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Catalytic, Enantioselective Sulfenylation of Ketone-Derived Enoxysilanes

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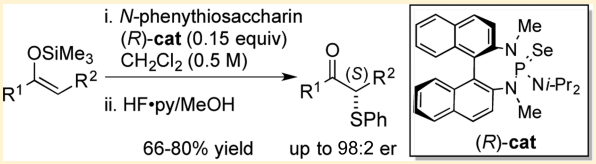
Supporting Information

ABSTRACT: A catalytic, enantioselective, Lewis base-catalyzed α-sulfenylation of silyl enol ethers has been developed. To avoid acidic hydrolysis of the silyl enol ether substrates, a sulfenylating agent that did not require additional Brønsted acid activation, namely *N*-phenylthiosaccharin, was developed. Three classes of Lewis bases—tertiary amines, sulfides, and selenophosphoramides—were identified as active catalysts for the α-sulfenylation reaction. Among a wide variety of chiral Lewis bases in all three classes, only chiral selenophosphoramides afforded α-phenylthio ketones in generally high yield and with good enantioselectivity. The selectivity of the reaction does not depend on the size of the silyl group but is highly sensitive to the double bond geometry and the bulk of the substituents on the double bond. The most selective substrates are those containing a geminal bulky substituent on the enoxysilane. Computational analysis revealed that the enantioselectivity arises from an intriguing interplay among sterically guided approach, distortion energy, and orbital interactions.



INTRODUCTION

Chiral sulfides are important for the synthesis of a wide range of biologically relevant molecules and are also versatile synthetic intermediates for a variety of organic transformations.[1] In recent years, a number of methods have been developed for the direct formation of stereogenic carbon centers bearing sulfur. The most successful is the α-sulfenylation of carbonyl coumpounds[2] such as ketones,[3a] lactams,[4] esters,[5] and amides.[3b] All of these methods involve the formation of a metalloenolate or enamine precursor[6] followed by reaction with sulfur-based electrophiles (e.g., sulfenyl chlorides, sulfenylamines, thiosulfonates, or disulfides) to produce α-thio-functionalized carbonyl compounds.

Already in 1979, Sato reported the enantioselective sulfenylation of 4-alkylcyclohexanones using chiral sulfonamides as sulfenylating reagents.[7] Six years later, Paterson reported the use of chiral *O*-silylated imide enolates derived from acyl oxazolidinones in the sulfenylation of masked ketones using phenylsulfenyl chloride.[8] Unfortunately, both methods afforded low to modest levels of enantioselection (45:55−17:83 er). Improved enantioselectivities for thiofunctionalization of ketones were reported some years later by Mukaiyama, who employed *in situ*-generated tin(II) enolates that reacted in the presence of a chiral diamine ligand to afford 25:75−8:92 er.[9]

Since these early reports, a wide variety of methods have been introduced, using a range of chiral auxiliaries for the synthesis of α-thiofunctionalized compounds (e.g., phenylethylamine,[10] imidazolidinones,[11] oxazolidines/oxazolines,[12] pyrrolidines,[13] and pyrazoles[14]). However, until recently, only a few examples that employ chiral sulfenylating reagents have been reported.[7,15]

A novel approach for the synthesis of α-thiofunctionalized β-dicarbonyl compounds was described by Togni and co-workers, who reported the first catalytic, asymmetric sulfenylation of β-keto esters using a Ti[TADDOL(ato)] complex that afforded products with good yields and high enantioselectivities (up to 94:6 er).[16]

Most recently, Feng reported a catalytic, enantioselective sulfenylation of unprotected 3-substituted oxindoles via cooperative catalysis of a chiral bispiperidine-*N*,*N*′-dioxide−$Sc(OTf)_3$ complex in the presence of a Brønsted base.[17] Using the readily available *N*-phenylthiophthalimide as the sulfur source, a wide range of enantiomerically enriched 3-phenylthio-oxindoles are obtained in excellent yields (82−98%) and excellent enantioselectivities (>99:1 er) under mild reaction conditions.

The asymmetric synthesis of 3-sulfenylated *N*-Boc-protected oxindoles has been demonstrated by Enders and co-workers, who reported the use of a hydrogen-bonding squaramide-based organocatalyst in combination with *N*-(sulfanyl)succinimides to be a highly efficient method for the preparation of a wide range of enantiomerically enriched 3-phenylthiooxindoles.[18] Using a similar and equally enantioselective approach, *N*-Bn-protected oxindoles could also be thiofunctionalized with a high level of enantioselectivity using $(DHQD)_2PHAL$ in the presence of a wide range of *N*-(sulfanyl)succinimides, as reported by Jiang,[19a] who also applied a closely related catalytic system to the enantioselective sulfenylation of azlactones.[19b]

Among the most recent advances is the enantioselective α-sulfenylation of aldehydes and ketones through the intermediacy of *in situ*-generated enamines. Wang and co-workers employed a chiral pyrrolidine trifluoromethanesulfonamide using *N*-phenylthiophthalimide as the sulfur source to produce

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racemic α-phenylthio ketones and α-phenylthio aldehydes.[20] Shortly thereafter, Jørgensen reported the first example of enantioselective α-sulfenylation of aldehydes using diphenyl-L-prolinol TMS ether as the catalyst together with benzylsulfenyl-1,2,4-triazole as the sulfenylating agent.[21] The corresponding sulfenylated products are obtained in high yields and excellent enantioselectivities (up to >99:1 er). Finally, Zhu and co-workers also demonstrated the direct sulfenylation of β-keto esters,[22a] β-keto phosphonates,[22b] and α-nitroesters[22c] using diaryl-L-prolinols.

Chiral Brønsted bases such as *cinchona* alkaloid derivatives can also catalyze the direct α-sulfenylation of other substrates such as lactones, lactams, and β-dicarbonyl compounds to afford enantiomerically enriched α-sulfenylated compounds in moderate to high yields (up to 95%) and enantioselectivities (up to 96:4 er).[23]

The highly enantioselective sulfenylation of β-keto esters via base-free asymmetric phase-transfer catalysis was reported by Maruoka and co-workers in 2013.[24] Using a novel, bifunctional quaternary phosphonium salt, in combination with an *N*-thioaryl- or *N*-thiobenzylphthalimide, the α-sulfenylated products can be isolated in excellent yields and excellent enantioselectivities (96:4−97.5:2.5 er).

α-Thiofunctionalized carbonyl compounds can also be prepared from silyl enol ethers of ketones as first reported by Murai, albeit to form only racemic products.[25] A catalytic version that employs TMSOTf was introduced by Saigo,[26] and the same Lewis acid was also employed by Kita[27] to promote the facile and efficient alkyl- and aryl-sulfenylation of ketones and esters in high yields but again in racemic form.

Finally, in a method that constructs the carbon−sulfur bond in an electronically reversed fashion compared to all those methods highlighted above, Coltart and co-workers reported the sulfenylation of nitrosoalkenes using a nucleophilic sulfur source.[28] In their report, *in situ*-derived cyclic and acyclic nitrosoalkenes, formed from their corresponding α-chloro oximes and base, are combined with a range of aromatic and heteroaromatic thiols in the presence of a hydrogen-bonding thiourea-based catalyst to give α-sulfenyl oximes, which could be oxidized to the corresponding α-sulfenyl ketones in high yields using 2-iodoxybenzoic acid (83:17−94:6 er).

Thus, despite considerable effort, no examples of catalytic, enantioselective α-sulfenylation of unactivated ketones are extant.

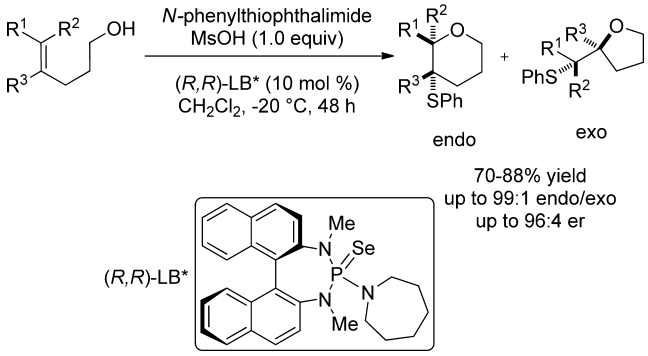
BACKGROUND

The mechanism of electrophilic addition and, in particular, the addition of arylsulfenyl chlorides to olefins, is well documented. It was first reported in the literature in 1937,[29] which was also the first time an "onium ion" was postulated. The classical mechanistic description of this process suggests a rate-determining formation of an episulfonium (thiiranium) ion that undergoes a nucleophilic, invertive opening by chloride ion to give an overall *anti* addition.[30] Other mechanisms have also been proposed, such as the formation of a sulfurane, but valid support for this hypothesis is lacking, especially when compared with all the structural and reactivity studies on thiiranium ions.[31]

Many examples of sulfenofunctionalizations via thiiranium ions have been reported. These processes can be divided into two main types: (1) sulfenocyclizations and (2) sulfeno-functionalizations of isolated alkenes. A third area, represented with few examples, is the sulfenylation of more reactive alkenes such as silyl enol ethers and silyl ketene acetals.

