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Catalytic Asymmetric Thiofunctionalization of Unactivated Alkenes

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Supporting Information

ABSTRACT: Catalytic asymmetric sulfenylation of double bonds has been achieved using a BINAM-based phosphoramide catalyst and an electrophilic sulfur source. Simple alkenes as well as styrenes afforded sulfenylated tetrahydrofurans and tetrahydropyrans by closure with pendant hydroxyl or carboxyl groups. Intermolecular thiofunctionalizations were also achieved with simple alcohols or carboxylic acids as the nucleophiles.

Olefins are among the most versatile building blocks in organic synthesis. Their utility largely derives from the myriad functionalization reactions that simultaneously form carbon−carbon or carbon−heteroatom bonds and create two new stereocenters.[1] This family of reactions includes the functionalization of alkenes with boron, nitrogen, and oxygen moieties stereo-, regio-, and enantioselectively.[2] However, the stereocontrolled transfer of sulfur[3] and selenium[4] to alkenes remains underdeveloped; in fact, no example of a catalytic, asymmetric thiofunctionalization of an unactivated olefin is extant.[5,6] Given the prevalence of sulfur in certain classes of natural products,[7] as well as the rich chemistry of sulfur that allows for further manipulations,[8] a reliable and highly enantioselective method for vicinal thiofunctionalization is of interest.

The successful development of a catalytic, enantioselective sulfenylation reaction requires that certain critical mechanistic features be established. First, the Ad_E thiofunctionalization of alkenes with electrophilic sulfur(II) sources is now universally accepted to involve thiiranium ions.[9] Because of the distribution of positive charge in these highly strained, electrophilic species, attack of a nucleophile can occur at both the carbon and the sulfur centers. Reaction at the carbon centers forms stereodefined, vicinally functionalized products by an invertive ring-opening,[10] whereas reaction at sulfur regenerates the alkene along with a sulfenylated nucleophile. Experimental data show that nucleophilic attack at the carbon atoms of thiiranium ions is preferred.[11] Second, the configurational stability of thiiranium ions must be sufficient that, if generated in enantiomerically enriched form under catalytic conditions, they could be intercepted by nucleophiles without erosion in enantiopurity. A recent report from these laboratories confirmed that enantiomerically enriched thiiranium ions, generated stoichiometrically *in situ*, are configurationally stable at −20 °C and can be captured by a variety of nucleophiles with complete enantiospecificity.[12] Furthermore, the configurational stability of thiiranium ions persists in the presence of an alkene, implying that racemization via olefin-to-olefin transfer is slow at −20 °C.[11,13] Hence, if enantiomerically enriched thiiranium ions could be formed catalytically, their rate of racemization would be sufficiently slow that capture by nucleophiles could form enantioenriched sulfides.[12]

Engineering a catalytic, enantioselective thiofunctionalization first requires a functioning catalytic process. Previous studies from these laboratories demonstrated that *seleniranium* ions could be generated catalytically from weakly electrophilic selenium(II) sources by Lewis bases to form reactive ionic selenylating species, in accord with the principle of Lewis base activation of Lewis acids.[4b,14] Subsequent studies showed that chiral Lewis bases were capable of delivering an arylselenium moiety to simple olefins with modest enantioselectivity.[4c] We envisioned designing an analogous system wherein judicious choice of a sulfur(II) electrophile, along with a chiral Lewis base, would allow for the formation of enantioenriched thiiranium ions, which would then be captured by a variety of nucleophiles to effect a catalytic asymmetric thiofunctionalization (Scheme 1).

