Preparative and Mechanistic Studies toward the Rational Development of Catalytic, Enantioselective Selenoetherification Reactions

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Abstract: A systematic investigation into the Lewis base catalyzed, asymmetric, intramolecular seleno-etherification of olefins is described. A critical challenge for the development of this process was the identification and suppression of racemization pathways available to arylseleniranium ion intermediates. This report details a thorough study of the influences of the steric and electronic modulation of the arylselenenyl group on the configurational stability of enantioenriched seleniranium ions. These studies show that the 2-nitrophenyl group attached to the selenium atom significantly attenuates the racemization of seleniranium ions. A variety of achiral Lewis bases catalyze the intramolecular selenoetherification of alkenes using *N*-(2-nitrophenylselenenyl)succinimide as the electrophile along with a Brønsted acid. Preliminary mechanistic studies suggest the intermediacy of ionic Lewis base−selenium(II) adducts. Most importantly, a broad survey of chiral Lewis bases revealed that 1,1′-binaphthalene-2,2′-diamine (BINAM)-derived thiophosphoramides catalyze the cyclization of unsaturated alcohols in the presence of *N*-(2-nitrophenylselenenyl)succinimide and methanesulfonic acid. A variety of cyclic seleno ethers were produced in good chemical yields and in moderate to good enantioselectivities, which constitutes the first catalytic, enantioselective selenofunctionalization of unactivated olefins.

Introduction

The selenofunctionalization of unactivated olefins represents an important method for the rapid introduction of vicinal functional groups, often with concomitant formation of rings and stereocenters.[1] Generally these transformations are characterized by the pairwise addition of a carbon or a heteroatomic selenium(II) electrophile and a nucleophile to an isolated double bond.[2] A diverse array of 1,2-difunctionalized products can be obtained from these transformations through the large number of different combinations of nucleophiles and selenium(II) precursors.[3−7] The mechanism of this family of reactions is believed to involve the formation of a discrete seleniranium ion

intermediate, followed by inter- or intramolecular nucleophilic attack at the carbon to release the isolated product (Scheme 1).[8] These transformations are stereospecific and as such afford the product via *anti* addition of the electrophile and the nucleophile.

Scheme 1
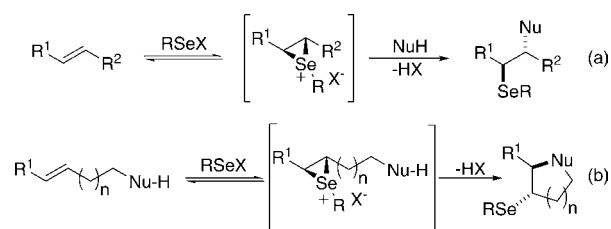
The most commonly utilized selenofunctionalization reactions for the synthesis of complex natural and non-natural compounds are intramolecular selenoetherifications and selenolactonizations.[9] These reactions involve the interception of the seleniranium ion by a pendant alcohol or carboxylic acid to generate

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cyclic ethers or lactones, respectively. Once introduced, the organoselenium moiety provides a versatile intermediate for further structural manipulation. Specifically, the C−Se bond can stabilize α-carbanions,[10] serve as a radical precursor,[11] or undergo *syn* oxidative elimination via the selenoxide.[12] Ultimately, the facile installation and subsequent elaboration of organoselenium functionalities in this manner allows for the rapid generation of structurally and stereochemically rich ring systems from simple olefins. As such, electrophilic selenofunctionalizations of alkenes have found widespread use as key steps in the total synthesis of complex biologically active molecules.[1]

Despite the established synthetic utility of these selenofunctionalization reactions, there is no report on a catalytic, enantioselective variant of these transformations.[13] To date, the synthesis of enantiomerically enriched selenofunctionalized products has relied upon either the presence of stereogenic centers on the olefin substrate[14] or the use of chiral selenylating agents.[15] Although both of these strategies have allowed for highly diastereoselective selenofunctionalizations, they do have drawbacks that limit their efficiency, cost effectiveness, and widespread application. The former approach necessitates the requirement of an appropriately positioned stereocontrolling element on the olefin substrate, which might not be readily accessible in the context of complex molecule synthesis. The latter strategy often requires lengthy syntheses of enantiomerically pure selenium electrophiles as well as the use of expensive chiral modifiers in stoichiometric amounts. Hence, the development of catalytic, enantioselective selenofunctionalization reactions remains an important challenge in organic chemistry.[16]

As part of a broadly based program for the development of asymmetric transformations mediated by main-group elements,[17] heavier chalcogens (S, Se, Te) have been identified as elements for which a rich chemistry is extant, albeit with a dearth of catalytic, asymmetric variants.[18] We describe here the inspiration, design, development, and mechanistic study of the first catalytic, asymmetric selenoetherification of unactivated olefins by harnessing the paradigm of "Lewis base activation of Lewis acids".[19]

Background

1. Lewis Base Catalysis. The concept of "Lewis base activation of Lewis acids" has been successfully exploited in the development of a myriad of catalytic, asymmetric reactions.[19] In general, these transformations involve the *in situ* generation of the catalytically active adduct of a Lewis basic donor and a Lewis acid acceptor, characterized by three-center, four-electron (3c-4e) hypervalent bonds (Scheme 2).[20] In the limit of polarization, ionization of one of the acceptor ligands can generate a cationic Lewis acid. As depicted in Scheme 2, such complex formation enhances the electrophilicity of the nascent Lewis acid, thereby providing the chemical potential for reactivity. Furthermore, the use of a chiral Lewis base generates a chiral adduct, which allows for asymmetric induction via the activated species. This concept has been most effectively applied to catalytic, asymmetric reactions involving silicon-based Lewis acids (e.g., $SiCl_4$).[21] However, recent work from these laboratories and others has demonstrated that this form of catalysis can be applied to the reactions of Group 17 Lewis acids as well,[22,23] such as halofunctionalization of alkenes. Catalytic, asymmetric selenofunctionalization of unactivated alkenes presents yet another opportunity for the application of Lewis base catalysis, in this case with Group 16 Lewis acids.

Scheme 2
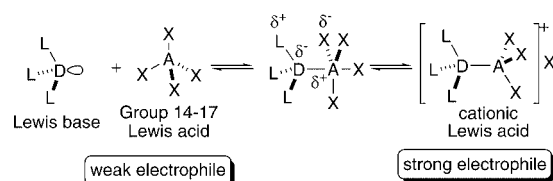
A hypothetical catalytic cycle for selenofunctionalization of olefins using a Lewis base catalyst and a selenium(II) source is depicted in Figure 1. Following the concept articulated above, the weak selenium(II) electrophile will combine with a chiral Lewis base to form adduct **1**. Such a chirally modified and kinetically activated complex can potentially discriminate the enantiotopic faces of a prochiral alkene to afford a diastereo-enriched seleniranium ion (**3**). Finally, nucleophilic capture of

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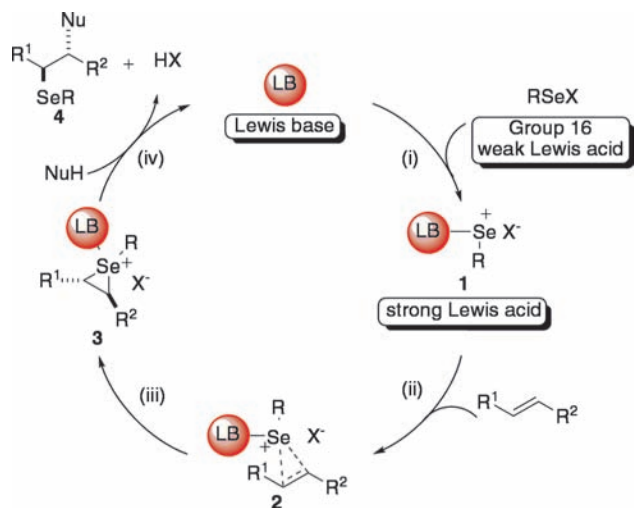
**Figure 1.** Hypothetical catalytic cycle for Lewis base catalyzed seleno-functionalization of olefins.

the seleniranium ion at carbon would release the product **4** and regenerate the Lewis base catalyst.

The feasibility of this catalytic cycle is predicated on the well-documented formation of 3c-4e hypervalent bonds between Lewis bases and electrophilic selenium(II) reagents to generate complexes analogous to **1** (Figure 1, step i).[24] Importantly, it is the enhanced electrophilicity at the central atom of the proposed adduct **1** (Figure 1) relative to that in the parent Lewis acid RSeX that is expected to minimize any contribution from RSeX to the overall reaction rate. More significantly, in the case of the chiral, nonracemic complex **1**, the enhanced kinetic potency of adduct **1** relative to the achiral Lewis acid is critical to achieve high levels of asymmetric induction in these transformations.[15]

2. Preliminary Studies. The critical proof of principle toward achieving the desired transformation depicted in Figure 1 was secured in 2007, in the first example of a Lewis base catalyzed selenolactonization reaction (Scheme 3).[25] The combination of an unsaturated acid (**5**) with *N*-phenylselenenylsuccinimide (NPSS, **6**) in the presence of substoichiometric amounts (10 mol %) of a Lewis base afforded seleno lactone **7** in excellent yields. A variety of Lewis bases such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), DMPU(S), PPh$_3$(S),

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PCy$_3$(S), hexamethylphosphorous triamide (HMPT), hexamethylphosphoramide (HMPA), HMPA(S), and HMPA(Se) served as efficient catalysts for this transformation. Importantly, the selenolactonization was completely suppressed when it was conducted with the *in situ* generated pyridinium carboxylate of **5**, indicating the need for a Brønsted acid coactivator in these reactions.
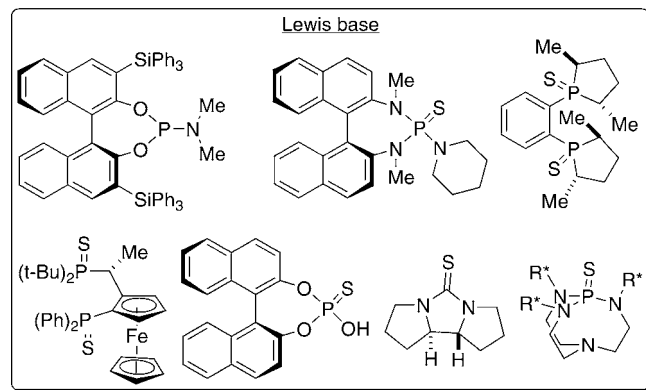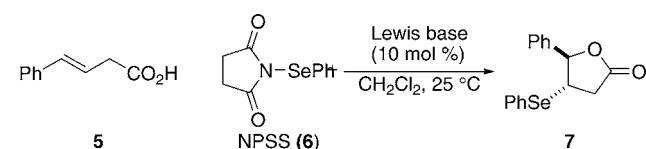
Scheme 3
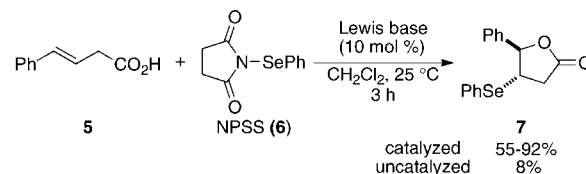
Lewis base: HMPA, DMPU, HMPA(S), DMPU(S), HMPT, Cy$_3$P(S), Ph$_3$P(S)

The successful demonstration of a Lewis base catalyzed selenolactonization reaction set the stage for the development of catalytic, enantioselective variants of this and other seleno-functionalizations.[26] The selenolactonization reactions were investigated with a wide variety of enantioenriched Lewis bases, a small subset of which are shown in Scheme 4. The products were obtained in good to excellent yields; however, *in all cases the products were racemic!* Although it is possible that none of the chiral Lewis bases were suitable for stereoinduction, this seemed unlikely because of the structural diversity of catalysts that were investigated. Importantly, control experiments demonstrated that enantioenriched seleno lactone product **7** obtained via an alternative route did not racemize under the reaction conditions. Hence, the failure to obtain any asymmetric induction using chiral Lewis bases demanded a careful understanding of processes that could be subverting the formation of enantioenriched products.