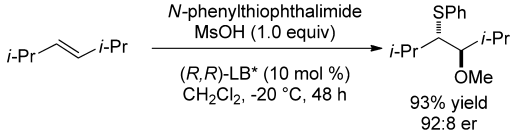
As part of our continuing program on Lewis base activation of Lewis acids, we have reported the catalytic, enantioselective thiofunctionalization of unactivated alkenes using oxygen, carbon, and nitrogen nucleophiles.[32] Thus, the combination of *N*-phenylthiophthalimide, a chiral Lewis base catalyst, and a Brønsted acid (MsOH) produces enantioenriched thiiranium ions that could be captured intramolecularly by either alcohols or electron-rich aromatic compounds (Scheme 1).

Scheme 1



Using this procedure, it is also possible promote the *intermolecular* capture of thiiranium ions by nucleophiles. Treatment of an olefin with *N*-phenylthiophthalimide at room temperature in the presence of 1.0 equiv of MeOH and the same chiral Lewis base/Brønsted acid combination produces the phenylthio methyl ether in 93% yield and 92:8 er (Scheme 2).

Scheme 2



These promising results stimulated the investigation of the direct, catalytic thiofunctionalization of enol derivatives, e.g., silyl enol ethers that formally can be considered as activated olefins.

RESEARCH OBJECTIVES

Consideration of the proposed catalytic cycle for the Lewis base-catalyzed α-sulfenylation of silyl enol ethers reveals a number of concerns that have not been addressed in the previous studies (Scheme 3). Initial protonation of the sulfenylating agent (Het-SPh) by a stoichiometric amount of Brønsted acid, in the presence of a catalytic amount of Lewis base, generates the activated catalytic complex **I**. Subsequent reaction of sulfenyl cation **I** with a silyl enol ether forms oxocarbenium ion **II**. It is important to highlight that this might occur directly or via an intermediate thiiranium ion **III**, the latter scenario more closely resembling our previous work on the catalytic asymmetric sulfenylation of unactivated alkenes (outlined above). Finally, the α-sulfenylated ketone would be isolated upon work-up.

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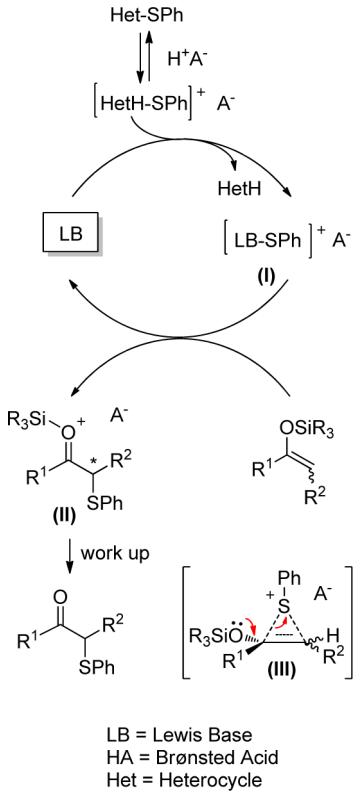
Scheme 3

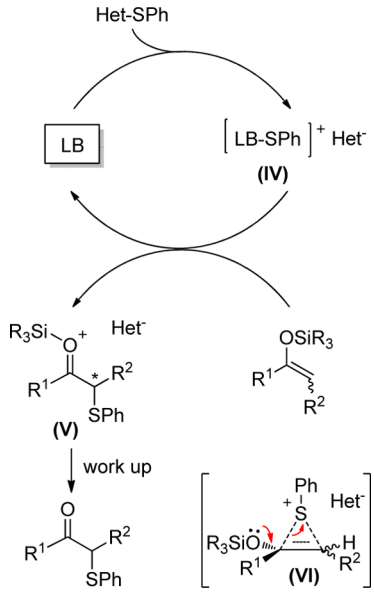


LB = Lewis Base
HA = Brønsted Acid
Het = Heterocycle

In the presence of a chiral Lewis base, the formation of oxocarbenium ion **II** would be the enantiodetermining step in the scenario not involving an intermediate thiiranium ion **III**. However, if **III** is generated, then its formation would be assumed enantiodetermining in the presence of a chiral Lewis base. Previous studies in these laboratories demonstrated that simple thiiranium ions are configurationally stable at −20 °C.[31d] The configurational stability of **III** is unknown, but its opening to form **II** is expected to be rapid and irreversible (perhaps driven by desilylation with the conjugate base of the Brønsted acid). Moreover, the greater nucleophilicity of the silyl enol ether compared to isolated alkenes raises the specter of a racemic background reaction. Finally, the requirement for a strong Brønsted acid (MsOH) is incompatible with the silyl enol ether due to rapid protonolysis.

Thus, the successful development of this transformation will require reevaluation of critical reaction parameters and scope: (1) the pK_a of the Brønsted acid and its effect on the activity of the electrophile, (2) the reactivity of the sulfenylating reagent, and (3) the ability of the Lewis base to generate adduct **I**, along with (4) the usual reaction parameters (time, temperature, solvent), (5) the identity of suitable Lewis bases that can catalyze the process and optimize their characteristics, e.g., the basicity, steric bulk, and type of chiral scaffold, and (6) the scope of the reaction with substrates having different characteristics, e.g., silyl groups, geometries (*E* vs *Z* double bond), steric factors, and nucleophilicity. The enhanced reactivity of silyl enol ethers raises the possibility that a sufficiently electrophilic sulfenylating agent could be employed that does not require activation with a Brønsted acid. This possibility obviates the incompatibility issue but increases the undesired intervention of a racemic background reaction.[33] The catalytic cycle for this variant is shown in Scheme 4.

Scheme 4

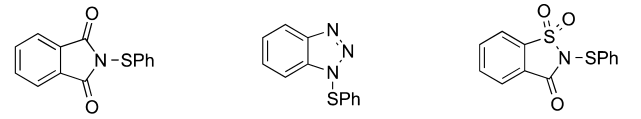


In this scenario, the role of the heteroaromatic nucleofuge, generated after the transfer of the sulfenium ion, requires more consideration. In the case of thiiranium ion formation (**VI**), the resulting ion pair could influence the lifetime of the ion before the rearrangement to **V**. However, its presence could also promote the desilylation of **V**, accelerating the formation of the final product and potentially reducing the lifetime of the thiiranium ion, if formed.

The *Z*-trimethylsilyl enol ether of propiophenone ((*Z*)-**1a**) was selected for orienting experiments. Using conditions described by Ireland,[34] the *Z* isomer can be generated selectively.[35]

RESULTS

1. Investigation of Sulfenylating Agents. On the basis of previous studies,[36] three different electrophiles were examined (Figure 1). *N*-Phenylthiophthalimide (**2**) is the least reactive toward isolated alkenes and requires the use of a strong Brønsted acid, e.g., CH_3SO_3H (pK_a = −2.6 in water), to activate the leaving group and thus increase the phenylsulfenium ion donor character. This feature also dictates that only weakly Brønsted basic Lewis bases can be employed (to avoid protonation of the Lewis base catalyst). *N*-1-Phenylthiobenzotriazole (**3**) is more reactive than **2** and thus requires the use of a weaker Brønsted acid, e.g., trifluoroacetic acid (TFA, pK_a = 0.23 in water), to be activated. Thus, a broader range of Lewis bases can be employed. Finally, *N*-phenylthiosaccharin (**4**) is the most reactive of the three and requires an even weaker acid, trichloroacetic acid (pK_a = 0.71 in water), to be activated.



N-phenylthiophthalimide (**2**) | *N*-phenylthiobenzotriazole (**3**) | *N*-phenylthiosaccharin (**4**)

Figure 1. Sulfenylating agents.