Scheme 1

Orienting experiments employed stable, crystalline, commercially available sulfenylating agent *N*-phenylsulfenyl-phthalimide (**1**) and alcohol **2a**.[4c,15] Because previous studies established the need for Lewis bases *and* Brønsted acids to effect chalcogenoetherifications,[4c] a survey of both components was undertaken. A suitable catalyst must balance sufficient Lewis basicity (to function as a sulfenyl-transfer agent) with low Brønsted basicity (to remain active in the presence of a Brønsted acid). Tetrahydrothiophene (THT) was selected to initiate the survey in view of its established competence as a group-transfer agent[16] along with its weak Brønsted basicity (Table 1).[17] Thus, **1**, **2a**, THT, and TFA were combined at room temperature, and thioether **4a** was detected in significant amounts (entry 1).[15b] The use of a stronger Brønsted acid, MsOH (pK_a(TFA) = 3.75, pK_a(MsOH) = 1.6, in DMSO),[18] allowed for complete conversion of **2a** in <3 h (entry 2). Importantly, barely any reaction was detected after 24 h with either TFA or MsOH alone, excluding the possibility of simple Brønsted acid catalysis (entries 3, 4). Next, a variety of Lewis bases containing different donor atoms were surveyed to determine their catalytic efficacy. HMPA proved ineffective, whereas DMPU(S), a thiourea, displayed moderate reactivity (entry 5). Considering the importance of phosphorus(V) compounds for selenofunctionalization,[4b,c] a number of phosphine chalcogenides were tested. Both $Ph_3P(S)$ and $Cy_3P(S)$ showed high catalytic activity, leading to complete conversion of **2a** within

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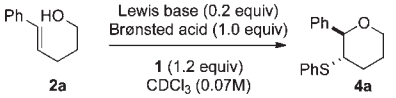
Table 1. Survey of Achiral Lewis Bases



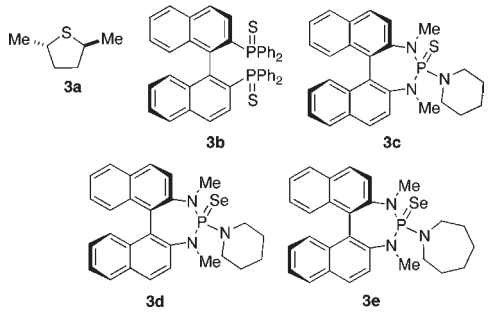
			conv,[a] %	
entry	acid	Lewis base	3 h	24 h
1	TFA	THT	33	70
2	MsOH	THT	100	100
3	TFA	none	0	0
4	MsOH	none	trace	10
5	MsOH	DMPU(S)	7	55
6	MsOH	$Ph_3P(S)$	100	100
7	MsOH	$Cy_3P(S)$	100	100
8	MsOH	HMPA(S)	trace	35
9	MsOH	HMPA(Se)	31	100

[a] Conversion was determined by assuming **2a** was converted only to **4a**, as no other significant product was detected by ^{1}H NMR spectroscopy.

3 h (entries 6, 7). Phosphoramides HMPA(S) and HMPA(Se) also showed potential; the HMPA(Se)-catalyzed reaction was complete within 24 h (entries 8, 9).

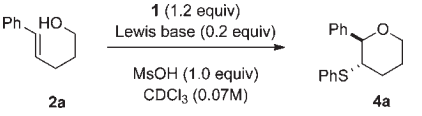
The next stage of reaction development was to identify structural elements that lead to high enantioselectivity in the thioetherification process. Because the softer sulfur and selenium donor atoms displayed good catalytic activity, chiral catalysts incorporating simple sulfides and phosphine sulfides (selenides) were investigated. Surprisingly, THT analogue **3a** (Chart 1) and phosphine sulfide **3b** both gave poor enantioselectivity (Table 2, entries 1, 2). Thiophosphoramide **3c** displayed good selectivity but poor reactivity (entry 3). Replacing sulfur with selenium (**3d**) increased the reactivity of the catalyst (entry 4), as expected. Further optimization identified **3e**, which afforded **4a** with useful enantioselectivity (84:16) in 3 h.[19] The enantioselectivity could be further improved by lowering the reaction temperature to −20 °C (with an attendant increase in reaction time, entries 6, 7). Finally, the catalyst loading could be lowered to 0.1 equiv without adversely affecting the enantioselectivity (entries 8, 9). Although sulfenylating agents other than **1** were tried, no difference in enantioselectivity was observed.[20]

