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Lewis Base Activation of Lewis Acids: Development of a Lewis Base Catalyzed Selenolactonization

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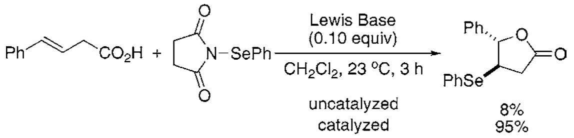
ABSTRACT



The concept of Lewis base activation of Lewis acids has been applied to the selenolactonization reaction. Through the use of substoichiometric amounts of Lewis bases with "soft" donor atoms (S, Se, P) significant rate enhancements over the background reaction are seen. Preliminary mechanistic investigations have revealed the resting state of the catalyst as well as the significance of a weak Brønsted acid promoter.

The asymmetric functionalization of prochiral olefins is one of the most powerful transformations in organic chemistry. From large-scale generation of bulk chemicals to the late stages of a complex molecule synthesis, asymmetric epoxidations,[1] dihydroxylations,[2] aminohydroxylations,[3] and hydroborations[4] are invaluable methods for the chemo-, regio-, and stereoselective introduction of functional groups. In addition to redox chemistry, stereoselective, electrophile-promoted, nucleophilic addition reactions to olefins are efficient methods for the preparation of a multitude of stereodefined, synthetically relevant acyclic and heterocyclic structures.[5] Despite the significance of these transformations, catalytic, enantioselective variants are, with few exceptions, outside of transition-metal-initiated processes, limited to the above-mentioned redox-based reactions.[6] Stereoselective, electrophilically initiated olefin additions have primarily relied on substrate- or reagent-controlled diastereoselectivity.

A case in point is the selenofunctionalization of olefins. To date, no catalytic, enantioselective variant of this reaction is known. This is particularly surprising, as selenium electrophiles efficiently promote intramolecular cyclization for the construction of functionalized rings.[7] Moreover, the resultant arylselenide is a versatile group that can undergo oxidative elimination as well as radical homologation reactions.[7] Thus far, efforts at stereocontrol in the selenofunctionalization of olefins have relied on the stoichiometric preparation and use of chiral selenium derivatives.[8] Although synthetically useful diastereoselectivities have been achieved for several selenylation reactions, the multistep preparation of the chiral selenide detracts from the utility of these methods.

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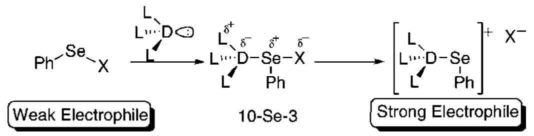
Recently, we have undertaken a broadly based program to investigate opportunities for catalysis within the Main Group.[9] In particular, we are interested in expanding the concept of Lewis base activation of Lewis acids[10] to include selenium-induced reactions (Scheme 1). By analogy to previous work from this laboratory,[11] coordination of a strong Lewis base donor to an arylselenium electrophile could enhance the electrophilicity at the selenium atom through a net polarization of the electron density of the resultant Lewis acid–base adduct.[12] In the limit of this polarization, ionization of a ligand on the arylselenium moiety could occur, resulting in a highly electrophilic selenium cation. After the Lewis base–selenium adduct has undergone successful reaction with an olefin, fission of the dative bond between the Lewis base and the selenium atom would allow for turnover. Finally, if the Lewis base is chiral, the catalyzed reaction pathway could occur in a chiral environment and thus might allow for enantiotopic face selection. Herein we report the first examples of Lewis base catalyzed selenolactonization and identify key features of the catalysts and reactive intermediates.

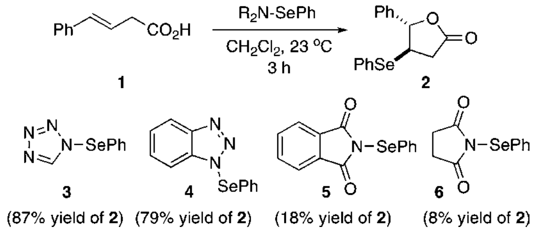
Scheme 1. Lewis Base Activation of a Selenium Electrophile



The selenolactonization of (*E*)-4-phenyl-3-butenoic acid **1** was chosen as the test reaction for the development of a Lewis base catalyzed process. Earlier mechanistic investigations[13] had shown that the most common selenylating agent, benzeneselenyl chloride, reacted with olefins spontaneously even at cryogenic temperatures. Additionally, the lactonization reaction was complicated by competitive trapping of the putative seleniranium species[14] with chloride ion as well as by reversible seleniranium ion formation. Thus, the study began by investigating whether judicious choice of the leaving group (X) could suppress both the background and side reactions.