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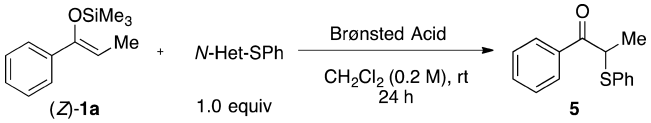
On the basis of these considerations, all three phenylthio transfer agents would be tested in the presence and in the absence of the corresponding Brønsted acid in the α-sulfenylation of (*Z*)-**1a**. This survey was conducted at room temperature using dichloromethane as solvent (0.2 M). The reaction was quenched with a pH 9 buffer solution in order to remove any acid present. The formation of 1-phenyl-2-(phenylthio)-propan-1-one (**5**) was monitored by gas chromatography (GC) with an internal standard after 2 and 24 h.

As shown in Table 1, when *N*-phenylthiophthalimide (**2**) was employed, no desired product was observed in the presence or absence of MsOH after 24 h. The absence of Brønsted acid allowed recovery of the silyl enol ether; however, the presence of MsOH resulted in complete hydrolysis to the corresponding ketone. Similarly, no reaction was observed in the case of *N*-1-phenylthiobenzotriazole (**3**) without an acid additive. In contrast, the addition of TFA generated the sulfenylated ketone **5** in 79.8% conversion (GC), accompanied by a small amount of hydrolyzed starting material. No further conversion was detected after 2 h.

Table 1. Survey of Sulfenylating Reagents



entry	*N*-Het-SPh	Brønsted acid[a]	conv,[b] % (ketone recovered) 2 h	24 h
1	**2**	–	0 (0)	0 (0)
2	**2**	CH_3SO_3H	0 (100)	0 (100)
3	**3**	–	0 (0)	0 (0)
4	**3**	TFA[c]	79.8 (13.8)	80.5 (15.0)
5	**4**	–	47.6 (12.3)	78.6 (21.3)
6	**4**	Cl_3CCO_2H[d]	17.0 (77.7)	17.2 (78.6)
7	**4**	Cl_3CCO_2H[c]	33.7 (62.8)	36.1 (63.2)

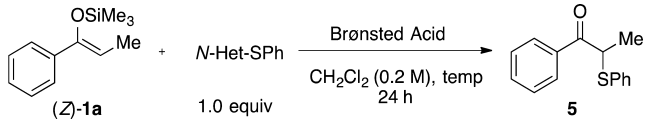
[a]1.0 equiv was used. [b]Monitored by GC with internal standard. [c]Brønsted acid added 10 min after the addition of the silyl enol ether. [d]Brønsted acid added 10 min before the addition of the silyl enol ether.

N-Phenylthiosaccharin (**4**) provided **5** in 47.6% conversion, even without an acid activator. The detrimental effect of acid is evident in the use of trichloroacetic acid, which causes extensive hydrolysis of (*Z*)-**1a**. As has been observed in previous entries, the starting material is consumed in 2 h. It should be noted that the order of addition of the acid is consequential to the amount of **5** produced: the addition of trichloroacetic acid to **4** gave a slightly higher conversion to **5** (33.7%) compared to that of the reversed sequence of addition (17.0%).

To minimize the formation of sulfenylated ketone **5** in the absence of Lewis base catalysis, the α-sulfenylation of (*Z*)-**1a** was investigated at low temperature (Table 2). At −10 °C, *N*-1-phenylthiobenzotriazole (**3**), together with a stoichiometric amount of TFA, gave the same conversion to **5** as was obtained at room temperature. Lowering the temperature to −78 °C gave only a small reduction in conversion (Table 2, entries 1 and 2).

Interestingly, in the absence of acid, *N*-phenylthiosaccharin (**4**) showed the same chemical efficiency at room temperature

Table 2. Investigation of Background Rate at Low Temperature



entry	*N*-Het-SPh	temp, °C	Brønsted acid[a]	conv,[b] (%) (ketone recovered) 2 h	24 h
1	**3**	−10	CF_3CO_2H	89.9 (9.2)	88.4 (11.6)
2	**3**	−78	CF_3CO_2H	61.5 (6.4)	73.7 (8.4)
3	**4**	25	–	47.6 (12.3)	78.6 (21.3)
4	**4**	−10	–	31.9 (6.1)	67.3 (8.7)
5	**4**	−10	Cl_3CCO_2H	50.1 (27.2)	49.8 (28.6)
6	**4**	−20/−25	–	3.1 (3.6)	19.6 (4.5)
7	**4**	−50	–	3.9 (2.8)	12.7 (2.9)
8	**4**	−78	–	5.4 (7.5)	8.8 (7.2)
9	**4**	−78	Cl_3CCO_2H	41.3 (52.9)	44.8 (51.1)

[a]1.0 equiv was used and added 10 min after the addition of the silyl enol ether. [b]Monitored by GC with internal standard.

and at −10 °C. However, when the reaction was conducted in the presence of trichloroacetic acid at −10 °C, the conversion was increased to 50%, due to the inhibition of the hydrolysis process (entry 5, cf. Table 1, entry 6). When the temperature was decreased to −25 °C, the α-sulfenylation of (*Z*)-**1a** was slow in the absence of acid (19.6% conversion after 24 h).

Finally, the reaction was investigated at −78 °C. In the presence of trichloroacetic acid, ketone **5** was obtained with a moderate conversion, but, interestingly, in the absence of acid, both the α-sulfenylation process and the hydrolysis process were significantly slowed (only 8.8% conversion after 24 h). On the basis of these results, it was now possible to almost completely suppress the background reaction at −78 °C, using **4** as electrophile, without a Brønsted acid. The stage was now set to evaluate the ability of Lewis bases to turn on the catalytic (and stereoselective) pathway.

2. Investigation of Achiral Lewis Bases. The survey of achiral Lewis bases was performed on a 0.2 mmol scale using dichloromethane as solvent in the presence of 10 mol % of a Lewis base. Product formation was monitored by GC analysis after 24 h at −78 °C. Biphenyl was used as an internal standard. An extensive survey of a wide range of more than 50 Lewis bases was carried out, and these results are presented in their entirety in the Supporting Information. A qualitative schematic of these data is presented in Figure 2 to allow for a general comparison of the efficiency of different Lewis bases to catalyze this process.

From this study it was clear that the most efficient Lewis bases were those derived from tertiary amines, sulfides, and selenophosphoramides. In particular, in the case of tertiary amine-based nucleophiles, the steric environment around the nitrogen atom was demonstrated to be important, with *N*-*i*-Pr-piperidine significantly less effective than *N*-Me-piperidine.

During the course of these studies, a highly effective quench procedure was developed to ensure rapid and complete hydrolysis of any remaining trialkylsilyl enol ether before warming the reaction, prior to work-up. An efficient quench was required not only to obtain accurate information on

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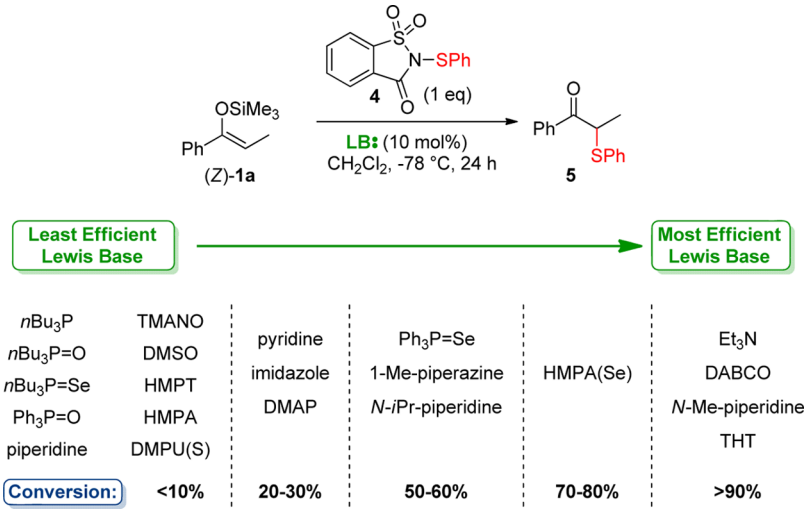


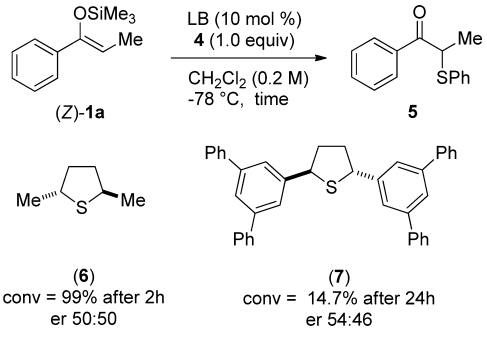
Figure 2. Survey of Lewis bases for the sulfenylation of (*Z*)-**1a**.

reaction conversion but also, upon the development of an enantioselective protocol, to prevent a racemic background reaction which could occur upon warming and therefore lead to an overall reduction in the enantioselectivity observed. The optimized quench procedure involved the addition of a precooled (−78 °C) solution of HF·pyridine in methanol (derived from a solution of HF in pyridine, ca. 70%) into the reaction mixture at −78 °C. Using this procedure, the extent of the uncatalyzed, background reaction amounted to 2.4% conversion to **5** after 24 h at −78 °C.