Chart 1



With the feasibility of the catalytic asymmetric thioetherification demonstrated, the next stage was to establish the sensitivity of the reaction to the steric and electronic properties of the

Table 2. Survey of Chiral Lewis Bases



entry	Lewis base	equiv	temp, °C	time,[a] h	er[b]
1	**3a**	0.2	23	24	40:60
2[c]	**3b**	0.2	23	1	46:54
3	**3c**	0.2	23	24	82:18
4	**3d**	0.2	23	3	79:21
5	**3e**	0.2	23	3	84:16
6	**3e**	0.2	−20	40	91:9
7	**3e**	0.2	−30	66[d]	91:9
8	**3e**	0.05	−20	24[e]	89:11
9	**3e**	0.1	−20	24[f]	91:9

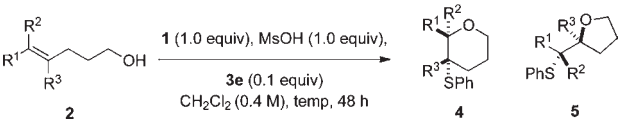
[a] Unless otherwise specified, reactions were completed at the time indicated. [b] Ratio of (2*R*,3*S*)/(2*S*,3*R*); absolute configuration established by independent synthesis of **4a** (see Supporting Information). [c] *N*-Phenylthiobenzotriazole and TFA were used. [d] 70% conversion. [e] 52% conversion. [f] 65% conversion.

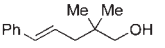
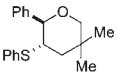
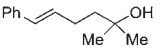
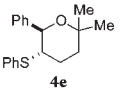
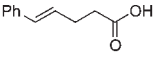
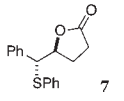
substrate. Under the optimal reaction conditions, substrate **2a** provided pyran **4a** in 80% yield with excellent constitutional and enantioselectivity (Table 3, entry 1).[21] Electron-deficient alkene **2b** reacted more sluggishly (41% conversion in 48 h), whereas electron-rich alkene **2c** behaved comparably to **2a**. On the other hand, the electronic character of the double bonds had only a minimal effect on enantioselectivity (entries 2, 3). Geminal dimethyl substituents in the tether did not significantly affect the rate or enantiomeric composition of the products, as both **2d** and **2e** afforded thioethers **4d** and **4e** in good yields and nearly identical enantioselectivities compared to **4a** (entries 4, 5). The constitutional selectivity was somewhat eroded for **4e**, most likely because of the increased sensitivity of the approaching alcohol to the steric difference between the alkyl and phenyl groups. Nonconjugated alkenes were also useful substrates. For *trans* nonconjugated alkenes, the constitutional selectivity was dependent on the difference in size of the alkene substituents (entries 6, 7). The increased compression in the *endo* transition state disfavors **4** for alkenes with bulkier C(5) substituents.[22,23] Excellent enantioselectivities were obtained with these substrates. For *cis* nonconjugated alkene **2h**, the reaction proceeded in 72% yield, 20:1 site selectivity, but poor enantioselectivity (entry 8).[24]

The generality of the thiofunctionalization reaction for different alkene types was also investigated. The substitution pattern of the double bond was found to have a major effect on the enantiomeric composition of the products. Geminally disubstituted alkene **2i** produced furan **5i** in 85% yield but only 62:38 er, whereas terminal olefin **2j** cyclized in 72% yield and 83:17 er. Trisubstituted olefin **2k** was the least reactive, necessitating running the reaction at rt which afforded many side products. On the other hand, isomer **2l** was more reactive, affording **5l** in 82% yield and 70:30 er. These results indicate that the presence of a substituent *cis* to the phenyl group is detrimental to the enantioselectivity and rate of the reaction. Notably, catalytic, asymmetric thiolactonization was possible as carboxylic acid **6** cyclized to form lactone **7** in high yield and with high endo selectivity and good enantioselectivity.