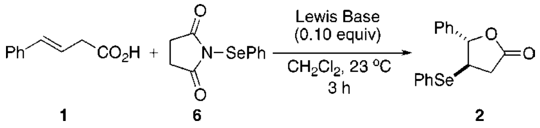
Selenenamides were particularly appealing choices at the outset of this study because of the ease of synthesis, the ability to tune the electronic character of the selenium electrophile, and the non-nucleophilicity of the amide counterion.[15] In the first experiment, *N*-phenylselenyltetrazole **3** combined with **1** at a rate and yield on par with that observed with benzeneselenyl chloride (Scheme 2). Modifying the selenium electrophile to incorporate a benzotriazole instead of the tetrazole qualitatively (as monitored by NMR) slowed the reaction slightly. Nonetheless, the *N*-phenylselenylbenzotriazole **4** still afforded **2** in 79% yield in 3 h. Only by changing to *N*-phenylselenylphthalimide **5** was a significant decrease in the background reaction seen, as **2** was isolated in only 18% yield. Finally, *N*-phenylselenylsuccinimide (NPSS) **6**, which lacks the electronically stabilizing arene ring of the phthalimide, afforded **2** in only 8% yield after 3 h at room temperature. Thus, near complete suppression of the background reaction could be achieved with the use of **6**.

Scheme 2. Selenenamide Background Reaction Survey with **1**



The key proof of principle experiment involved identifying a viable Lewis base activator for the NPSS-promoted reaction. Gratifyingly, using only 10 mol % of HMPA (**7**) brought about a considerable rate enhancement.[16] After 3 h, **2** was isolated in 55% yield (Table 1). To our knowledge, this is the first example of a Lewis base catalyzed selenofunctionalization reaction.

Table 1. Lewis Base Catalyzed Selenolactonization of **1**



entry	Lewis base catalyst	yield,[a] %
1	$(Me_2N)_3P{=}O$ (**7**)	55
2	$(Me_2N)_3P{=}S$ (**8**)	89
3	$(Me_2N)_3P{=}Se$ (**9**)	95

[a] Isolated yield of chromatographically homogeneous material

Kinetic analysis of the interactions of a variety of Lewis bases with *o*-nitrobenzeneselenyl halides shows that sulfur-

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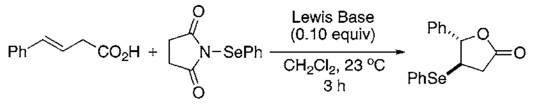
(16) The reactions were monitored by in situ ReactIR spectroscopy. The increase in the selenolactone signal allowed for qualitative rate comparisons of these reactions. See the Supporting Information.

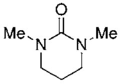
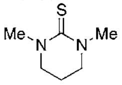
based donors generally have a stronger interaction than the corresponding oxygen-based donors. These studies suggest that the highly polarizable selenium center might bind more strongly to soft, polarizable chalcogen donors.[17] Thus, the thio- (**8**) and selenophosphoramide (**9**) analogues were prepared and tested (Table 1). The increased efficacy of these catalysts was immediately apparent. Whereas with HMPA the selenolactonization reaction went to ~60% conversion in 3 h, with 10 mol % of the HMPA(S) (**8**) the reaction went nearly to completion in 10 min. After workup, an 89% yield of the lactone **2** was isolated. Utilizing HMPA(Se) (**9**) had an even more dramatic effect as the reaction went rapidly to completion in under 5 min, providing a 95% yield of lactone **2**!

An expanded set of structurally diverse Lewis base donors were next tested under the selenolactonization reaction conditions (Table 2). With 10 mol % of either triphenylphosphine oxide or tricyclohexylphosphine oxide as the donor the selenolactonization reaction did not proceed much further than the background reaction. Employing a substoichiometric amount of the cyclic urea DMPU gave slightly better results (Table 2, entry 3), comparable to those with HMPA (Table 1, entry 1). On the other hand, the sulfide derivatives of these Lewis bases gave much better results. Thus, employing 10 mol % of either triphenylphosphine sulfide, tricyclohexylphosphine sulfide, or the sulfur analogue of DMPU, lactone **2** could be isolated in excellent yield.

