely shut down the reactivity. Furthermore, the reaction was found to be not very sensitive to concentration (entries 9 and 10).

Table 2: Evaluation of different protective groups and other parameters



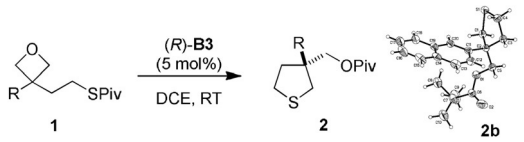
1aa-1af **2aa-2af**

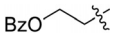
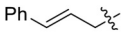
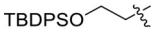
Entry	R	Solvent	*t* [h]	Yield [%][a]	*ee* [%][b]
1	Me	DCE	24	69	72
2	^{i}Pr	DCE	44	87	80
3	^{t}Bu	DCE	24	84	91
4	1-Ad	DCE	28	69	89
5	Ph	DCE	30	56	57
6	^{t}Bu	DCM	32	45	86
7	^{t}Bu	$CHCl_3$	32	< 10	–
8	^{t}Bu	toluene	32	< 10	–
9[c]	^{t}Bu	DCE	32	78	89
10[d]	^{t}Bu	DCE	32	80	88

[a] Yield based on ^{1}H NMR analysis of the crude reaction mixture with CH_2Br_2 as an internal standard. [b] The *ee* value based on HPLC analysis. [c] Concentration = 0.2 M. [d] Concentration = 0.05 M. 1-Ad = 1-adamantyl, DCE = 1,2-dichloroethane. DCM = dichloromethane.

With the optimized reaction conditions (Table 2, entry 3), we next examined the substrate generality (Table 3). A wide variety of oxetanes reacted smoothly to afford the desired

Table 3: Scope for the synthesis of chiral tetrahydrothiophenes

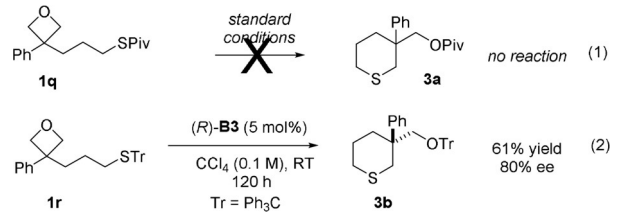


Entry	R	*t* [h]	2	Yield [%][a]	*ee* [%][b]
1	Ph	24	**2a**	82	91
2	2-naphthyl	22	**2b**	85	92
3	*p*-(MeO)C_6H_4	27	**2c**	76	92
4	*p*-(MeS)C_6H_4	30	**2d**	81	92
5[c]	*p*-ClC_6H_4	30	**2e**	72	92
6[d]	*m*-ClC_6H_4	30	**2f**	76	93
7		15	**2g**	67	91
8	Me	10	**2h**	61	82
9	Et	10	**2i**	67	84
10	Bn	10	**2j**	65	88
11	^{i}Pr	10	**2k**	73	82
12		10	**2l**	82	84
13		10	**2m**	81	86
14		10	**2n**	72	84
15		14	**2o**	50	90
16	BnS	15	**2p**	91	90

[a] Yield of isolated product. [b] The *ee* value was determined by chiral-phase HPLC. [c] Run with 8 mol% of the catalyst. The crystal structure of **2b** is shown with thermal ellipsoids at 40% probability.[19] Piv = pivaloyl, TBDPS = *t*-butyldiphenylsilyl.

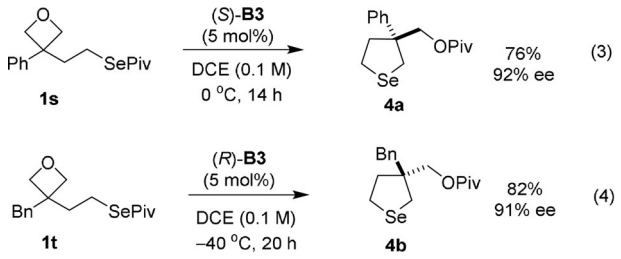
chiral tetrahydrothiophenes with high efficiency, generating all-carbon quaternary stereocenters with good to excellent enantioselectivities.[12] The absolute configuration of **2b** was confirmed by X-ray crystallography. Both electron-donating and electron-withdrawing groups on the 3-aryl substituents were suitable, although the latter cases showed slightly low reactivity and thus required a slightly higher catalyst loading (entries 5 and 6). Heterocycles can also be incorporated into the product (entry 7). Substrates with aliphatic substituents at the 3-position were more reactive, since they went to completion within a shorter reaction time, however some products were obtained in moderate yields because of the formation of byproducts. This mild reaction also exhibited good functional-group compatibility. Finally, an oxetane bearing a heterosubstituent (SBn) also reacted to form chiral bis(sulfide) product **2p** in excellent enantiopurity, and could serve as a potential bidentate ligand.

