JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

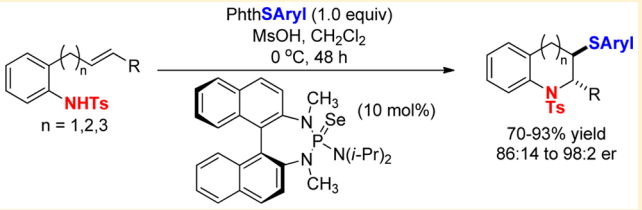
Catalytic, Enantioselective, Intramolecular Sulfenoamination of Alkenes with Anilines

Scott E. Denmark* and Hyung Min Chi

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801, United States

Supporting Information

ABSTRACT: A method for the catalytic, enantioselective, intramolecular sulfenoamination of alkenes with aniline nucleophiles has been developed. The method employs a chiral, Lewis basic selenophosphoramide catalyst and a Brønsted acid co-catalyst to promote stereocontrolled C−N and C−S bond formation by activation of an achiral sulfenylating agent. Benzoannulated nitrogen-containing heterocycles such as indolines, tetrahydroquinolines, and tetrahydrobenzazepines were prepared with high to excellent enantioselectivities. The impact of tether length and electron density of both the nucleophile and olefin on the reactivity, site selectivity, and enantioselectivity were investigated and interpreted in terms of substrate-dependent stereodetermining thiiranium ion formation or capture.



INTRODUCTION

As an important member of the class of nitrogen-containing biologically relevant motifs, the tetrahydroquinoline ring system is common to a wide range of natural and synthetic compounds that exhibit biological activities (Chart 1).[1] These compounds display, inter alia, antitumor, antiarrhythmic, antibiotic, antidepressant, cardiovascular, antithrombotic, antiallergenic, antiheumatic, immunosuppressant, and antifertility activity.[1]

Synthesis of Tetrahydroquinolines. Due to their diverse applications in pharmaceutical and medicinal chemistry, the development of novel strategies for the synthesis of tetrahydroquinolines has been an active area of research. Traditional approaches to the synthesis of the tetrahydroquinoline core can be classified into three categories: (1) construction of the tetrahydropyridine fragment, (2) construction of the aryl ring, and (3) reduction/hydrogenation of quinolines (Figure 1). Among these, the first strategy is the most common and involves the formation of C−C or C−N bonds with creation of stereogenic sp^3 carbon centers. A few reports employ the second strategy of which the intramolecular Diels−Alder reaction of a furan as the diene followed by thermal aromatization is a representative example.[2] On the other hand, the third strategy (partial hydrogenation of quinolines) is often more direct and can be accomplished enantioselectively. Indeed, many enantioselective hydrogenation methods have been developed for the synthesis of *syn*-2,3-substituted tetrahydroquinolines.[3] Of course, the preparation of the starting quinolines then becomes the challenge.[1b]

Enantioselective Syntheses of Tetrahydroquinolines. Numerous strategies for the synthesis of the tetrahydropyridine fragment have been developed that target different bond disconnections and stereocontrol elements. The enantioselective syntheses of the tetrahydropyridine ring can be further divided into two subcategories by the number of bonds formed in the key step. The first category is a cyclization that forms one bond, and the second is an annulation that forms two or more bonds. Most enantioselective methods leverage facile cyclization, whereas only a few enantioselective variants of annulation processes have been reported.

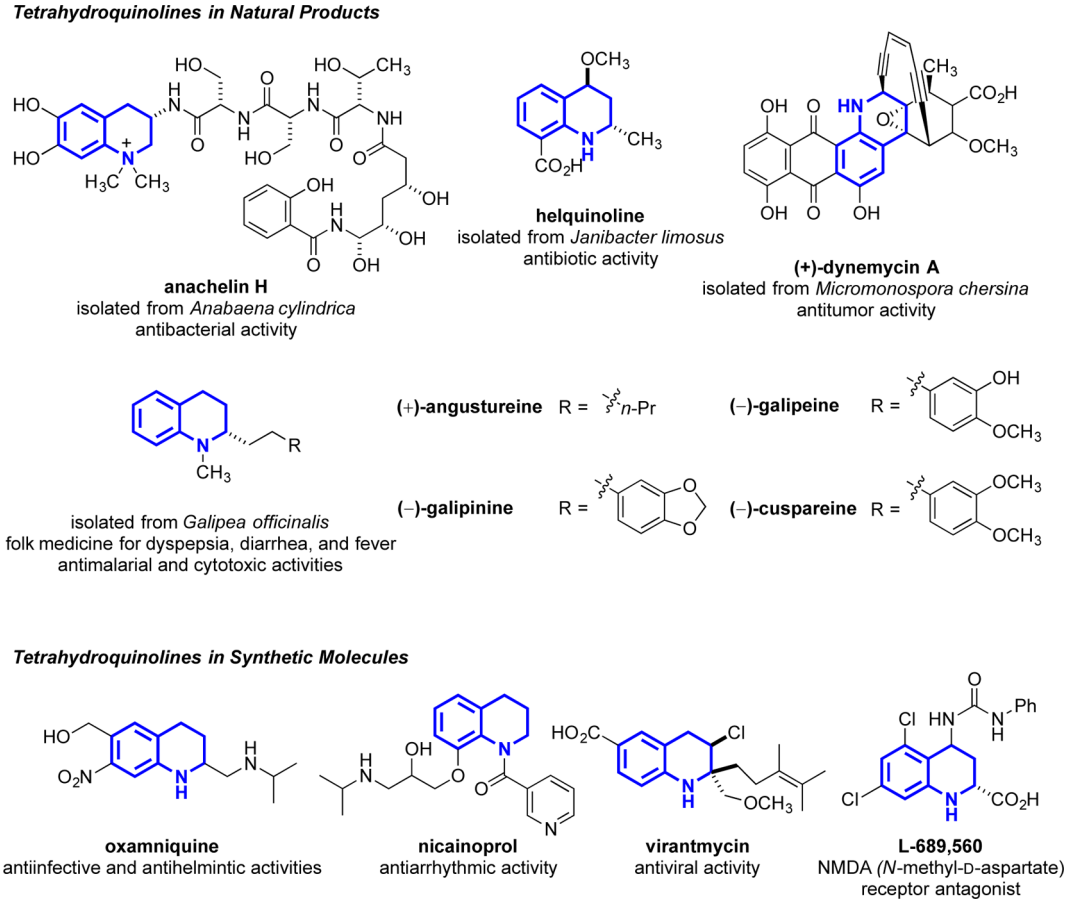
Enantioselective, intramolecular, one-bond construction of tetrahydroquinolines can be categorized into four types based on the bond that is formed: (1) N−C_2, (2) C_2−C_3, (3) C_3−C_4, and (4) C_4−C_{4a} (Figure 2). Disconnection strategy of N−C_{8a} is also well described and represented by transition-metal-catalyzed amination reactions,[4] but they inherently cannot be enantioselective.

For disconnection (1), Hamada and co-workers reported an enantioselective amination of an allylic acetate catalyzed by $Pd(dba)_2$ in the presence of a chiral phosphabicyclononane ligand (Scheme 1).[5] The reaction is speculated to proceed through an intermediate chiral, π-allyl palladium complex. For disconnection (2), addition of chiral lithium amides to α,β-unsaturated esters was described by Davies and co-workers to furnish 2,3,4-functionalized tetrahydroquinoline derivatives.[6] The lithium amide initiates a tandem conjugate addition/cyclization reaction connecting C_2−C_3 bond with excellent diastereo- and enantioselectivity. For disconnection (3), Nishibayashi and co-workers developed a catalytic, enantioselective synthesis of 3,4-functionalized tetrahydroquinolines with excellent enantioselectivity.[7] In this process, a propargylic alcohol undergoes an intramolecular ene reaction with a pendant allyl amine under catalysis by a thiolate-bridged diruthenium complex. Finally, for disconnection (4), Lu and co-workers reported an enantioselective Friedel−Crafts alkylation using a prolinol silyl ether catalyst.[8]

Received: February 18, 2017

DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX−XXX

Chart 1. Tetrahydroquinolines in Natural and Synthetic Compounds



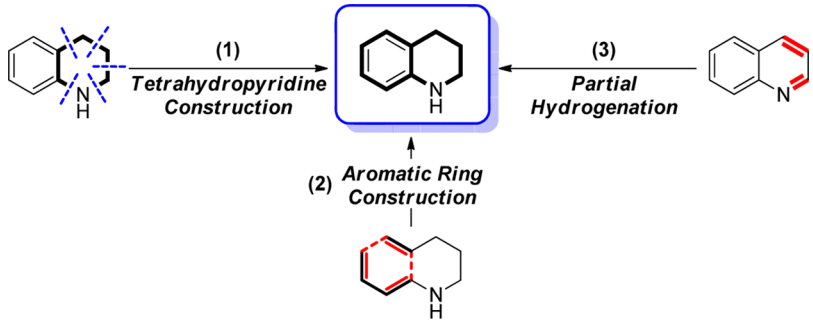


Figure 1. Three strategies for the synthesis of tetrahydroquinolines.

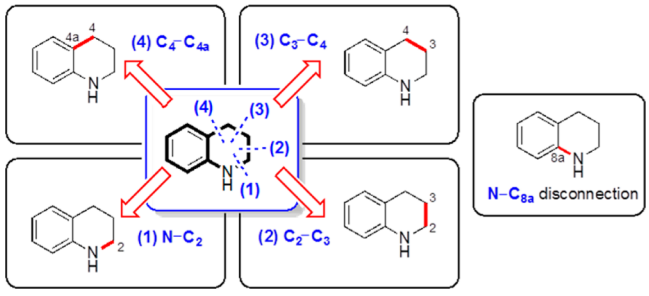


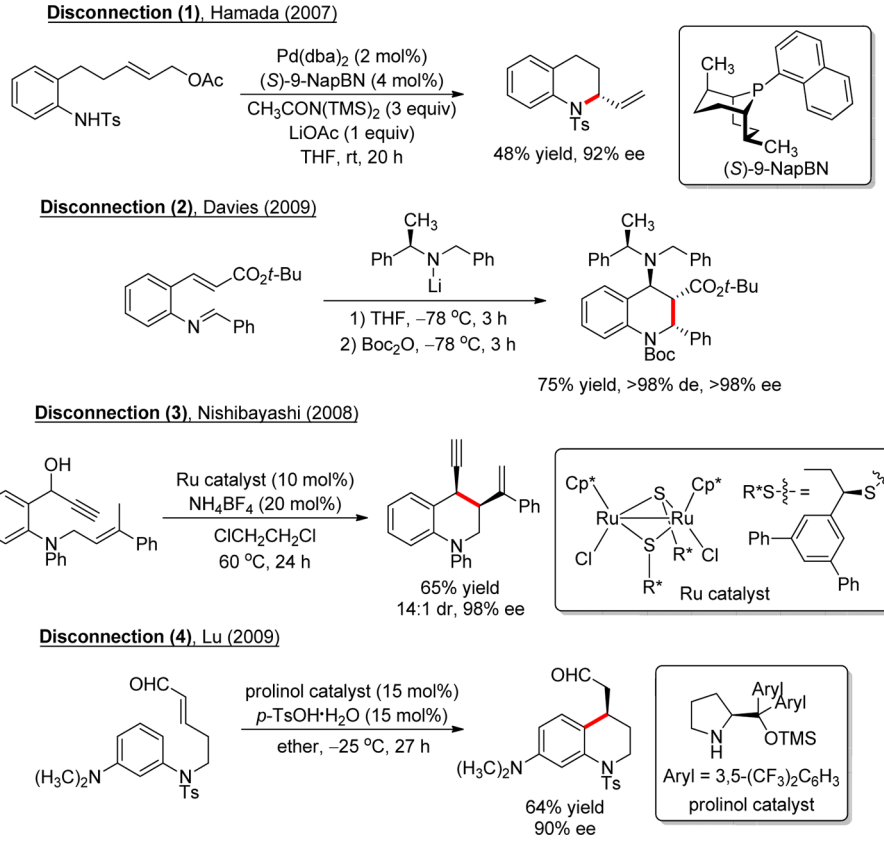
Figure 2. Different connectivity-based approaches to tetrahydroquinoline ring construction.

Enantioselective, intermolecular tetrahydroquinoline syntheses involving multibond construction have also been developed (Scheme 2). Nenajdenko and co-workers described synthesis of tetrahydroquinolines via a two-bond formation approach using a (*S*)-methoxymethyl pyrrolidine chiral auxiliary.[9] Tunge and co-workers reported the Pd-catalyzed synthesis of tetrahydroquinoline from benzoxazinanones and benzylidene malononitriles in the presence of chiral bidentate phosphine ligands.[10]

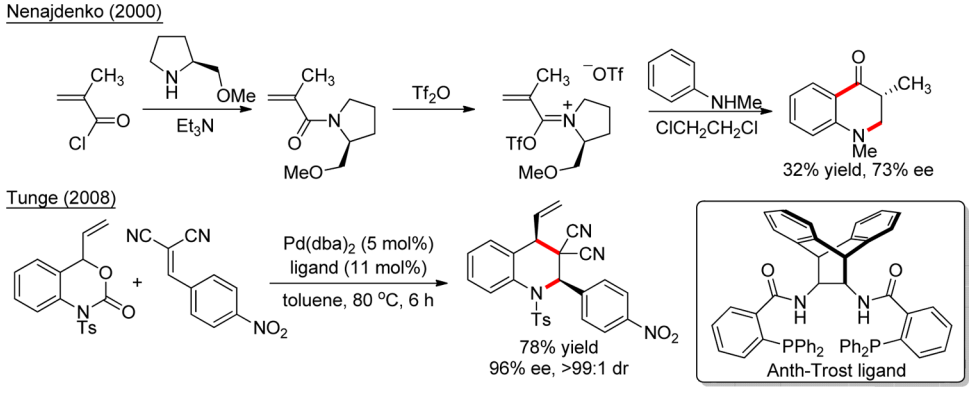
Unfortunately, application of these methods to the construction of enantioenriched *anti*-2,3-difunctionalized tetrahydroquinolines is not trivial, with most existing methods requiring multiple steps. In 2013, Zhou and co-workers reported a two-step sequence of asymmetric transfer hydrogenation followed by epimerization to afford *anti*-2,3-difunctionalized tetrahydroquinoline with high enantioselectivity (Scheme 3).[3d]

DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX−XXX

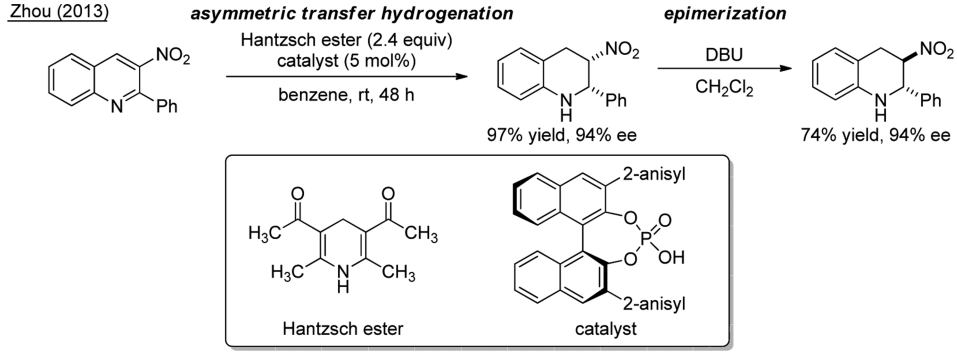
Scheme 1. Example Reactions of Disconnections 1−4



Scheme 2. Examples of Two-Bond-Forming Reactions



Scheme 3. Zhou's Two-Step Sequence Strategy

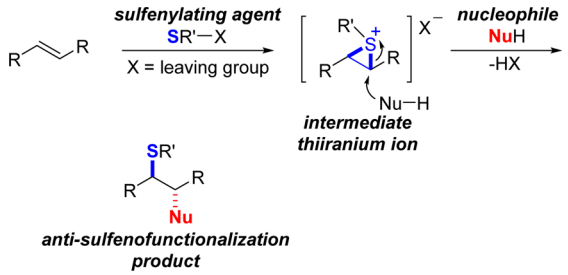


DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX−XXX

BACKGROUND

Sulfenofunctionalization of alkenes with electrophilic sulfur reagents has been known since the 1960s in the context of thiiranium ion chemistry.[11] Thiiranium ions (also called episulfonium ions) are analogous to epoxides and aziridinium ions in their ability to undergo ring opening with a variety of nucleophiles to install stereogenic centers (Scheme 4).[12] Thiiranium ions are typically generated from reaction of alkenes with electrophilic sulfur reagents, such as sulfenyl halides, thiosulfonium salts, and disulfides.[11,13] Despite the high reactivity of thiiranium ions, they are configurationally stable at low temperature and undergo stereospecific S_N2 ring opening by nucleophiles, thus leading to *anti*-sulfenofunctionalized products.[14]

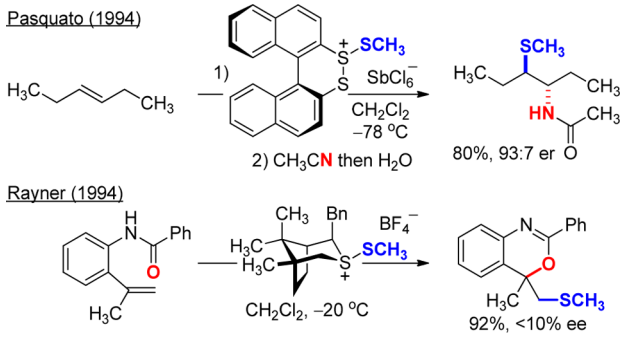
Scheme 4. Intermediacy of the Thiiranium ions in Sulfenofunctionalization Reactions