4. Investigation of Chiral Lewis Bases. The selection of suitable chiral Lewis bases was guided by the results of the initial catalyst survey. Because tertiary amines, tetrahydrothiophene, and selenophosphoramides showed the best catalytic activity, the use of chiral Lewis bases derived from these three classes was chosen for initial investigation.

4.1. Sulfur-Containing Chiral Lewis Bases. Following previous experience,[36] chiral C_2-symmetric tetrahydrothiophenes **6** and **7** were tested first (Scheme 5). As anticipated, the use of (2*R*,5*R*)-2,5-dimethyltetrahydrothiophene (**6**) led to the formation of **5** with quantitative conversion after 2 h at −78 °C—unfortunately, however, in racemic form. It is presumed that the stereocenters are too far away from the catalytic site and that the methyl groups are too small for a preferential selection of one of the two enantiotopic faces of the silyl enol ether. The bulkier tetrahydrothiophene (**7**) was also investigated. However, this Lewis base promoted the α-sulfenylation of (*Z*)-**1a** to only 15% conversion after 24 h at −78 °C again with negligible control over the stereochemical outcome (er, 54:46). Raising the temperature to −20 °C afforded the desired product with 80% conversion after 24 h but with similar enantiomeric ratio (57:43).

Scheme 5



4.2. Nitrogen-Containing Chiral Lewis Bases. A preliminary survey of readily available tertiary amines was carried out. Initially, (−)-sparteine and (+)-*N*-methylephedrine along with a variety of monomeric and dimeric dihydrocinchonine and cinchonidine derivatives were examined: $(DHQD)_2PHAL$, $(DHQ)_2PHAL$, and $(DHQ)_2AQN$, nicotine, (*R*,*R*)-1,2-bis(dimethylamino)cyclohexane, (*R*,*R*)-2,2′-bis(*N*-methyl)pyrrolidine, and (*S*,*S*)-2,5-dimethyl-*N*-benzylpyrrolidine. The most encouraging results were obtained from $(DHQ)_2PHAL$, which afforded an 84% conversion of (*Z*)-**1a** to **5** under standard conditions with a 61:39 er.

4.3. Selenophosphoramide Chiral Lewis Bases. The use of chiral selenophosphoramides as catalysts for stereoselective transformations was first reported from these laboratories for the asymmetric thiofunctionalization of unactivated alkenes.[32] Following the same synthetic route, a family of different selenophosphoramides was prepared for subsequent evaluation in the enantioselective α-sulfenylation of **1** (Scheme 6). (*S*)-BINAM (**9**) was prepared from 2-naphthylamine[37a] and was converted, in two steps, to the *N*-methylated BINAM (*S*)-**10**.[37b,38] Following a protocol developed in these laboratories,[37c] this precursor was transformed into a variety of selenophosphoramides that possessed various substituents on the external nitrogen.

The catalytic efficiency and selectivity of the different selenophosphoramides were investigated in the α-sulfenylation of (*Z*)-**1a** (Figure 3). Conversion was measured by GC analysis with an internal standard, and the enantiomeric ratios were determined after chromatographic purification by CSP-HPLC.

Gratifyingly, selenophosphoramides derived from BINAM bearing a cyclic amine, e.g., piperidine (**12a**), azepane (**12b**), and azocane (**12c**), were able to promote the reaction with good conversions and high levels of enantioselection (up to 13:87 er for **12c**). It is noteworthy that the reduced rate observed using these Lewis bases meant that 24 h was required. Interestingly, the use of **12d**, bearing a less basic amine, was able to maintain the same level of stereoselection but with a decreased rate. This observation confirms that the use of more-basic, aliphatic amines is important for the chemical efficiency

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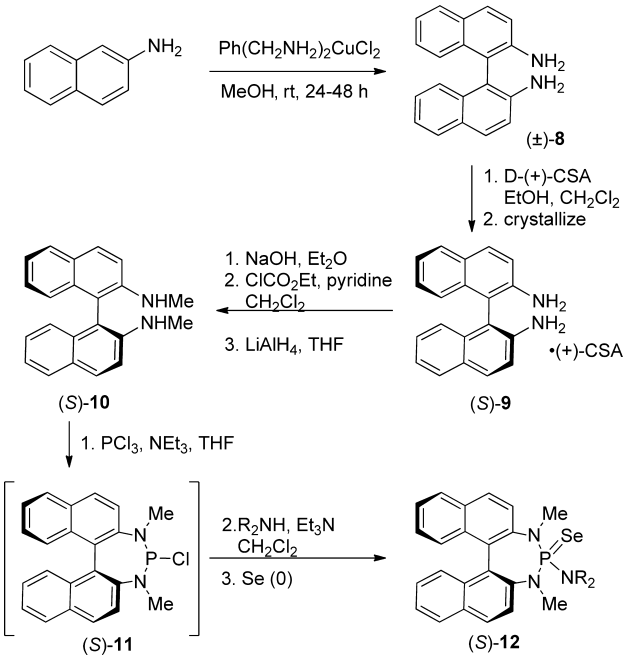
Scheme 6



of the catalyst. On the basis of these results, other selenophosphoramides bearing aliphatic amines were investigated. In all cases, **5** was produced with comparable conversions. Using the selenophosphoramide **12e**, derived from diethylamine, afforded **5** with 79% conversion in 86:14 er. Modification or elongation of the amine chain, e.g., **12f** and **12g**, afforded the product with comparable efficiencies and selectivities.

The incorporation of branched amines led to an increase in enantioselection. The use of selenophosphoramides **12h** and **12i** afforded **5** with ca. 77% conversion and 10:90 er. The selectivity improved to 7:93 when the diisopropylamino-derived catalyst **12j** was employed. The use of Lewis base **13**, wherein the binaphthyl backbone was substituted with the less bulky biphenyl system, led to decreases in catalytic efficiency and selectivity.

5. Development of a Catalytic, Enantioselective Sulfenylation Protocol. In view of the highly encouraging results described above, the substrate scope in the α-sulfenylation process was next investigated. However, at this stage, a number of significant challenges had been identified that would need to be addressed as part of this endeavor.

5.1. Large-Scale Preparation of Catalyst (R)-12j. Because selenophosphoramide **12j** afforded this highest enantioselectivity for the conversion of (*Z*)-**1a** to **5**, it was chosen for the survey of the remaining substrates. However, the general preparation outlined in Scheme 6 was not suitable for the bulky diisopropylamine needed in the last step. Thus, an improved preparation was developed that installs the diisopropylamino group as part of the diazaphosphepine ring formation (Scheme 7). The reaction is somewhat scale-dependent, but yields up to 78% have been achieved.[32e]