Scheme 4

3. Challenges. The stereodetermining step for the Lewis base catalyzed asymmetric selenolactonization of alkene **5** is most likely the formation of the seleniranium ion.[27] The formation of racemic seleno lactone products with all the chiral Lewis

(26) Collins, W. R. Ph.D. thesis, University of Illinois, Urbana−Champaign, 2009.

bases investigated was attributed to the racemization of the intermediate seleniranium ion prior to intramolecular capture by the pendant acid. Racemization of the seleniranium ion requires epimerization of both of the carbon−selenium bonds simultaneously or in rapid succession.[28] Mechanistically, this process could occur by attack of a nucleophile on the selenium atom of the seleniranium ion instead of the carbon atom to yield an alkene and an achiral selenium species (Scheme 5). The subsequent redelivery of the electrophilic selenium species to the olefin would diminish or eliminate any enantioenrichment. The two most likely candidates for causing racemization by this pathway under these selenolactonization reaction conditions are the pendant nucleophile, namely the carboxylate anion (Scheme 5, path a), and the alkene (Scheme 5, path b).

Scheme 5
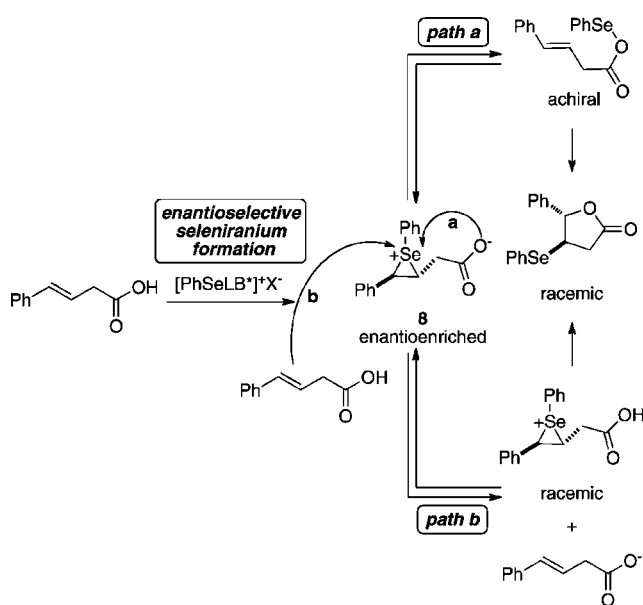
Configurational scrambling of seleniranium ions by nucleophiles has been well documented in the literature.[29] For example, Gruttadauria and co-workers have shown that the reaction of diastereomerically enriched seleno alcohols **9a** and **9b** both afforded **10** after elimination of water (Scheme 6a).[29d,e] This result is explained by invoking fast equilibration of **11a** to **11b** via reversible selenylation−deselenylation by the pendant alcohol. Similarly, Wirth has reported that the reaction of diastereomerically enriched **12** with triflic acid in methanol generated a significant amount (25%) of ether **13b** via deselenylation−selenylation of the initially generated seleniranium ion **14a** (Scheme 6b).[30] Finally, Toshimitsu has demonstrated that the enantiospecificity[31] of the seleno-Ritter reaction

of β-hydroxy selenides with triflic acid in acetonitrile is highly sensitive to the nature of the aryl group on the selenium atom.[32] Increased steric hindrance around the selenium atom increases the enantiospecificities, as exemplified by the reaction of substrates **15a−d** (Scheme 6c). Furthermore, almost complete enantiospecificity is observed in the seleno-Ritter reaction of **15e**, bearing the electron-deficient 2-trifluoromethylphenylselenenyl group.

Scheme 6
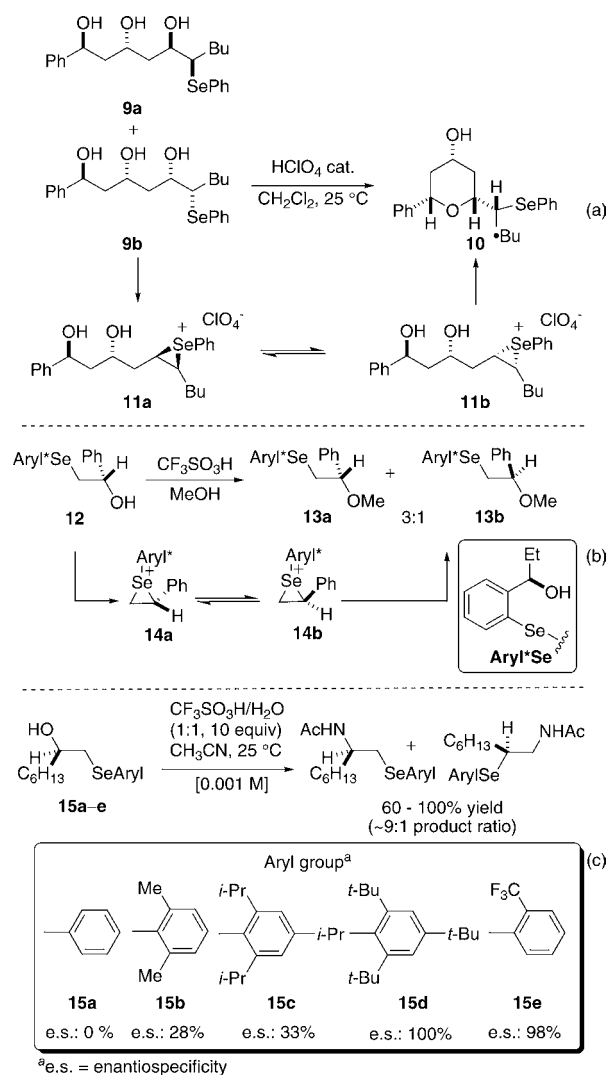
As detailed below, both computational and experimental studies have unambiguously demonstrated the feasibility of olefin transfer to iranium ions. The computationally calculated barrier for direct transfer of olefins to thiiranium ions is relatively

(27) Alternatively, as in Wirth's system, capture could be stereodetermining and cannot be ruled out at this time.

(28) (a) Schmid, G. H.; Garratt, D. G. In *The Chemistry of Double Bonded Functional Groups*, Supplement A, Part 2; Patai, S. Ed.; Wiley: New York, 1977; pp 854−866. (b) Garratt, D. G.; Kabo, A. *Can. J. Chem.* **1980**, *58*, 1030–1041. (c) Pannecoucke, X.; Outurquin, F.; Paulmier, C. *Eur. J. Org. Chem.* **2002**, 995–1006.

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(31) The term "enantiospecificity" [es = (ee_product/ee_starting material) × 100%] provides a convenient method for describing the conservation of configurational purity of a reaction.

(32) (a) Toshimitsu, A.; Ito, M.; Uemura, S. *J. Chem. Soc., Chem. Commun.* **1989**, 530–531. (b) Toshimitsu, A.; Nakano, K.; Mukai, T.; Tamao, K. *J. Am. Chem. Soc.* **1996**, *118*, 2756–2757. (c) Toshimitsu, A.; Terada, M.; Tamao, K. *Chem. Lett.* **1997**, 733–734. (d) Okamoto, K.; Nishibayashi, Y.; Uemura, S.; Toshimitsu, A. *Tetrahedron Lett.* **2004**, *45*, 6137–6139. (e) Toshimitsu, A. *Phosphorus, Sulfur Silicon* **2005**, *180*, 935–937.

low (11 kcal/mol).[33] Additionally, in 2009, the first spectroscopic observation of the direct transfer of selenium cations from one olefin to another was reported from these laboratories (Scheme 7).[16a] For example, seleniranium ion **16a** reacted rapidly and completely with alkene (E)-**17** to generate **16b** and (Z)-**17**.

Scheme 7
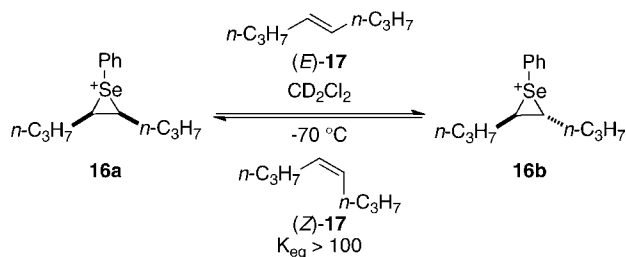
4. Objectives of this Study. The realization of Lewis base catalyzed, enantioselective selenofunctionalization reactions is contingent on the suppression of the above-mentioned racemization pathways available to seleniranium ions (Scheme 5). In recognition of this fundamental requirement for success, the goals for this program were the following:

(1) to systematically elucidate the effect of the electronic and steric properties of the selenium atom on the configurational stability of seleniranium ions analogous to **8** (Scheme 5);
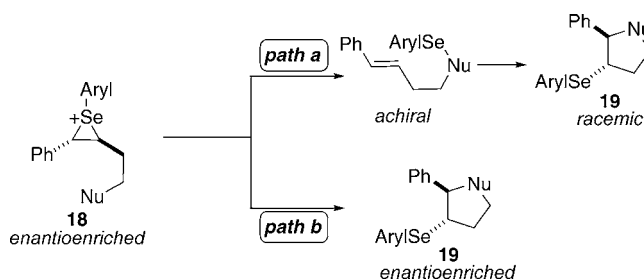
(2) to judiciously select a selenium(II) electrophile with optimum steric and electronic properties for Lewis base catalyzed selenofunctionalization to minimize racemization of putative seleniranium ion intermediates; and

(3) to demonstrate the application of the selected electrophile toward the development of Lewis base catalyzed asymmetric selenofunctionalization of unactivated olefins.

