

Lewis Base Catalyzed, Enantioselective, Intramolecular Sulfenoamination of Olefins

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S Supporting Information

ABSTRACT: A method for the enantioselective, intramolecular sulfenoamination of various olefins has been developed using a chiral BINAM-based selenophosphoramidate, Lewis base catalyst. Terminal and *trans* disubstituted alkenes afforded pyrrolidines, piperidines, and azepanes in high yields and high enantiomeric ratios via enantioselective formation and subsequent stereospecific capture of the thiiranium intermediate with the pendant tosyl-protected amine.

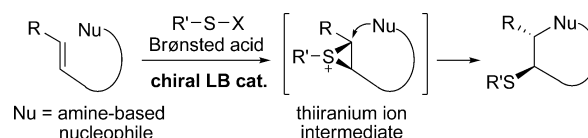
Nitrogen-containing, saturated heterocycles such as piperidines, pyrrolidines, and azepanes are commonly found in many biologically active natural products and pharmaceutical compounds.^{1,2} The chemical and biological properties of these molecules can be greatly influenced by the location and configuration of carbon and heteroatom substituents.^{2d} Accordingly, numerous strategies have been developed to generate stereodefined, saturated, nitrogen heterocycles with various types of substitution.³

As a part of an ongoing program in these laboratories on the concept of Lewis base activation of Lewis acids,⁴ we have focused on the activation of group 16 electrophiles with chiral Lewis bases.⁵ Recent reports have described the catalytic, enantioselective sulfenoetherification⁶ and carbosulfenylation⁷ of olefins (Scheme 1). These reactions proceed via the enantioselective generation of thiiranium ions⁸ that are constitutionally and configurationally stable at low temperatures which allows them to be captured by nucleophiles without racemization.⁹

The research reported herein expands upon the previous sulfenofunctionalization reactions to develop a catalytic method

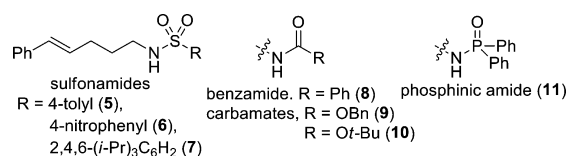
for the enantioselective, intramolecular sulfenoamination of olefins.¹⁰ Using an achiral sulfonylating reagent in concert with a chiral Lewis base catalyst, an intermediate thiiranium ion is generated which is subsequently captured with a pendant amine-based nucleophile (Scheme 2).

Scheme 2



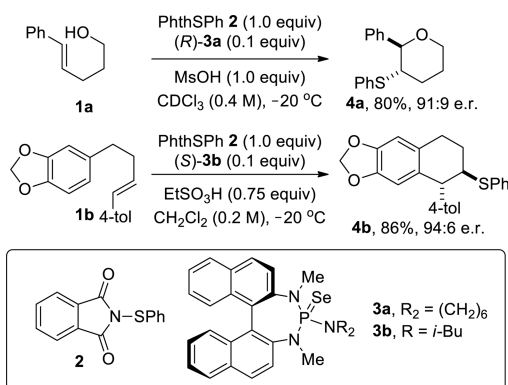
In the studies of sulfenoetherification and carbosulfenylation reactions, it was shown that a Brønsted acid coactivator was required. As a result, for the sulfenoamination reactions, the amine-based nucleophile needed to be not only sufficiently nucleophilic to form the C–N bond but also sufficiently non-basic to avoid protonation under the acidic conditions. To satisfy those criteria, a series of amines were selected as candidates for the nucleophile: sulfonamides, benzamides, carbamates, and phosphinic amides (Chart 1).

Chart 1



To evaluate the reactivity of the nucleophiles, each substrate was subjected to the reaction conditions developed for the sulfenofunctionalization reactions (Table 1).^{6,7} Preliminary evaluation of the protected amine substrates 5–11 with sulfonylating agent 2 (phenylthiophthalimide, PhthSPh) in the presence of an achiral Lewis base catalyst (tetrahydrothiophene, THT) and a Brønsted acid (MsOH) at room temperature showed that sulfonamides 5–7 rapidly formed piperidines in good yields (entries 1, 3, and 5). Although both tosylamide 5 and nosylamide 6 displayed excellent reactivity in the presence of THT, tosylamide 5 possessed a lower background rate when the Lewis base was omitted (entries 2 and 4). Cyclizations of benzamide 8 (entry 7) and benzyl carbamate 9 (entry 8) were slow under the reaction conditions such that 48 h were required

Scheme 1



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to reach high conversions. Unsurprisingly, *tert*-butylcarbamate **10** (entry 9) and diphenylphosphinic amide **11** (entry 10) decomposed under the acidic reaction conditions.