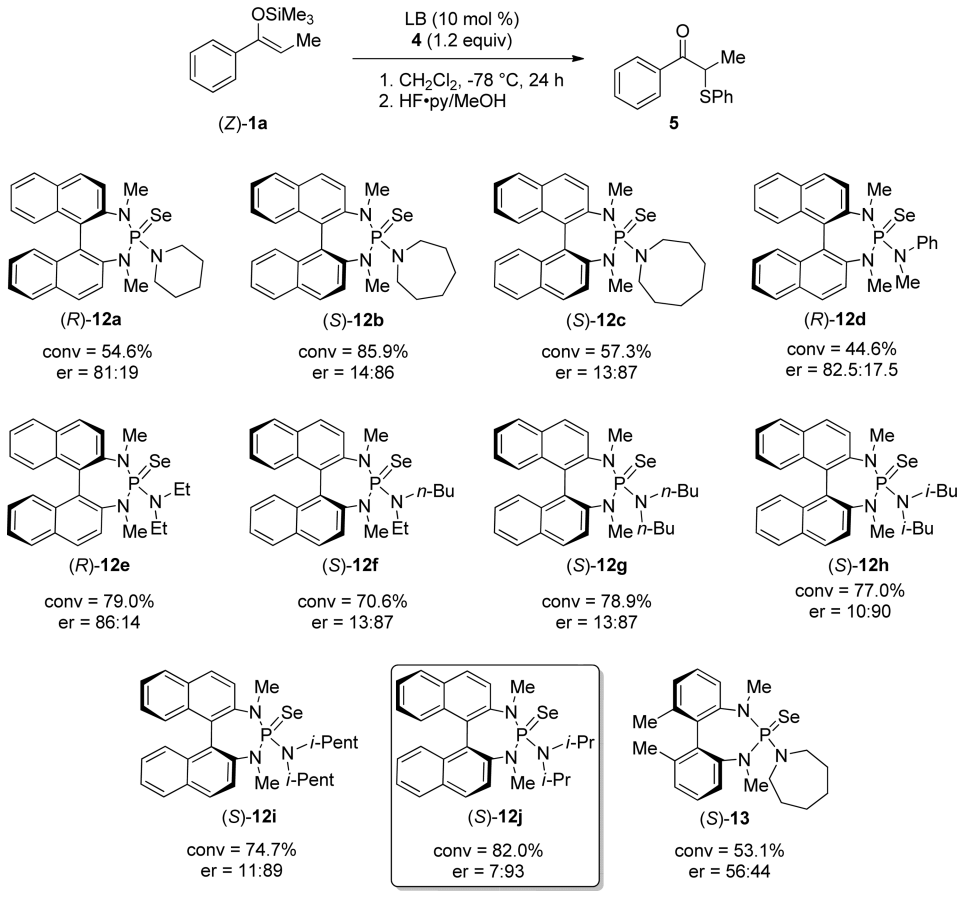


Figure 3. Survey of chiral selenophosphoramides in the sulfenylation of (*Z*)-**1a**.

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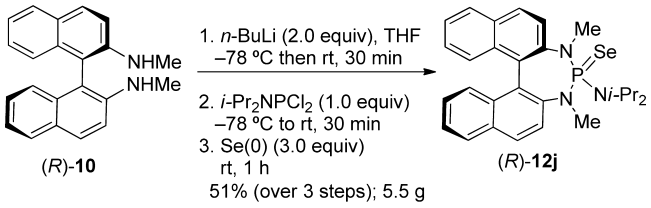
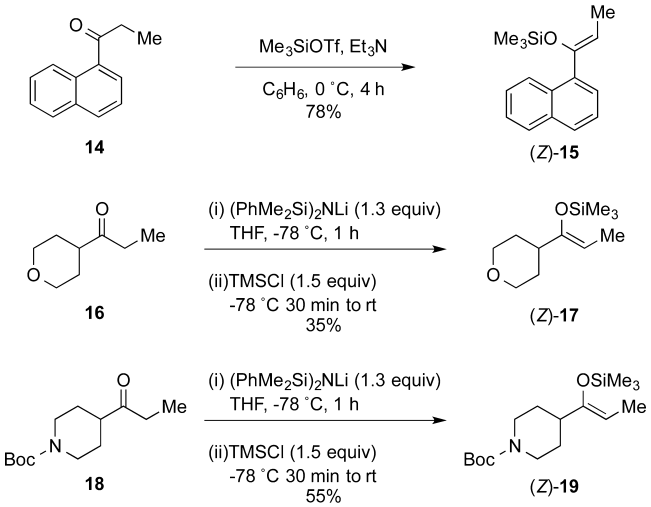
Scheme 7



5.2. Preparation of Silyl Enol Ethers. The syntheses of a large number of the silyl enol ethers used in this work are known and are therefore not described here.[39] However, for a number of substrates, preparative methods had to be developed. Importantly, they had to provide enol ethers in high purity and high (*Z*)-diastereoselectivity. High purity was required to aid final purification of the α-sulfenylated products, and high (*Z*)-diastereoselectivity was found to have an impact on the enantiomeric purity of the products. The developed preparative methods are detailed below.[39b] The configuration of all enol ethers shown below was confirmed by nuclear Overhauser enhancement (NOE) spectroscopy.

Although trimethylsilyl enol ether (*Z*)-**15**, derived from 1-(naphthalenyl)-1-propanone (**14**), is known,[40] the method reported was found to be irreproducible, and therefore alternative conditions were developed with the combination of TMSOTf and Et_3N, giving complete conversion of **14** to (*Z*)-**15** as a 95:5 *Z*/*E* mixture. Trimethylsilyl enol ether (*Z*)-**15** was isolated in a 78% yield (Scheme 8). ^{1}H NMR spectroscopic analysis of enol ether (*Z*)-**15** was not in accordance with that reported[40] but was confirmed by NOE spectroscopy.

Scheme 8



The use of lithium 1,1,3,3-tetramethyl-1,3-diphenyldisilazide was first reported by Masamune and co-workers for the highly (*Z*)-selective synthesis of silyl enol ethers derived from dialkyl ketones bearing one small and one medium-sized substituent.[41] This protocol was successfully applied to the synthesis of tetrahydropyranyl-based silyl enol ether (*Z*)-**17**. Complete conversion and excellent diastereoselectivity (*Z*/*E* > 25:1) were possible, and the method was amenable to scale-up. Separation of the enol ether from disilazane and disilazane-related materials proved nontrivial but was possible by column chromatography using basic alumina, activity grade III, allowing isolation of enol ether (*Z*)-**17** in 35% yield (Scheme 8). The *N*-*t*-Boc-piperidine-based silyl enol ether (*Z*)-**19** could also be prepared, using the lithiodisilazide base, in excellent diastereoselectivity (*Z*/*E* > 25:1).

5.3. Purification of the Sulfenylation Product. The fate of any unreacted enol ether, upon reaction work-up, was hydrolysis to the parent ketone. Separation of this ketone from the α-sulfenylation product proved to be difficult, especially as the chiral Lewis base also showed very similar interactions with all stationary phases during attempts to purify using column chromatography. Silica gel, basic alumina, and reverse-phase C-18 chromatography were all evaluated, with silica gel showing the best resolution. Radial chromatography was also found to be very effective. However, the increased acidity of the silica gel required to prepare the chromatography plates used for radial chromatography caused epimerization of the products. The solution to this issue required (1) the preparation of enol ethers of high purity (i.e., not contaminated with parent ketone), (2) that the reaction be as close to completion as possible upon work-up, and (3) careful chromatographic purification of the product (SiO_2 and reverse-phase C-18).

5.4. Accurate Reaction Monitoring. The low temperatures at which the reactions were conducted (typically −78 °C) rendered accurate reaction monitoring difficult because of the difficulties associated with removing a sample from the reaction mixture and quenching it before it had the opportunity to warm up (from −78 °C). Direct quench of the entire reaction mixture at −78 °C would ensure an accurate result; however, this would mean multiple reaction runs per substrate. The long reaction times of 24−48 h would make this an even less efficient approach. The solution to this issue was to sample using precooled, narrow-bore needles (−78 °C) with precooled quench solutions (also −78 °C). This optimized technique could allow, after work-up of the aliquot and ^{1}H NMR analysis, an accurate understanding of the reaction. This approach was validated by comparison to a direct reaction quench.

6. Substrate Scope Evaluation. With a set of standard reaction conditions and a wide range of enol ethers prepared, we then evaluated the efficiency of the α-sulfenylation procedure (Table 3). As detailed above, (*Z*)-**1a** was fully converted to **5** after 24 h at −78 °C to afford a high isolated yield (72%) with excellent er (93:7, entry 1). It should be noted that the catalyst loading was increased to 15 mol % to ensure full conversion of substrates to the α-sulfenylated products. As noted earlier, if not fully converted, residual enol ether would be hydrolyzed to the parent ketone upon work-up, complicating purification.

Enol ether (*E*)-**1a** also showed full conversion after 24 h at −78 °C, but in racemic form (entry 2). It was therefore decided to not explore acyclic (*E*)-enol ethers further.

Investigation of the effect of the R^2 substituent of the silyl enol ether was then carried out (Table 3, entries 3 and 4). With an ethyl substituent, full conversion was observed after 24 h at −78 °C, and product **21** was obtained in a similar yield (75%) and enantiomeric composition (er 90:10). However, increasing size of the R^2 substituent beyond an ethyl substituent caused a dramatic reduction in rate at −78 °C, and the reaction had to be warmed to −50 °C to give high conversion (entry 4). Fortunately, the high level of enantioselectivity was retained (er 91:9).