Results

1. Configurational Stability of Seleniranium Ions. 1.1. Strategy. The first phase of these studies was the investigation of the effect that the steric and electronic environment at the selenium atom had on the configurational stability of seleniranium ions bearing a tethered nucleophile. As such, enantioenriched seleniranium ions tethered to a nucleophile with diverse sterically and electronically differentiated arylselenenyl groups in the absence of any other nucleophile were needed (Scheme 8). Because seleniranium ions are not stable in the presence of even weak nucleophiles for any spectroscopically observable period of time, they had to be generated in situ.[34] The enantiomeric purity of product **19**, formed upon capture by the tethered nucleophile, would provide insight into the relative rates of ring closure versus deselenylation of **18** (Scheme 8). If the nucleophile preferentially attacks the seleniranium ion **18** at the carbon, then the products will be formed with preserved configurational purity (Scheme 8, path b). If, instead, the nucleophile attacks at the selenium atom of **18**, the enantiopurity will be lost via deselenylation pathways, and the enantioenrichment of product **19** will be compromised (Scheme 8, path a). Additionally, this study could be performed in the presence

(33) (a) Solling, T. I.; Wild, S. B.; Radom, L. *Chem. Eur. J.* **1999**, *5*, 509–514. For seleniranium ions, see: (b) Borodkin, G. I.; Chernyak, E. I.; Shakirov, M. M.; Shubin, V. G. *Russ. J. Org. Chem.* **1997**, *33*, 470–471. (c) Borodkin, G. I.; Chernyak, E. I.; Shakirov, M. M.; Shubin, V. G. *Russ. J. Org. Chem.* **1998**, *34*, 1563–1568.
(34) Denmark, S. E.; Edwards, M. G. *J. Org. Chem.* **2006**, *71*, 7293–7306.

Scheme 8

of an olefin to investigate any racemization pathways introduced by the alkene.

The initial studies focused on accessing enantioenriched seleniranium ions tethered to an alcohol (instead of an acid) because of their ease of accessibility. It was envisioned that carbonates **20** could serve as suitable precursors to the desired seleniranium ions for several reasons (Scheme 9). First, they could be readily accessed with diverse aryl groups on the selenium atom. Second, Brønsted acid activation of carbonates in conjunction with anchimeric assistance from the selenium atom could generate the desired enantioenriched seleniranium ions in situ with concomitant extrusion of carbon dioxide (Scheme 9). Subsequent invertive displacement at the benzylic position by the tethered alcohol in **21** would produce the 3-arylselenotetrahydrofurans **22**. Finally, the only byproduct in the formation of the seleniranium ion is carbon dioxide, precluding any complications with additional nucleophiles in solution.

Scheme 9
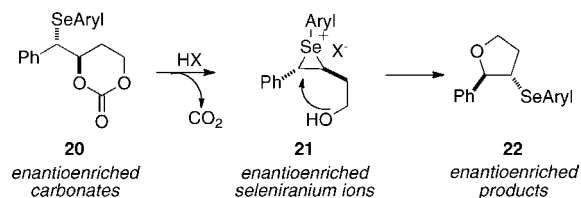
1.2. Synthesis of Carbonates. The synthetic strategy to access the desired arylseleno carbonates with diverse electronic and steric environments at the selenium atom is outlined in Scheme 10. The desired (3R,4S)-arylseleno carbonates **25a−g** were obtained in modest to good yields. The enantiomeric ratios (er's) of the carbonates were assumed to be the same as those of epoxide **23** (93:7).[35]

1.3. Choice of Brønsted Acid for the Carbonate Opening. The execution of the proposed carbonate-opening experiments required a Brønsted acid that generated the seleno ethers at appreciable rates (Scheme 9). Additionally, to attribute the results of the experiment solely to the configurational stability of the intermediate seleniranium ions, it was imperative to ensure that the acid did not racemize the seleno ether products. Thus, the configurational stability of 3-arylselenotetrahydrofurans toward Brønsted acids was investigated. Because the racemization of seleno ethers requires the acid-assisted formation of seleniranium ions, it is reasonable to posit that the stability of 3-phenylseleno-2-phenyltetrahydrofuran **28a** (Scheme 11) closely reflects that of other seleno ethers with electron-rich selenenyl

(35) The er's of **25a** and **25f** were checked against the racemates and were found to be 95:5 and 96:4, respectively. Therefore, it is reasonable to assume that the er's of **25b−e** and **25g** are not significantly different than that of the starting epoxide **23**.

Scheme 10

Scheme 11
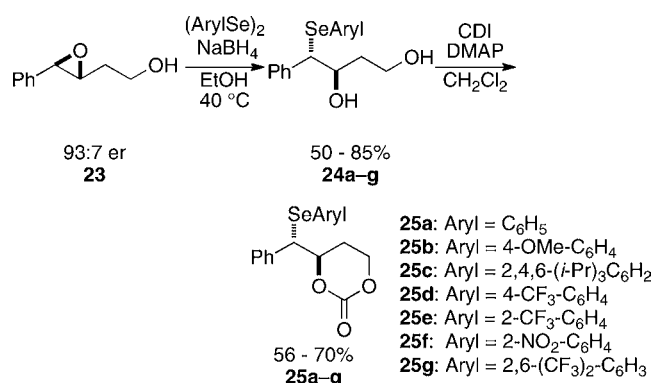
moieties. Additionally, racemization of ethers containing electron-deficient selenenyl groups should be further attenuated under otherwise identical conditions because of destabilization of the corresponding selenium cations. As such, the enantioenriched 3-phenylselenotetrahydrofuran **28a** was synthesized in >99:1 er, as determined by chiral stationary phase, supercritical fluid chromatographic (CSP-SFC) analysis of the product (Scheme 11).
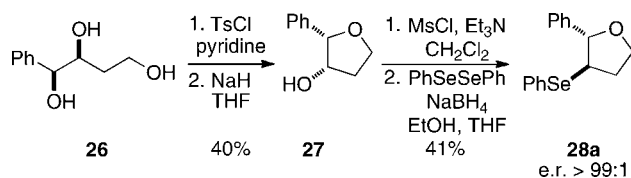
Next, selenide **28a** was treated with 10 mol % of Brønsted acids of varying pK_a values[36] at 25 °C in dichloromethane. As summarized in Table 1, racemization of **28a** was highly dependent on the acid strength. Triflic acid (pK_a in DMSO = −14) and methanesulfonic acid (pK_a in DMSO = −2.6) led to significant racemization of **28a** (Table 1, entries 1 and 3). Gratifyingly, **28a** was configurationally stable in the presence of trifluoroacetic acid (pK_a in DMSO = −0.25) over 24 h, thus making it the acid of choice for the carbonate-opening studies (Table 1, entries 4 and 5).

1.4. Carbonate Opening Experiments. Treatment of the arylseleno carbonates **25a**−**g** with trifluoroacetic acid (TFA) led to the formation of cyclic ethers at varying rates and with variable enantiospecificities (Table 2). The enantiopurity of the 3-arylselenotetrahydrofurans thus formed was determined by CSP-SFC analysis. The enantiospecificities (es's) of these transformations were obtained by comparing the enantiomeric excess of the carbonate substrates and the 3-arylselenotetrahydrofuran products.[31] On the basis of the working mechanistic hypothesis for these reactions, the major enantiomer of the seleno ethers formed from completely stereospecific carbonate opening would be of 2*R*,3*S* absolute configuration. Whereas 10 mol % of TFA was sufficient to generate significant amounts of 3-arylselenotetrahydrofurans from electron-rich seleno carbonates **25a**−**c** over 24 h (Table 2, entries 1−3), the reaction of arylseleno carbonates bearing electron-deficient aryl groups

(36) (a) Bordwell, F. G.; Van der Puy, M.; Vanier, N. R. *J. Org. Chem.* **1976**, *41*, 1883–1885. (b) Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; Drucker, G. E.; Gerhold, J.; McCollum, G. J.; Van der Puy, M.; Vanier, N. R.; Matthews, W. S. *J. Org. Chem.* **1977**, *42*, 326–332.

Table 1. Configurational Stability of **28a** toward Brønsted Acids

entry	acid, equiv	conc, M	time, h	es,[a] %
1	CF₃SO₃H, 0.1	0.01	0.5	0
2	CH₃SO₃H, 0.1	0.01	0.5	100
3	CH₃SO₃H, 0.1	0.01	3	77
4	CF₃CO₂H, 0.1	0.01	24	100
5[b,c]	CF₃CO₂H, 0.1	0.10	24	100
6[b,c]	CF₃CO₂H, 1.0	0.10	24	0

[a] Determined by CSP-SFC analysis. [b] The er of the starting seleno ether was >99:1. [c] Conducted in CDCl₃.

required an equivalent amount of TFA or methanesulfonic acid (MsOH) (Table 2, entries 4−7). Importantly, control experiments showed that, unlike seleno ether **28a**, **28d**−**f** did not racemize to any significant extent with an equivalent amount of TFA. Hence, the enantiomeric ratios of **28d**−**f** solely reflect the relative configurational stability of the intermediate seleniranium ions without contribution from the product racemization. Both electron-deficient and sterically hindered arylselenenyl groups were modestly effective at preventing racemization of seleniranium ions (entries 3−5), whereas electron-rich (entry 1) and -neutral (entry 2) substrates resulted in nearly racemic products. As shown in Table 2, arylseleno ethers **28f** and **28g** were obtained with the highest enantiospecificities, suggesting that the 2-nitrophenyl and 2,6-bis(trifluoromethyl)phenyl groups[37] (entries 6 and 7, respectively) are most effective at preventing the racemization of the corresponding seleniranium ions in the presence of a tethered nucleophile.
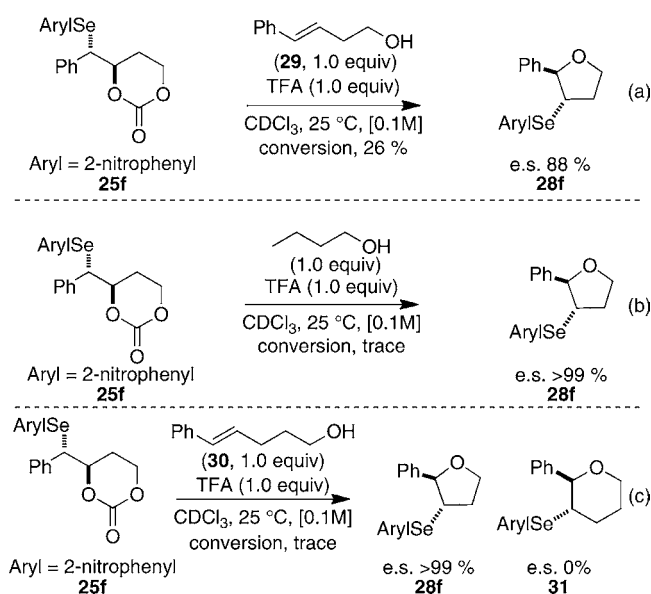
Table 2. Carbonate-Opening Experiments

entry	aryl	carbonate	acid, equiv	ether	conv,[a] %	er[b]	es, %
1[c]	4-MeOC₆H₄	**25b**	TFA, 0.1	**28b**	46	52.5:47.5	5
2[c]	Ph	**25a**	TFA, 0.1	**28a**	17	57.4:42.6	17
3[c]	2,4,6-(*i*-Pr)₃C₆H₂	**25c**	TFA, 0.1	**28c**	48	62.8:37.2	30
4[c]	4-CF₃C₆H₄	**25d**	TFA, 1.0	**28d**	100	61.8:38.2	27
5[c]	2-CF₃C₆H₄	**25e**	TFA, 1.0	**28e**	100	67.2:32.8	40
6[c]	2-NO₂C₆H₄	**25f**	TFA, 1.0	**28f**	54	93.6:6.4	>99
7[d]	2,6-(CF₃)₂C₆H₃	**25g**	MsOH, 1.0	**28g**	94	93.7:6.3	>99

[a] Conversion determined by monitoring reaction progress by ¹H NMR spectroscopy. [b] Determined by CSP-SFC analysis. [c] Reaction time was 24 h. [d] Reaction time was 2 h.