Table 1. Survey of Amine Protecting Groups

entry	substrate (R)	Lewis base	time ^a	yield, % ^d
1	5 (Ts)	THT	5 min ^b	93
2	5 (Ts)	none	48 h ^c	4 ^f
3	6 (Ns)	THT	5 min ^b	95
4	6 (Ns)	none	48 h ^c	11 ^f
5	7 (Tris)	THT	5 min ^b	84
6	7 (Tris)	none	48 h ^c	2 ^f
7	8 (Bz)	THT	48 h ^b	86
8	9 (Cbz)	THT	48 h ^b	81
9	10 (Boc)	THT	— ^e	— ^e
10	11 (DPP)	THT	— ^e	— ^e

^aConversion monitored by TLC. ^bThe time full conversion observed. ^cThe time reaction was quenched. ^dIsolated yields. ^eDecomposed under the reaction conditions. ^fDetermined by integration of the ¹H NMR spectra of crude reaction mixtures.

Identification of the optimal catalyst involved a survey of various BINAM-derived selenophosphoramides bearing different dialkylamine substituents (Table 2). Azepane-substituted selenophosphoramide (*R*)-**3a**, which was employed in the analogous sulfenoetherification reaction,⁶ afforded **12** with an 11:89 e.r. (entry 1). The reaction with diisobutylamine-substituted selenophosphoramide (*S*)-**3b**, which was employed in the carbosulfonylation reaction, afforded the same yield and selectivity as (*R*)-**3a** (entry 2). Selenophosphoramides with less bulky substituents, (*S*)-**3c**, resulted in a slightly eroded enantiomeric ratio (entry 3). Azocane-substituted catalyst (*S*)-**3d** and diisopentylamine-substituted selenophosphoramide (*S*)-**3e** afforded the product in lower yields but improved the enantioselectivities of 91:9 and 93:7 e.r., respectively (entries 4 and 5). Interestingly, diisopropylamine-substituted selenophosphoramide (*S*)-**3f**, bearing the most sterically encumbered substituent adjacent to the nitrogen, afforded the best enantiomeric ratio of 95:5 e.r. but at a lower rate. The absolute

Table 2. Survey of Chiral Lewis Base Catalysts

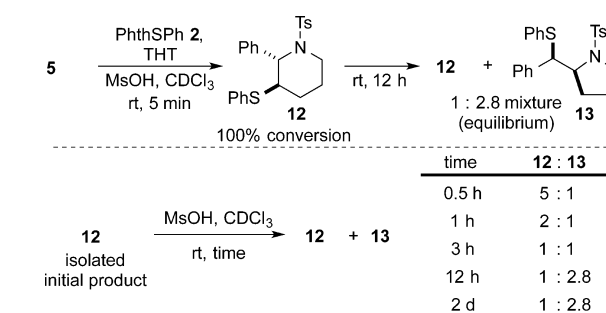
entry	catalyst, R ₂	yield, % ^a	e.r. ^b
1	(<i>R</i>)- 3a , (CH ₂) ₆	90	11.5:88.5
2	(<i>S</i>)- 3b , (<i>i</i> -Bu) ₂	88	89.4:10.6
3	(<i>S</i>)- 3c , <i>n</i> -Bu, Et	79	88.1:11.9
4	(<i>S</i>)- 3d , (CH ₂) ₇	67	91.4:8.6
5	(<i>S</i>)- 3e , (<i>i</i> -amyl) ₂	82	92.8:7.2
6	(<i>S</i>)- 3f , (<i>i</i> -Pr) ₂	75	94.6:5.4

^aIsolated yields. ^bThe enantiomeric ratio was determined by CSP-SFC analysis.

configuration of **12** was determined by reductive removal of the sulfide group and comparison of the optical rotation of the resulting piperidine to literature values.¹¹

During the reaction optimization studies, isomerization of piperidine **12** to a pyrrolidine was observed. The combination of THT and 1.0 equiv of MsOH afforded piperidine **12** quantitatively in 5 min at rt (Scheme 3). However, piperidine **12** isomerized into a 1:2.8 mixture of **12** and pyrrolidine **13** by allowing the mixture to stir for 12 h. Independent treatment of either **12** or **13** with 1.0 equiv of MsOH at rt resulted in the establishment of an equilibrium mixture of **12**/**13** (1:2.8) after 12 h.¹² The isomerization of **12** to **13** alleviates the steric interactions between the *N*-tosyl group and the 2-phenyl group in piperidine **12**.¹³

Scheme 3



In view of the MsOH-induced isomerization of the product, additional studies were performed to evaluate the optimal acid loading for the sulfenoamination reaction (Table 3). With 1.0 equiv of MsOH at 0 °C, isomerization of **12** to **13** was observed. However, using less than 1.0 equiv of MsOH greatly reduced the amount of product isomerization. Whereas reactions with loadings of 0.5 and 0.75 equiv of MsOH afforded comparable results (entries 2 and 3), 0.5 equiv led to slightly higher enantioselectivity. The reaction with 0.25 equiv of MsOH displayed a slightly slower reaction rate, reaching full conversion at 24 h (entry 4). Although the reaction with 0.10 equiv gave high e.r., the reaction rate was unacceptably slow (entry 5).