While this protocol is successful for chiral tetrahydrothiophene synthesis, direct extension to the formation of six-membered tetrahydrothiopyrans proved not to be straightforward [Eqs. (1) and (2)]. Under the standard reaction conditions, the pivalate **1q** showed no reactivity, which is presumably due to the increased barrier in six-membered (vs. five-membered) ring formation [Eq. (1)]. Nevertheless, after considerable efforts in manipulating the protective groups, we found that the use of the trityl protection in **1r** led to smooth formation of the tetrahydrothiopyran **3b** at room temperature [Eq. (2)]. It is worth noting that chiral tetrahydrothiopyrans are also important structural units in biologi-

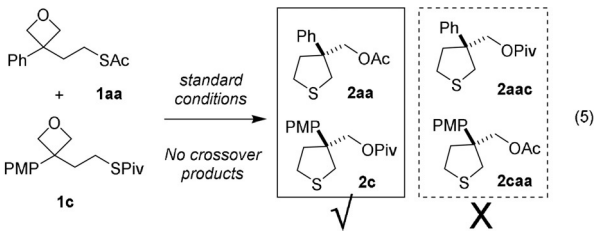


cally important molecules, but general and efficient access to them is lacking.[13]

The same catalytic protocol could also be extended to the synthesis of chiral tetrahydroselenophenes. The selenoesters **1s** and **1t** underwent facile oxetane ring opening, even at relatively low temperature [Eqs. (3) and (4)]. The desired products **4a** and **4b** were both formed with excellent enantioselectivities, and is the first demonstration of catalytic asymmetric synthesis of chiral tetrahydroselenophenes.[5] These chiral products are potential organocatalysts for electrophilic halogenation reactions.[3b]



In our reaction, the sulfur proting group in the substrates was transferred to the hydroxy group in the products. To probe the nature of this acyl transfer, either intramolecular or intermolecular, we carried out a crossover experiment. In fact, a mixture of **1aa** and **1c** reacted independently to form **2aa** and **2c** without crossover products, suggesting an intramolecular acyl transfer [Eq. (5)].



To explore the mechanism and the origins of stereoselectivity, density-functional theory (DFT) calculations at the M06-2X/6-311 + G(d,p)-SMD (dichloroethane)//B3LYP/6-31G(d) level of theory[14] in the Gaussian 09 package[15] were carried out. We first investigated the free-energy profile of the intramolecular desymmetrization of the oxetane **CP1**, with **CP2** as the catalyst (Figure 2). The catalyst **CP2** establishes a hydrogen bond with the oxygen atom of the reactants to afford the complexes **CP3-*S*** and **CP3-*R***. This reaction is endergonic by 3.9 and 4.8 kcal mol^{-1}, respectively, because of the unfavorable entropy of this bimolecular reaction. The

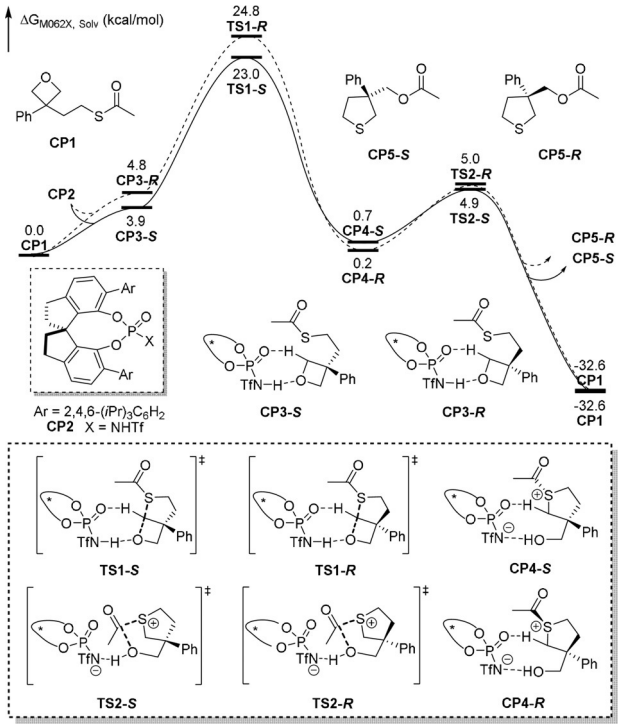


Figure 2. Free-energy profiles of chiral N-triflyl phosphoramide catalyzed enantioselective intramolecular desymmetrization of oxetane by a thioester. Values are given in kcal mol^{-1}.