To determine whether the 2-nitrophenylseleniranium ion was stable to racemization via olefin transfer of selenium cations, carbonate **25f** was treated with TFA (1.0 equiv) in the presence of *trans*-4-phenyl-3-buten-1-ol (**29**) (1.0 equiv) (Scheme 12a). The decreased enantiospecificity of this reaction versus that in Table 2, entry 6, implies that **29** effects the racemization of the

(37) A >100% es was observed for the reactions for which es is reported as >99%. This is likely because the er's of carbonate in these cases were higher than the assumed er (93:7).

Scheme 12[37]

intermediate seleniranium ion to some extent. To distinguish whether the double bond or the hydroxy group in **29** is responsible for this racemization, the carbonate opening of **25f** was performed in the presence of 1-butanol. This reaction generated arylseleno ether **28f** with high enantiospecificity (Scheme 12b), suggesting that the erosion of specificity in Scheme 12a is mediated by the olefin of **29**. This racemization was further investigated by a crossover experiment in which the opening of **25f** was conducted in the presence of *trans*-5-phenyl-4-penten-1-ol (**30**) (Scheme 12c). In this system, two different products, **28f** and **31**, resulted from the capture of the seleniranium ions generated by carbonate opening and olefin transfer, respectively. The lack of enantioselectivity for the formation of seleno ether **31** confirmed that the attenuated selectivity in Scheme 12a results from olefin transfer of seleniranium ions to olefins.[38]

2. Selection and Synthesis of the Electrophile for Lewis Base Catalyzed Selenoetherifications. The carbonate-opening study (Table 2) suggested that the 2-nitrophenyl and the 2,6-bis(trifluoromethyl)phenylseleniranium ions are the most configurationally stable intermediates among all the precursors tested. These results are particularly significant because they suggest that the use of 2-nitrophenylselenenyl or 2,6-bis(trifluoromethyl)phenylselenenyl electrophiles in place of NPSS (**6**) in the chiral Lewis base catalyzed selenofunctionalization reactions might furnish enantioenriched products (Scheme 4). The 2-nitrophenylselenenyl electrophiles were selected for several reasons. First, the 2-nitrophenyl diselenide precursor for the synthesis of 2-nitrophenylselenenyl electrophiles is commercially available and is readily prepared in multigram quantities in good yields from 2-nitrophenylselenocyanate.[39] Second, the 2-nitrophenylselenenyl group has been extensively used in synthesis.[1a] Finally, the olefin-to-olefin transfer observed with the 2-nitrophenylselenenyl carbonate (Scheme 12a) could potentially be minimized further if the catalytic, enantioselective

selenoetherification were performed at lower temperatures or by syringe pump addition of the substrate.[16]

On the basis of the previous report from these laboratories on the ability of NPSS (**6**) to promote selenolactonization under catalysis with Lewis bases, *N*-(2-nitrophenylselenenyl)succinimide (**34**) was selected as the selenenylating reagent for subsequent investigations. Electrophile **34** was easily obtained in good yield following the synthetic sequence analogous to that used for the synthesis of *N*-phenylselenenylsuccinimide.[40] Allylation of **32**, followed by reaction of **33** with *N*-chlorosuccinimide, afforded **34** as an air- and moisture-stable solid (Scheme 13).[41]

Scheme 13
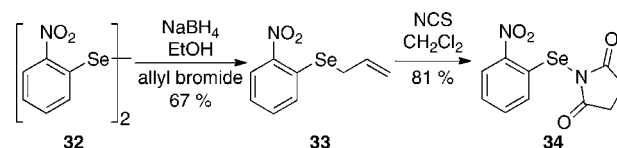
3. Selenoetherification with Achiral Lewis Bases. The carbonate-opening experiments gave insight into the racemization of seleniranium ions in the presence of a tethered alcohol (not an acid). Although Lewis base catalysis for selenolactonization had been demonstrated,[25] catalysis of the corresponding selenoetherification had not. Thus, before implementing the use of chiral Lewis bases with **34**, it was deemed prudent to establish suitable reaction conditions for catalysis with simple Lewis bases. The observation that the tethered carboxylic acid moiety in substrate **5** serves as the Brønsted acid for these reaction was critical for the development of selenoetherifications (Scheme 4). Combination of substrate **29** with **34** and HMPA(S) did not afford any of the desired 3-arylselenotetrahydrofuran product (Table 3, entry 1). Gratifyingly, however, the use of TFA resulted in good to excellent conversions[42] of **29** to **28f** in the presence of a variety of achiral Lewis base catalysts (Table 3, entries 3 and 5−10). Importantly, acetic acid was completely ineffective in promoting this transformation (Table 3, entry 2). Additionally, reactions with MsOH generally proceeded faster than with TFA under otherwise identical conditions (Table 3, entries 4 versus 3). The thiophosphoryl Lewis bases (Table 3, entries 3 and 8−10) were more effective than the corresponding phosphoryl oxides (HMPA) (Table 3, entry 6), selenophosphoryl (HMPA(Se)) (Table 3, entry 5), or a phosphorus(III) catalyst (HMPT) (Table 3, entry 7). Importantly, **28f** was not formed in the absence of the Lewis base catalyst with or without TFA (Table 3, entries 11 and 12).

4. Selenoetherification with Chiral Lewis Bases. At this juncture, the ability of 2-nitrophenyl groups to significantly attenuate the racemization of the corresponding seleniranium ions was firmly secured. The critical task ahead was to validate the hypothesis that the identification and suppression of racemization pathways available to seleniranium ions was the key to the development of Lewis base catalyzed asymmetric

(38) The ratio of **28f** to **31** could not be determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture due to overlapping resonances. However, ^{1}H NMR spectroscopic analysis of the isolated product showed approximately a 2:1 ratio of **28f**:**31**.

(39) Casar, Z.; Leban, I.; Majcen-Le Marechal, A.; Lorcy, D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1568–1573.

(40) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 4208–4210.

(41) For a reference on ^{1}H, ^{13}C, ^{15}N, ^{17}O, and ^{77}Se NMR of selenamides bearing 2-nitrophenyl groups, see: Paulmier, C.; Lerouge, P.; Outurquin, F.; Chapelle, S.; Granger, P. *Magn. Reson. Chem.* **1987**, *25*, 955–959.

(42) The major side product in these reactions results from trifluoroacetylation of the alcohol of the alkenol. Conversions were calculated by monitoring the relative integrations of the diagnostic peaks of the olefin substrate, the seleno ether product, and the trifluoroacetylated side product in ^{1}H NMR spectra of unpurified reaction mixtures.

Table 3. Achiral Lewis Base Survey with **34**
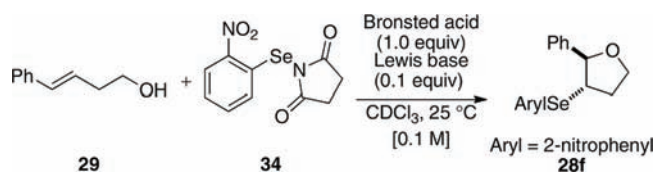
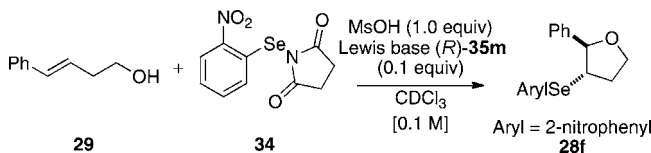|			conv,[a] %	
entry	acid	Lewis base	3.5 h	24 h
1	none	HMPA(S)	0	0
2	AcOH	HMPA(S)	0	0
3	TFA	HMPA(S)	73	95
4	MsOH	HMPA(S)	100	—
5	TFA	HMPA(Se)	21	72
6	TFA	HMPA	trace	trace
7	TFA	HMPT	45	85
8	TFA	Ph$_3$P(S)	100[b]	—
9	TFA	Cy$_3$P(S)	100	—
10	TFA	DMPU(S)	12	75
11	none	none	0	0
12	TFA	none	trace	trace
13	MsOH	none	3	38

[a] Conversion of **29** to **28f** determined by ^{1}H NMR spectroscopic analysis of the reaction mixture. [b] Complete conversion within 1.5 h.

selenoetherification reactions. In anticipation of testing this premise, the successful demonstration of Lewis base catalyzed selenoetherification using the 2-nitrophenylselenenyl-containing electrophile **34** set the stage to embark on the crucial experiments implementing the use of chiral Lewis bases. A wide variety of chiral, nonracemic Lewis bases, including phosphine sulfides, thiophosphoramides, and thioureas, were efficient at catalyzing the selenoetherification of **29** (see Supporting Information, Figure S1). In general, the reactions proceeded with good to excellent conversions of **29** to **28f** after 24 h, as determined by ^{1}H NMR spectroscopic analysis of crude reaction mixtures.[42] Although, disappointingly, the products were racemic in most cases, we were pleased to discover that the 1,1′-binaphthalene-2,2′-diamine (BINAM)-derived thiophosphoramide (*R*)-**35a** delivered the first nonracemic sample of **28f** in a modest 61.6:38.4 enantiomeric ratio (Figure 2). The use of the NPSS electrophile with (*R*)-**35a** as the catalyst led to seleno ether **28a** in nearly racemic form (er 54:46), thus emphasizing the importance of the 2-nitrophenyl moiety for enantioselectivity.