Variation of the R^1 substituent of the silyl enol ether was far better tolerated (entries 5−7). The (*Z*)-enol ether derived from

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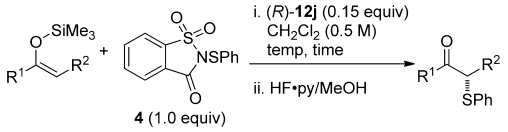
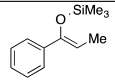
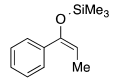
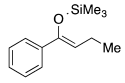
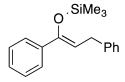
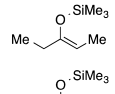
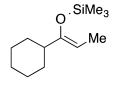
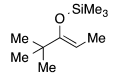
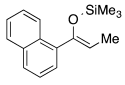
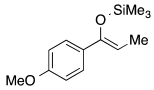
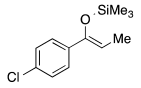
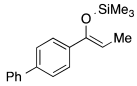
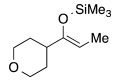
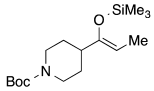
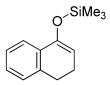
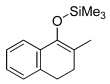
Table 3. Enantioselective Sulfenylation of Various Silyl Enol Ethers



entry	substrate		temp, °C	time, h	yield, %[a]	product	er after work up[b]	er after purification[b]
1		(*Z*)-**1a**	–78	24	72%	**5**	-	93:7
2[c]		(*E*)-**1a**	–78	24	100%[d]	**5**	50:50	-
3		(*Z*)-**20**	–78	24	75%	**21**	-	90:10
4		(*Z*)-**22**	–50	48	71%	**23**	91:9	91:9
5		(*Z*)-**24**	–78	24	75%	**25**	91:9	87:13
6		(*Z*)-**26**	–78	36	78%	**27**	-	94:6
7[c]		(*Z*)-**28**	–78	24	74%	**29**	-	98:2
8		(*Z*)-**15**	–50	48	76%	**30**	81:19	-
9		(*Z*)-**31**	–78	24	79%	**32**	90:10	90:10
10		(*Z*)-**33**	–78	48	66%	**34**	88:12	88:12
11		(*Z*)-**35**	–78	36	77%	**36**	94:6	94:6
12		(*Z*)-**17**	–78	48	80%	**37**	97:3	88:12
13		(*Z*)-**19**	–78	48	78%	**38**	97:3	94:6
14[c]		**39**	–78	24	92%[d]	**40**	56:44	-
15[c]		**41**	–78	24	97%[d]	**42**	75:25	-
16		**43**	–40	48	65%	**44**	85:15	99:1[e]

[a]Yield of isolated, analytically pure product. All reactions were carried out on a 1.0 mmol scale. [b]The enantiomeric ratio was determined by CSP-SFC analysis or CSP-HPLC analysis, as required. [c]10 mol % Lewis base was used in this instance. [d]% conversion determined by GC analysis using biphenyl as an internal standard. [e]After one recrystallization from MeOH.

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pentan-3-one (entry 5) showed a rate similar to that of (*Z*)-**1** and afforded **25** in good enantiomeric purity (er 91:9) and isolated yield (75%). Unfortunately, epimerization was observed during column chromatography, and the enantiomeric composition was compromised (er 87:13). Increasing the steric bulk of the R^1 group to cyclohexyl had little effect on the rate of the reaction, which was close to complete after 24 h (>90%) but was allowed to proceed for an additional 12 h to ensure complete conversion. Again, the isolated yield and enantioenrichment of the product were very good (entry 6, 78%, 94:6 er). Further increasing the steric bulk with a *tert*-butyl substituent at the 1-position was again well tolerated (entry 7). In fact, in this case only 10 mol % of (*R*)-**12j** was required to achieve very good isolated yield and er after 24 h at −78 °C (74%, 98:2 er).

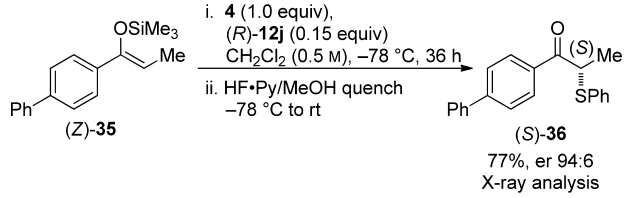
The next phase of the survey evaluated the effect of electronically modulating the enol ether by varying the substituents on the R^1 aromatic substituent. A 4-methoxy-substituted silyl enol ether was observed to give quantitative conversion at −78 °C after 24 h with very good er (90:10, entry 9). The reduction in selectivity, relative to (*Z*)-**1**, may be a result of increased background reaction or Lewis base catalysis by the methoxy substituent. Attenuation in electron density of the enol ether by the attachment of a 4-chlorophenyl substituent led to a significant reduction in reaction rate: after 48 h at −78 °C, the conversion was only 87% (entry 10). A moderate isolated yield of **34** could still be obtained (66%), with slightly reduced enantiopurity (er 88:12) relative to entry 1. Although the reason for the lower selectivity is not clear, the electron-deficient ketone would be more easily epimerized upon work-up. The 4-phenyl-substituted enol ether behaved well to afford **36** in good yield and high selectivity (entry 11).

The compatibility of Lewis basic functionalities in the substrates was then examined (entries 12 and 13). Both the tetrahydropyranyl- and *N*-*t*-Boc-piperidinyl-substituted silyl enol ethers were good substrates and afforded products with yields and enantiomeric purities very similar to those observed with the cyclohexyl-based substrate (compare entries 6, 12, and 13).[42]

Cyclic enol ethers were also examined (entries 16−18). Substrates **39** and **41** reacted in the same way previously seen with acyclic enol ether (*E*)-**1a**; conversion was complete at 24 h, but the er was found to be very poor. Next, to investigate the possibility of preparing of tertiary sulfides, the trimethylsilyl enol ether of 2-methyltetralone **43** was tested. This enol ether was targeted specifically to serve as a comparison to previous results with **41**. The rate of sulfenylation of **43** was much reduced in comparison to that of **41**, presumably a consequence of increased hindrance; only 77% conversion was obtained after 48 h at −40 °C. Interestingly, the selectivity in this case was higher than for silyl enol ether **41** (85:15 vs 75:25). The enantiomeric ratio could be upgraded to >99:1 after a single recrystallization from MeOH.

7. Determining the Absolute Configuration of the Sulfenylation Products. The absolute configuration of the products was established for product **36** from the sulfenylation of (*Z*)-**35**, which gave a crystalline product (Scheme 9). After 36 h at −78 °C, complete conversion of (*Z*)-**35** was achieved, and product **36** was obtained in very good yield and enantioenrichment (77%, 94:6 er). After purification, the *α*-sulfenyl ketone provided crystals from MeOH suitable for single-crystal X-ray analysis.[43] The refinement demonstrated that (*R*)-**12j** produced (*S*)-**36**. The configurations of the other

Scheme 9



products were assigned by analogy and confirmed via circular dichroism spectroscopy; comparison demonstrated that all substrates displayed a negative Cotton effect.

8. Mechanistic Considerations. *8.1. Proposed Catalytic Cycle and Structure of Intermediates.* The proposed mechanism of the reaction is detailed in Figure 4. Reaction of the chiral, enantioenriched Lewis base with *N*-phenylthiosaccharin **4** is proposed to give the Lewis base-bound sulfenyl cation **IV**.[32d] This active sulfenylating agent then reacts with the silyl enol ether to produce silyloxycarbenium ion **V** or thiiranium ion **VI**. Finally, nucleophilic removal of the trimethylsilyl group from either **V** or **VI** by the saccharin anion affords the *α*-sulfenylated product and *N*-trimethylsilylsaccharin. Although detailed kinetic studies have not been carried out with this system, in the related sulfenylation of isolated alkenes, thiiranium ion formation is rate-determining and intramolecular capture is rapid.[44] Since this variant does not have a capture step and the rate of reaction is not dependent upon the size of the silyl group,[45a] it is safe to assume that electrophilic attack on the silyl enol ether is rate- and stereo-determining here as well. Furthermore, the rate of the reaction decreases dramatically with increasing steric bulk at the 2-position of the enol ether, further supporting the notion that sulfenyl group transfer is rate-determining.