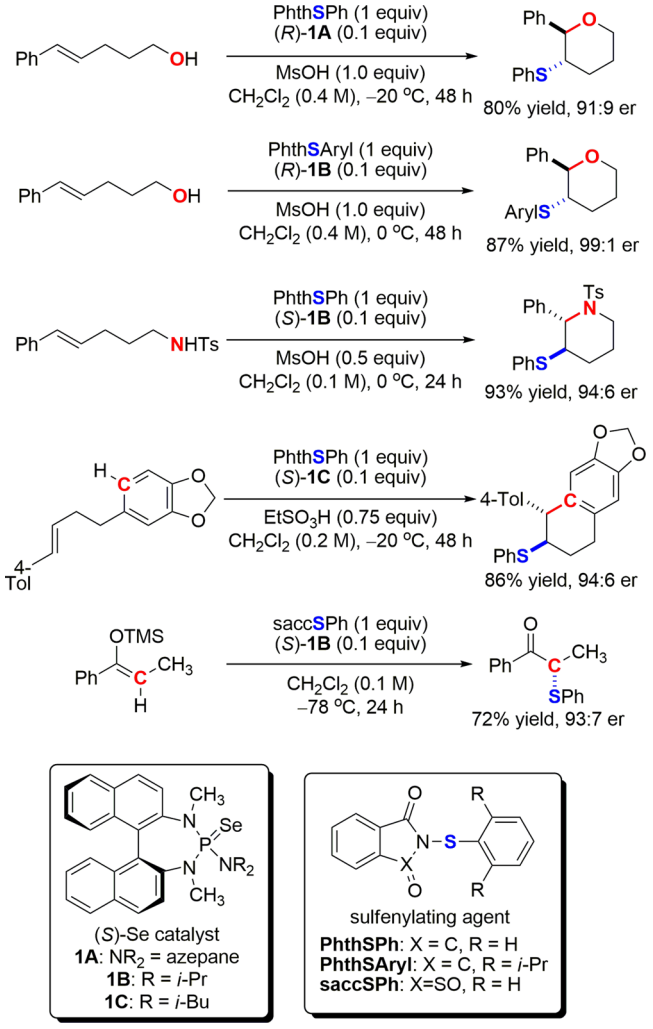
Enantioselective Sulfenofunctionalization. Only two enantioselective sulfenofunctionalization reactions that proceed via enantioenriched thiiranium ions have been reported (Scheme 5). In 1994, Pasquato and co-workers described the enantioselective sulfenoamination of *trans*-3-hexene by employing a stoichiometric amount of a binaphthyl-derived sulfenylating agent.[15] Thiiranium ions are captured by acetonitrile in the presence of water to afford acetamides by a Ritter-type reaction. Generating the thiiranium ions at lower temperatures led to products with higher enantiomeric purities, consistent with temperature dependence on the configurational stability. Rayner reported the intramolecular capture of thiiranium ions generated from a chiral methylthiosulfonium salt to afford benzoxazines.[16] While the reaction proceeded cleanly with high yield, it only gave marginal stereoselection at −20 °C.

Lewis Base Catalysis of Sulfenofunctionalization. Foregoing studies from these laboratories have described catalytic, enantioselective sulfenofunctionalizations of isolated alkenes with oxygen-,[17,18] carbon-,[19] and nitrogen-based[18,20] nucleophiles (Scheme 6). These reactions employ chiral Lewis bases **1** and proceed with high selectivities to provide access to tetrahydropyrans, tetralins, and piperidines, respectively.

Scheme 5. Previously Reported Enantioselective Sulfenofunctionalization Reactions



Scheme 6. Lewis Base Catalyzed Sulfenofunctionalization Reactions



Enantioselective α-sulfenylation of silyl enol ethers has also been developed using a saccharin-derived sulfenylating agent.[21] More recently, a sterically encumbered sulfenylating agent ((2,6-diisopropylphenyl)thiophthalimide, PhthSAryl) has been introduced to provide improved enantioselectivities for these sulfenylation reactions.[18] To recapitulate, in all of these reports on sulfenofunctionalizations, selenophosphoramide catalysts showed superior selectivity on *trans*-disubstituted alkenes compared to *cis*-disubstituted or trisubstituted alkenes.

The mechanistic details of this process have been thoroughly investigated by kinetic, spectroscopic, crystallographic, and computational analysis.[18,22] The catalytic cycle begins with the protonation of the Lewis acid (PhthSAryl) by a Brønsted acid (MsOH) (Figure 3). This step is followed by transfer of the arylsulfenium group to the chiral Lewis base catalyst to form the catalytically active complex ***i***. This sulfenylated complex ***i*** is the resting state of the catalyst and has been characterized by NMR spectroscopic and X-ray crystallographic analysis.[18] The complex ***i*** then transfers the sulfenium ion to the carbon−carbon double bond to generate the enantioenriched thiiranium

DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX−XXX

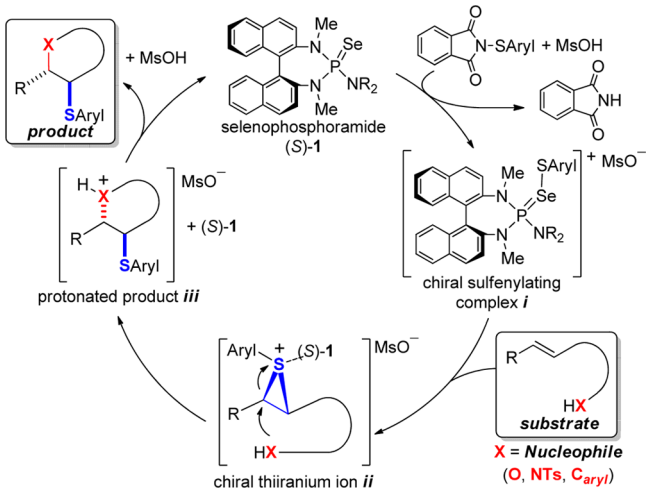


Figure 3. Catalytic cycle for enantioselective sulfenofunctionalization reaction.

ion intermediate ***ii***. Lastly, capture of the thiiranium ion with a tethered nucleophile forms the protonated species ***iii*** with release of the catalyst; subsequent proton transfer affords the enantioenriched, sulfenofunctionalized product.

Among the series of above-mentioned sulfenofunctionalization reactions, the enantioselective sulfenoamination of alkenes have demonstrated the synthesis of *anti*-2,3-disubstituted *piperidines* and *azepanes* with high enantioselectivity (Scheme 7).[20] Therefore, it was logical that *anti*-2,3-disubstituted tetrahydroquinolines could be analogously accessed by substituting aniline nucleophiles in place of the established amines. Anilines are unique functional groups in both their steric and electronic properties when compared to the aliphatic amines. While the conformational restriction from the planar geometry of aniline influences the cyclization, the variable substitution pattern allows evaluation of the electronic properties of the nucleophiles. Their utilization would expand the scope of the reaction for the construction of other chiral nitrogen-containing heterocycles as well, such as indolines and tetrahydrobenzazepines.

RESULTS

Previously, the influence of the electronic and steric properties of the *alkenes* on the rate, site selectivity, and enantioselectivity of the enantioselective sulfenoamination reaction was investigated.[20] The electronic properties of the amine were varied by installing different protecting groups on the amine. Also, the tether length between the alkene and amine was varied to examine the accessibility of medium-sized rings. In a similar manner, the following goals were set for this study to investigate the effect of (1) the electronic properties of the aniline nucleophile, (2) the steric and electronic properties of the olefin, and (3) the tether length for the sulfenoamination reaction of olefins with anilines.

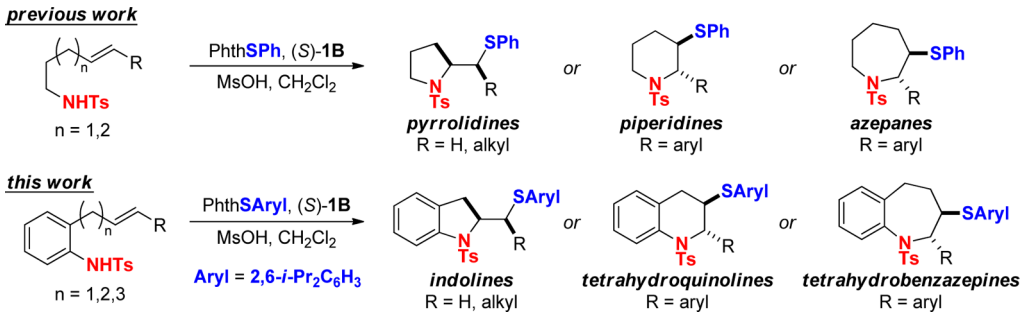
To evaluate all of these structural parameters required efficient access to range of aniline-containing substrates. These substrates were prepared by three general routes: (1) 3-aza-Cope rearrangement of *N*-allylic anilines, (2) metathesis of terminal olefins, and (3) Pd-catalyzed C–N coupling (Scheme 8). Detailed syntheses and characterizations of these substrates have been described in a separate report.[23]

Optimization of the Sulfenoamination Reaction. To investigate the properties of aniline substrates, reaction conditions were adapted from the previously reported enantioselective sulfenoamination reaction: PhthSAryl was employed as the sulfenylating agent, MsOH as the Brønsted acid, and selenophosphoramide (*S*)-**1B** as the Lewis base catalyst,[20] at room temperature at 0.1 M in substrate.[18]

2-Cinnamyl-*N*-tosylanisidine (**2a**) was selected as the test substrate for reaction optimization. Initially, the reaction was carried out in NMR tubes to monitor the rate profile at room temperature over 2 days (Table 1, entries 1–4). The reaction reached full conversion after 48 h under the above conditions to afford tetrahydroquinoline **3a**, favoring 6-*endo* cyclization exclusively. However, the enantiomeric composition of the product was much lower than expected, 90:10 er. To ensure that no competing racemic pathway was operative, the reaction was carried out in the absence of the selenophosphoramide catalyst (entry 5). No product was formed, suggesting that the attenuated selectivity arose from other factors. Therefore, the reaction was performed at a lower temperature (0 °C) to enhance the configurational stability of the thiiranium ion intermediate, which resulted in an improved enantiomeric ratio of 94:6 er (entry 6). However, the conversion over the monitored time dropped to 80%, comparable to the 12 h time point at room temperature reaction. To improve the conversion, the overall concentration was increased to 0.4 M (entry 7). Gratifyingly, the reaction showed full conversion to tetrahydroquinoline **3a** with excellent *endo* selectivity and negligible enantiomeric erosion.

2. Sulfenoamination of Olefins with One-Methylene Tether. Both indoline and tetrahydroquinoline scaffolds were accessible with single-methylene tethered substrates, depending on the mode of cyclization (5-*exo* vs 6-*endo*). To evaluate the influence of electronic properties of the aniline nucleophile on reaction outcome, a series of substrates with varying substitutions on the nucleophile was prepared. The model substrate, electron-rich anisidine **2a** afforded 2,3-difunctional-

Scheme 7. Sulfenoamination of Amines and Anilines



DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX–XXX

Scheme 8. Three Main Routes for the Preparation of 2-Alkenylaniline Substrates

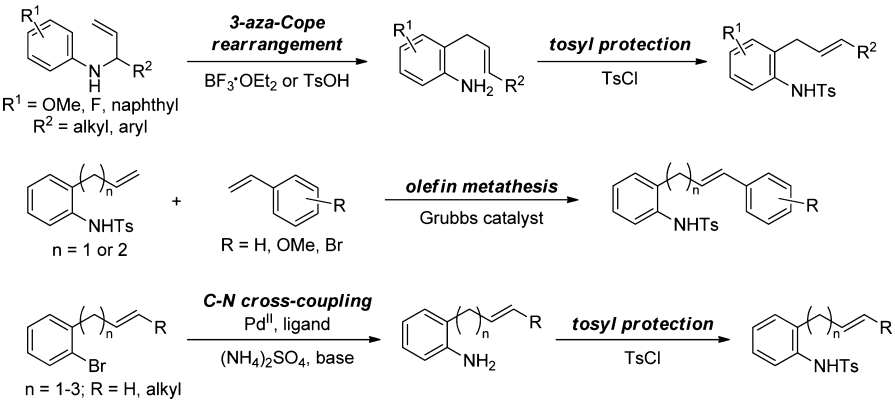
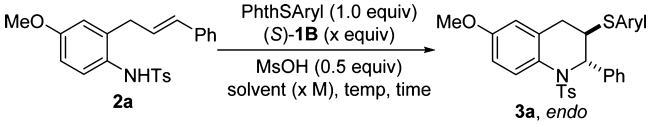


Table 1. Optimization of the Sulfenoamination Reaction



entry	catalyst loading (equiv)	solvent, conc (M)	cond: T (°C), time (h)	conv/ yield[b] (%)	er[c]
1	0.1	$CDCl_3$, 0.1	20, 6	52/–	–
2	0.1	$CDCl_3$, 0.1	20, 12	77/–	–
3	0.1	$CDCl_3$, 0.1	20, 24	94/–	–
4	0.1	$CDCl_3$, 0.1	20, 48	100/82	90:10
5	0	$CDCl_3$, 0.1	20, 48	no conv	–
6	0.1	CH_2Cl_2, 0.1	0, 48	80[a]/64	94:6
7	0.1	CH_2Cl_2, 0.4	0, 48	100[a]/80	93:7

[a]Conversion and constitutional selectivity determined by ^{1}H NMR spectroscopy of the crude mixture. [b]Yields of isolated purified products; low yields due to difficulty in separation from the residual starting materials in the case of incomplete conversion. [c]The enantiomeric ratio of the major constitutional isomer was determined by CSP–HPLC analysis.

ized tetrahydroquinoline **3a** with high site- and enantioselectivity (Table 2, entry 1). Electron-neutral and electron-deficient anilines **2b** and **2c** both cyclized into tetrahydroquinolines **3b** and **3c** with comparable enantioselectivity to **3a** (entries 2 and 3). However, the cyclization of 4-fluoroaniline **2c** was much slower in contrast to anilines **2a** and **2b**, requiring 6 days to reach full conversion (compared to 2 days). Cyclization of naphthyl substrate **2d** cleanly furnished tetrahydrobenzo[*f*]-quinoline **3d** with high enantioenrichment (entry 4). In all single-methylene tethered styrenyl cases, excellent site selectivity was observed for 6-*endo* cyclization.

The influences of the electronic properties of the olefin were also investigated. Styrenes with electron-donating substituents **2e** and **2f** afforded tetrahydroquinolines via *endo* cyclization with high yields and enantioselectivities (entries 5 and 6). The reaction times required for full conversion were comparable to the model substrate **2a**. Electron-deficient styrenes are known to exhibit poor reactivity and therefore not examined.[17,19,20]

Next, dialkyl-substituted olefins were tested to explore the steric influences of the olefin on the reaction outcome. Cyclization of the nitrile-appended aliphatic olefin **2g** afforded a 4:1 mixture of *exo* and *endo* cyclized products, with diminished enantiomeric ratio of 86:14 (entry 7). However, olefin **2h**, having a sterically demanding isopropyl group, cyclized with improved constitutional selectivity favoring 5-*exo* cyclization (*exo*:*endo* = 12:1) and excellent enantioselectivity (98:2 er) (entry 8).

Olefins with different numbers of substitutions were also examined. In the previous sulfenofunctionalization studies, cyclizations of terminal olefins resulted in high enantioselectivities, whereas cyclizations of trisubstituted olefins did not.[17,19,20] Terminal olefin-containing substrate **2i** transformed cleanly into 2-substituted indoline **3i** via 5-*exo* cyclization with excellent enantioselectivity (entry 9). In contrast, trisubstituted olefin substrate **2j** afforded 2,2-dimethyl-substituted tetrahydroquinoline **3j** via 6-*endo* cyclization with a reduced enantiomeric ratio (88:12 er) (entry 10).

Lastly, a substrate was devised to compare the relative reactivity of the two different types of nucleophiles, amines and anilines, toward the capture of the thiiranium ion. Substrate **2k**, containing competing aniline and amine nucleophiles afforded pyrrolidine **3k** as the major product (entry 11). This result trivially shows the superior thiiranium ion capturing ability of the aliphatic amines.

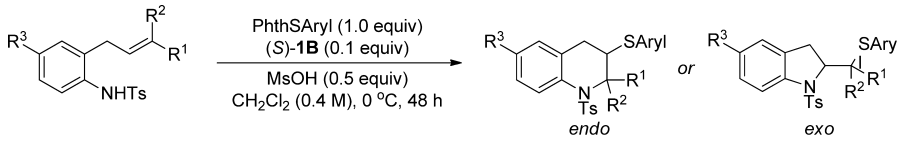
3. Sulfenoamination of Olefins with Longer Tethers. Substrates with longer tethers were explored to gauge the potential to access larger *N*-containing heterocycles such as tetrahydrobenzazepines. In Table 2, tetrahydroquinolines with 2-aryl substituents were accessible from 2-cinnamyl anilines with excellent site selectivity, while those with aliphatic substituents at the 2-position were generated with reduced selectivity. To address this problem, substrates bearing longer tethers were examined.[23] Specifically, dialkyl-substituted olefin **2l** cleanly afforded 2-alkyltetrahydroquinoline **3l** by 6-*exo* cyclization with excellent enantioselectivity (98:2 er) (Table 3, entry 1). On the other hand, electronically biased styrenyl olefin substrate **2m** furnished 2-phenyltetrahydrobenzazepine **3m** via 7-*endo* cyclization with high site and enantioselectivity (entry 2).