The intermolecular capture of thiiranium ions by nucleophiles can also be achieved with this catalytic system. Exposure of 4-octene to the reaction conditions in the presence of 1.0 equiv of

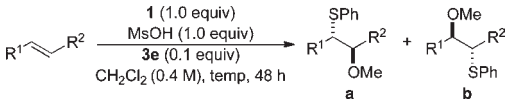
Table 3. Scope of the Intramolecular Asymmetric Sulfenylation Reaction



entry	substrate	R^1	R^2	R^3	temp,°C	product	yield,[a] %	4/5 [b]	er [c,d,e]
1	**2a**	Ph	H	H	-20	**4a**	80	49:1	91:9
2	**2b**	4-$CF_3C_6H_4$	H	H	-10	**4b**	36[f]	25:1	88:12
3	**2c**	4-MeO-C_6H_4	H	H	-20	**4c**	84	>10:1	91:9
4	**2d**				-20	 **4d**	94	19:1	92:8
5	**2e**				-20	 **4e**	84	13:1	92:8
6	**2f**	CH_2CH_2Ph	H	H	-20	**4f**	88	5:1	96:4 (**4f**) 96:4 (**5f**)
7	**2g**	*i*-Pr	H	H	-20	**4g**	71	17:1	96:4
8	**2h**	H	CH_2CH_2Ph	H	-10	**5h**	81	1:20	54:46
9	**2i**	H	H	Ph	-20	**5i**	85	<1:99	62:38
10	**2j**	H	H	H	-10	**5j**	72	1:50	83:17
11	**2k**	Ph	H	Me	23	**5k**	24	18:1	60:40
12	**2l**	Ph	Me	H	-20	**4l**	82	17:1	70:30
13	**6**				-10	 **7**	83	<1:99	91:9

[a] Yield of isolated products. [b] Pyran/furan selectivity was determined by ^{1}H NMR spectroscopy on the product mixture prior to chromatographic separation. [c] The enantiomeric ratio for the major constitutional isomer **4** or **5**. [d] The enantiomeric ratio was determined by CSP-SFC analysis (see Supporting Information). [e] The absolute configuration of **4a** was assigned by X-ray crystallographic analysis (see Supporting Information); all other compounds are assigned by analogy. [f] 55% of unreacted **2b** was recovered.

Table 4. Intermolecular Sulfenylation of Simple Alkenes



entry	R^1	R^2	NuH	temp, °C	product	yield,[a] %	a/b ratio[b]	er[c]
1	*n*-Pr	*n*-Pr	MeOH	−20	**8**	93	—	92:8
2	H	*n*-Hex	MeOH	23	**9**	77	10:1	82:18
3	*i*-Pr	*n*-Pr	MeOH	−20	**10**	58	4:1	84:16 (**a**) 84:16 (**b**)
4	*n*-Pr	*n*-Pr	AcOH	−20	**11**	77	—	91:9

[a] Yield of combined isomers. [b] Isomer ratio determined by ^{1}H NMR spectroscopy on samples prior to chromatographic separation. [c] Enantiomeric ratio of major isomer determined by CSP-SFC analysis (see Supporting Information).

MeOH afforded phenylthio methyl ether **8** in 93% yield and 92:8 er (Table 4, entry 1). Whereas 1-octene was unreactive at −20 °C, at room temperature the reaction was complete within 48 h, producing **9** in 77% yield and 82:18 er (entry 2). In the reaction of (*E*)-2-methyl-3-heptene, a 4:1 mixture of constitutional isomers **10a** and **10b** was obtained with 58% overall yield. Acetic acid was an effective nucleophile for the intermolecular thiofunctionalization as well (entry 4).

Preliminary mechanistic experiments were performed to determine whether the composition of the constitutionally isomeric products (**4** vs **5**) was established under kinetic control. A wide spectrum of behavior was noted at rt, ranging from no isomerization (**5j**) to slow isomerization (**5h**), to rapid isomerization (**5f**). However, **5h** did not isomerize at −10 °C, and **5f** slowly isomerized at −20 °C. Thus, the ratios of constitutional isomers listed in Table 3 may not represent products of kinetic control.[25] Nonetheless, the enantiomeric composition of the products in the isomerization experiments was maintained.