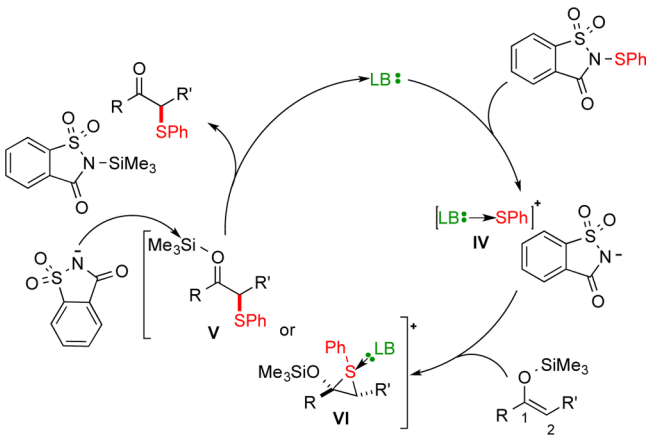


Figure 4. Proposed catalytic cycle.

To establish whether thiiranium ion **VI** is a reasonable intermediate in this process, DFT calculations (B3LYP/6-31G(d)) were performed on the two limiting reaction profiles shown in Scheme 10. For computational simplicity, the phenylsulfenylating agent derived from HMPA(Se) (**VII**) was employed in combination with (*Z*)-**5**. Mechanism 1 posits the formation of thiiranium ion **VI** as a stable intermediate that may open to silyloxycarbenium ion **V** or undergo direct collapse to the sulfenylated product. Mechanism 2 posits the direct formation of silyloxycarbenium ion **V**. Computationally, thiiranium ion **VI** could not be located as a stationary state

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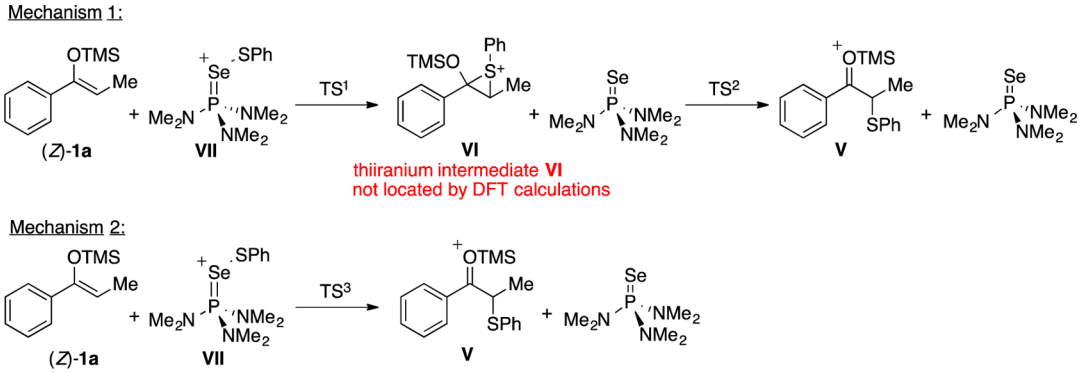
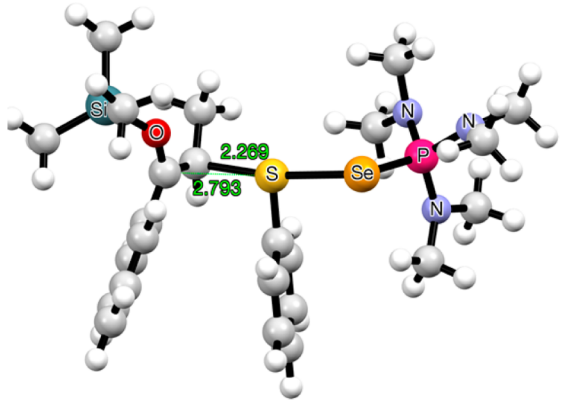
Scheme 10



starting from a number of different geometries, whereas silyloxycarbenium ion **V** was found to be a stable entity. The transition structure for formation of **V** from (*Z*)-**1a** and **VII** was located and (as expected) was highly unsymmetrical, with significantly different distances between the sulfur atom and the two carbons of the enol ether (Figure 5).[45b]



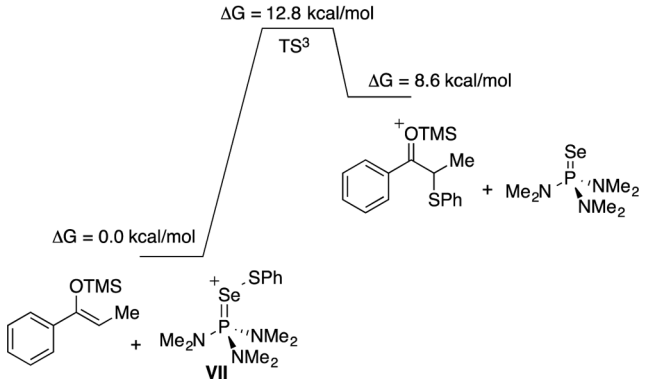
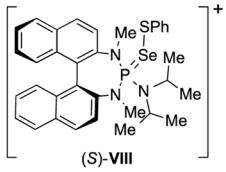


Figure 5. Energy profile and transition structure for sulfenyl group transfer.

8.2. Origin of Enantioselectivity. To provide more detailed insight into the origin of enantioselectivity, the structures of the catalytically active species and the transition states for the various stereochemical pathways for the α-sulfenylation reaction were investigated by computational analysis. Previous studies strongly suggested that the catalytically active species (**I**, Scheme 3 or **IV**, Scheme 4) is the sulfenylated selenophosphoramide (*S*)-**VIII** (Figure 6). The calculations on this species were performed by first establishing a rough structure with



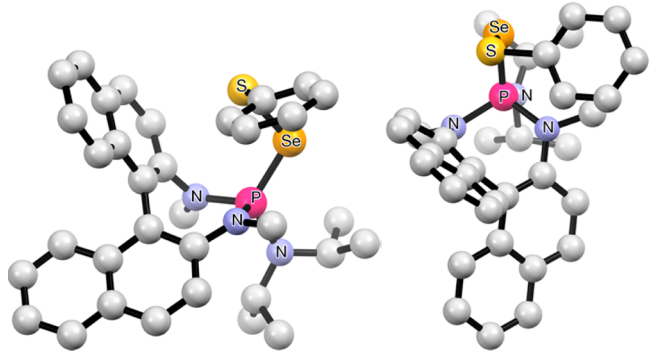


Figure 6. DFT-minimized structure of (*S*)-**VIII** (hydrogens removed for clarity).

molecular mechanics and then refining the structure prior to DFT calculations. The DFT method employed the B3LYP-D3 hybrid functional, with a LACVP(+)* basis set. Optimizations of the geometry were performed in dichloromethane using the PBF solvation model.

The first calculations focused on the geometry of the phenylsulfenyl group with respect to the Lewis base. Interestingly, the diisopropylamino group is turned such that the phenylsulfenyl group is pointing toward the binaphthyl moiety and perpendicular to the naphthyl ring. This structural feature provides an important insight for the high selectivity seen with branched dialkylamino-derived catalysts.

Using the optimized geometry of the catalytically active species (*S*)-**VIII**, four different α-sulfenylation transition states for the sulfenyl group transfer to (*Z*)-**1a** were located using B3LYP/6-31G(d) at −78 °C in the gas phase, and their structures are shown in Figure 7. All four transition states have highly unsymmetrical structures with significantly different distances between the sulfur atom and the two carbons of the enol ether, consistent with the conclusions from the foregoing analysis. The transition-state structures **TS *Re*-1** and **TS *Re*-2** will lead to product (*R*)-**5**, whereas **TS *Si*-1** and **TS *Si*-2** lead to (*S*)-**5**. The most stable transition state leading to (*R*)-**5** (**TS *Re*-1**) is 0.9 kcal/mol more stable than the lowest energy transition state leading to (*S*)-**5** (**TS *Si*-1**), which agrees with the