The modest but promising result with *N*-(2-nitrophenylselenenyl)succinimide and (*R*)-**35a** prompted an examination of other thiophosphoramide catalysts with structural variations. As shown in Figure 2, the use of selenophosphoramide (*R*)-**35b** in place of (*R*)-**35a** led to racemic **28f**. The lower enantiomeric ratio (50:50) of the product obtained using (*R*)-**35c** versus (*R*)-**35d** suggests that substitution at the 3,3′ positions is detrimental to enantioselectivity. The replacement of the methyl group on the internal nitrogen with an ethyl group (*R*)-**35e** resulted in decreased selectivity. Additionally, the thiophosphoramidite catalyst (*R*)-**35f** led to poor conversion (15%) to **28f** over 3 days. Finally, a variety of cyclic and acyclic dialkylamino groups, including *N*-methylphenylamino (*R*)-**35g**, diethylamino (*R*)-**35h**, pyrrolidino (*R*)-**35i**, azepino (*R*)-**35j**, indolino (*R*)-**35k**, tetrahydroquinolino (*R*)-**35l**, and morpholino (*R*)-**35m**, were introduced in place of piperidine. These thiophosphoramide catalysts ((*R*)-**35g**–**m**) resulted in good conversions of **29** to **28f**, albeit with modest effects of these peripheral modifications on enantioselectivity. The highest selectivity, 66:34, was obtained using

the morpholine-derived thiophosphoramide catalyst (*R*)-**35m**, which was thus selected for further optimization.

In the next phase of optimization, MsOH was used in place of TFA. The reaction of **29** and **34** with (*R*)-**35m** as the catalyst afforded similar enantioselectivities with significantly faster reaction rates (Table 4, entry 1). Lowering the reaction temperature to −12 °C led to increased selectivity, albeit with only partial conversion after 24 h (Table 4, entry 2).[42] Additionally, syringe pump addition of the substrate resulted in only a small increase in selectivity (Table 4, entry 3).

Table 4. Optimization of Selenoetherification with (*R*)-**35m**

entry	time, h	temp, °C	conv,[a] %	er[b]
1	0.33	25	100	68:32
2	24	−12	50	73:27
3[c]	14	25	100	69:31

[a] Conversion of **29** to **28f** determined by ^{1}H NMR spectroscopic analysis of the reaction mixture. [b] Determined by CSP-SFC analysis of the product. [c] 20 mol % of catalyst used, and the substrate was added via syringe pump addition over 14 h.

At this point, the reaction conditions in Table 4, entry 1, were deemed sufficient to explore the generality of this transformation with respect to other substrates. Gratifyingly, those conditions could be applied to a number of *trans* disubstituted olefins to obtain the *trans* products in excellent yields and diastereoselectivities (>20:1), with modest to good enantioselectivities (Table 5). The reactions of olefinic substrates bearing an alkyl group at the terminal position were more enantioselective than those with a phenyl substituent (Table 5, entries 1 and 2 versus 3 and 4). Additionally, (*E*)-**36** and (*E*)-**39** afforded a mixture of *endo* and *exo* cyclization products. Finally, the *cis*-3-arylselenotetrahydrofuran **42** was obtained in good yields and high diastereoselectivity (>20:1) from the reaction of the *cis*-olefin (*Z*)-**29**, albeit in racemic form. The absolute configuration of the major enantiomer of product **28f** was determined to be 2*R*,3*S* by comparison of its CSP-SFC trace with that of the same product obtained from the carbonate-opening experiment. The absolute configurations of the other products are assigned by analogy.

5. Mechanistic Studies on the Selenoetherification with *N*-(2-Nitrophenylselenenyl)succinimide. BINAM-derived thiophosphoramides have enabled the discovery of the first catalytic, asymmetric selenocyclization reaction. To foster future design of catalysts with higher activity and selectivity, an understanding of the reactive intermediates involved in these transformations was initiated. As detailed in the preceding sections, the thiophosphoryl Lewis bases exhibit exquisite activity in catalyzing the selenoetherification reactions with **34**. The catalytically active intermediate postulated in these transformations is the Lewis acid−base adduct between the electrophile and the Lewis base. Although several phosphorus(III)−selenium(II) adducts have been spectroscopically characterized,[24] analogous studies on complex formation between phosphorus(V) Lewis bases and selenium(II) Lewis acids are not known. Accordingly, the identification of acid−base adduct formation between thiophosphoramides and **34** was undertaken. Additionally, the effect of the strength of the Lewis bases and Brønsted acids on
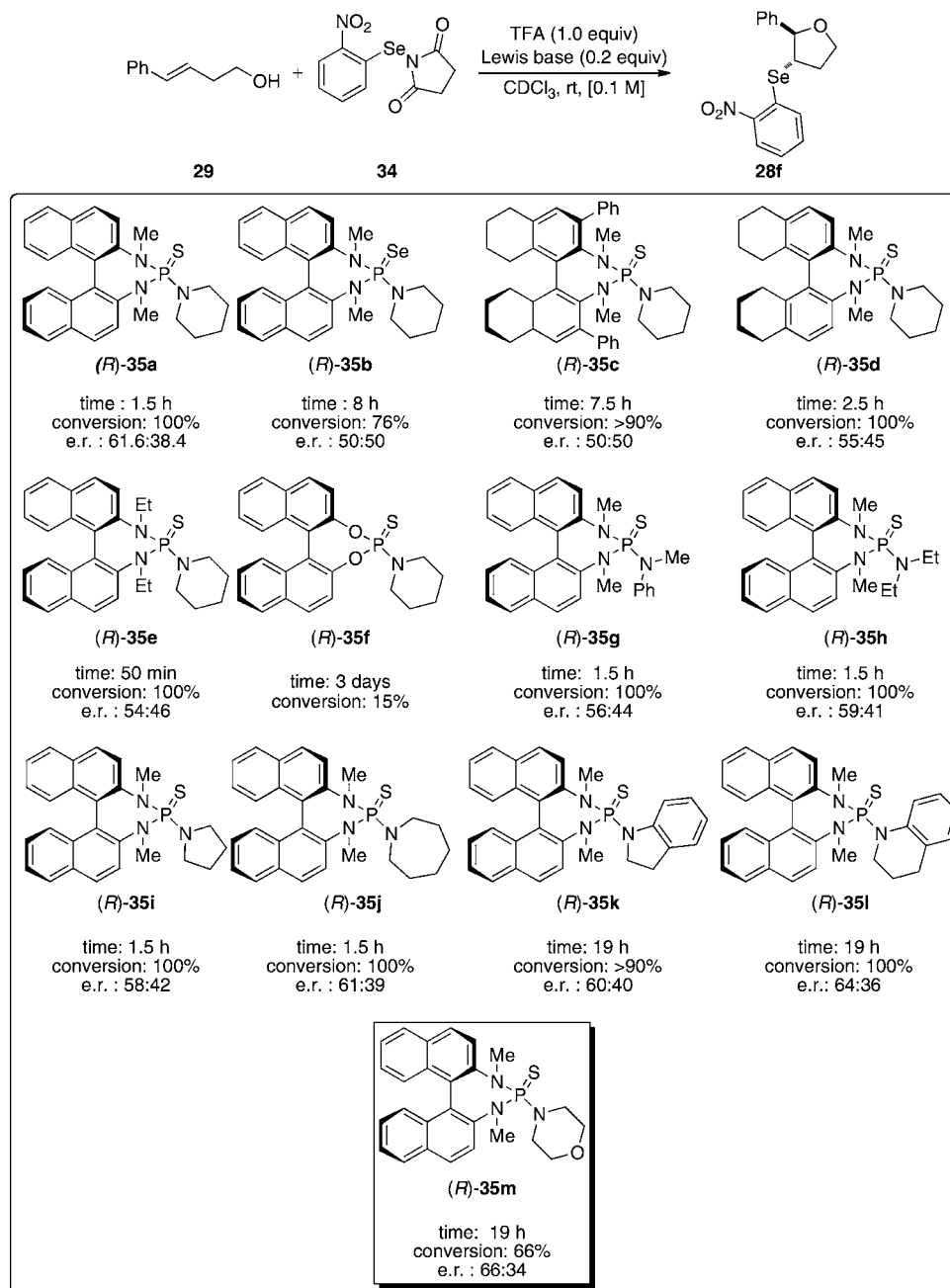
Figure 2. Catalytic, asymmetric selenoetherification with BINAM-derived thiophosphoramides.

the rate and equilibrium position of adduct formation was examined to elucidate the origin of the effect of these parameters on the catalytic reaction.

These studies began by examining the ^{1}H, ^{31}P, and ^{77}Se NMR spectra of the stoichiometric reaction between the phosphorus(V) Lewis bases and **34**. A 1.0:1.0 mixture of HMPA(S) with **34** in CDCl$_3$ at room temperature did not produce spectroscopically observable changes. However, the addition of MsOH (1.0 equiv) to this solution led to instantaneous observation of new resonances in both the ^{1}H NMR and the ^{31}P NMR spectra (see Supporting Information). The ^{1}H NMR spectrum clearly depicted four new signals in the aromatic region, corresponding to the 2-nitrophenyl moiety. Integration of the new resonances to those of **34** revealed a 2.0:1.0 ratio favoring the new species. Importantly, this ratio remained constant over 24 h. ^{31}P NMR spectroscopic analysis of this mixture at room temperature

showed a broad resonance around δ 60 ppm, implying that the species observed were fluxional. When the ^{31}P NMR spectrum was recorded at −50 °C, two sharp, well-resolved signals corresponding to HMPA(S) (δ 82 ppm) and a new species (δ 62 ppm) could be observed in a 2.0:1.0 ratio. On the basis of the similarity of shifts of the ^{31}P resonance of the new species and the HMPT−NPSS complex (δ 60 ppm), and the previously reported HMPA(S)−dihalogen[43] and HMPA(Se)−dihalogen adducts,[44] the new species is most likely the ionized complex **43** depicted in Scheme 14.

(43) Cross, W. I.; Godfrey, S. M.; Jackson, S. L.; McAuliffe, C. A.; Pritchard, R. G. *J. Chem. Soc., Dalton Trans.* **1999**, 2225−2230.
(44) Godfrey, S. M.; Jackson, S. L.; McAuliffe, C. A.; Pritchard, R. G. *J. Chem. Soc., Dalton Trans.* **1997**, 4499−4502.

Table 5. Substrate Scope for Catalytic, Asymmetric Selenoetherification with (*R*)-**35m**

| entry	substrate	product[a]	yield,[b] %	e.r.[d]
1.	(*E*)-**29**	**28f**	97%	68.9:31.1
2.	(*E*)-**30**	**31**	86%	74.9:25.1
3.	(*E*)-**36**	**37**	94%	78.8:21.2
		38	**37:38** = 1.4:1[c]	85.1:14.9
4.	(*E*)-**39**	**40**	86%	82.6:17.4
		41	**40:41** = 4.5:1[c]	83.8:16.2
5.	(*Z*)-**29**	**42**	80%	50.9:49.1

[a] Aryl = 2-nitrophenyl. *[b]* Reaction conditions: alkene (1.0 mmol), **34** (1.1 mmol), MsOH (1.0 equiv), (*R*)-**35m** (0.1 mmol), CHCl₃ (0.1 M), 25 °C. *[c]* *Exo:endo* ratios determined by ¹H NMR spectroscopic analysis of the crude reaction mixture. *[d]* Determined by CSP-SFC analysis.