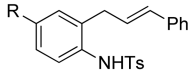
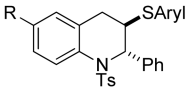
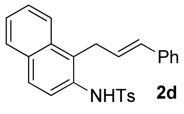
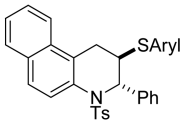
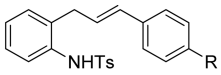
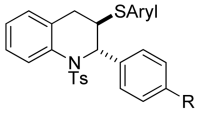
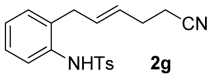
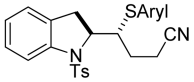
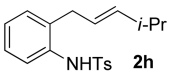
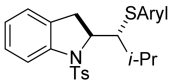
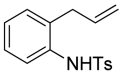
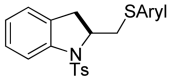
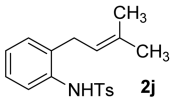
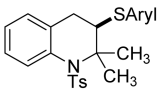
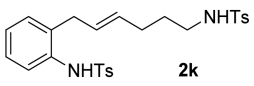
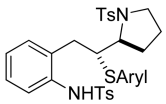
Terminal olefins with longer tethers were also examined. Cyclization of 2-homoallyl aniline **2n** furnished 2-alkyltetrahydroquinoline **3n** also via 6-*exo* closure with excellent constitutional and enantioselectivity (entry 3). Lastly, aniline **2o** bearing an *ortho*-4-pentenyl chain cyclized to form 2-alkyltetrahydrobenzazepine **3o** via the 7-*exo* mode with high enantioselectivity (entry 4).

Desulfurization of the Sulfenoamination Products. In contrast to phenyl sulfides, which are easily cleaved with nickel boride under mild conditions,[24] 2,6-diisopropylphenyl sulfides required more forcing desulfurization conditions. The 2,6-

DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX–XXX

Table 2. Scope of the Sulfenoamination of Substrates with One-Methylene Tether



entry	substrate	major product		yield (%)[a]	endo : exo[b]	er[c]
1	 **2a**, R = OMe **2b**, R = H **2c**, R = F		**3a**, R = OMe	87	>20 : 1	94 : 6
2			**3b**, R = H	92	>20 : 1	95 : 5
3			**3c**, R = F	86[d]	>20 : 1	96 : 4
4	 **2d**		**3d**	93	>20 : 1	98 : 2
5	 **2e**, R = OMe **2f**, R = Br		**3e**, R = OMe	93	>20 : 1	96 : 4
6			**3f**, R = Br	88	>20 : 1	97 : 3
7	 **2g**		**3g**	86	1 : 4	86 : 14
8	 **2h**		**3h**	85	1 : 12	98 : 2
9	 **2i**		**3i**	90	1 : >20	98 : 2
10	 **2j**		**3j**	89	>20 : 1	88 : 12
11	 **2k**		**3k**	70	1 : 4	95 : 5

[a]Isolated yields of analytically pure material. [b]Constitutional selectivity determined by ^{1}H NMR spectroscopy of the crude mixture. [c]The enantiomeric ratio of the major constitutional isomer was determined by CSP−HPLC analysis, and the absolute configurations of the products were assigned by comparison of their CD spectra with **3i**. [d]Reaction time of 6 d.

diisopropylphenyl sulfide moiety was cleanly reduced by lithium naphthalenide, along with the concomitant reductive cleavage of the tosyl protecting group (Scheme 9).[25] The absolute configuration of the reduced product, 2-methylindoline, was compared to literature values and assigned the (*R*)-configuration.[26]

DISCUSSION

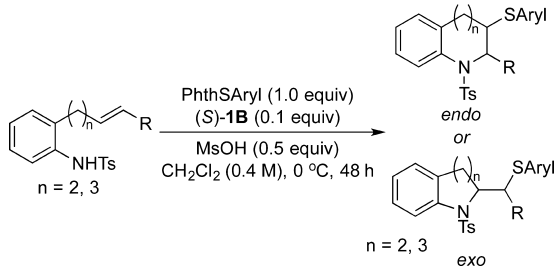
The primary objective for this project was to expand the scope of the enantioselective, catalytic sulfenoamination of olefins to tethered aniline nucleophiles to synthesize enantioenriched benzannulated nitrogen-containing heterocycles, e.g., indolines, tetrahydroquinolines, and tetrahydrobenzazepines. The influence of nucleophile, alkene environment, and tether length on the rate, enantioselectivity, and site selectivity is discussed.

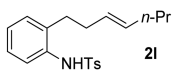
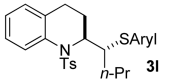
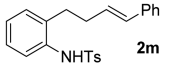
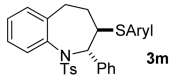
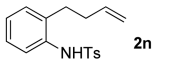
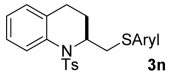
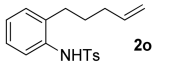
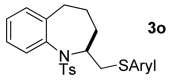
Optimization of the Sulfenoamination Reaction. *Overall Concentration.* During the optimization surveys, the overall concentration was the only factor altered from the typical reaction condition, which was increased 4-fold to 0.4 M from 0.1 M. The main concern with this alteration was that higher concentration could result in racemization via "olefin-to-olefin" transfer of the sulfenium group.[14] However, in contrast to the effects of elevated temperature, increased concentration showed enhanced conversion with no significant enantiomeric erosion, indicating that olefin-to-olefin transfer is disfavored at 0 °C.

Catalyst and Brønsted Acid. An extensive catalyst survey was unnecessary, having been performed in the preceding studies. The third-generation, diisopropylamine-substituted selenophosphoramide catalyst (*S*)-**1B** provided the best selectivity for all O-,[17] C-,[19] and N-nucleophile[20] sulfenofunctionalization reactions. The improved performance of the PhthSAryl relative to other sulfenylating agents (e.g., PhthSPh) attributed to its enhanced steric environment that leads to the

DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX−XXX

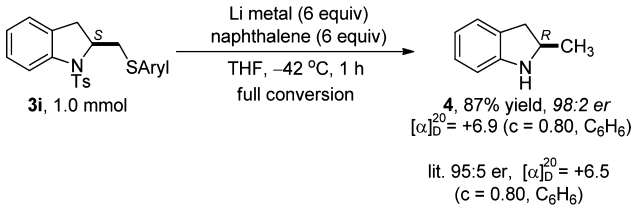
Table 3. Scope of the Sulfenoamination of Substrates with Longer Tethers



entry	substrate	product	yield (%)[a]	endo : exo[b]	er[c]
1	 **2l**	 **3l**	93	1 : >20	98 : 2
2	 **2m**	 **3m**	91	>20 : 1	95 : 5
3	 **2n**	 **3n**	93	1 : >20	98 : 2
4	 **2o**	 **3o**	89	1 : >20	93 : 7

[a]Isolated yields of analytically pure material. [b]Constitutional selectivity determined by ^{1}H NMR spectroscopy of the crude mixture. [c]The enantiomeric ratio of the major constitutional isomer was determined by CSP–HPLC analysis, and the absolute configurations of the products were assigned by comparison of their CD spectra with **3i**.

Scheme 9. Reductive Cleavage of the Sulfide Moiety



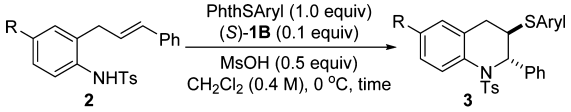
distortion of the catalyst for better differentiation of the two enantiotopic faces of the olefin, ultimately resulting in excellent enantioselectivies in most cases.[18]

The Brønsted acid loading was adopted unchanged from the previous sulfenoamination reaction conditions. According to the titration studies, the catalytically active species ***i*** reached saturation above 4.0 equiv of Brønsted acid with respect to the catalyst (Figure 3).[22] In this sulfenoamination study, 0.5 equiv of MsOH was sufficient for full activation of the catalytically active species ***i*** (^{31}P NMR at 60 ppm) and showed anticipated reactivity for the cyclization. Therefore, the acid loading required no further optimization.

Structural Effects on Rate and Selectivity. *Influence of the Nucleophile.* Many factors can influence the rate, enantioselectivity, and site selectivity of the sulfenoamination reaction, such as electronic and steric properties of the olefin and the nucleophile, or the length of the tether connecting them. Because these factors were also explored in the preceding cyclization studies with aliphatic tosylamides, the results from this work will be compared to those previous results.

Reaction Rate. Anilines with electron-donating (**2a**) and -withdrawing (**2c**) substituents on the *para*-position were both examined (Scheme 10). Whereas no noticeable enhancement on rate was observed with more electron-rich nucleophile relative to the electron-neutral substrate **2b**, the reaction slowed significantly with electron-poor nucleophile **2c**, which required 6 days to reach full completion.

Scheme 10. Effect of the Electron Density of Nucleophile on Sulfenoamination



R	time (d)	yield (%)	er
OMe (**a**)	2	93	94:6
H (**b**)	2	92	95:5
F (**c**)	6	88	96:4

This observation may be explained by a change in the turnover-limiting step (TOLS) (Figure 4). For sulfenofunctionalization reactions involving thiiranium ion intermediates, the formation of the thiiranium ion is typically considered to be turnover limiting.[18] Therefore, electron-rich anilines do not enhance the reaction rate because the formation of the thiiranium ion is not affected by the electronic character of the aniline ring. However, with a 4-fluoro substituent, which is π-donating but σ-withdrawing,[27] the rate was substantially retarded. This outcome can be interpreted as an inductive effect of the 4-fluoro group, resulting in decreased nucleophilicity of the nitrogen atom and thus disfavored capture of the thiiranium ion. Since the thiiranium ion formation should not be affected by the electron-withdrawing character of the aniline ring, the observed rate deceleration can be interpreted as a change of TOLS for **2c** from thiiranium ion formation to nucleophilic capture.

Enantioselectivity. The enantiomeric compositions of the sulfenoamination products were consistently high and exhibited the same absolute configuration across a range of nucleophiles possessing varying electronic properties. This behavior is consistent with the formation of the thiiranium ion being the enantiodetermining step. However, the shift in the turnover-limiting step, as discussed in the previous section, implies an extended lifespan of the thiiranium ion species. According to the previous studies in the configurational stability of thiiranium ions, *S*-phenyl thiiranium ions are known to be configurationally unstable at 0 °C toward "olefin-to-olefin" sulfenium group transfer (Scheme 11).[14] Therefore, decreased enantioselectivity would be expected for slow cyclizations implying a slow capture of the thiiranium ion.

However, for the cyclization of 4-fluoroaniline substrate **2c**, high enantioselectivity was observed despite the slow capture of the thiiranium ion (Scheme 12). This result implied that the *S*-2,6-diisopropylphenyl thiiranium ion preserved its enantioenrichment at 0 °C. Therefore, it may be safely argued that the configurational stability of *S*-2,6-diisopropylphenyl thiiranium ion is much greater than that of *S*-phenyl thiiranium ion at 0 °C.

Site Selectivity. The site selectivity of the cyclization reaction is heavily dominated by the electronic properties of the alkenes. (*E*)-2-Cinnamylaniline derivatives **2a**, **2b**, **2c**, and **2d** afforded 6-*endo*-cyclized products exclusively, regardless of the electronic properties of the nucleophile. Therefore, the variation on

DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX–XXX

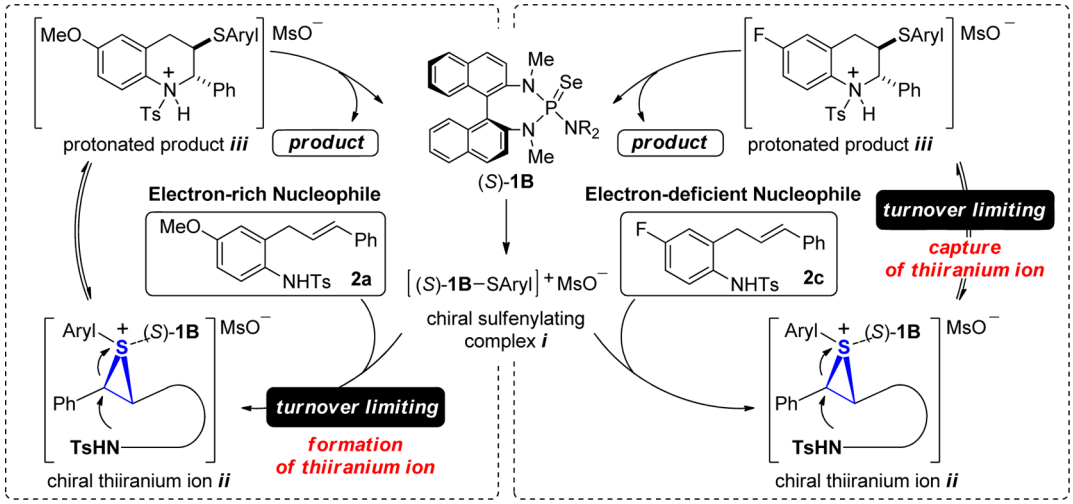
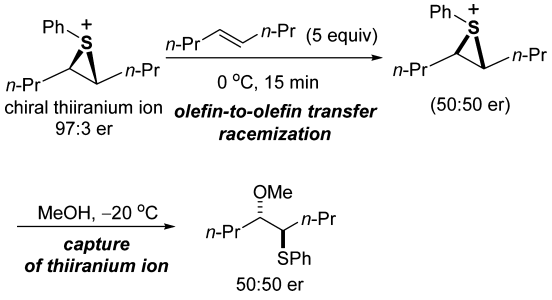
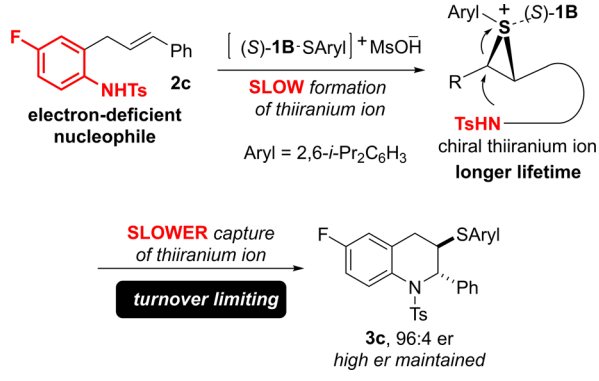


Figure 4. Unified mechanistic scheme for different TOLS.

Scheme 11. Configurational Stability of *N*-Phenyl Thiiranium Ion



Scheme 12. Shift in Turnover-Limiting Step of Substrate 2c



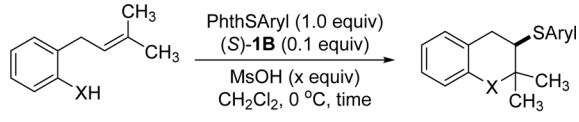
electron density of the nucleophile had no observable influence on the site selectivity of sulfenoamination reaction.

Influence of Alkene Substitution. In the previous sulfenofunctionalization studies, the alkene environment had a profound influence on both rate and selectivity.[17,19,20] The reaction rate is heavily dependent on the electron density of the olefin because the formation of the thiiranium ion is generally the TOLS, while the enantioselectivity is mainly governed by the geometrical and steric environment of the olefin. These properties dictate the affinity of the olefin for the catalytically active species ***i***. On the basis of the assumption that the formation of the thiiranium ion is typically the TOLS, the overarching reactivity trend on the alkene for the sulfenofunctionalizations was established. Therefore, it seemed unnecessary to explore the individual rate of the each reaction; the reactions were set up for 48 h to reach completion by default based on the results from the initial reactivity optimization.

Enantioselectivity. During the examination of substrate scope, the enantiomeric ratios of the cyclized products were mostly unaffected by the alkene environment, with the exception of nitrile substrates **2g**[28] and trisubstituted olefin **2j**. Various aryl- and alkyl-substituted *trans*-alkenes were sulfenoaminated with high (95:5 er) to excellent (98:2 er) enantioselectivities. The consistency of enantiomeric composition observed for the cyclized products implies that the sulfenoamination proceeds through a common, enantioenriched thiiranium ion intermediate. This is strong evidence for the current understanding of the thiiranium ion formation being the enantiodetermining step.

In the case of the trisubstituted olefin **2j**, several hypotheses may account for the diminished enantioselectivity. The first possibility is the lower inherent facial selectivity of the catalyst toward this class of olefin, and the second is the existence of a competitive racemic pathway. However, in contrast to the case of **2j**, high enantioselectivity has recently been obtained for oxysulfenylation of 2-prenylphenol employing (*S*)-**1B**, PhthSAryl, and 0.25 equiv of MsOH (Scheme 13),[29] which strongly suggests that the first possibility is not likely.