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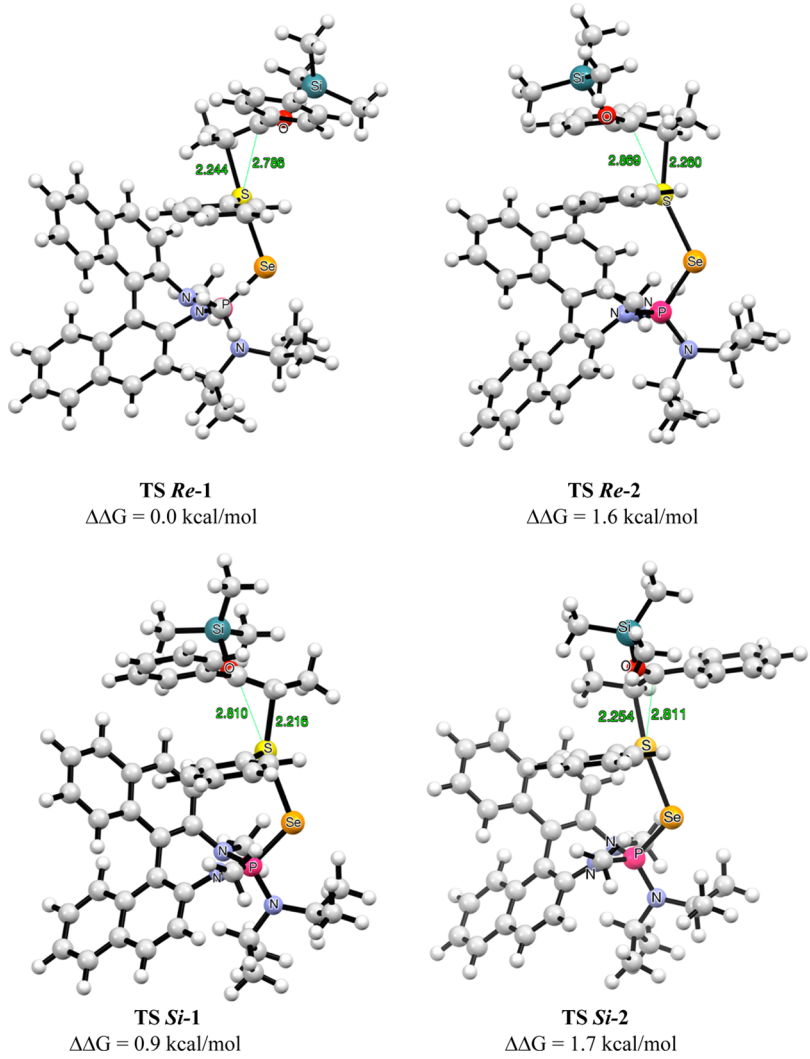

TS *Re*-1
ΔΔG = 0.0 kcal/mol

TS *Re*-2
ΔΔG = 1.6 kcal/mol

TS *Si*-1
ΔΔG = 0.9 kcal/mol

TS *Si*-2
ΔΔG = 1.7 kcal/mol

Figure 7. Optimized structures and energies of **TS *Re*-1**, **TS *Re*-2**, **TS *Si*-1**, and **TS *Si*-2**.

Table 4. Distortion–Interaction and NBO Analysis for the Diastereomeric Transition States

	$\Delta E_{dist\_}\mathbf{A}^a$	$\Delta E_{dist\_}\mathbf{B}^a$	ΔE_d	ΔE_i	$\Delta E_{act}{}^b$	ΔH	ΔG	π(C=C)–σ*(S–Se)^c
TS*Re*-1	**10.8**	**19.6**	**30.4**	**−26.7**	**3.7 (0.0)**	**4.5 (0.0)**	**13.2 (0.0)**	**76.7 (6.2)**
TSRe-2	11.2	20.4	31.6	−26.3	5.4 (1.7)	6.2 (1.7)	14.8 (1.6)	70.5 (0.0)
TS*Si*-1	**11.1**	**20.5**	**31.6**	**−27.3**	**4.3 (0.6)**	**5.3 (0.8)**	**14.1 (0.9)**	**76.8 (6.3)**
TS*Si*-2	10.2	21.1	31.3	−26.4	4.9 (1.2)	5.7 (1.2)	14.9 (1.7)	71.7 (1.2)

^{a}**A** = silyl enol ether (*Z*)-**1a**. **B** = catalytically active species (*S*)-**VIII**. $^b\Delta E_{act} = \Delta E_d + \Delta E_i$ ($\Delta E_d = \Delta E_{dist\_}\mathbf{A} + \Delta E_{dist\_}\mathbf{B}$). $^c\pi$(C=C)–σ*(S–Se) orbital interaction energy is calculated by NBO analysis.

experimental stereochemical outcome (91:9 calcd; 93:7 obsd).[46] However, careful inspection of these competing transition structures failed to identify any obvious interactions that would disfavor **TS *Si*-1** with respect to **TS *Re*-1**. The highly unsymmetrical transition states allow for a significant distance between the aryl residue and the catalytically active species, obviating any severe nonbonding interactions.

To provide additional insight into the origin of enantioselectivity, distortion–interaction[47] and NBO[48] analyses were carried out (Table 4). These results mirror those from the DFT analysis and suggest that a more subtle effect may be operative. As highlighted in bold type, **TS *Re*-1** possesses the lowest activation energy, 0.6 kcal/mol lower than that of **TS *Si*-1**. Interestingly, even though **TS *Si*-1** benefits from a greater interaction energy ($\Delta\Delta E_i$ = −0.6 kcal/mol), this advantage is offset by a greater distortion energy ($\Delta\Delta E_d$ = 1.2 kcal/mol). The greater interaction energy associated with **TS *Re*-1** was substantiated by the NBO analysis, which provided the stabilization energies arising from orbital overlap from the π-bond of the silyl enol ether to the antibonding (σ*) orbital of the sulfur–selenium bond. The stabilization energies for **TS *Re*-1** and **TS *Si*-1** are nearly identical (and are the largest of the four transition states), indicating similar levels of orbital overlap. However, to achieve those levels of overlap requires greater distortion of the orbitals in **TS *Si*-2** (likely resulting from nonideal approach of the silyl enol ether). Thus, whereas unfavorable steric interactions are not the apparent cause of the enantioselectivity, it is likely that the avoidance of unfavorable

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steric interactions leads to a nonideal approach of the silyl enol ether that manifests in the greater distortion energy contribution to that transition state.

The composite picture gleaned from empirical results reveals the sensitivity of the catalytic species to the shape of the olefin substrate (Figure 8). These characteristics comport well with the trends deduced from analysis of the intramolecular carbosulfenylation of alkenes using the same catalyst and presumably the same catalytically active species.[44] The superior performance of (*E*)-alkenes in that analysis is reflected in the higher selectivities observed with (*Z*)-silyl enol ethers in this work, as the carbon-based substituents on the double bond are effectively trans. Moreover, the observed decrease in selectivity with decreasing size of the R^1 substituent also agrees with the poor selectivity seen with (*Z*)-alkenes, because with a small R^1 group, the silyloxy substituent becomes the sterically dominant substituent on that side of the double bond, leading to a net (*Z*)-alkene shape.

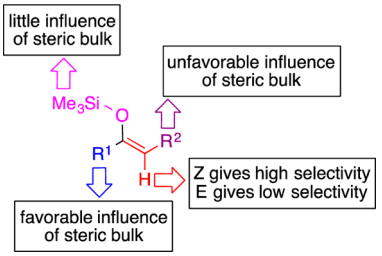

Figure 8. Composite influence of substrate shape on selectivity.

CONCLUSIONS

The development of a catalytic, asymmetric, Lewis base-catalyzed α-sulfenylation of silyl enol ethers has been described. To establish the conditions for a successful catalytic process, a new sulfenylating agent was developed that did not require activation by a Brønsted acid because of the sensitivity of silyl enol ether to acidic hydrolysis. These investigations identified *N*-phenylthiosaccharin to be a suitable electrophile and highlighted three classes of suitable Lewis bases: tertiary amines, sulfides, and selenophosphoramides. In addition, reaction monitoring and quench procedures were developed to ensure the suppression of background reaction and that the catalytic process went to completion.

Chiral selenophosphoramides served to effectively catalyze the α-sulfenylation with generally good enantioselectivity. The success of the reaction does not depend on the size of the silyl group but is highly sensitive to the double bond geometry and the bulk of the substituents on the double bond. Extension of this process to the α-sulfenylation of ketene acetals and related nucleophiles is ongoing and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Full experimental procedures and characterization data; X-ray coordinates and CIF file for (*S*)-**36**; copies of ^{1}H and ^{13}C NMR spectra; CSP-HPLC and CSP-SFC traces; and Cartesian coordinates and energies for (*S*)-**VIII** and **TS *Re*-1**, **TS *Re*-2**, **TS *Si*-1**, and **TS *Si*-2**. 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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(43) The crystallographic coordinates of **36** have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 959716. These data can be obtained free of charge via from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK; fax (+44) 1223-336-033, or via www.ccdc.cam.ac.uk/conts/retrieving.html or E-mail to deposit@ccdc.cam.ac.uk.
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