***Scheme 14***
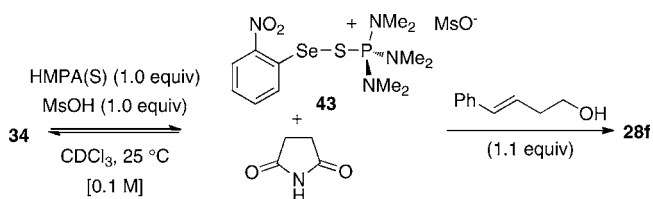
The absence of selenium satellites in the ³¹P NMR spectra suggests a small $^{2}J_{Se-P}$ for complex **43**.[45] Furthermore, the ⁷⁷Se NMR spectra also showed two sharp singlets at δ 723 ppm (**34**) and δ 582 ppm (**43**) at room temperature and −50 °C. Importantly, the upfield shifts of complex **43** relative to HMPA(S) and **34** in the ³¹P and ⁷⁷Se NMR spectra, respectively, are similar to those observed for known Lewis base—selenium(II)[43] and Lewis base—halogen adducts.[44] Addition of olefin (*E*)-**29** (1.1 equiv) to this mixture at room temperature resulted in the quantitative (with respect to the electrophile **34**) formation of **28f** within 1 h, with concomitant regeneration of HMPA(S) (sharp signal at δ 82 ppm in the ³¹P NMR spectrum).

Next, a similar study with TFA in place of MsOH was conducted to gain insight into the position of these Lewis

(45) Duddeck, H. *Prog. Nucl. Magn. Reson. Spectrosc.* **1995**, *27*, 1–323.

acid—base equilibria as a function of the strength of the Brønsted acids. The reaction between HMPA(S) and **34** with TFA in place of MsOH under otherwise identical conditions also resulted in the formation of a new complex (**44**) (Scheme 15). The ³¹P NMR (δ 63 ppm) and ⁷⁷Se NMR (δ 587 ppm) resonances of **44** were very similar to those observed in the experiment with MsOH. However, in contrast to the reaction with MsOH, this experiment produced a 0.9:1.0 mixture of **44** to **34**. Additionally, treatment of this mixture with alkene (*E*)-**29** proceeded at a slightly slower rate, leading to a 74% conversion of (*E*)-**29** to **28f** in 1 h at room temperature. Importantly, ³¹P NMR signals at δ 62 and 63 ppm were the only observable signals in the HMPA(S)-catalyzed 2-nitrophenylselenoetherification of (*E*)-**29** with MsOH and TFA, respectively, suggesting the relevance of these stoichiometric reactions to the catalytic transformations.

Scheme 15
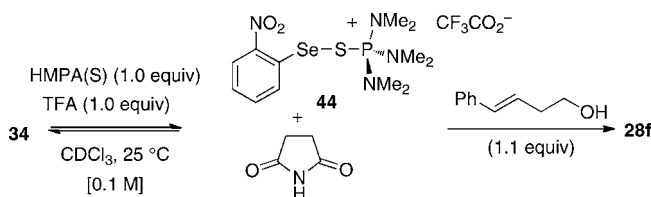
Finally, the stoichiometric reaction between the morpholine-derived chiral thiophosphoramide (*R*)-**35m** and electrophile **34** was investigated to glean insights on the effect of the Lewis base strength. Thiophosphoramide is a weaker Lewis base than HMPA(S) because the lone pairs on the internal nitrogen atoms of (*R*)-**35m** are in conjugation with the binaphthyl ring. A 1.0:1.0 mixture of (*R*)-**35m** and **34** and MsOH (1.0 equiv) in CDCl₃ at room temperature resulted in a 0.28:1.0 (³¹P) mixture of the putative complex **45** to **34**, as determined by ³¹P NMR spectroscopic analysis (Scheme 16). Importantly, the unfavorable equilibrium for the complexation with (*R*)-**35m** is manifested in the catalytic reaction, in which the resonance at δ 87 ppm (*R*)-**35m** is the only spectroscopically observable phosphorus species. ³¹P NMR spectroscopic analysis of the reaction revealed two separate, broad resonances at δ 87 and 65 ppm, corresponding to (*R*)-**35m** and **45**, respectively. The observation of two separate resonances at room temperature suggests the diminished fluxional behavior of these species relative to the HMPA(S) system. As was the case with HMPA(S), the resonances in the ³¹P NMR spectrum sharpened at −50 °C. The ⁷⁷Se NMR spectrum also revealed the existence of two major species with signals at δ 723 and 620 ppm. Subsequent reaction with olefin (*E*)-**29** led to quantitative formation of **28f** in 1 h at room temperature.

Scheme 16
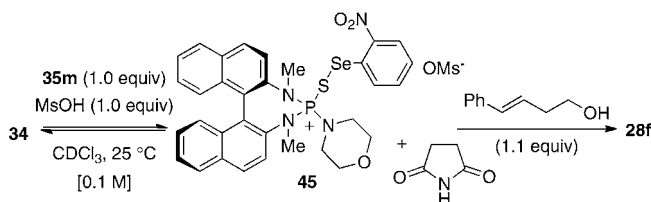
Discussion

1. Configurational Stability of Seleniranium Ions. The reaction of carbonates **25a**—**g** with a Brønsted acid proceeded with varying enantiospecificities to generate the 3-arylselenotetra-

hydrofurans **28a**−**g** (Table 2). If the conversion of the carbonates to the seleno ethers proceeded without racemization of the intermediate seleniranium ion, the 3-arylselenotetrahydrofurans would consequently be produced with complete enantiospecificity. If, instead, the intermediate seleniranium ions underwent racemization, the enantiopurity of the tetrahydrofuran products would be compromised.

Previous reports suggest that electron-deficient and sterically hindered arylselenenyl groups are effective at attenuating the racemization of the corresponding seleniranium ions (Scheme 6c).[32] Electron-deficient aryl groups on the selenium atom enhance the electrophilicity of the benzylic carbon via inductively polarizing electron density away from the carbon. This polarization thereby attenuates the racemization by increasing the propensity of nucleophilic capture at carbon. On the other hand, sterically encumbering aryl groups suppress racemization by preventing nucleophilic attack at the selenium atom. The results of the carbonate-opening studies are confluent with these observations (Table 2). Whereas the ring-opening of arylseleno carbonates **25a** and **25b**, bearing electron-neutral, electron-rich, and sterically undemanding aryl groups, led to the formation of nearly racemic 3-arylselenotetrahydrofurans **28a** and **28b**, respectively (Table 2, entries 2 and 1), the reaction of **25d**, bearing a 4-trifluoromethyl group, proceeded with modest enantiospecificity (es = 27%). Additionally, the sterically congested 2,4,6-triisopropylphenyl group in **25c** also generated 3-arylselenotetrahydrofuran **28c** with modest enantiospecificity (Table 2, entry 3). These results suggested that a combination of steric and electronic influences was needed to prevent racemization of seleniranium ions. Consistent with this hypothesis, the reaction of arylseleno carbonate **25g**, bearing the 2,6-bis(trifluoromethylphenyl)selenenyl group, occurred with complete enantiospecificity (Table 2, entry 7). Importantly, the modest enantiospecificity observed in the formation of **28e** with a 2-trifluoromethylphenylselenenyl group (Table 2, entry 5) revealed that both trifluoromethyl groups in **25g** were necessary to prevent racemization. Interestingly, however, the ring-opening of 2-nitrophenylselenenyl-containing precursor **25f** also proceeded with high enantiospecificity (Table 2, entry 6). The significantly enhanced enantiospecificity of this reaction versus that of carbonate **25e** (Table 2, entry 5) could be a result of the increased electron-withdrawing nature of the nitro group versus the trifluoromethyl group ($\sigma_{para}CF_3 = 0.46$, $\sigma_{para}NO_2 = 0.71$).[46] The 2-nitrophenyl group might also be preventing racemization by blocking a coordination site on the selenium.[47] Intramolecular bonding between the nitro group and the selenium atom has been cited as the reason for the significantly slower rates of nucleophilic substitution reactions of 2-nitrobenzeneselenenyl halides relative to those of benzeneselenenyl halides (Figure 3).[48,49]

Although these studies established the configurational stability of 2-nitrophenylseleniranium ions in the presence of a tethered hydroxyl group, it was deemed prudent to demonstrate their stability under pseudocatalytic conditions in which seleniranium ions are generated in low concentration in relation to the parent alkene. The carbonate opening of **25f** in the presence of *trans*-
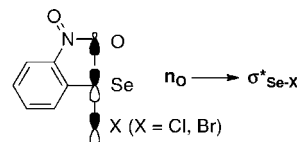
Figure 3. Hypervalent bonding between the nitro group and the selenium center in 2-nitrobenzeneselenenyl halides.

4-phenyl-3-buten-1-ol ((*E*)-**29**) exhibited a modest erosion of enantiospecificity as a result of racemization of the intermediate seleniranium ion via arylselenenyl cation transfer (Scheme 12a). Two limiting mechanisms can be envisioned for this transfer in which either the arylselenenium ion departs unassisted from the seleniranium ion (dissociative, Scheme 17a) or another alkene assists in the deselenylation process (associative, Scheme 17b). The formation of racemic **31** in the crossover experiment in Scheme 12c does not distinguish between these possibilities. However, the calculated enthalpic barrier (32.2 kcal/mol) for the direct dissociation of uncoordinated selenium cations from seleniranium ions is prohibitively high at room temperature in the gas phase.[50] This factor, along with the recent report from these laboratories on the modest enantiospecificity that is observed for thiiranium ion transfer to an olefin, supports an associative mechanism for olefin transfer to selenium cations.[16b]