Table 2. Extended Survey of Lewis Bases



1 **6** **2**

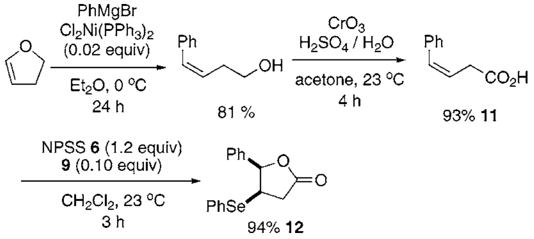
entry	Lewis Base	yield %[a]
1	$Ph_3P{=}O$	6
2	$(Cy)_3P{=}O$	20
3		51
4	$Ph_3P{=}S$	93
5	$(Cy)_3P{=}S$	88
6		87
7	$(Me_2N)_3P$	92
8	$(PhO)_2(Me_2N)P$	0[b]
9	$(PhO)_3P$	0[b]

[a] Isolated yield of chromatographically homogeneous material. [b] Isolation of ~10% of the selenol ester, with oxidation of the P(III) catalyst to the P(V) species.

The superior behavior of the "soft" sulfur and selenium Lewis base derivatives could be extended also to phosphorus(III) species (Table 2, entries 7−9). Hexamethylphosphorous triamide (HMPT) proved to be a very effective catalyst affording lactone **2** in a 92% yield. Interestingly, both *N*,*N*′-dimethyl diphenylphosphoramidite and triphenyl phosphite afforded no lactone product. Closer inspection of the ^{31}P NMR spectra of the crude reaction mixtures showed that these reagents underwent oxidation to the phosphorus(V) compounds with concomitant formation (ca. 10%) of the corresponding selenol ester. These reactions most likely proceed via a mechanism similar to that invoked by Grieco.[18]

The stereospecificity of the selenolactonization was investigated next with the stereoisomeric (*Z*)-4-phenyl-3-butenoic acid **11** (Scheme 3). Previous mechanistic studies by Schmid and Garratt as well as by Luh and co-workers showed that the nucleophilic trapping of the seleniranium ion is a stereospecific anti ring opening.[14,19] Thus, (*E*)-olefins should generate trans lactones, and (*Z*)-olefins should give the cis isomers.

Scheme 3. Stereospecific Selenolactonization



The synthesis of geometrically homogeneous **11** proceeded according to the procedure developed by Sullivan.[20] The sequence consisted of a stereoselective nickel-catalyzed addition of phenylmagnesium bromide to 2,3-dihydrofuran followed by a Jones oxidation of the primary alcohol. With the acid in hand, treatment of **11** with 1.2 equiv of NPSS and 10 mol % of HMPA(Se) provided a 94% yield of the *cis*-lactone **12** exclusively. This result implies that the reaction proceeds via a mechanism similar to the uncatalyzed process.

The divergence of pathways in the phosphorus(III)-catalyzed reactions stimulated an investigation aimed at identifying the nature of the reactive intermediates to obtain a clearer mechanistic picture of the catalytic cycle. Many phosphorus(III)−selenium(II) adducts have been spectroscopically characterized and thus provided good reference points for a multinuclear, solution NMR study (Scheme 4). Combining HMPT in a 1:1 stoichiometry with NPSS (**6**) in $CDCl_3$ led to an instantaneous disappearance of the ^{31}P NMR resonance of HMPT (δ ^{31}P, 122 ppm). The parent signal was replaced with a new doublet at 60.2 ppm with $^{1}J_{Se-P}$ of 488 Hz. Additionally, the ^{77}Se NMR spectrum revealed the absence of the signal for **6** at 1181 ppm[21] and the appearance of a doublet at 290.4 ppm with a $^{1}J_{Se-P}$ of 488 Hz. These

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(18) (a) Grieco, P. A.; Jaw, J. Y. *J. Org. Chem.* **1981**, *46*, 1215−1217. (b) Grieco, P.; Yokoyama, Y.; Williams, E. *J. Org. Chem.* **1978**, *43*, 1283−1285.

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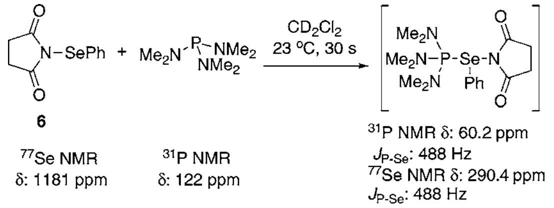
(20) Baumgartner, H.; Sullivan, A. C.; Schneider, J. *Heterocycles* **1997**, *45*, 1537−1549.

data are nearly identical to the spectroscopic data given for the phenylselenyl iodide−HMPT adduct prepared by Godfrey and co-workers.[22,23] It is therefore reasonable to assume that the HMPT·**6** complex **13** exists as a hypervalent 10-Se-3 charge-transfer species. Importantly, the same spectroscopic change occurs when the HMPT was used in a substoichiometric quantity during the course of a selenolactonization reaction. The new ^{31}P NMR peak at ca. 61 ppm persists throughout the time course of the reaction and is currently believed to be the resting state of the catalyst.