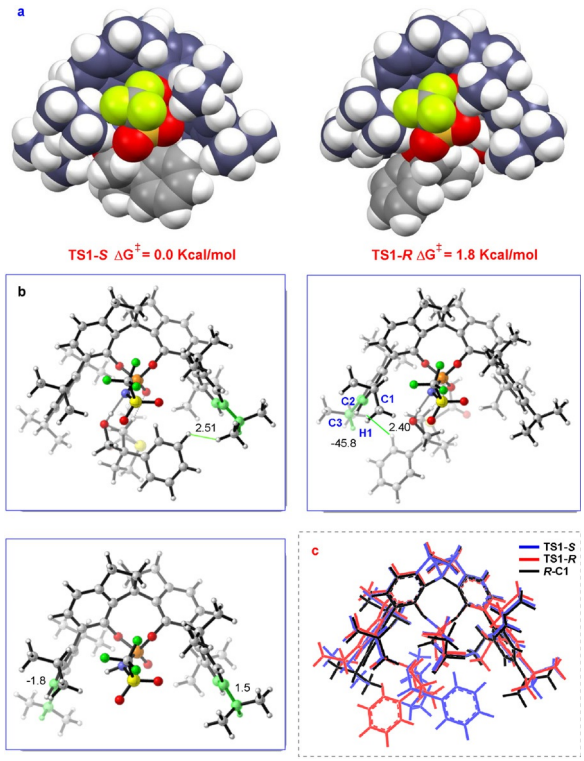


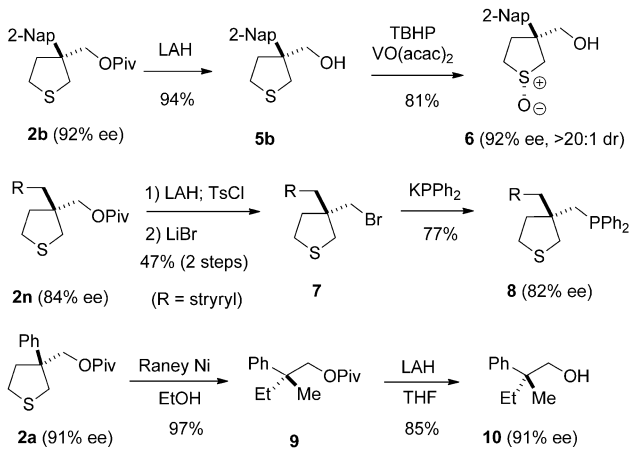
Figure 3. a) Space-filling models of **TS1-*S*** and **TS1-*R***. b) Axial projection of **TS1-*S***, **TS1-*R*** and **(*R*)-C1**. Key bond lengths and angles are given. c) Superimposition of the axial projections of **(*R*)-C1** (black lines), **TS1-*S*** (blue lines), and **TS1-*R*** (red lines).

oxetane complex then undergoes a S_N2 attack by the sulfur atom of the thioester at the 2-position of the oxetane via the transition-states **TS1-*S*** and **TS1-*R*** to generate the intermediates **CP4-*S*** and **CP4-*R***, respectively. The optimized transition-state **TS1-*S*** has a barrier of 23.0 kcal mol^{-1} and is 1.8 kcal mol^{-1} lower than **TS1-*R***. Intermediate ion pairs (**CP4**) undergo the intramolecular acyl transfer via transition-states **TS-2-*S*** and **TS-2-*R*** to obtain the final products (**CP5**). **TS-2-*R*** is only 0.1 kcal mol^{-1} less stable than **TS-2-*S***. The overall rate- and stereodetermining step is the S_N2 attack of the sulfur atom at the 2-position of oxetane via **TS1-*S*** and **TS1-*R***. The optimized 91% *ee* is reasonably consistent with the 72% *ee* observed experimentally.