Scheme 13. Sulfenofunctionalization of Phenol and Aniline



X	MsOH (equiv)	time (h)	yield (%)	er
O	0.25	24	93	95:5
NTs (**2j**)	0.5	48	92	88:12

The disparity between these two similar trisubstituted substrates may be explained by pH-dependent reactivity differences. During optimization of the oxysulfenylation reaction, comparable rates and enantioselectivities were observed employing 0.25, 0.50, and 0.75 equiv of MsOH; hence, 0.25 equiv of MsOH was chosen as the optimal condition.[29] However, the optimization process of the sulfenoamination reaction with anisidine **2a** showed that 0.5

DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX−XXX

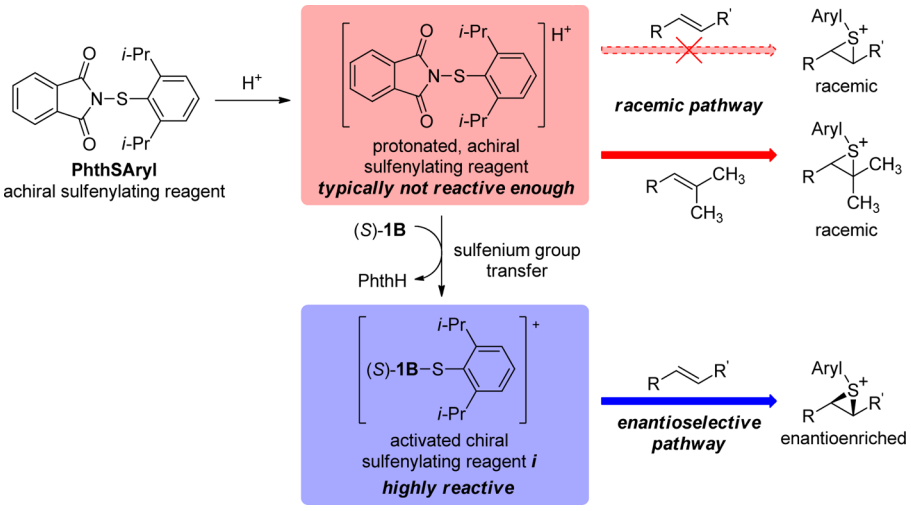


Figure 5. Two pathways for generation of the thiiranium ion intermediates.

equiv of MsOH was adequate without observing a background reaction.

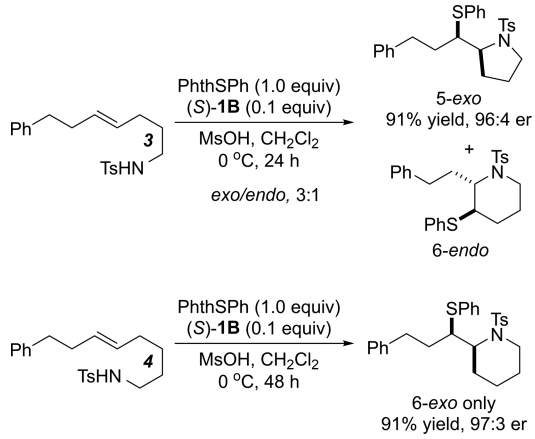
From a titration study, as mentioned earlier, it was found that 4.0 equiv of Brønsted acid with respect to the catalyst was required to fully generate the catalytically active species ***i***.[22] This implies that employing 5.0 equiv of Brønsted acid with respect to the catalyst (the amount of acid loading found to be operative from optimizations) leaves an extra 1.0 equiv of the acid as a free state. This extra free acid can increase the population of protonated, achiral sulfenylating species [PhthSAryl]·H^+.

In the initial step of the catalytic cycle, PhthSAryl is protonated under the acidic conditions (Figure 5). Typically, these protonated sulfenylating species are not reactive enough to effect direct thiiranium ion formation with unactivated disubstituted olefins, evidenced by no conversion in absence of the Lewis base catalyst (Table 1, entry 5). However, trisubstituted alkenes are more electron-rich than disubstituted alkenes, and the subsequent transfer of the sulfenium group to the alkene could generate a racemic thiiranium ion intermediate. Therefore, under stronger acidic conditions, a small quantity of racemic thiiranium ion may be generated from trisubstituted alkenes that may attenuate the observed enantioselectivity.

Site Selectivity. Among the factors governing the site selectivity of the nucleophilic attack, the electron-density distribution in the thiiranium ion appears to be the most important. For example, styrenyl substrates **2b** and **2m** cyclized into tetrahydroquinoline **3b** and tetrahydrobenzazepine **3m** with complete *endo* selectivity. In contrast, aliphatic alkenes cyclized with *exo* selectivity. Steric factors seem to be less important than electronic factors, yet the influence of the olefin steric environment on site selectivity is evident in highly hindered substrates. Isopropyl-substituted olefin **2h** afforded an enhanced *exo*/*endo* ratio compared to other alkyl-substituted olefins, possibly due to the increased steric repulsion between the olefin substituent and the incoming nucleophile. 2-Prenylaniline **2j** cyclized to 2,2-dimethyltetrahydroquinoline **3j** via a 6-*endo* pathway, demonstrating that the site selectivity is governed by the electronic, not steric, factors (Markovnikov rule).

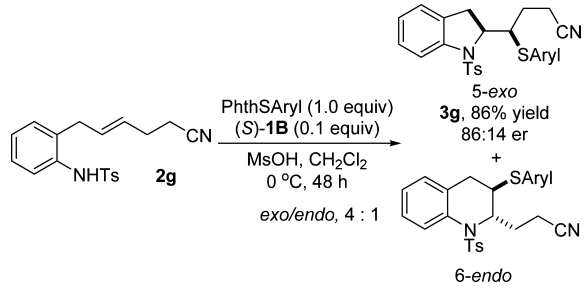
Influence of the Tether Length. From previous studies on sulfenoamination reactions, influence of the tether length was found to be an important factor in controlling the site selectivity (Scheme 14).[20] As is now commonly observed, the enantioselectivities are not affected by the tether length if the alkene substitution pattern is the same.

Scheme 14. Impact of Tether Length on Site Selectivity with Tosylamides



These trends were also observed in the sulfenoamination with aniline substrates. In the case of electronically and sterically unbiased, aliphatic olefins **2g** and **2l**, indoline **3g** (5-*exo* vs 6-*endo*) and tetrahydroquinoline **3l** (6-*exo* vs 7-*endo*) are generated, respectively (Scheme 15). Whereas **3g** was generated in a 4:1 mixture of constitutional isomers favoring

Scheme 15. Effect of Olefin Substitution on Site Selectivity



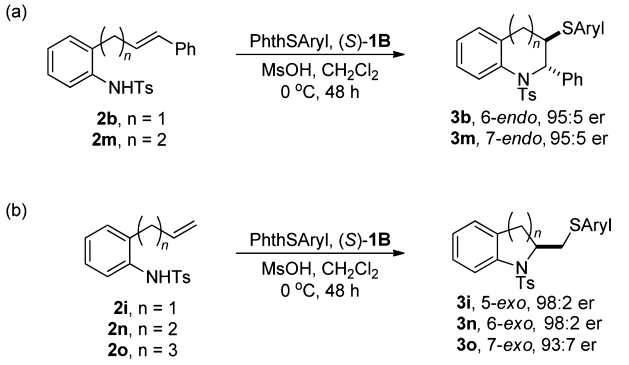
DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX−XXX

the *exo* approach, **3l** was formed with exclusive *exo* selectivity. However, in terms of enantioselectivity comparison, substrate **2g** was an unfortunate choice of selection. Enantioselectivity for cyclization of **2g** was much lower, presumably due to the interference of the nitrile moiety.[28]

This difference in site selectivity is likely attributed to higher activation entropy required for the formation of larger size rings. The site selectivity for a cyclization of an electronically nonbiased alkene should be dependent on the size of the rings that are formed. The rates for the cyclization of *N*-tosylazacycloalkanes are known in the order of 5- > 6- > 7-membered rings.[30] Therefore, the cyclization of **2g** should favor the formation of an indoline over a tetrahydroquinoline via 5-*exo* closure. The cyclization of substrate **2l** also shows good agreement with the reported rate (6-membered ring formation is 200 fold faster than 7-membered ring formation), affording only tetrahydroquinoline **3l** via 6-*exo* closure.

Electronically biased alkene substrates with different tethers were also investigated. Both cinnamyl substrates **2b** and **2m** afforded tetrahydroquinoline **3b** and tetrahydrobenzazepine **3m**, respectively, with a kinetic preference of *endo* cyclization (Scheme 16a). Similar to the trend observed in the previous studies, the enantioselectivities were comparable for both heterocyclic products. The alkenes in substrates **2i**, **2n**, and **2o** bearing different length tethers are electronically biased in the opposite direction (Scheme 16b). All three terminal olefins cyclized via *exo* closure into indolines, tetrahydroquinolines, and tetrahydrobenzazepines with excellent site selectivity. Both of the cinnamyl and terminal alkene substrates demonstrated that the site selectivity is governed by the Markovnikov rule.

Scheme 16. Site Selectivity Following the Markovnikov Rule



CONCLUSION

In conclusion, the catalytic, enantioselective sulfenoamination of olefins with aniline nucleophiles has been developed using a chiral selenophosphoramide Lewis base catalyst. This method allows rapid access to highly enantioenriched *N*-heterocycles, including biologically relevant indolines, tetrahydroquinolines, and tetrahydrobenzazepines with excellent site selectivity. Systematic investigation of the nucleophile component and tether enabled identification of their influence on rate, enantioselectivity, and site selectivity. Whereas rates on cyclizations of electron-neutral and -rich anilines were comparable, those of electron-deficient anilines were greatly decelerated, suggesting a change in the TOLS. Enantioselectivity was unaffected with modifications in nucleophile component or tether length. Excellent site selectivity for styrenyl alkenes was observed, favoring nucleophilic capture at the benzylic carbon. Site-selectivity for cyclization of electronically nonbiased alkenes was low for one-methylene tethers but high for longer tethers. The configurational stability of the thiiranium ions was increased by employing *N*-[(2,6-diisopropylphenyl)thio]phthalimide, leading to enhanced enantioselectivities. Utilization of the arylsulfenyl moiety of the cyclized product is currently under investigation. In addition, development of new catalyst designs suitable for the enantioselective sulfenofunctionalization of *cis*- and higher order substituted alkenes is underway.

EXPERIMENTAL SECTION

General Experimental Procedures. All reactions were performed in oven-dried (140 °C) and/or flame-dried glassware under an atmosphere of dry argon, unless noted. Internal temperatures of low-temperature reactions were measured using Teflon-coated thermocouples unless otherwise noted. A ThermoNesLab CC-100 or a ThermoNesLab IBC-4A cryocool with an attached cryotrol was used for reactions at subambient temperatures.

Boiling points for Kugelrohr distillations correspond to corrected air bath temperatures (ABT). Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus in sealed tubes under vacuum and are corrected. Analytical thin-layer chromatography was performed on Merck silica gel plates with QF-254 indicator. R_f values reported were measured using a 10 × 2 cm TLC plate in a developing chamber containing the solvent system described. Visualization was accomplished with UV (254 nm), potassium permanganate ($KMnO_4$), and/or ceric ammonium molybdate (CAM). Column chromatography was performed using Merck silica 60 (40−63 μm particle size) gel purchased from Aldrich.

Normal-phase HPLC was performed on an Agilent 1100 HPLC equipped with AD-H, OJ-H, IB-3, naphtholeucine, and *R*,*R*-Beta-Gem columns. Reversed-phase HPLC was performed on an Agilent 1100 HPLC using a Chiralpak AD-RH or Chiralcel OJ-RH column. Optical rotations were measured using a JASCO DIP-360 digital polarimeter in Fischer spectranalyzed grade $CHCl_3$ containing approximately 0.75% EtOH as a preservative and are reported as follows: concentration (c = g/dL), a solvent.

^{1}H and ^{13}C NMR spectra were recorded on Varian Unity (400 MHz, ^{1}H; 101 MHz, ^{13}C) or Inova (500 MHz, ^{1}H; 126 MHz, ^{13}C) spectrometers. ^{31}P and ^{19}F NMR spectra were recorded on Inova (202 MHz) and Inova (470 MHz) spectrometers, respectively.^{1}H and ^{13}C NMR spectra were acquired in $CDCl_3$ referenced to residual $CHCl_3$ at 7.26 and 77.00 ppm, respectively. Assignments were obtained by reference to COSY, HSQC, and HMBC correlations. Chemical shifts are reported in ppm, and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sext (sextet), sept (septet), m (multiplet) and br (broad). Coupling constants, J, are reported in hertz, integration is provided, and assignments are indicated.

Mass spectroscopy (MS) was performed by the University of Illinois Mass Spectrometry Center. ESI mass spectra were performed on a Waters or Micromass Q-Tof Ultima instrument. EI mass spectra were performed on a 70-VSE instrument. Data are reported in the form of (m/z) versus intensity. Infrared spectra (IR) were recorded on a PerkinElmer FT-IR system. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 67−100%); m (medium, 34−66%); w (weak, 0−33%). Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory and Robertson Microlit Laboratories, Inc.

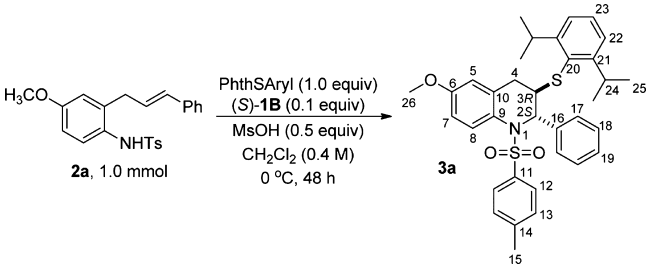
Commercial Chemicals. Reaction solvents tetrahydrofuran (Fisher, HPLC grade) and CH_2Cl_2 (Fisher, unstabilized HPLC grade) were dried by passage through two columns of neutral alumina in a solvent-dispensing system. Reaction solvent deuterated chloroform ($CDCl_3$, Cambridge Isotope Laboratories, D 99.8%) was dried by keeping it with activated 4 A MS at least over 24 h. Solvents for chromatography, filtration, and recrystallization were CH_2Cl_2 (Aldrich, ACS grade),

DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX−XXX

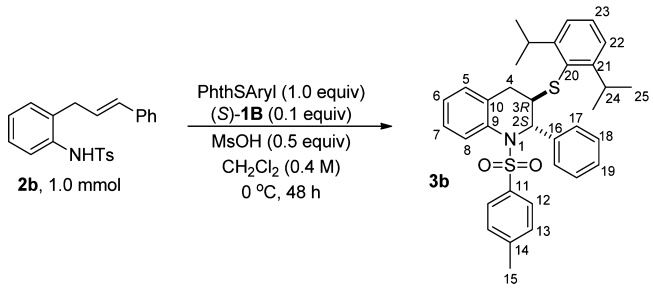
ethyl acetate (Fisher, ACS grade), pentane (Fisher, HPLC grade), and hexanes (Fisher, Optima) and used as received.

Literature Preparations. Substrates **2a–h**,[23] **2i**,[31] **2j**,[32] **2k–m**,[23] **2n**,[33] **2o**,[23] catalyst (*S*)-**1B**,[20] and sulfenylating agent *N*-(2,6-diisopropyl)thiophthalimide (PhthSAryl)[18] were prepared according to literature procedures.

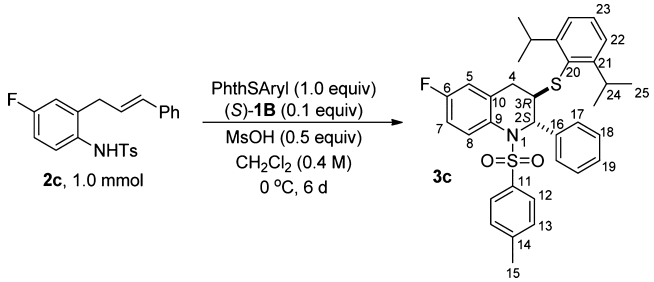
General Procedure I: Sulfenoamination of Anilines. An oven-dried, 10 mL Schlenk flask equipped with a stir bar was charged with substrate **2** (1.0 mmol, 1.0 equiv), PhthSAryl (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**1B** (52.1 mg, 0.1 mmol, 0.10 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M) then capped with a rubber septum followed by argon purge. The flask was placed in a 0 °C isopropyl alcohol bath cooled via a Cryocool unit. The temperature of the mixture was monitored via a thermocouple digital temperature probe. After the temperature stabilized, MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) was added slowly via syringe (internal temperature was maintained below 4 °C during addition of MsOH, and MsOH was dropped carefully far from the top to prevent freezing in the syringe), and the mixture was allowed to stir for the indicated time. The reaction was quenched while cold by addition of precooled satd $NaHCO_3$ aq solution (5 mL) upon vigorous stirring. The biphasic resulting mixture was extracted with CH_2Cl_2 (5 mL × 3). The combined organic extracts were dried over Na_2SO_4, filtered through glass wool, and then concentrated in vacuo (23 °C, 10 mmHg) to afford the crude solid product. The product **3** was purified via silica gel flash column chromatography.