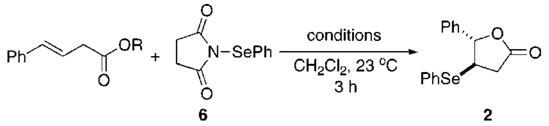
Scheme 4. HMPT−Selenium Adduct



If the resting state of the catalyst is the putative hypervalent 10-Se-3 species, the selenium atom is coordinatively saturated. Therefore, one of two events must occur prior to olefin coordination: (1) ionization of the nitrogen selenium bond directly to form a contact ion pair or (2) activation of the succinimide leaving group to form a selenium cation. That activation could come from the weak Brønsted acidity of the carboxylic acid.

This possibility was tested by sequestering the proton with a stoichiometric amount of the bulky base 2,6-di(*tert*-butyl)-4-methylpyridine (DTBMP) **14** (Table 3). Under standard reaction conditions (10 mol % of **9**, 3 h, rt), the salt afforded no lactone product. Similarly, by employing the trimethylsilyl (*E*)-4-phenyl-3-butenoate ester **15** instead of a carboxylic acid, the catalyzed reaction did not proceed. Further support for a critical role of the carboxylic acid proton was secured from a reaction of ester **15** in the presence of 1.0 equiv of acetic acid.[24] Without a Lewis base catalyst, the lactone could be isolated in only 13% yield, similar to the background reaction of **10**. However, with 10 mol % of **9**, the reaction went to completion in 3 h.

Table 3. Effect of the Carboxylate Proton on Reactivity



entry	R	conditions	yield,[a] %
1	H (**1**)	1.0 equiv of DTBMP, 0.1 equiv of $(Me_2N)_3P{=}Se$	0
2	$SiMe_3$ (**15**)	0.1 equiv of $(Me_2N)_3P{=}Se$	0
3	$SiMe_3$ (**15**)	1.0 equiv of AcOH	13
4	$SiMe_3$ (**15**)	1.0 equiv of AcOH, 0.1 equiv of $(Me_2N)_3P{=}Se$	91

[a] Isolated yield of chromatographically homogeneous material.

Taken together, all of this data reveals a consistent mechanistic picture of the Lewis base catalyzed selenolactonization reaction (Figure 1). The Lewis base catalyst coordinates to the selenium electrophile producing a hypervalent Lewis base−selenium complex. Subsequent protonation of the succinimide by a carboxylic acid forms the fully ionized phenylselenyl cation. Nucleophilic attack on the selenium by the olefin forms the putative seleniranium species with concomitant ejection of the Lewis base. The seleniranium is then trapped by the pendant carboxylate to afford the selenolactone product.

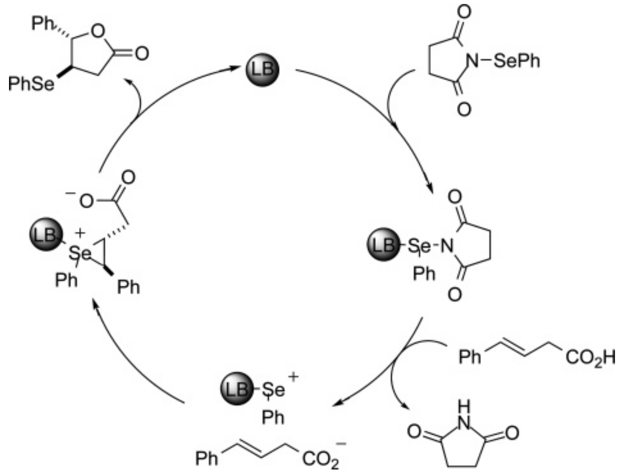


Figure 1. Proposed catalytic cycle.

Current efforts are focused on the expansion of this concept to other reactions with selenium as an electrophile as well other Main Group elements. Through structural modification of these catalysts we are also in the process of developing asymmetric variants of these reactions.

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Supporting Information Available: Detailed procedures for the preparation and characterization of all new compounds along with ReactIR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) NMR experiments confirmed that the metathetical reaction between the TMS ester and acetic acid is slow and does not reach equilibrium within 8 h.