Scheme 17

Dissociative Mechanism

Associative Mechanism
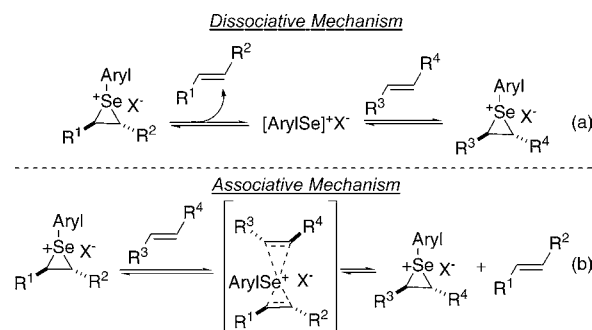
2. Selenoetherifications Catalyzed by Achiral Lewis Bases. 2.1. Mechanistic Hypothesis. The central tenet of the mechanistic hypothesis for Lewis base catalyzed selenofunctionalization of olefins is that the catalytically active species is a Lewis base coordinated, cationic arylselenium species such as **1** (Figure 1). This postulate is supported by the results of both the catalytic and stoichiometric selenoetherification reactions and is discussed below. The stoichiometric reaction between thiophosphoramides (HMPA(S) and (*R*)-**35m**) and electrophile **34** in the presence of a Brønsted acid effected the formation of the Lewis base−selenium(II) complexes **43**−**45** (Schemes 14−16). The ionic nature of the complexes is suggested by the similarity of the chemical shifts in the ^{31}P NMR spectra (δ 62, 63, and 65 ppm) to those of $[(Me_2N)_3P=Se-Me]^+SbCl_6^-$ (δ 63.2 ppm).[51] Furthermore, a previous report from these laboratories has demonstrated the feasibility for the complexation of HMPT with NPSS to generate the ionic complex **46** (Scheme 18).[25] Complexes **43**−**45** reacted with olefin (*E*)-**29** to furnish the 3-selenoaryltetrahydrofuran **28f**. Additionally, complexes **43** and **44** are the resting states of the catalyst in the HMPA(S)-

(46) Ritchie, C. D. *Prog. Phys. Org. Chem.* **1964**, *2*, 323–400.
(47) Eriksen, R.; Hauge, S. *Acta Chem. Scand.* **1972**, *26*, 3153–3164.
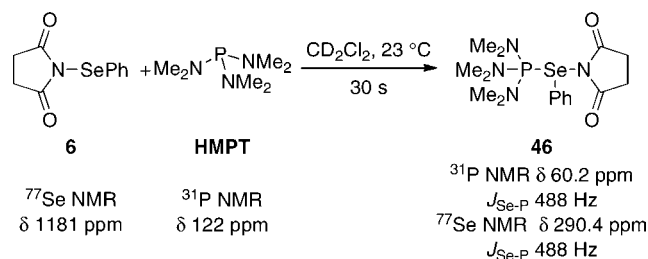(48) Lindgren, B. *Acta Chem. Scand. B* **1977**, *31*, 1–6.
(49) (a) Austad, T. *Acta Chem. Scand.* **1975**, *29*, 895–906. (b) Austad, T. *Acta Chem. Scand.* **1976**, *30*, 579–585. (c) Austad, T. *Acta Chem. Scand.* **1977**, *31*, 227–231. (d) Austad, T. *Acta Chem. Scand.* **1977**, *31*, 93–103.

(50) Wang, X.; Houk, K. N.; Spichty, M.; Wirth, T. *J. Am. Chem. Soc.* **1999**, *121*, 8567–8576.
(51) Krawczyk, E.; Skowronska, A.; Michalski, J. *J. Chem. Soc., Dalton Trans.* **2002**, 4471–4478.

promoted selenoetherification. These data suggest the potential of a hypervalent Lewis base−selenium complex as a key intermediate in these transformations. Importantly, a crucial component for the stoichiometric complexation of **34** with HMPA(S) (or (*R*)-**35m**) to proceed is a Brønsted acid. These results support the observation that both a Lewis base and a Brønsted acid are required for significant rates of catalytic selenoetherification with **34** (Table 3), indicating a critical role of a Brønsted acid coactivator in these reactions.

Scheme 18

6   HMPT   46

^{77}Se NMR ^{31}P NMR
δ 1181 ppm   δ 122 ppm

^{31}P NMR δ 60.2 ppm
J_{Se-P} 488 Hz
^{77}Se NMR δ 290.4 ppm
J_{Se-P} 488 Hz

Taken together, these data allow the formulation of a self-consistent mechanism for the Lewis base catalyzed selenoetherifications (Figure 4). The cycle commences with the reversible binding of the Lewis base to the selenimide to form adduct **47**. Protonation of the succinimide in **47** generates the putative reactive intermediate **48**. Subsequent formation of the seleniranium ion **49** and nucleophilic capture releases the product and regenerates the Lewis base catalyst. A slight modification of this mechanism involves protonation of the succinimide prior to binding of the Lewis base with strong acids (TFA or MsOH). In either case, species **48** is proposed to be the key reactive intermediate. Importantly, the proposed acid-assisted removal of the succinimide in the coordinatively saturated intermediate **47** is likely necessary to allow for the binding of the olefin and the subsequent reaction to occur (Figure 4, step ii). A similar mechanism has been postulated previously for the Lewis base catalyzed selenolactonizations.[25]
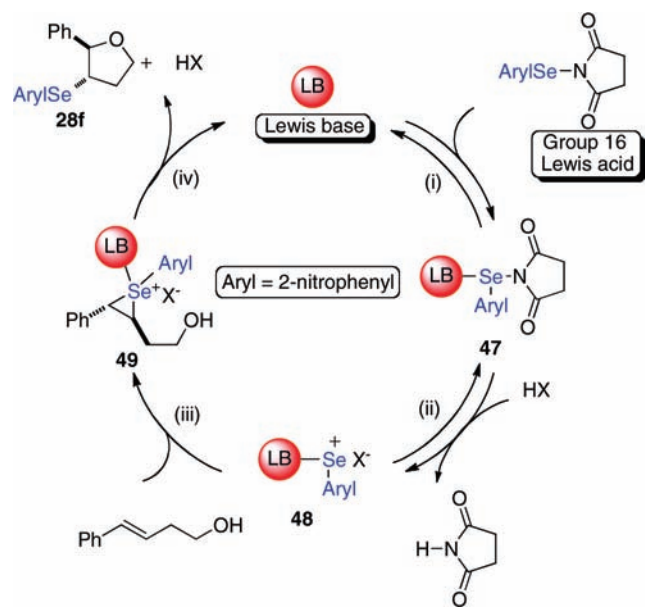

Figure 4. Proposed catalytic cycle for Lewis base catalyzed selenoetherification.

2.2. Analysis of the Effect of the Bronsted Acid Strength on the Catalytic Reaction Rates. The equilibrium position for complex formation in the stoichiometric reactions of **34** with HMPA(S) was sensitive to the strength of the Brønsted acid employed. Whereas the equilibrium in the reaction of HMPA(S) and **34** with MsOH (1.0 equiv) favored the ionized complex **43** (Scheme 14), the analogous reaction with TFA (1.0 equiv) slightly favored free HMPA(S) (Scheme 15). Because the rates of the catalyzed reactions are faster with MsOH than with TFA (Table 3, entries 3 and 4), the results of the stoichiometric studies suggest that the rate of catalytic selenoetherification is dependent on the concentration of the ionized complex **48** (Figure 4). This conclusion is further corroborated by the need for a significantly stronger acid (TFA or MsOH) in reactions with the weaker electrophile **34** (Table 3) than with NPSS (AcOH) (see Supporting Information). Previous reports have demonstrated that nucleophilic substitution reactions of 2-nitrobenzeneselenenyl halides proceeds 10^6 times slower that those of benzeneselenenyl halides. This difference in reactivity is attributed to the intramolecular n−σ* interaction between the selenium atom and an oxygen of the nitro group (Figure 3).[49] As such, the less reactive electrophile **34** requires a stronger acid to form the ionized complex in concentrations that would allow the catalytic reactions to proceed at observable rates.

2.3. Analysis of the Effect of the Lewis Base Strength on Catalytic Reaction Rates. A variety of Lewis bases were effective at catalyzing the selenoetherification with **34**. However, the rates of these reactions were highly dependent on the polarizability of the donor atom and the substituent attached to it (Table 3). The reactivity trend of the Lewis bases in the order of decreasing rates of selenoetherification is Ph$_3$PS > Cy$_3$PS > HMPA(S) > HMPA(Se) > DMPU(S) > HMPA. Previous reports have shown that the rate of nucleophilic S$_N$2 displacement of halides from arylselenenyl halides decreases in the order Se donor > S donor > O donor.[49] Consistent with these reports, the softer chalcogens donors, namely HMPA(Se) and HMPA(S), were much more effective than HMPA in the selenoetherification reactions. However, unlike the nucleophilic substitutions of arylselenenyl halides, reactions promoted by the stronger Lewis base, HMPA(Se), were significantly slower than those with HMPA(S). Additionally, the above trend implies that the rate of the selenoetherification is inversely proportional to the Brønsted/Lewis basicity of the catalyst. Among the thiophosphoryl catalysts, this behavior is exemplified by the fastest and the slowest rates for Ph$_3$PS and HMPA(S), respectively.[52] Additionally, reaction with a strong Lewis base such as HMPT is relatively slow. Two scenarios can be envisaged to explain these results on the basis of the postulated mechanism for these transformations. First, the strong Brønsted acids required for selenoetherification with **34** might be protonating the stronger Lewis bases (also Brønsted bases), rendering them less available for the formation of the catalytically active ionized complex **48** (Figure 4). However, this reasoning is not consistent with the stoichiometric reactions of thiophosphoryl Lewis bases and **34**. The stoichiometric complexation of HMPA(S) with **34** proceeded to a greater extent with MsOH than with TFA (Scheme 14 versus 15). Moreover, the equilibria for Lewis

(52) (a) Henderson, W. A., Jr.; Streuli, C. A. *J. Am. Chem. Soc.* **1960**, *82*, 5791–5794. (b) Matrosov, E. I.; Tsvetkov, E. N.; Mironova, Z. N.; Malevannaya, R. A.; Kabachnik, M. I. *Russ. Chem. Bull.* **1975**, *24*, 1231–1234. (c) Li, T. S.; Lough, A. J.; Morris, R. H. *Chem. Eur. J.* **2007**, *13*, 3796–3803.

base−selenium(II) complexation lies far to the left for the weaker Lewis base (*R*)-**35m** (Scheme 14 versus 16).

A second explanation to reconcile the results of the stoichiometric and the catalytic reactions is that the activation barrier for the reaction with weaker Lewis bases is lower than that with stronger Lewis bases. To postulate a reason for the different activation barriers, an understanding of the rate-determining step is critical. On the basis of the preceding discussions, it is reasonable to posit that the ionized complex **48** (Figure 4) is involved at or before the turnover-limiting step of the catalytic cycle. The rate-determining step for the addition of benzeneselenenyl halides to alkenes is believed to be the formation of the seleniranium ion.[2,8] Hence, it is reasonable to propose that the rate-determining step of the Lewis base catalyzed selenoetherification involves the reaction of the alkene with the ionized complex **48**. In this scenario, the influence of the Lewis base strength on the activation barriers for the reaction could stem from the varying energies required for the seleniranium ion formation between complex **48** and the olefin (Figure 4).[53] In the transition state for seleniranium ion formation, both the olefin and the Lewis base are in competition for the positive charge on the selenium atom. The higher energy needed for the association of olefins to adducts with stronger Lewis bases increases the barrier for seleniranium ion formation and thus consequently decreases the rate of the overall transformation.