*Preparation of (2S,3R)-3-[(2,6-Diisopropylphenyl)thio]-6-methoxy-2-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (**3a**).* Following general procedure I, a 10 mL Schlenk flask was charged with **2a** (393.5 mg, 1.0 mmol, 1.0 equiv), PhthSAryl (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**1B** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) at 0 °C, and the mixture was stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm ⌀, hexanes/EtOAc, 19:1–9:1) to afford 510 mg (87%) of a **3a** as a white solid. An analytically pure sample was obtained by recrystallization of the solid with boiling EtOAc/pentane (1:10 mixture, 10 mL) to afford **3a** as white crystals. Data for **3a**: mp 157–158 °C (EtOAc/pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 8.5 Hz, 1 H, HC(8)), 7.54 (d, J = 8.0 Hz, 2 H, HC(12)) 7.39–7.27 (m, 8 H, HC(aryl)), 7.10 (d, J = 7.5 Hz, 2 H, HC(22)), 6.87 (dd, J = 9.0, 3.0 Hz, 1 H, HC(7)), 6.40 (d, J = 3.0 Hz, 1 H, HC(5)), 5.15 (d, J = 9.0 Hz, 1 H, HC(2)), 3.79 (s, 3 H, HC(26)), 3.35 (brs, 2 H, HC(24)), 2.83 (ddd, J = 12.5, 9, and 4.0 Hz, 1 H, HC(3)), 2.48 (s, 3 H, HC(15)), 2.18 (dd, J = 14.0, 4.0 Hz, 1 H, HC(4)), 1.52 (t, J = 13.0 Hz, 1 H, HC(4)), 1.06 (d, J = 7.0 Hz, 6 H, HC(25)), 0.98 (d, J = 7.0 Hz, 6 H, HC(25)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0 (C6), 153.7 (C20), 143.5 (C11), 142.5 (C16), 136.3 (C14), 135.7 (C10), 129.5 (C19), 129.5 (C13), 129.2 (C9), 128.9 (C8), 128.8 (C21), 128.3 (C17), 127.5 (C23), 127.2 (C12), 127.0 (C18), 123.6 (C22), 112.9 (C7), 112.6 (C5), 64.6 (C2), 55.5 (C26), 55.4 (C3), 33.8 (C4), 31.2 (C24), 24.5 (C25), 23.8 (C25), 21.6 (C15); MS (ESI) 148 (13), 236 (11), 431 (100), 432 (31), 586 (M + H, 11), 608 (22); HRMS calcd for $C_{35}H_{40}NO_3S_2$ 586.2450, found 586.2440; TLC R_f 0.34 (hexanes/EtOAc, 4:1) [UV]; IR 2965 (w), 1495 (m), 1457 (w), 1354 (m), 1343 (w), 1222 (m), 1164 (s), 1089 (w), 1053 (m), 1032 (w), 960 (w), 868 (m), 811 (w), 802 (m), 750 (w); $[\alpha]_D^{24}$ −35.7 (c = 0.90, $CHCl_3$); CD (−), Cotton sign, 230–280 nm; HPLC (2*R*,3*S*)-**3a**, t_R 7.1 min (6.3%); (2*S*,3*R*)-**3a**, t_R 8.2 min (93.7%) (Chiralpak AD, 220 nm, 90:10, hexanes/i-PrOH, 1 mL/min). Anal. Calcd for $C_{35}H_{39}NO_3S_2$ (585.82): C, 71.76; H, 6.71; N, 2.39. Found: C, 71.63; H, 6.59; N, 2.26.



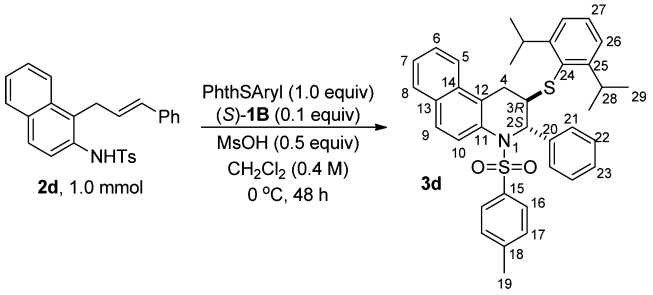
*Preparation of (2S,3R)-3-[(2,6-Diisopropylphenyl)thio]-2-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (**3b**).* Following general procedure I, a 10 mL Schlenk flask was charged with **2b** (363.5 mg, 1.0 mmol, 1.0 equiv), PhthSAryl (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**1B** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) at 0 °C, and the mixture was stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm ⌀, hexanes/EtOAc, 19:1–9:1) to afford 510 mg (92%) of a **3b** as a white solid. An analytically pure sample was obtained by recrystallization of the solid with boiling pentane (20 mL) to afford **3b** as white crystals. Data for **3b**: mp 172–173 °C (pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 1 H, HC(8)), 7.56 (d, J = 8.0 Hz, 2 H, HC(12)) 7.37–7.25 (m, 9 H, HC(aryl)), 7.14 (td, J = 7.5, 1.0 Hz, 1 H, HC(6)), 7.10 (d, J = 7.5 Hz, 2 H, HC(22)), 6.88 (d, J = 7.5 Hz, 1 H, HC(5)), 5.26 (d, J = 8.5 Hz, 1 H, HC(2)), 3.37 (brs, 2 H, HC(24)), 2.89 (ddd, J = 11.5, 8.5, and 4.0 Hz, 1 H, HC(3)), 2.46 (s, 3 H, HC(15)), 2.31 (dd, J = 14.0, 4.0 Hz, 1 H, HC(4)), 1.71 (dd, J = 14.0, 12.0 Hz, 1 H, HC(4)), 1.07 (d, J = 7.0 Hz, 6 H, HC(25)), 0.99 (d, J = 7.0 Hz, 6 H, HC(25)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0 (C6), 153.7 (C20), 143.7 (C11), 142.2 (C16), 136.3 (C14), 135.8 (C10), 131.0 (C9), 129.6 (C19), 129.5 (C13), 129.0 (C8), 128.7 (C21), 128.3 (C17), 127.6 (C23), 127.2 (C12), 127.0 (C18), 123.7 (C22), 113.4 (C7), 113.4 (C5), 64.6 (C2), 55.3 (C3), 33.6 (C4), 31.2 (C24), 24.5 (C25), 23.8 (C25), 21.6 (C15); MS (ESI) 169 (17), 259 (22), 286 (28), 440 (95), 442 (100), 522 (41), 556 (M + H, 10), 636 (40); HRMS calcd for $C_{34}H_{38}NO_2S_2$ 556.2344, found 556.2340; TLC R_f 0.43 (hexanes/EtOAc, 4:1) [UV]; IR 2965 (w), 1487 (w), 1461 (w), 1356 (m), 1169 (s), 1093 (w), 1054 (w), 1005 (w), 960 (m), 817 (m), 807 (m), 761 (w), 753 (w); $[\alpha]_D^{24}$ −43.0 (c = 0.90, $CHCl_3$); CD (−), Cotton sign, 230–280 nm; HPLC (2*R*,3*S*)-**3b**, t_R 8.5 min (5.2%); (2*S*,3*R*)-**3b**, t_R 10.1 min (94.8%) (Chiralpak AD, 220 nm, 90:10, hexanes/i-PrOH, 1 mL/min). Anal. Calcd for $C_{34}H_{37}NO_2S_2$ (555.79): C, 73.47; H, 6.71; N, 2.52. Found: C, 73.23; H, 6.53; N, 2.30.



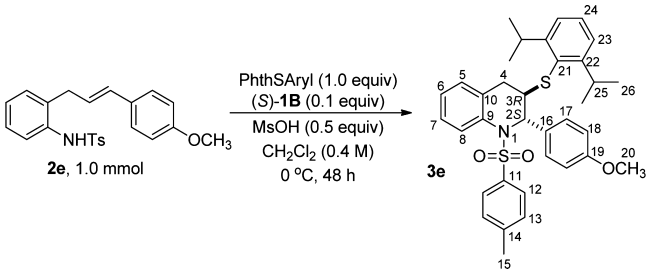
*Preparation of (2S,3R)-3-[(2,6-Diisopropylphenyl)thio]-6-fluoro-2-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (**3c**).* Following general procedure I, a 10 mL Schlenk flask was charged with **2c** (381.5 mg, 1.0 mmol, 1.0 equiv), PhthSAryl (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**1B** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) at 0 °C, and the mixture was stirred for 6 d. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm ⌀, hexanes/EtOAc, 19:1–9:1) to afford 493 mg (86%) of a **3c** as a white solid. An analytically pure sample was obtained by recrystallization of the solid with boiling

DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX–XXX

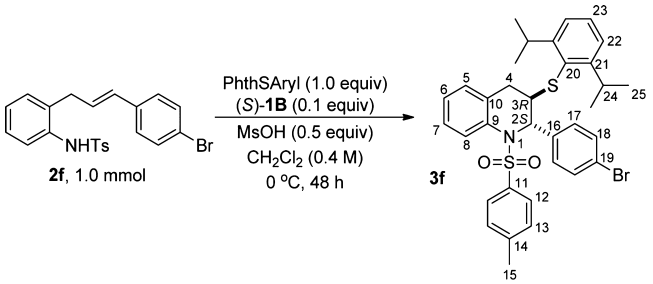
pentane (20 mL) to afford **3c** as white crystals. An analytically pure sample was obtained by recrystallization of the solid with boiling pentane (20 mL) to afford **3c** as white crystals. Data for **3c**: mp 198–199 °C (pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (ddd, J = 9.0, 5.0, and 2.0 Hz, 1 H, HC(8)), 7.56 (d, J = 8.0 Hz, 2 H, HC(12)) 7.38–7.28 (m, 8 H, HC(aryl)), 7.11 (d, J = 7.5 Hz, 2 H, HC(22)), 7.03 (td, J = 8.5, 3.0 Hz, 1 H, HC(7)), 6.62 (dd, J = 8.5, 3.0 Hz, 1 H, HC(5)), 5.21 (dd, J = 9.0, 2.5 Hz, 1 H, HC(2)), 3.35 (brs, 2 H, HC(24)), 2.90–2.83 (m, 1 H, HC(3)), 2.49 (s, 3 H, HC(15)), 2.28–2.21 (m, 1 H, HC(4)), 1.60 (d, J = 14.0, 12.0 Hz, 1 H, HC(4)), 1.07 (d, J = 6.5 Hz, 6 H, HC(25)), 0.99 (d, J = 7.0 Hz, 6 H, HC(25)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.7 (d, J = 248.3 Hz, C6), 153.6 (C20), 143.8 (C11), 142.1 (C16), 136.2 (C14), 136.0 (d, J = 7.4 Hz, C10), 132.4 (d, J = 2.8 Hz, C9), 129.7 (C19), 129.6 (C13), 129.0 (d, J = 8.3 Hz, C8), 128.6 (C21), 128.4 (C17), 127.7 (C23), 127.2 (C12), 126.9 (C18), 123.7 (C22), 114.6 (d, J = 22.6 Hz, C7), 114.2 (d, J = 22.8 Hz, C5), 64.5 (C2), 55.1 (C3), 33.4 (C4), 31.2 (C24), 24.5 (C25), 23.8 (C25), 21.6 (C15); ^{19}F NMR δ −115.42 (app q, J = 7.2 Hz); MS (ESI) 181 (19), 224 (35), 380 (100), 381 (25), 574 (M + H, 42), 596 (M + Na, 36); HRMS calcd for $C_{34}H_{37}NO_2S_2F$: 574.2250, found 574.2245; TLC R_f 0.45 (hexanes/EtOAc, 4:1) [UV]; IR 2965 (w), 1490 (m), 1356 (m), 1347 (m), 1184 (w), 1168 (s), 1141 (m), 1042 (m), 940 (w), 872 (m), 818 (w), 799 (m), 747 (m); $[\alpha]_D^{24}$ −17.9 (c = 0.90, $CHCl_3$); CD (−), Cotton sign, 230–280 nm; HPLC (2*R*,3*S*)-**3c**, t_R 6.9 min (4.4%); (2*S*,3*R*)-**3c**, t_R 8.5 min (95.6%) (Chiralpak AD, 220 nm, 90:10, hexanes/i-PrOH, 1 mL/min). Anal. Calcd for $C_{34}H_{36}NO_2S_2F$ (573.78): C, 71.17; H, 6.32; N, 2.44. Found: C, 71.17; H, 6.30; N, 2.36%.



*Preparation of (2S,3R)-3-[(2,6-Diisopropylphenyl)thio]-2-phenyl-1-tosyl-1,2,3,4-tetrahydrobenzo[f]quinoline (**3d**).* Following general procedure I, a 10 mL Schlenk flask was charged with **2d** (413.5 mg, 1.0 mmol, 1.0 equiv), PhthSAryl (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**1B** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) at 0 °C, and the mixture was stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm ⌀, hexanes/EtOAc, 19:1–9:1) to afford 563 mg (93%) of a **3d** as a white solid. An analytically pure sample was obtained by recrystallization of the solid with boiling EtOAc/pentane (1:10 mixture, 10 mL) to afford **3d** as white crystals. Data for **3d**: mp 214–215 °C (EtOAc/pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 9.0 Hz, 1 H, HC(9)), 7.86 (d, J = 8.0 Hz, 1 H, HC(5)) 7.81 (d, J = 9.0 Hz, 1 H, HC(10)), 7.59 (d, J = 8.5 Hz, 2 H, HC(16)), 7.50 (d, J = 8.5 Hz, 1 H, HC(8)), 7.45 (t, J = 7.0 Hz, 1 H, HC(6)), 7.40 (t, J = 7.0 Hz, 1 H, HC(7)), 7.35–7.27 (m, 6 H, HC(aryl)), 7.22 (d, J = 8.0 Hz, 2 H, HC(17)), 7.11 (d, J = 7.5 Hz, 1 H, HC(26)), 5.41 (d, J = 7.5 Hz, 1 H, HC(2)), 3.44 (brs, 2 H, HC(28)), 3.05–2.96 (m, 2 H, HC(3,4)), 2.43 (s, 3 H, HC(19)), 1.84 (td, J = 12.0, 4.0 Hz, 1 H, HC(4)), 1.07 (d, J = 7.0 Hz, 6 H, HC(29)), 0.97 (d, J = 7.0 Hz, 6 H, HC(29)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7 (C24), 143.7 (C15), 142.1 (C20), 136.5 (C18), 134.4 (C12), 131.7 (C14), 130.5 (C13), 129.7 (C23), 129.5 (C17), 128.9 (C25), 128.6 (C5), 128.4 (C21), 127.9 (C11), 127.6 (C10), 127.5 (C27), 127.3 (C16), 126.9 (C22), 126.3 (C7), 125.5 (C6), 125.1 (C9), 123.7 (C26), 122.4 (C8), 64.3 (C2), 55.2 (C3), 31.3 (C28), 27.6 (C4), 24.4 (C29), 23.9 (C29), 21.6 (C19); MS (ESI) 167 (34), 168 (59), 256 (48), 257 (25), 412 (58), 413 (17), 451 (100), 452 (34), 606 (M + H, 91), 607 (41), 628 (M + Na, 68), 629 (29); HRMS calcd for $C_{38}H_{40}NO_2S_2$ 606.2500, found 606.2501; TLC R_f 0.40 (hexanes/EtOAc, 4:1) [UV]; IR 2965 (w), 1455 (w), 1358 (s), 1239 (w), 1170 (s), 1091 (w), 1048 (w), 1025 (w), 990 (m), 807 (m), 762 (w), 747 (m); $[\alpha]_D^{24}$ −92.5 (c = 0.90, $CHCl_3$); CD (−), Cotton sign, 230–280 nm; HPLC (2*R*,3*S*)-**3d**, t_R 9.5 min (2.3%); (2*S*,3*R*)-**3d**, t_R 13.3 min (97.7%) (Chiralpak AD, 220 nm, 90:10, hexanes/i-PrOH, 1 mL/min). Anal. Calcd for $C_{38}H_{39}NO_2S_2$ (605.85): C, 75.33; H, 6.49; N, 2.31. Found: C, 74.93; H, 6.37; N, 2.41.



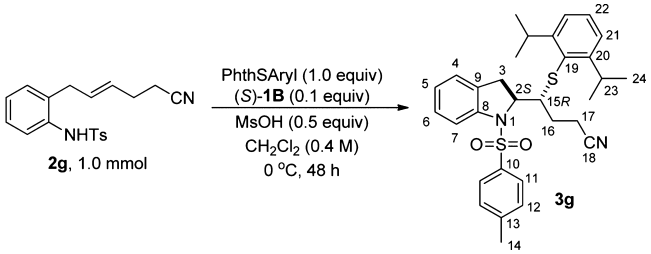
*Preparation of (2S,3R)-3-[(2,6-Diisopropylphenyl)thio]-2-(4-methoxyphenyl)-1-tosyl-1,2,3,4-tetrahydroquinoline (**3e**).* Following general procedure I, a 10 mL Schlenk flask was charged with **2e** (393.5 mg, 1.0 mmol, 1.0 equiv), PhthSAryl (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**1B** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) at 0 °C, and the mixture was stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm ⌀, hexanes/EtOAc, 19:1–9:1) to afford 546 mg (93%) of a **3e** as a white solid. An analytically pure sample was obtained by recrystallization of the solid with boiling EtOAc/pentane (1:10 mixture, 10 mL) to afford **3e** as white crystals. Data for **3e**: mp 161–162 °C (EtOAc/pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.0 Hz, 1 H, HC(8)), 7.55 (d, J = 8.0 Hz, 2 H, HC(12)) 7.33–7.23 (m, 6 H, HC(aryl)), 7.15–7.08 (m, 3 H, HC(aryl)), 6.89–6.85 (m, 3 H, HC(aryl)), 5.22 (d, J = 8.5 Hz, 1 H, HC(2)), 3.84 (s, 3 H, HC(20)), 3.41 (brs, 2 H, HC(25)), 2.89 (ddd, J = 11.5, 8.5, and 4.0 Hz, 1 H, HC(3)), 2.45 (s, 3 H, HC(15)), 2.29 (dd, J = 14.0, 4.0 Hz, 1 H, HC(4)), 1.68 (dd, J = 14.0, 11.5 Hz, 1 H, HC(4)), 1.08 (d, J = 7.0 Hz, 6 H, HC(26)), 1.00 (d, J = 7.0 Hz, 6 H, HC(26)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0 (C19), 153.6 (C21), 143.5 (C11), 136.5 (C14), 136.4 (C16), 134.6 (C10), 133.4 (C9), 129.5 (C7), 129.4 (C13), 128.9 (C22), 128.1 (C17), 127.7 (C24), 127.5 (C5), 127.2 (C12), 126.7 (C8), 126.1 (C6), 123.6 (C23), 113.7 (C18), 64.2 (C2), 55.3 (C3), 55.3 (C20), 33.2 (C4), 31.2 (C25), 24.5 (C26), 23.9 (C26), 21.6 (C15); MS (ESI) 114 (44), 121 (100), 142 (17), 150 (28), 236 (64), 392 (70), 608 (M + Na, 78), 609 (31), 624 (20); HRMS calcd for $C_{35}H_{39}NO_3S_2Na$ 608.2269, found 608.2257; TLC R_f 0.35 (hexanes/EtOAc, 4:1) [UV]; IR 2965 (w), 1497 (m), 1455 (w), 1347 (m), 1341 (w), 1225 (w), 1163 (s), 1090 (w), 1053 (m), 1030 (w), 958 (w), 853 (m), 812 (w), 800 (m), 749 (w); $[\alpha]_D^{24}$ −27.6 (c = 0.90, $CHCl_3$); CD (−), Cotton sign, 230–280 nm; HPLC (2*R*,3*S*)-**3e**, t_R 10.5 min (3.9%); (2*S*,3*R*)-**3e**, t_R 14.6 min (96.1%) (Chiralpak AD, 220 nm, 90:10, hexanes/i-PrOH, 1 mL/min). Anal. Calcd for $C_{35}H_{39}NO_3S_2$ (585.82): C, 71.76; H, 6.71; N, 2.39. Found: C, 71.68; H, 6.89; N, 2.41.