Table 3. Survey of Acid Loadings

entry	MsOH, equiv	conv, % ^{a,b}	endo:exo ^b	e.r. ^c
1	1.00	100	85.7:14.3	91.6:8.4
2	0.75	100	98.9:1.1	92.9:7.1
3	0.50	100	99.2:0.8	93.5:6.5
4	0.25	98	99.4:0.6	93.6:6.4
5	0.10	69	99.5:0.5	93.9:6.1

^aThe conversion was monitored by ¹H NMR spectroscopy (6, 12, and 24 h). ^bDetermined by ¹H NMR spectroscopy of the crude mixture. ^cThe enantiomeric ratio was determined by CSP-SFC analysis.

The scope of the reaction with various olefins was investigated next (Table 4). The influence of the electronic properties of the alkene on reaction rate and stereoselectivity was examined first. Substrate **14**, with a 4-anisyl-substituted double bond possessing greater electron density than **5**, showed comparable reactivity with a slight drop in enantioselectivity (entry 2). In contrast,

Table 4. Scope of the Enantioselective Intramolecular Sulfenoamination Reaction

entry	substrate	product	time	yield, % ^a	endo : exo ^b	e.r. ^c
1	Ph-CH=CH-CH ₂ -CH ₂ -CH ₂ -NHTs (<i>E</i>)-5	12 R = Ph	24 h	93	>99 : 1	93.6 : 6.4
2	MeO-C ₆ H ₄ -CH=CH-CH ₂ -CH ₂ -CH ₂ -NHTs 14	15 R = 4-MeOC ₆ H ₄	24 h	91	46 : 1	91.8 : 8.2
3	CF ₃ -C ₆ H ₄ -CH=CH-CH ₂ -CH ₂ -CH ₂ -NHTs 16	17 R = 4-CF ₃ C ₆ H ₄	48 h	39 ^d	27 : 1	91.9 : 8.1
4	Ph-CH=CH-CH ₂ -CH ₂ -CH ₂ -CH ₂ -NHTs 18	19 R = PhCH ₂ CH ₂	24 h	91	1 : 3	95.9 : 4.1 (<i>exo</i>) 95.8 : 4.2 (<i>endo</i>)
5	Me-CH=CH-CH ₂ -CH ₂ -CH ₂ -NHTs 20	21 R = <i>i</i> -Pr	48h	89	1 : 15	96.8 : 3.2
6	Ph-CH=CH-C(Me) ₂ -CH ₂ -CH ₂ -NHTs 22	23	24 h	91	80 : 1	96.3 : 3.7
7	Ph-CH=CH-C(Me) ₂ -CH ₂ -NHTs 24	25	24 h	93	20 : 1	91.8 : 8.2
8	Ph-CH=CH-CH ₂ -CH ₂ -NHTs (<i>Z</i>)-5	26	48 h	68 ^d	12 : 1	62.8 : 37.2
9	CH ₂ =CH-CH ₂ -CH ₂ -NHTs 27	28	36 h	93	1 : >99	92.5 : 7.5
10	Ph-CH=CH-CH ₂ -C(=O)-NHTs 29	30	48 h	85	20 : 1	83.7 : 16.3
11	Ph-CH=CH-CH ₂ -NHTs 31	32	36 h	86	>99 : 1	91.3 : 8.7
12	Ph-CH=CH-CH ₂ -CH ₂ -CH ₂ -NHTs 33	34	36 h	84	>99 : 1	92.7 : 7.3
13	Me-CH=CH-CH ₂ -CH ₂ -CH ₂ -NHTs 35	36 R = <i>i</i> -Pr	48 h	87	1 : >99	95.4 : 4.6
14	Ph-CH=CH-CH ₂ -CH ₂ -CH ₂ -NHTs 37	38 R = PhCH ₂ CH ₂	48 h	91	1 : >99	97.4 : 2.6

^aIsolated yields of analytically pure material. ^bConstitutional selectivity determined by ¹H NMR spectroscopy of the crude mixture. ^cThe enantiomeric ratio of the major constitutional isomer was determined by CSP-SFC analysis, and the absolute configurations of the products were assigned by analogy to **12**. ^dIncomplete conversion on quenching at 48 h.