3. Selenoetherification Catalyzed by Chiral Lewis Bases.
3.1. Effect of Catalyst Structure. The diversity of the Lewis bases that catalyzed the selenoetherification reactions with *N*-(2-nitrophenylselenenyl)succinimide enabled a good deal of versatility in the design of potential chiral catalysts. A broad survey of catalyst structure was critical because the constitutional and stereochemical details of the Lewis base−selenium(II) complex as well as the precise trajectory of the approach of the olefin to the ionized adduct are unknown. Most of the initial catalysts were chosen because of the demonstrated efficiency of their analogues in other asymmetric transformations. However, among all the chiral Lewis bases investigated thus far, only the BINAM-derived thiophosphoramide catalysts led to the formation of seleno ethers in nonracemic form. Additionally, structural variations on the BINAM backbone led to only modest effects on enantioselectivity (Figure 2). The morpholine-derived thiophosphoramide (*R*)-**35m** generated the 3-arylselenotetrahydrofurans with the highest, albeit still modest, enantioselectivity at appreciable rates and was thus employed to explore the generality of this transformation. Substrates were chosen to evaluate the effect of conjugation ((*E*)-**29** and (*E*)-**30** versus (*E*)-**36** and (*E*)-**39**), tether length ((*E*)-**29** versus (*E*)-**30**), and alkene geometry ((*E*)-**29** versus (*Z*)-**29**) on the rate, yield, site-selectivity, stereospecificity, and enantioselectivity of these transformations (Table 5). These results and their implications are discussed in detail below. The insights gleaned from these studies are critical for an understanding of the transition state structure as well as for the future design of catalyst structures for these transformations.

3.2. Stereospecificity. The reaction of *cis*- and *trans*-alkenols with catalyst (*R*)-**35m** and electrophile **34** furnished the products in excellent yields in 4 h at room temperature (Table 5). The exclusive formation of *cis*- and *trans*-tetrahydrofurans and pyrans from *cis*- and *trans*-olefins, respectively, exemplifies the

stereospecificity of these selenoetherification reactions (Table 5, entries 1−4 versus 5). Importantly, these results suggest that the Lewis base catalyzed selenoetherification reactions proceed via discrete cyclic seleniranium ion intermediates, analogous to the uncatalyzed transformations.[1f]

3.3. Effect of Olefin Structure on Constitutional Site Selectivity. The conjugated alkenols (*E*)-**29** and (*E*)-**30** afforded **28f** and **31**, respectively, by nucleophilic capture of the intermediate seleniranium ion at the benzylic position. This site selectivity is believed to be a result of the greater stability of the incipient positive charge on benzylic carbons (Table 5, entries 1 and 2). In contrast, nonconjugated alkenes (*E*)-**36** and (*E*)-**39** led to mixtures of constitutional isomers arising from competitive *exo* and *endo* cyclization modes (Table 5, entries 3 and 4). Importantly, the *exo* and *endo* products do not interconvert under the reaction conditions, thus assuring that the product ratios were the result of kinetically controlled selectivity (see the Supporting Information). The preference for 5-*exo* versus 6-*endo* cyclization observed with (*E*)-**36** and (*E*)-**39** is confluent with the calculated activation barriers for cyclization of seleniranium ions derived from nonconjugated alkenes tethered to a hydroxy group (5-*endo* > 6-*endo* > 5-*exo*).[54] Additionally, the constitutional site preference for furan formation in nonconjugated alkenols is typical for a variety of selenocyclizations.[1g]

3.4. Effect of Olefin Structure on Enantioselectivity. The enantioselectivity of this reaction was highly dependent on the substrate structure. As is the case in asymmetric selenofunctionalizations with chiral selenides,[50] the varying steric demands presented by the substitution patterns and the geometry of the olefins dictate the intrinsic facial selectivity of the catalyst for different substrates. The exact nature of the factors influencing the facial selectivities in the stereodetermining transition structure is unknown at this time.

In addition to the intrinsic facial selectivities for different olefins, the enantioselectivities will also be influenced by the rates of intramolecular capture of the different seleniranium ion intermediates. This contribution arises because the carbonate-opening studies showed that the 2-nitrophenyl group does not completely suppress arylselenenium cation transfer to olefins (Scheme 12). Thus, higher enantioselectivities would be expected in reactions of substrates for which cyclization is faster than racemization by arylselenenium cation transfer. The varying degrees of nonbonding interactions associated with the transfer process for different alkenols may in part be influencing the enantioselectivities in the Lewis base catalyzed selenoetherifications. This conclusion is consistent with reports by Modena and co-workers, who have demonstrated that the rate of nucleophilic attack at the sulfur of thiiranium ions by disulfides is sensitive to the substitution pattern on the ring carbons.[55] In general, for *trans*-substituted thiiranium ions, the sterically bulky substituents on the carbons attenuate the degree of nucleophilic attack at the sulfur, thereby allowing for product formation by attack at the carbon atoms. However, the lack of asymmetric induction for the selenoetherification of *cis*-alkenol (*Z*)-**29** (Table 5, entry 5) cannot be explained on the basis of these arguments because the extent of nucleophilic attack at the carbon is postulated to be significantly greater for *cis*-thiiranium ions than for their *trans* counterparts.[56] Hence, the observed lack of

(53) For analogy in silicon chemistry, see: Denmark, S. E.; Eklov, B. M.; Yao, P. J.; Eastgate, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 11770–11787.

(54) (a) Gruttadauria, M.; Noto, R. *Tetrahedron Lett.* **1999**, *40*, 8477–8481. (b) Gruttadauria, M.; Lo Meo, P.; Noto, R. *Tetrahedron* **2001**, *57*, 1819–1826.

enantioselectivity for (Z)-**29** likely stems from the poor facial selectivity of the catalyst for *cis*-alkenols.

The higher enantioselectivities for reactions of nonconjugated alkenols (E)-**36** and (E)-**39** (Table 5, entries 3 and 4) could be attributed to faster closure to nonstabilized, alkyl-substituted seleniranium ions versus the benzylic seleniranium intermediates for (E)-**29** and (E)-**30** (Table 5, entries 1 and 2). Furthermore, consistent with the higher activation barrier for 5-*endo* versus 6-*endo* cyclization, the enantiomeric purity of the 5-*endo* product **28f** (Table 5, entry 1) is lower than that of the 6-*endo* product **31** (Table 5, entry 2). Contrary to expectations, however, 5-*exo* product **37** had a lower enantiomeric ratio than the corresponding 6-*endo* constitutional isomer **38** (Table 5, entry 3). This discrepancy can be reconciled if the intrinsic rates of closure are overridden by the effect of the Lewis base on the relative rates of various cyclization modes. Importantly, for this argument to hold, the Lewis base must be present in the coordination sphere of the selenium atom at the time of intramolecular capture of the seleniranium intermediate.[22b]

3.5. Speculation on the Transition-State Structure. The absolute configuration of the major enantiomer of the seleno ethers formed under catalysis with (R)-**35m** was confirmed to be 2R,3S. A plausible transition-state structure for the approach of the olefin to the Lewis base−**34** adduct is illustrated in Figure 5. The selenium−aryl bond is perpendicular to the plane of the three-membered ring on the basis of the calculated structures for seleniranium and thiiranium ions.[50,55a] Additionally, the approximate T-shaped structure of the Lewis acid−base adduct is implied on the basis of similar geometries of the ionic HMPT−selenium(II) adducts.[24a] Two critical features of this transition state are the involvement of a seleniranium ion and the presence of the Lewis base. These features corroborate the experimentally observed stereospecificity and the enantioselectivity of these transformations, respectively. Importantly, the details of the transition-state structure are limited by the lack of knowledge on both the constitutional and stereochemical details of the Lewis base−selenium(II) adduct as well as the precise trajectory of the approach of the olefin to the complex. As such, the proposed transition-state structure will guide the computational modeling to elucidate these details for future development of catalyst architectures to engender enhanced enantioselectivities for the Lewis base catalyzed selenoetherification reactions.
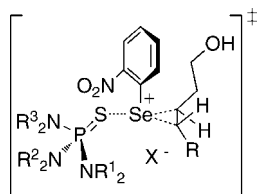

Figure 5. Transition structure hypothesis for catalytic, asymmetric selenoetherification.

Conclusion and Outlook

This full account traces the conceptual development, proof of principle, exploration of scope, and mechanistic investigation of the first catalytic, asymmetric selenofunctionalization of unactivated olefins. Critical to this success was the suppression of racemization of seleniranium ion intermediates in these transformations. An investigation of the effect of the steric and electronic nature of the aryl group on the selenium atom on the configurational stability of *in situ* generated, enantioenriched arylseleniranium ions revealed that the 2-nitrophenyl-bearing seleniranium ion is significantly stabilized toward racemization by nucleophiles. This result culminated in the selection of *N*-2-nitrophenylselenosuccinimide as the selenylating agent of choice for the development of catalytic, enantioselective selenoetherifications. A thorough screen of catalyst structures revealed that the BINAM-derived thiophosphoramides are able to catalyze the enantioselective selenoetherification of a variety of olefins in modest to good enantioselectivities. Among the catalysts examined, the thiophosphoryl(V) Lewis bases are the most efficient at catalyzing the selenoetherifications. Additionally, these reactions are sensitive to the strength of the Brønsted acids employed. Preliminary mechanistic studies support the intermediacy of hypervalent Lewis acid−base adducts in these transformations. Furthermore, these studies suggest that both the concentration of the putative Lewis base−selenium(II) intermediates and their reactivity toward olefins are playing a role in dictating the overall rate of the catalytic selenoetherification reactions. In all, the study described herein exemplifies the importance of understanding the mechanistic underpinnings governing chemical transformations to bring to fruition novel forms of reactivity.

Having demonstrated the feasibility of Lewis base catalyzed asymmetric selenoetherifications, it is now possible to undertake the challenge of rationalizing the origin of enantioselectivities in these transformations. As such, future efforts will focus on extensive computational modeling to achieve this goal. Furthermore, the lessons gleaned from these studies will be applied to expanding the scope and selectivities for the selenofunctionalization of olefins by novel catalyst design. Most importantly, these investigations will be invaluable for the development of a broader class of catalytic, enantioselective chalcogen functionalization reactions of alkenes.

Supporting Information Available: Experimental details and spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA106837B

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(56) (a) Lucchini, V.; Modena, G.; Pasquato, L. *J. Am. Chem. Soc.* **1988**, *110*, 6900–6901. (b) Lucchini, V.; Modena, G.; Pasi, M.; Pasquato, L. *J. Org. Chem.* **1997**, *62*, 7018–7020. (c) Pasquato, L.; Modena, G. *Chem. Commun.* **1999**, 1469–1470.