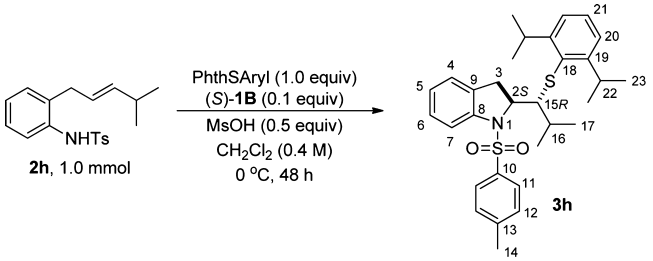
*Preparation of (2S,3R)-2-(4-Bromophenyl)-3-[(2,6-diisopropyl)-phenylthio]-1-tosyl-1,2,3,4-tetrahydroquinoline (**3f**).* Following general procedure I, a 10 mL Schlenk flask was charged with **2f** (442.4 mg, 1.0 mmol, 1.0 equiv), PhthSAryl (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-

DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX–XXX

1B (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) at 0 °C, and the mixture was stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm ⌀, hexanes/EtOAc, 19:1−9:1) to afford 557 mg (88%) of a **3f** as a white solid. An analytically pure sample was obtained by recrystallization of the solid with boiling pentane (20 mL) to afford **3f** as white crystals. Data for **3f**: mp 183−184 °C (pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 1 H, HC(8)), 7.53 (d, J = 8.5 Hz, 2 H, HC(12)), 7.47 (d, J = 8.5 Hz, 2 H, HC(18)), 7.35−7.22 (m, 6 H, HC(7,13,17,23)), 7.14 (td, J = 7.5, 1.0 Hz, 1 H, HC(6), 7.11 (d, J = 7.5 Hz, 2 H, HC(22)), 6.87 (d, J = 7.5 Hz, 1 H, HC(5)), 5.16 (d, J = 9.0 Hz, 1 H, HC(2)), 3.34 (brs, 2 H, HC(24)), 2.79 (ddd, J = 11.5, 9.0, and 4.0 Hz, 1 H, HC(3)), 2.46 (s, 3 H, HC(15)), 2.30 (dd, J = 14.0, 4.0 Hz, 1 H, HC(4)), 1.66 (dd, J = 14.0, 11.5 Hz, 1 H, HC(4)), 1.08 (d, J = 7.0 Hz, 6 H, HC(25)), 0.99 (d, J = 7.0 Hz, 6 H, HC(25)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.6 (C20), 143.8 (C11), 141.5 (C16), 136.2 (C14), 136.1 (C10), 133.4 (C9), 131.4 (C18), 129.7 (C7), 129.5 (C13), 128.7 (C17), 128.5 (C21), 127.9 (C23), 127.5 (C5), 127.2 (C12), 126.8 (C8), 126.4 (C6), 123.7 (C22), 121.5 (C19), 64.2 (C2), 55.2 (C3), 33.3 (C4), 31.2 (C21), 24.5 (C25), 23.9 (C25), 21.6 (C15); MS (ESI) 169 (14), 171 (16), 259 (22), 261 (21), 284 (27), 286 (28), 287 (10), 440 (96), 441 (24), 442 (100), 443 (24), 634 (M + H, 39), 635 (17), 636 (45), 637 (17), 656 (M + Na, 30), 657 (12), 658 (34), 659 (13); HRMS calcd for $C_{34}H_{37}NO_2S_2Br$: 634.1449, found 634.1448; TLC R_f 0.43 (hexanes/EtOAc, 4:1) [UV]; IR 2963 (w), 1488 (w), 1350 (m), 1342 (m), 1180 (m), 1167 (s), 1139 (m), 1047 (m), 1041 (m), 960 (w), 940 (w), 867 (m), 815 (w), 799 (m), 746 (m); $[\alpha]_D^{24}$ −51.2 (c = 0.90, $CHCl_3$); CD (−), Cotton sign, 230−280 nm; HPLC (2*R*,3*S*)-**3f**, t_R 6.5 min (3.3%); (2*S*,3*R*)-**3f**, t_R 8.8 min (96.7%) (Chiralpak AD, 220 nm, 90:10, hexanes/i-PrOH, 1 mL/min). Anal. Calcd for $C_{34}H_{36}BrNO_2S_2$ (634.69): C, 64.34; H, 5.72; N, 2.21. Found: C, 64.53; H, 5.58; N, 2.17.

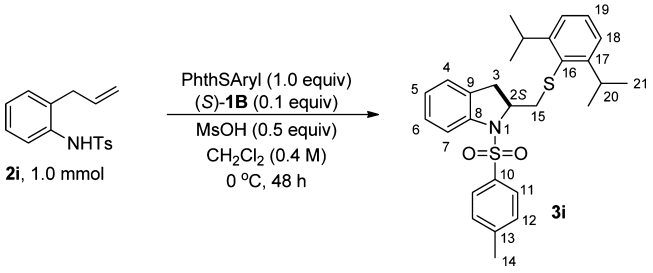


*Preparation of (2S,15R)-2-{3-[1-(2,6-Diisopropyl)phenylthio]-cyanopropyl}-1-tosylindoline (**3g**).* Following general procedure I, a 10 mL Schlenk flask was charged with **2g** (340.4 mg, 1.0 mmol, 1.0 equiv), PhthSAryl (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**1B** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) at 0 °C and the mixture was stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm ⌀, hexanes/EtOAc, 19:1−9:1) to afford 457 mg (86%) of a **3g** as a white solid. An analytically pure sample was obtained by recrystallization of the solid with boiling EtOAc/pentane (1:10 mixture, 10 mL) to afford **3g** as white crystals. Data for **3g**: mp 144−145 °C (EtOAc/pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.0 Hz, 1 H, HC(7)), 7.39 (t, J = 7.5 Hz, 1 H, HC(22)), 7.33 (d, J = 8.5 Hz, 2 H, HC(11)), 7.27−7.21 (m, 3 H, HC(6,21)), 7.18−7.05 (m, 4 H, HC(4,5,12)), 4.03 (dd, J = 11.0, 9.5 Hz, 1 H, HC(2)), 3.93 (sept, J = 7.0 Hz, 2 H, HC(23)), 3.39 (dd, J = 13.5, 3.0 Hz, 1 H, HC(15)), 2.95 (dd, J = 16.0, 3.0 Hz, 1 H, HC(3)), 2.94 (dd, J = 16.0, 9.0 Hz, 1 H, HC(3)), 2.47−2.33 (m, 4 H, HC(16,17)), 2.38 (s, 3 H, HC(14)), 1.30 (d, J = 7.0 Hz, 6 H, HC(24)), 1.22 (d, J = 7.0 Hz, 6 H, HC(24)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2 (C19), 144.0 (C10), 141.5 (C8), 134.2 (C13), 130.7 (C9), 129.8 (C20), 129.2 (C12), 129.1 (C22), 127.6 (C6), 126.8 (C11), 125.0 (C4), 124.8 (C5), 123.8 (C21), 119.1 (C18), 117.4 (C7), 61.5 (C2), 43.1 (C15), 33.9 (C3), 31.5 (C23), 28.3 (C16), 24.3 (C24), 24.2 (C24), 21.4 (C14), 17.5 (C17); MS (ESI) 169 (14), 171 (16), 259 (22), 261 (21), 284 (27), 286 (28), 287 (10), 440 (96), 441 (24), 442 (100), 443 (24), 634 (M + H, 39), 635 (17), 636 (45), 637 (17), 656 (M + Na, 30), 657 (12), 658 (34), 659 (13); HRMS calcd for $C_{31}H_{37}N_2O_2S_2$: 533.2296, found 533.2293; TLC R_f 0.49 (hexanes/EtOAc, 4:1) [UV]; IR 2965 (w), 2249 (s), 1456 (w), 1323 (m), 1159 (s), 1089 (w), 1054 (m), 1029 (m), 961 (m), 921 (w), 816 (w), 807 (m), 755 (w), 749 (w); $[\alpha]_D^{24}$ −21.4 (c = 0.90, $CHCl_3$); CD (−), Cotton sign, 230−280 nm; HPLC (2*R*,15*S*)-**3g**, t_R 7.3 min (13.6%); (2*S*,15*R*)-**3g**, t_R 9.1 min (86.4%) (Chiralpak AD, 220 nm, 90:10, hexanes/i-PrOH, 1 mL/min). Anal. Calcd for $C_{31}H_{36}N_2O_2S_2$ (532.76): C, 69.89; H, 6.81; N, 5.26. Found: C, 69.71; H, 6.64; N, 5.21.

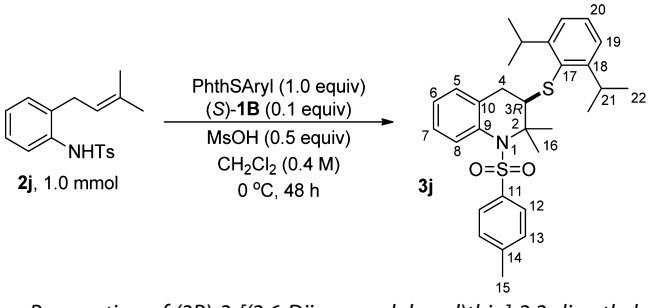


*Preparation of (2S,15R)-2-{2-[(2,6-Diisopropylphenyl)thio]-isobutyl}-1-tosylindoline (**3h**).* Following general procedure I, a 10 mL Schlenk flask was charged with **2h** (329.5 mg, 1.0 mmol, 1.0 equiv), PhthSAryl (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**1B** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) at 0 °C, and the mixture was stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm ⌀, hexanes/EtOAc, 19:1−9:1) to afford 443 mg (85%) of a **3h** as a white solid. An analytically pure sample was obtained by recrystallization of the solid with boiling EtOAc/pentane (1:10 mixture, 10 mL) to afford **3h** as white crystals. Data for **3h**: mp 131−132 °C (EtOAc/pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, J = 7.5 Hz, 1 H, HC(7)), 7.44 (t, J = 8.0 Hz, 1 H, HC(21)), 7.31 (d, J = 8.5 Hz, 2 H, HC(11)), 7.29−7.05 (m, 7 H, HC(4,5,6,12,20)), 4.06 (ddt, J = 11.5, 9.5, and 2.0 Hz, 1 H, HC(2)), 3.95 (sept, J = 7.0 Hz, 2 H, HC(22)), 3.53 (m, 1 H, HC(15)), 2.99 (dd, J = 16.5, 3.5 Hz, 1 H, HC(3)), 2.91 (dd, J = 16.5, 9.0 Hz, 1 H, HC(3)), 2.36 (s, 3 H, HC(14)), 2.10 (sept, 1 H, HC(16)), 1.30 (d, J = 7.0 Hz, 6 H, HC(23)), 1.23 (d, J = 7.0 Hz, 6 H, HC(23)), 1.11 (d, J = 6.5 Hz, 3 H, HC(17)), 1.09 (d, J = 6.5 Hz, 3 H, HC(17)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.0 (C18), 144.1 (C10), 141.5 (C8), 134.2 (C13), 130.1 (C19), 129.9 (C9), 129.5 (C12), 129.4 (C21), 127.7 (C6), 126.5 (C11), 125.4 (C4), 124.7 (C5), 123.6 (C20), 117.0 (C7), 61.3 (C2), 60.0 (C15), 33.9 (C3), 32.1 (C16), 31.4 (C22), 24.4 (C23), 24.1 (C23), 21.5 (C14), 21.1 (C17), 20.5 (C17); MS (ESI) 169 (14), 171 (16), 259 (22), 261 (21), 284 (27), 286 (28), 287 (10), 440 (96), 441 (24), 442 (100), 443 (24), 634 (M + H, 39), 635 (17), 636 (45), 637 (17), 656 (M + Na, 30), 657 (12), 658 (34), 659 (13); HRMS calcd for $C_{31}H_{40}NO_2S_2$: 522.2500, found 522.2504; TLC R_f 0.47 (hexanes/EtOAc, 4:1) [UV]; IR 2964 (w), 1486 (w), 1356 (m), 1160 (s), 1093 (w), 1076 (w), 1054 (m), 1029 (m), 1002 (w), 961 (m), 813 (m), 805 (m), 761 (w), 751 (m); $[\alpha]_D^{24}$ −31.2 (c = 0.90, $CHCl_3$); CD (−), Cotton sign, 230−280 nm; HPLC (2*R*,15*S*)-**3h**, t_R 7.8 min (2.2%); (2*S*,15*R*)-**3h**, t_R 10.4 min (97.8%) (Chiralpak AD, 220 nm, 90:10, hexanes/i-PrOH, 1 mL/min). Anal. Calcd for $C_{31}H_{39}NO_2S_2$ (521.78): C, 71.36; H, 7.53; N, 2.68. Found: C, 71.51; H, 7.72; N, 2.70.

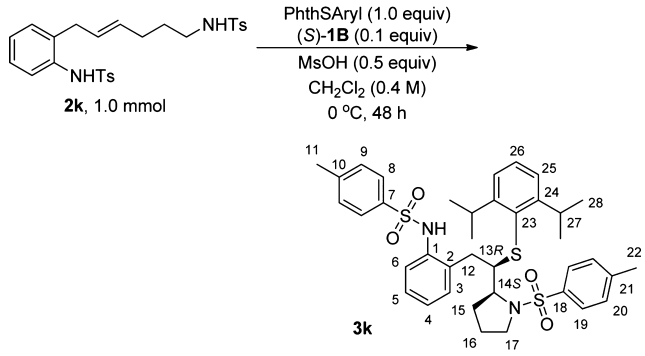
DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX−XXX



*Preparation of (2S)-2-{[(2,6-Diisopropylphenyl)thio]methyl}-1-tosylindoline (**3i**).* Following general procedure I, a 10 mL Schlenk flask was charged with **2i** (287.4 mg, 1.0 mmol, 1.0 equiv), PhthSAryl (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**1B** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) at 0 °C, and the mixture was stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm ⌀, hexanes/EtOAc, 19:1−9:1) to afford 432 mg (90%) of a **3i** as a white solid. An analytically pure sample was obtained by recrystallization of the solid with boiling pentane (20 mL) to afford **3i** as white crystals. Data for **3i**: mp 127−128 °C (pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 8.0 Hz, 1 H, HC(7)), 7.42 (t, J = 7.5 Hz, 1 H, HC(19)), 7.30 (d, J = 8.5 Hz, 2 H, HC(11)), 7.28−7.20 (m, 3 H, HC(6,18)), 7.16−7.04 (m, 4 H, HC(4,5,12)), 4.06 (ddt, J = 11.0, 9.5, and 2.5 Hz, 1 H, HC(2)), 3.95 (sept, J = 7.0 Hz, 2 H, HC(20)), 3.28 (dd, J = 13.0, 3.5 Hz, 1 H, HC(15)), 3.00 (dd, J = 16.5, 3.5 Hz, 1 H, HC(3)), 2.92 (dd, J = 16.5, 9.0 Hz, 1 H, HC(3)), 2.80 (dd, J = 12.5, 11.0 Hz, 1 H, HC(15)), 2.38 (s, 3 H, HC(14)), 1.31 (d, J = 7.0 Hz, 6 H, HC(21)), 1.24 (d, J = 7.0 Hz, 6 H, HC(21)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4 (C16), 143.8 (C10), 141.4 (C8), 134.4 (C13), 130.9 (C9), 129.8 (C17), 129.5 (C12), 129.4 (C19), 127.8 (C6), 126.9 (C11), 125.2 (C4), 124.7 (C5), 123.8 (C18), 117.1 (C7), 61.1 (C2), 43.0 (C15), 33.8 (C3), 31.5 (C20), 24.4 (C21), 24.2 (C21), 21.5 (C14); MS (ESI) 272 (15), 318 (40), 325 (46), 326 (11), 480 (M + H, 100), 481 (31), 482 (14), 502 (M + Na, 55), 503 (18), 518 (12); HRMS calcd for $C_{28}H_{34}NO_2S_2$: 480.2031, found 480.2027; TLC R_f 0.46 (hexanes/EtOAc, 4:1) [UV]; IR 2965 (w), 1480 (w), 1458 (w), 1358 (s), 1331 (w), 1169 (s), 1104 (m), 1091 (w), 1021 (m), 997 (w), 955 (m), 811 (m), 803 (s), 763 (m), 752 (s); $[\alpha]_D^{24}$ +34.6 (c = 0.90, $CHCl_3$); CD (−), Cotton sign, 230−280 nm; HPLC (2*R*,15*S*)-**3i**, t_R 8.1 min (1.8%); (2*S*,15*R*)-**3i**, t_R 9.6 min (98.2%) (Chiralpak AD, 220 nm, 90:10, hexanes/i-PrOH, 1 mL/min). Anal. Calcd for $C_{28}H_{33}NO_2S_2$ (479.70): C, 70.11; H, 6.93; N, 2.92. Found: C, 69.90; H, 6.95; N, 2.83.