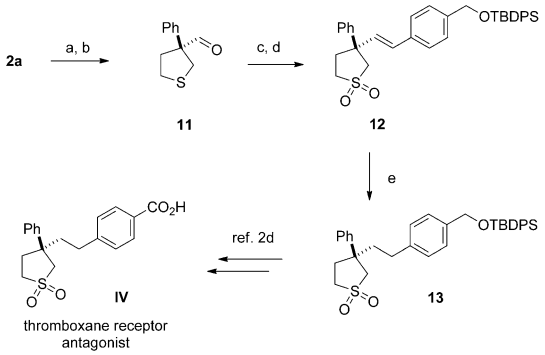
To better understand the origins of stereoselectivity, the structures of **TS1-*S*** and **TS1-*R*** were compared (Figure 3). The theoretical analysis of analogous phosphoric acid and phosphoramide catalyzed transition states by the groups of Goodman, Paton, Sunoj, Wheeler, and ourselves has been reviewed recently by Wheeler et al.[16] The key factor for determining selectivity is the orientation of the phenyl groups of the substrates relative to the isopropyl groups of the catalyst. In the disfavored **TS1-*R***, the aryl groups on the oxetane and the isopropyl groups of the triisopropylphenyl catalyst are close to each other and the H–H bond distance (2.40) is shorter than that in **TS1-*S*** (2.51). Moreover, to minimize unfavorable steric clashes between the aryl groups and 4-isopropyl group in **TS1-*R***, the dihedral angle C1-C2-C3-H1 on the substituents is rotated to −46° compared with that in the free catalyst (−2°). The methyl groups on the 4-isopropyl group have undergone an unfavored conformational change (Figure 3a). By contrast, the isopropyl groups in **TS1-*S*** have no steric interaction with the substrate. To better illustrate this distortion of the catalyst geometry, the axial projections of **(*R*)-C1**, **TS1-*R***, and **TS1-*S*** are overlaid in Figure 3c. The catalyst in **TS1-*R*** is distorted away from the favored catalyst structure. Steric factors are responsible for the observed enantioselectivities. To compare the enantioselectivities optimized with dispersion corrections, structure optimizations were also performed using B3LYP-D3[17] and the 6-31G(d) basis set. The detailed free-energy profile is summarized in the Supporting Information, and is in agreement with the computed results using B3LYP and the 6-31G(d) basis set.

Finally, we carried out some product derivatizations (Scheme 2). The pivalate unit in **2b** could be easily removed to form the free alcohol **5** in 94% yield. Next, oxidation of the thioether motif by TBHP (^{t}BuOOH) and $VO(acac)_2$ resulted in highly diastereoselective formation of the chiral sulfoxide **6**. Moreover, after some simple steps, **2n** was easily converted into the phosphine **8**, a potential chiral P,S-ligand.[18] Moreover, **2a** underwent clean desulfuration mediated by Raney Ni to give acyclic pivalate **9**. Further reduction afforded the alcohol **10**, bearing an acyclic all-carbon quaternary stereocenter.[12b] Notably, the product enantiopurity remains essentially intact in all these transformations.

The enantioenriched 3,3-*gem*-disubstituted tetrahydrothiophene products could also serve as versatile synthetic intermediates toward biologically active molecules (Scheme 3). For example, simple deprotection and oxidation



Scheme 2. Product derivatizations.



Scheme 3. Synthesis of the bioactive compound **IV**. a) $LiAlH_4$, THF, 0 °C to RT, 3 h, 84% yield; b) oxalyl chloride, DMSO, DCM, −78 °C; then $^{i}Pr_2NEt$, −78 °C to 0 °C, 48% yield; c) diethyl (4-(hydroxymethyl)-benzyl)phosphonate, $^{t}BuOK$, THF, 0 °C to RT, 4 h, 52% yield; d) Oxone, THF/H_2O (1:1), RT, 12 h, 84% yield; e) H_2, Pd/C, EtOH, RT, 2 h, 65% yield. DMSO = dimethylsulfoxide, THF = tetrahydrofuran.

of **2a** afforded the α-chiral aldehyde **11**, which was then converted into the olefin **12** by Horner–Wadsworth-Emmons olefination. Subsequent hydrogenation of the olefin provided the chiral sulfone **13**. Additional simple steps could deliver the chiral sulfone **IV**, a known thromboxane receptor antagonist.[2d]

Conclusion

We have developed a new catalytic asymmetric approach for the synthesis of chiral tetrahydrothiophenes and tetrahydroselenophenes, both are highly useful structures with limited efficient access previously. By proper choice of a suitable chiral Brønsted acid catalyst, the intramolecular oxetane desymmetrization by a well-positioned sulfur or selenium nucleophile proceeded efficiently to generate all-carbon quaternary stereocenters with excellent enantioselectivities. It is worth noting that taming the sulfur and selenium nucleophile in the forms of a thioester and selenoester, respectively, is crucial to the success of the reaction. Minor modifications to the reaction conditions also allowed the synthesis of chiral tetrahydrothiopyrans. This approach is also complementary to known strategies in forming a remote stereocenters at the 3-position in the absence of C2 chirality. This mild process features a broad scope, mild reaction conditions, and good functional-group compatibility. Mechanistic studies suggested an intramolecular acyl-transfer pathway. DFT calculations also rationalized the stereochemical outcomes. Finally, the chiral products generated from our reaction are useful precursors for other chiral molecules, including bioactive molecules.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · desymmetrization · organocatalysis · selenium · sulfur heterocycles

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[19] CCDC 1871523 (**2b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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