substrate **16**, bearing a strongly electron-withdrawing 4-trifluoromethylphenyl substituent, afforded only a 39% yield after 48 h (54% conv., entry 3). Interestingly, the observed e.r. (91.9:8.1) for **17** was comparable to that for **15**. It is important to note that substrates **5**, **14**, and **16** (entries 1, 2, and 3) afforded piperidines, as established by ¹H NMR spectroscopy. Substrate **18** bearing a non-conjugated olefin afforded a mixture of *endo* and *exo* products in a 1:3 ratio in good yields and excellent e.r.'s (entry 4). The reduced *endo* to *exo* ratio is likely due to the less-biased electron density of the alkene. In contrast, isopropyl-

substituted olefin **20** showed a much greater *exo* selectivity (along with a high yield and e.r.), thus implicating an important role for the steric bulk of the substituent (entry 5). Interestingly, the reaction of **22**, containing 2,2-dimethyl substitution on the tether, afforded a good yield and retained the excellent enantioselectivity (entry 6). However, substrate **24**, with 1,1-dimethyl substitution in the tether, resulted in a lower enantioselectivity (entry 7). Other olefins with different substitution patterns were also investigated. Olefin (*Z*)-**5** reacted slowly (75% conv. in 48 h) with poor enantioselectivity

(62.8:37.2) (entry 8). The reaction of terminal olefin **27** gave a good yield and high enantioselectivity of 92.5:7.5 with exclusive *exo* cyclization (entry 9). Carboxamide **29** afforded the product in good yield with constitutional selectivity, but showed diminished e.r. (entry 10). Presumably, protonation of the carbonyl group attenuates the nucleophilicity of the nitrogen and prevents rapid capture of the intermediate thiiranium ion, thus allowing racemization.

The influence of tether length on cyclization was also investigated. Two-carbon-tethered substrate **31** cyclized to pyrrolidine **32** in 86% yield and 91.3:8.7 e.r. with complete *endo* selectivity (entry 11). Interestingly, four-carbon-tethered substrate **33** showed the impact of conjugation on biasing the two olefinic carbons by affording exclusively azepane **34** (entry 12). The structure and the absolute configuration of **34** were established by X-ray crystallography.¹⁴ In contrast, the non-conjugated substrates **35** and **37** afforded only piperidine products via *exo* cyclization, indicating the preference to form the six-membered rings for dialkyl-substituted olefins. Additionally, reactions with both **35** and **37** gave the products in good yields and excellent enantioselectivities.

The proposed catalytic cycle for the sulfenoamination reaction is shown in Figure 1.¹⁵ Sulfenylating agent **2** is activated with MsOH and then transfers the sulfenyl moiety to the Lewis base (S)-**3f**, forming the chiral sulfenylating complex **i**.^{7c} Subsequent transfer of the sulfenium ion from **i** to the alkene furnishes the enantioenriched chiral thiiranium ion intermediate **ii**. Finally, capture of the thiiranium ion with the pendant tosylamide and subsequent deprotonation affords the enantioenriched product.

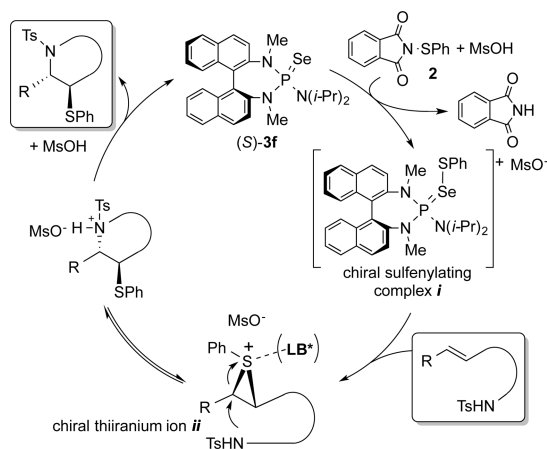


Figure 1. Proposed catalytic cycle for the sulfenoamination.

In conclusion, a Lewis base catalyzed, enantioselective, intramolecular sulfenoamination of unactivated olefins has been developed. The reaction produces saturated *N*-heterocyclic rings with high enantioselectivities for a wide range of *trans* olefins. Extensions to intermolecular sulfenoamination reactions are under investigation.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures, characterization data, and X-ray coordinates for **34**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (14) The crystallographic coordinates of **34** have been deposited with the CCDC; deposition no. 981943. These data can be obtained free of charge via from the Cambridge Crystallographic Data Centre, at www.ccdc.cam.ac.uk/conts/retrieving.html or deposit@ccdc.cam.ac.uk.
- (15) The kinetic, spectroscopic, structural, and computational characterization of this catalytic cycle has been completed and submitted for publication.