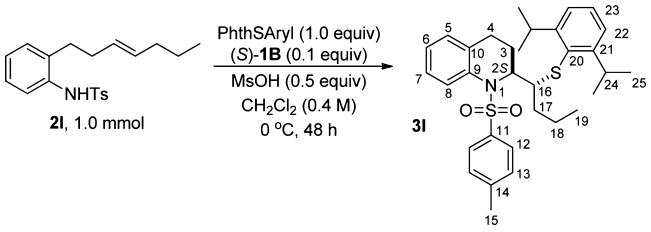
*Preparation of (3R)-3-[(2,6-Diisopropylphenyl)thio]-2,2-dimethyl-1-tosyl-1,2,3,4-tetrahydroquinoline (**3j**).* Following general procedure I, a 10 mL Schlenk flask was charged with **2j** (315.4 mg, 1.0 mmol, 1.0 equiv), PhthSAryl (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**1B** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) at 0 °C, and the mixture was stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm ⌀, hexanes/EtOAc, 19:1−9:1) to afford 451 mg (89%) of a **3j** as a white solid. An analytically pure sample was obtained by recrystallization of the solid with boiling pentane (20 mL) to afford **3j** as white crystals. Data for **3j**: mp 167−168 °C (pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.0 Hz, 1 H, HC(8)), 7.37 (d, J = 8.5 Hz, 2 H, HC(12)), 7.34 (t, J = 8.0 Hz, 1 H, HC(20)), 7.22 (t, J = 7.5 Hz, 1 H, HC(7)), 7.18 (d, J = 7.5 Hz, 2 H, HC(19)), 7.11 (d, J = 8.0 Hz, 2 H, HC(13)), 7.07 (t, J = 7.5 Hz, 1 H, HC(6)), 7.05 (d, J = 6.5 Hz, 1 H, HC(5)), 4.36 (dd, J = 9.0, 1.5 Hz, 1 H, HC(3)), 3.97 (sept, J = 7.0 Hz, 2 H, HC(21)), 3.20 (dd, J = 16.5, 1.5 Hz, 1 H, HC(4)), 2.63 (dd, J = 17.0, 9.0 Hz, 1 H, HC(4)), 2.35 (s, 3 H, HC(15)), 1.31 (brd, J = 47.0 Hz, 6 H, HC(22)), 1.31 (s, 3 H, HC(16)), 1.07 (brd, J = 32.5 Hz, 6 H, HC(22)), 0.90 (s, 3 H, HC(16)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.4 (C17, broadened due to slow rotation), 143.8 (C14), 142.8 (C9), 134.8 (C10), 134.7 (C11), 129.8 (C20), 129.3 (C13), 127.7 (C18), 127.5 (C7), 127.3 (C12), 125.8 (C6), 124.1 (C5), 123.5 (C19), 119.3 (C8), 70.2 (C3), 55.3 (C2), 32.0 (C21), 31.7 (C4), 26.5 (C16), 26.0 (C22), 23.7 (C16), 22.7 (C22), 22.3 (C22), 21.5 (C15); MS (ESI) 158 (16), 272 (11), 314 (100), 315 (20), 353 (11), 508 (M + H, 17), 530 (M + Na, 30), 531 (10); HRMS calcd for $C_{30}H_{38}NO_2S_2$: 508.2344, found 508.2339; TLC R_f 0.48 (hexanes/EtOAc, 4:1) [UV]; IR 2964 (w), 1458 (w), 1356 (s), 1168 (s), 1131 (w), 1115 (w), 1090 (m), 998 (m), 956 (m), 812 (m), 804 (m), 767 (s), 757 (w), 747 (m); $[\alpha]_D^{24}$ −87.1 (c = 0.90, $CHCl_3$); CD (−), Cotton sign, 230−280 nm; HPLC (2*R*,3*S*)-**3j**, t_R 7.5 min (11.8%); (2*S*,3*R*)-**3j**, t_R 9.9 min (88.2%) (Chiralpak AD, 220 nm, 90:10, hexanes/i-PrOH, 1 mL/min). Anal. Calcd for $C_{30}H_{37}NO_2S_2$ (507.75): C, 70.96; H, 7.34; N, 2.76. Found: C, 70.87; H, 7.25; N, 2.71.



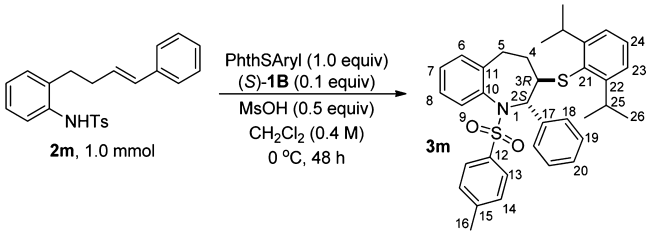
*Preparation of (13R,14S)-N-(2-{2-[(2,6-Diisopropylphenyl)thio]-2-(1-tosylpyrrolidin-2-yl)ethyl}phenyl)-4-toluenesulfonamide (**3k**).* Following general procedure I, a 10 mL Schlenk flask was charged with **2k** (498.7 mg, 1.0 mmol, 1.0 equiv), PhthSAryl (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**1B** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) at 0 °C and the mixture was stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm ⌀, hexanes/EtOAc, 19:1−9:1) to afford 451 mg (89%) of a **3k** as a white solid. An analytically pure sample was obtained by recrystallization of the solid with boiling pentane (20 mL) to afford **3k** as white crystals. Data for **3k**: mp 184−185 °C (pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.0 Hz, 2 H, HC(19)), 7.64 (d, J = 8.5 Hz, 2 H, HC(8)), 7.38 (d, J = 7.5 Hz, 1 H, HC(6)), 7.33−7.23 (m, 5 H, HC(9,20,26)), 7.20−7.09 (m, 5 H, HC(3,4,5,25)), 6.39 (brs, 1 H, HN), 4.08 (sept, J = 7.0 Hz, 2 H, HC(27)), 4.01 (ddd, J = 8.5, 5.5, and 4.0 Hz, 1 H, HC(14)), 3.41−3.30 (m, 3 H, HC(13,17)), 2.43 (s, 3 H, HC(22)), 2.42 (s, 3 H, HC(11)), 2.41−2.35 (m, 2 H, HC(12)), 1.89 (dtd, J = 13.0, 7.5, and 5.5 Hz, 1 H, HC(15)), 1.79 (dtt, J = 12.0, 5.5, and 5.5 Hz, 1 H, HC(16)), 1.67 (dtd, J = 13.0, 8.0, and 5.5 Hz, 1 H, HC(15)), 1.31 (d, J = 7.0 Hz, 6 H, HC(28)), 1.24 (d, J = 7.0 Hz, 6 H, HC(28)), 1.24 (m, 1 H, HC(16)); ^{13}C NMR (126 MHz, $CDCl_3$) 153.9 (C23), 143.7 (C10), 143.3 (C(18)), 136.6 (C7), 135.1 (C2), 134.9 (C(21)), 134.0 (C1), 130.3 (C24), 129.9 (C6), 129.7 (C(20)), 129.6 (C9), 128.9 (C26), 127.5 (C(19)), 127.1 (C8), 126.9 (C5), 126.2 (C4), 124.5 (C3), 123.6 (C25), 62.2 (C(14)), 57.5 (C13), 49.6 (C(17)), 31.2 (C27), 30.9 (C12), 28.6 (C(15)), 24.9 (C(16)), 24.6 (C28), 24.2 (C28), 21.5 (C(22)), 21.5 (C11); MS (ESI) 342 (25), 691 (M + H, 100), 692 (18), 713 (19), 729 (11); HRMS calcd for $C_{38}H_{47}N_2O_4S_3$: 691.2698, found 691.2694; TLC R_f 0.32 (hexanes/EtOAc, 4:1) [UV]; IR 3025 (m), 2946 (w), 1598 (w), 1475 (w), 1451

DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX−XXX

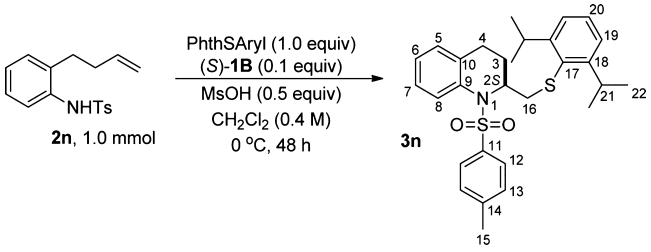
(w), 1343 (m), 1303 (w), 1216 (m), 1157 (s), 1091 (m), 1028 (m), 990 (w), 927 (w), 813 (w), 745 (m); $[\alpha]_D^{24}$ −45.9 (c = 0.90, $CHCl_3$); CD (−), Cotton sign, 230−280 nm; HPLC (13*S*,14*R*)-**3k**, t_R 9.6 min (5.5%); (13*R*,14*S*)-**3k**, t_R 12.0 min (94.5%) (Chiralpak AD, 220 nm, 90:10, hexanes/i-PrOH, 1 mL/min). Anal. Calcd for $C_{38}H_{46}N_2O_4S_3$ (690.98): C, 66.05; H, 6.71; N, 4.05. Found: C, 65.91; H, 6.55; N, 3.98.



*Preparation of (2S,16R)-2-{1-[(2,6-Diisopropylphenyl)thio]butyl}-1-tosyl-1,2,3,4-tetrahydroquinoline (**3l**).* Following general procedure I, a 10 mL Schlenk flask was charged with **2l** (343.5 mg, 1.0 mmol, 1.0 equiv), PhthSAryl (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**1B** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) at 0 °C, and the mixture was stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm ⌀, hexanes/EtOAc, 19:1−9:1) to afford 499 mg (93%) of a **3l** as a white solid. An analytically pure sample was obtained by recrystallization of the solid with boiling pentane (20 mL) to afford **3l** as white crystals. Data for **3l**: mp 158−159 °C (pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.0 Hz, 1 H, HC(8)), 7.33−7.26 (m, 4 H, HC(7,12,23)), 7.19−7.13 (m, 5 H, HC(6,13,22)), 6.94 (d, J = 7.5 Hz, 1 H, HC(5)), 4.41−4.36 (m, 1 H, HC(2)), 4.08 (sept, J = 7.0 Hz, 2 H, HC(24)), 3.35 (dt, J = 9.5, 5.0 Hz, 1 H, HC(16)), 2.39 (s, 3 H, HC(15)), 2.19 (dt, J = 15.0, 4.5 Hz, 1 H, HC(4)), 2.01−1.93 (m, 1 H, HC(3)), 1.83−1.74 (m, 1 H, HC(3)), 1.67−1.51 (m, 2 H, HC(17)), 1.49−1.35 (m, 2 H, HC(17)), 1.35−1.27 (m, 1 H, HC(4)), 1.25 (d, J = 7.0 Hz, 6 H, HC(25)), 1.24 (d, J = 7.0 Hz, 6 H, HC(25)), 0.85 (t, J = 7.0 Hz, 3 H, HC(19)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.9 (C20), 143.3 (C14), 136.5 (C11), 135.7 (C9), 135.5 (C10), 130.3 (C21), 129.3 (C13), 128.9 (C23), 128.5 (C8), 127.1 (C5), 127.0 (C12), 126.9 (C7), 126.1 (C6), 123.6 (C22), 58.8 (C2), 57.5 (C16), 36.0 (C17), 31.2 (C24), 25.3 (C4), 25.2 (C3), 24.6 (C25), 24.2 (C25), 21.5 (C15), 20.1 (C18), 14.0 (C19); MS (ESI) 132 (22), 342 (17), 381 (54), 382 (15), 536 (M + H, 100), 537 (37), 538 (16), 558 (51), 559 (19); HRMS calcd for $C_{32}H_{42}NO_2S_2$: 536.2657, found 536.2657; TLC R_f 0.48 (hexanes/EtOAc, 4:1) [UV]; IR 2966 (w), 1463 (w), 1350 (m), 1163 (s), 1092 (w), 1054 (w), 1025 (w), 966 (m), 817 (w), 805 (m), 759 (w), 748 (m); $[\alpha]_D^{24}$ +57.9 (c = 0.90, $CHCl_3$); CD (−), Cotton sign, 230−280 nm; HPLC (2*R*,3*S*)-**3l**, t_R 6.1 min (1.7%); (2*S*,3*R*)-**3l**, t_R 8.7 min (98.3%) (Chiralpak AD, 220 nm, 90:10, hexanes/i-PrOH, 1 mL/min). Anal. Calcd for $C_{32}H_{41}NO_2S_2$ (535.80): C, 71.73; H, 7.71; N, 2.61. Found: C, 71.61; H, 7.84; N, 2.47.



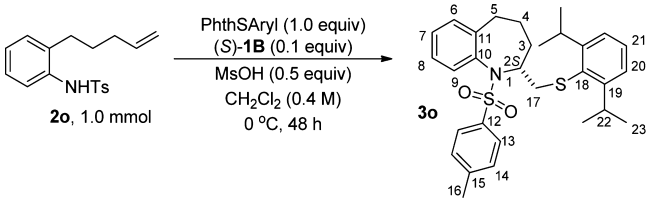
*Preparation of (2S,3R)-3-[(2,6-Diisopropylphenyl)thio]-2-phenyl-1-tosyl-2,3,4,5-tetrahydrobenzazepine (**3m**).* Following general procedure I, a 10 mL Schlenk flask was charged with **2m** (377.5 mg, 1.0 mmol, 1.0 equiv), PhthSAryl (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**1B** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) at 0 °C, and the mixture was stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm ⌀, hexanes/EtOAc, 19:1−9:1) to afford 516 mg (91%) of a **3m** as a white solid. An analytically pure sample was obtained by recrystallization of the solid with boiling pentane (20 mL) to afford **3m** as white crystals. Data for **3m**: mp 143−144 °C (pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 7.5 Hz, 2 H, HC(13), 7.32−7.27 (m, 3 H, HC(19,20)), 7.25−7.18 (m, 2 H, HC(7,24)), 7.22−7.16 (m, 2 H, HC(18)), 7.12−7.00 (m, 6 H, HC(6,8,14,23), 6.73 (d, J = 7.0 Hz, 1 H, HC(9)), 5.43 (d, J = 10.5 Hz, HC(2)), 3.51 (brs, 2 H, HC(25)), 3.02−2.89 (m, 2 H, HC(3,5)), 2.43−2.36 (m, 1 H, HC(5)), 2.36 (s, 3 H, HC(16)), 2.09−1.98 (m, 1 H, HC(4)), 1.80−1.69 (brs, 1 H, HC(4)), 1.05 (brs, 6 H, HC(26)), 0.93 (d, J = 5.0 Hz, 6 H, HC(26)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.5 (C21), 143.0 (C15), 140.3 (C11), 140.2 (C17), 138.8 (C12), 135.0 (C10), 131.3 (C9), 129.7 (C6,22), 129.1 (C14), 129.0 (C24), 128.9 (C7), 128.1 (C19), 128.0 (C20), 127.7 (C18), 127.3 (C13), 126.8 (C8), 123.6 (C23), 65.4 (C2), 50.2 (C3), 31.2 (C25), 29.4 (C5), 28.4 (C4), 24.5 (C26), 23.7 (C26), 21.5 (C16); MS (ESI) 220 (15), 376 (100), 377 (26), 570 (M + H, 22), 571 (9), 592 (21); HRMS calcd for $C_{35}H_{40}NO_2S_2$: 570.2500, found 570.2495; TLC R_f 0.41 (hexanes/EtOAc, 4:1) [UV]; IR 2965 (w), 1455 (w), 1345 (m), 1153 (s), 1117 (w), 1091 (m), 1054 (w), 1042 (w), 1026 (m), 980 (w), 960 (w), 815 (w), 800 (w), 749 (m); $[\alpha]_D^{24}$ +41.2 (c = 0.90, $CHCl_3$); CD (−), Cotton sign, 230−280 nm; HPLC (2*R*,3*S*)-**3m**, t_R 8.1 min (5.3%); (2*S*,3*R*)-**3m**, t_R 10.3 min (94.7%) (Chiralpak AD, 220 nm, 90:10, hexanes/i-PrOH, 1 mL/min). Anal. Calcd for $C_{35}H_{39}NO_2S_2$ (569.82): C, 73.77; H, 6.90; N, 2.46. Found: C, 73.79; H, 6.85; N, 2.58.