A catalytic cycle for the thiofunctionalization is proposed in Figure 1. Sulfenylation of the Lewis base **3e** by **1** mediated by MsOH generates the active catalytic species **12**. Evidence for this species is provided by ^{31}P NMR spectroscopy, in which the diagnostic signal for **3e** disappears (91.6 ppm) and a new signal at 60.4 ppm is observed. This value is in good agreement with related $[(R_2N)_3PX\text{-}YAr]^+$ compounds that have been prepared.[4c,26] Transfer of the sulfenium ion from **12** to an alkene forms intermediate thiiranium ion **13**, which, under control of the catalyst architecture, represents the enantiodetermining step.[4c] The enantioenriched thiiranium ion then undergoes intra- or intermolecular nucleophilic capture to deliver the corresponding enantioenriched thioether.

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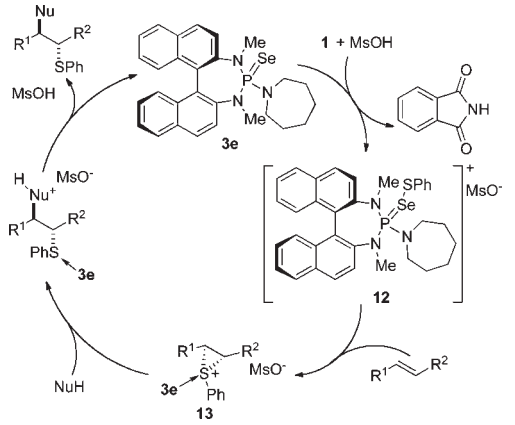

Figure 1. Proposed catalytic cycle for asymmetric sulfenofunctionalization.

In conclusion, the first catalytic, asymmetric sulfenylation of simple alkenes has been achieved using a chiral selenophosphoramide catalyst. Both inter- and intramolecular thiofunctionalizations are possible for a variety of olefin types. Efforts are underway to expand the substrate scope, improve the selectivity of the reaction, and elucidate the origins of enantioselectivity.

■ ASSOCIATED CONTENT

Supporting Information. Full experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) (a) No background reaction was observed between these two components at room temperature. (b) No reaction was observed in the absence of TFA at room temperature.

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(19) Other modifications of the BINAM structure, including substitution at the 3,3′ positions and saturation of the rings, did not increase enantioselectivity.

(20) *N*-Thiophenylbenzotriazole and *N*-thiophenylsaccharin gave 78:22 and 79:21 er, respectively, with 0.2 equiv of catalyst **3c** at 23 °C compared to 79:21 for **1**.

(21) Reactions proceeded to full conversion unless otherwise noted. Reactions that were not complete within 48 h at −20 °C were instead executed at −10 °C.

(22) For transition-state calculations and cyclization rates of the analogous seleniranium ions, see: Gruttadauria, M.; Lo Meo, P.; Noto, R. *Tetrahedron* **2001**, *57*, 1819–1826.

(23) However, as discussed below, the ratios may not represent reactions under kinetic control.

(24) With *cis*-styrenes, extremely long reaction times (20% conv at 4 d) were observed even at room temperature.

(25) For a recent demonstration of the Brønsted acid dependence of constitutional site selectivity, see: Wang, H.; Huang, D.; Cheng, D.; Li, L.; Shi, Y. *Org. Lett.* **2011**, *13*, 1650–1653. See also: (b) Fox, D. J.; House, D.; Warren, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2462–2482.

(26) A ^{31}P chemical shift of a species containing a cationic $(R_3N)_3$P-Se-S-R subunit could not be found. The closest analogy is the cationic $(R_3N)_3$P-S-Se-Aryl subunit in ref 4c. See also: Godfrey, S. M.; Ollerenshaw, R. T. A.; Pritchard, R. G.; Richards, C. L. *J. Chem. Soc., Dalton Trans.* **2001**, 508–509.