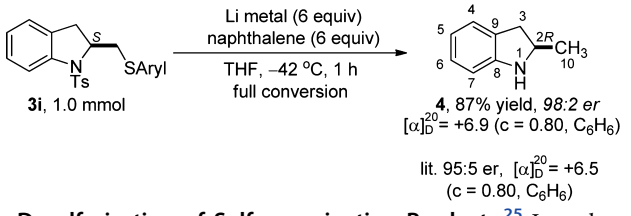
*Preparation of (2S)-3-[(2,6-Diisopropylphenyl)thio]-2,2-dimethyl-1-tosyl-1,2,3,4-tetrahydroquinoline (**3n**).* Following general procedure I, a 10 mL Schlenk flask was charged with **2n** (301.4 mg, 1.0 mmol, 1.0 equiv), PhthSAryl (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**1B** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) at 0 °C, and the mixture was stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm ⌀, hexanes/EtOAc, 19:1−9:1) to afford 459 mg (93%) of a **3n** as a white solid. An analytically pure sample was obtained by recrystallization of the solid with boiling pentane (20 mL) to afford **3n** as white crystals. Data for **3n**: mp 129−130 °C (pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 8.0 Hz, 1 H, HC(8)), 7.31 (d, J = 8.5 Hz, 2 H, HC(12)), 7.30 (t, J = 8.0 Hz, 1 H, HC(20)), 7.23 (t, J = 7.5 Hz, 1 H, HC(7)), 7.16 (d, J = 7.5 Hz, 2 H, HC(19)), 7.15 (d, J = 8.0 Hz, 2 H, HC(13)), 7.12 (t, J = 7.5 Hz, 1 H, HC(6)), 6.98 (d, J = 7.5 Hz, 1 H, HC(5)), 4.39−4.31 (m, 1 H, HC(2)), 3.88 (sept, J = 7.0, 2 H, HC(21)), 2.98 (dd, J = 12.0, 5.0 Hz, 1 H, HC(16)), 2.77 (dd, J = 12.0, 8.5 Hz, 1 H, HC(16)), 2.43−2.34 (m, 1 H, HC(4)), 2.38 (s, 3 H, HC(15)), 2.11−2.02 (m, 1 H, HC(3)), 1.83−1.75 (m, 1 H, HC(4)), 1.68−1.59 (m, 1 H, HC(3)), 1.22 (d, J = 7.0 Hz, 6 H, HC(22)), 1.20 (d, J = 7.0 Hz, 6 H, HC(22)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.1 (C18), 143.0 (C15), 142.5 (C11), 138.6 (C12), 135.4 (C10), 131.3 (C9), 131.1 (C19), 129.8 (C6), 129.4 (C14), 129.1 (C21), 128.4 (C8), 127.2 (C13), 126.6 (C7), 123.7 (C20), 56.4 (C2), 40.0 (C17), 33.7 (C5), 32.9 (C3), 31.4 (C22), 24.4 (C23), 24.3 (C23), 21.5 (C16), 20.8 (C4); MS (ESI) 132 (37), 339 (91), 340 (23), 494 (M + H, 100), 495 (34), 496 (15), 516 (72), 517 (24), 518 (11), 532 (13); HRMS calcd for $C_{29}H_{36}NO_2S_2$: 494.2187, found 494.2183; TLC R_f 0.44 (hexanes/EtOAc, 4:1) [UV]; IR 2965 (w), 1347 (s), 1161 (s), 1089 (m), 1053 (m), 966 (m), 818 (m), 801 (m), 767 (m), 760 (m), 748 (m); $[\alpha]_D^{24}$ +71.2 (c = 0.90, $CHCl_3$); CD (−), Cotton sign, 230−280 nm; HPLC (2*R*,3*S*)-**3n**, t_R 5.4 min (2.0%);

DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX−XXX

(2*S*,3*R*)-**3n**, t_R 7.7 min (98.0%) (Chiralpak AD, 220 nm, 90:10, hexanes/i-PrOH, 1 mL/min). Anal. Calcd for $C_{29}H_{35}NO_2S_2$ (493.72): C, 70.55; H, 7.15; N, 2.84. Found: C, 70.55; H, 7.03; N, 3.05.



*Preparation of (2S)-2-{[(2,6-Diisopropylphenyl)thio]methyl}-1-tosyl-2,3,4,5-tetrahydrobenzazepine (**3o**).* Following general procedure I, a 10 mL Schlenk flask was charged with **2o** (315.4 mg, 1.0 mmol, 1.0 equiv), PhthSAryl (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**1B** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) at 0 °C, and the mixture was stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm ⌀, hexanes/EtOAc, 19:1−9:1) to afford 450 mg (89%) of a **3o** as a white solid. An analytically pure sample was obtained by recrystallization of the solid with boiling pentane (20 mL) to afford **3o** as white crystals. Data for **3o**: mp 60−61 °C (pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 2 H, HC(13)), 7.29 (t, J = 7.5 Hz, 1 H, HC(21)), 7.22 (d, J = 8.0 Hz, 1 H, HC(9)), 7.21 (t, J = 8.0, 1 H, HC(8)), 7.20 (d, J = 8.0 Hz, 2 H, HC(14)), 7.14 (t, J = 8.0 Hz, 1 H, HC(7)), 7.11 (d, J = 7.5 Hz, 2 H, HC(20)), 7.10 (d, J = 8.0 Hz, 1 H, HC(6)), 4.63 (tt, J = 7.5, 4.0 Hz, 1 H, HC(2)), 3.69 (sept, J = 7.0 Hz, 2 H, HC(22)), 2.53 (dd, J = 12.5, 7.5 Hz, 1 H, HC(17)), 2.47 (t, J = 5.0 Hz, 2 H, HC(5)), 2.41 (s, 3 H, HC(16)), 2.28 (ddd, J = 12.0, 7.5, and 1.0 Hz, 1 H, HC(17)), 2.12 (ddt, J = 16.0, 12.5, and 4.0 Hz, 1 H, HC(3)), 1.91 (dd, J = 14.5, 4.5 Hz, 1 H, HC(3)), 1.71 (dt, J = 14.0, 4.5 Hz, 1 H, HC(4)), 1.35 (dtt, J = 14.0, 5.0, and 2.5 Hz, 1 H, HC(4)), 1.14 (d, J = 7.0 Hz, 6 H, HC(23)), 1.13 (d, J = 7.0 Hz, 6 H, HC(23)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.1 (C18), 143.0 (C15), 142.5 (C11), 138.6 (C12), 135.4 (C10), 131.3 (C9), 131.1 (C19), 129.8 (C6), 129.4 (C14), 129.1 (C21), 128.4 (C8), 127.2 (C13), 126.6 (C7), 123.7 (C20), 56.4 (C2), 40.0 (C17), 33.7 (C5), 32.9 (C3), 31.4 (C22), 24.4 (C23), 24.3 (C23), 21.5 (C16), 20.8 (C4); MS (ESI) 314 (20), 353 (15), 508 (M + H, 100), 509 (34), 510 (15), 530 (44), 531 (15); HRMS calcd for $C_{30}H_{38}NO_2S_2$: 508.2344, found 508.2345; TLC R_f 0.45 (hexanes/EtOAc, 4:1) [UV]; IR 2960 (w), 1455 (w), 1345 (m), 1158 (s), 1092 (m), 1053 (m), 1029 (m), 923 (w), 813 (w), 801 (m), 763 (m), 744 (m); $[\alpha]_D^{24}$ +27.4 (c = 0.90, $CHCl_3$); CD (−), Cotton sign, 230−280 nm; HPLC (2*R*)-**3o**, t_R 8.7 min (6.9%); (2*S*)-**3o**, t_R 10.8 min (93.1%) (Chiralpak AD, 220 nm, 90:10, hexanes/i-PrOH, 1 mL/min). Anal. Calcd for $C_{30}H_{37}NO_2S_2$ (507.75): C, 70.96; H, 7.34; N, 2.76. Found: C, 70.69; H, 7.39, N, 2.99.



Desulfurization of Sulfenoamination Products.[25] In a glovebox, to an oven-dried, 10 mL Schlenk flask equipped with a stir bar were added lithium metal (42 mg, 6.0 mmol, 6 equiv, cut into parts smaller than 3 mm) and naphthalene (769 mg, 6.0 mmol, 6 equiv). The flask was capped with a septum and transferred to a Schlenk line after exiting the glovebox. To the flask was added THF (2 mL) via syringe at −42 °C. The resulting mixture was stirred for 30 min at −42 °C with development of green color. To the lithium−naphthalenide solution was added a solution of sulfenylated product **3i** in THF (1.0 mmol in 2 mL, 0.5 M) via syringe at −42 °C. The color of the reaction mixture gradually turned to yellow during stirring for 1 h at −42 °C. The reaction mixture was decanted into a suspension of hexanes, water, and NH_4Cl (10 mL: 5 mL: 5 mL). Residual lithium in the Schlenk flask was rinsed with TBME (5 mL × 2). The biphasic mixture was separated, and the organic layer was washed with 1 M KOH solution (10 mL × 2) and brine (10 mL). The resulting organic layer was dried over Na_2SO_4 and evaporated under reduced pressure (25 °C, 10 mmHg) to yield a yellow odorous oil. Purification via silica gel flash column chromatography (SiO_2, 40 g, 25 mm ⌀, hexanes to hexanes/EtOAc, 9:1) afforded 116 mg (87%) of **4** as a colorless oil. The spectroscopic data matched those reported in the literature.[26] Data for **4**: bp: 110 °C (at 15 mmHg); ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.07 (d, J = 7.0 Hz, 1 H), 7.01 (t, J = 7.5 Hz, 1 H), 6.69 (td, J = 7.5, 1.0 Hz, 1 H), 6.60 (d, J = 7.5 Hz, 1 H), 3.99 (ddq, J = 8.5, 8.0, and 6.0 Hz, 1 H, HC(2)), 3.14 (dd, J = 15.5, 8.5 Hz, 1 H, HC(3)), 2.64 (ddt, J = 15.5, 8.0, and 1.0 Hz, 1 H, HC(3)), 1.29 (d, J = 6.0 Hz, 3 H, HC(10)); $[\alpha]_D^{24}$ +6.9 (c = 0.80, C_6H_6).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00391.

Optimization experiments and ^{1}H, and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sdenmark@illinois.edu.

ORCID

Scott E. Denmark: 0000-0002-1099-9765

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Mr. Zain Yousaf and Mr. Guanqun Zhang are thanked for their assistance with substrate synthesis. Dr. David J. P. Kornfilt, Dr. Eduard Hartmann, and Dr. Scott Barraza are thanked for providing helpful preparative advice and technical assistance. We are grateful to the National Institutes of Health for generous financial support (R01 GM08525)

■ REFERENCES

(1) (a) Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. *Chem. Rev.* **2011**, *111*, 7157−7259. (b) Katritzky, A.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031−15070. (c) Nammalwar, B.; Bunce, R. A. *Molecules* **2014**, *19*, 204−232. (d) Muñoz, G. D.; Dudley, G. B. *Org. Prep. Proced. Int.* **2015**, *47*, 179−206.

(2) (a) Padwa, A.; Brodney, M. A.; Dimitroff, M.; Liu, B.; Wu, T. *J. Org. Chem.* **2001**, *66*, 3119−3128. (b) Boonsombat, J.; Zhang, H.; Chughtai, M. J.; Hartung, J.; Padwa, A. *J. Org. Chem.* **2008**, *73*, 3539−3550.

(3) (a) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683−3686. (b) Rueping, M.; Theissmann, T.; Raja, S.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 1001−1006. (c) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2012**, *112*, 2557−2590. (d) Cai, X.-F.; Chen, M.-W.; Ye, Z.-S.; Guo, R.-N.; Shi, L.; Li, Y.-Q.; Zhou, Y.-G. *Chem. - Asian J.* **2013**, *8*, 1381−1385.

(4) (a) Chen, B.-L.; Wang, B.; Lin, G.-Q. *J. Org. Chem.* **2010**, *75*, 941−944. (b) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529−3533.

(5) Hara, O.; Koshizawa, T.; Makino, K.; Kunimune, I.; Namiki, A.; Hamada, Y. *Tetrahedron* **2007**, *63*, 6170−6181.

(6) Davies, S. G.; Mujtaba, N.; Roberts, P. M.; Smith, A. D.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 1959−1962.

(7) Fukamizu, K.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 10498−10499.

(8) Lu, H.-H.; Liu, H.; Wu, W.; Wang, X.-F.; Lu, L.-Q.; Xiao, W.-J. *Chem. - Eur. J.* **2009**, *15*, 2742−2746.

DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX−XXX

(9) Baraznenok, I. L.; Nenajdenko, V. G.; Churakov, A. V.; Nesterenko, P. N.; Balenkova, E. S. *Synlett* **2000**, *4*, 514−516.
(10) Wang, C.; Tunge, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 8118−8119.
(11) (a) Schmid, G. H.; Garratt, D. G. *The Chemistry of Double-Bonded Functional Groups*; John Wiley & Sons: London, 1977; Part 2, pp 725−912;. (b) Schmid, G. H. *The Chemistry of Double-Bonded Functional Groups, Part 1*; John Wiley & Sons: London, 1989; Part 1, Supplement A, Vol. *2*, pp 679−731. (c) Capozzi, G.; Modena, G.; Pasquato, L. In *The Chemistry of Sulphenic Acids and Their Derivatives*; Patai, S., Ed.; John Wiley & Sons, Ltd.: West Sussex, UK, 1990; pp 403−516. (d) Rayner, C. M. In *Organosulfur Chemistry: Synthetic Aspects*; Page, P., Ed.; Academic Press: London, 1995; pp 89−131. (e) Capozzi, G.; Modena, G. In *Organic Sulfur Chemistry: Theoretical and Experimental Advances*; Bernardi, F., Csizmadia, I. G., Mangini, A., Eds.; Elsevier: Amsterdam, 1985; Vol. *19*, pp 246−298.
(12) (a) Padwa, A.; Murphree, S. S. *Arkivoc* **2006**, *3*, 6−33. (b) Aggarwal, V. K.; Badine, D. M.; Moorthie, V. A. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006.
(13) (a) Modena, G.; Pasquato, L.; Lucchini, V. *Phosphorus, Sulfur Silicon Relat. Elem.* **1994**, *95*, 265−282. (b) Drabowicz, J.; Lyzwa, P.; Mikolajczyk, M. In *The Chemistry of Sulphenic Acids and Their Derivatives*; Patai, S., Ed.; John Wiley & Sons Ltd.: West Sussex, UK, 1990; pp 187−292.
(14) Denmark, S. E.; Vogler, T. *Chem. - Eur. J.* **2009**, *15*, 11737−11745.
(15) Lucchini, V.; Modena, G.; Pasquato, L. *J. Chem. Soc., Chem. Commun.* **1994**, 1565−1566.
(16) Archer, N. J.; Rayner, C. M.; Bell, D.; Miller, D. *Synlett* **1994**, *1994*, 617−619.
(17) Denmark, S. E.; Kornfilt, D. J. P.; Vogler, T. *J. Am. Chem. Soc.* **2011**, *133*, 15308−15311.
(18) Denmark, S. E.; Hartmann, E.; Kornfilt, D. J. P.; Wang, H. *Nat. Chem.* **2014**, *6*, 1056−1064.
(19) Denmark, S. E.; Jaunet, A. *J. Org. Chem.* **2014**, *79*, 140−171.
(20) Denmark, S. E.; Chi, H. M. *J. Am. Chem. Soc.* **2014**, *136*, 8915−8918.
(21) Denmark, S. E.; Rossi, S.; Webster, M. P.; Wang, H. *J. Am. Chem. Soc.* **2014**, *136*, 13016−13028.
(22) Denmark, S. E.; Chi, H. M. *J. Am. Chem. Soc.* **2014**, *136*, 3655−3663.
(23) Denmark, S. E.; Chi, H. M. Manuscript submitted.
(24) Back, T. G.; Yang, K. *J. Chem. Soc., Chem. Commun.* **1990**, 819−820.
(25) Göhl, M.; Seifert, K. *Eur. J. Org. Chem.* **2015**, *2015*, 6249−6258.
(26) Xiao, Y.-C.; Wang, C.; Yao, Y.; Sun, J.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10661−10664.
(27) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.
(28) Possible explanations that may be account for the diminished enantioselectivity of **3g** are as follows: (a) the formation of an achiral sulfenylating species with the Lewis basic nitrile moiety; (b) precoordination of the nitrile to the catalytically active species ***i***, thus disrupting the interaction between the alkene and ***i***; and (c) the reversing of the thiiranium ion formation by attacking with nitrile moiety. The viability of thiophilic attack by nitriles has been reported.[15]
(29) Denmark, S. E.; Kornfilt, D. J. K. *J. Org. Chem.* **2017**, DOI: 10.1021/acs.joc.7b00295.
(30) Di Martino, A.; Galli, C.; Gargano, P.; Mandolini, L. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1345−1349.
(31) Yamamoto, H.; Ho, E.; Namba, K.; Imagawa, H.; Nishizawa, M. *Chem. - Eur. J.* **2010**, *16*, 11271−11274.
(32) (a) Cooper, M. A.; Lucas, M. A.; Taylor, J. M.; Ward, A. D.; Williamson, N. M. *Synthesis* **2001**, 621−625. (b) Cooper, M. A.; Francis, C. L.; Holman, J. W.; Kasum, B.; Taverner, T.; Tiekink, E. R. T.; Ward, A. D. *Aust. J. Chem.* **2000**, *53*, 123−129.
(33) Jiang, F.; Wu, Z.; Zhang, W. *Tetrahedron* **2011**, *67*, 1501−1505.

DOI: 10.1021/acs.joc.7b00391
J. Org. Chem. XXXX, XXX, XXX−XXX