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Selenophosphoramide-Catalyzed Diamination and Oxyamination of Alkenes

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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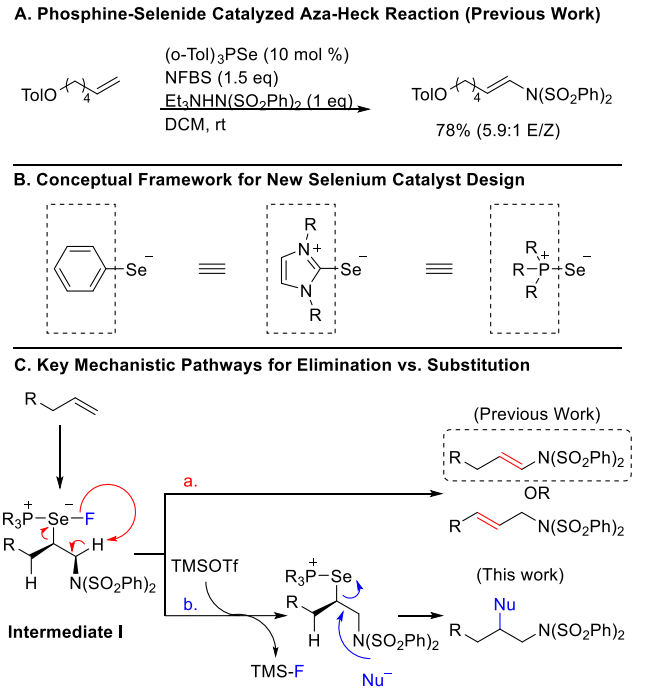
A new selenophosphoramide-catalyzed diamination of terminal- and trans-1,2-disubstituted olefins is presented. Key to the success of this transformation was the introduction of a fluoride scavenger, trimethylsilyl trifluoromethanesulfonate (TMSOTf), to prevent a competitive syn-elimination pathway, as was the use of a phosphoramide ligand on selenium to promote the desired substitution reaction. A screen of catalysts revealed that more electron-rich phosphine ligands resulted in higher yields of the desired product, with selenophosphoramides giving the optimal results. A broad range of substrates and functional groups were tolerated and yields were generally good to excellent. For (*E*)-1,2-disubstituted olefins, diastereoselectivities were always high, giving exclusively anti products. The conditions were also applied to substrates bearing internal nucleophiles such as esters and carbonates, giving rise to 1,2-aminoesters and cyclic carbonates, respectively.

Introduction

Organoselenium compounds have been useful reagents in organic synthesis for decades, enabling new reactivity and providing access to a diverse array of products.[1] One powerful set of applications of these reagents is in promoting oxidative transformations of alkenes. However, the efficiency and utility of these reactions has been limited by the requirement that the organoselenium reagent be used in stoichiometric quantities, necessitating multi-step procedures to obtain the desired end products. In recent years, attention has turned to using organoselenium compounds as catalysts, and several new catalytic protocols have emerged.[2,3] Despite these efforts, organoselenium catalysis still remains underexplored when compared to other catalyst classes, especially those based on transition metals. This disparity is more striking given the fact that selenium is potentially capable of promoting many of the same transformations as transition metal catalysts, but at lower cost. Consequently, it is important to continue to explore ways to expand the range of reactivity that can be achieved using selenium-based catalysts.

To this end, we recently developed a new class of phosphine selenide catalysts and employed them in the aza-Heck reaction of terminal alkenes to correct issues of stereo- and regioselectivity in existing transition metal- and diphenyl diselenide-catalyzed methods (Scheme 1A).[4] Key to our success was the innovative idea of treating the groups on selenium as ligands rather than substituents, allowing us to envision a variety of new selenium-based catalysts with a broad range of steric and electronic properties (Scheme 1B). Using this framework, we developed a diverse library of catalysts and observed that the ligand on selenium could indeed be used to improve reactivity and selectivity.



Scheme 1 Conceptual Evolution from Selenium-Catalyzed Addition/Elimination to Diaddition

To expand the versatility of selenium catalysis, we imagined that it should be possible to divert the typical addition/elimination mechanism to promote a new class of transformations of alkenes. We previously established that a key step in this mechanism is the concerted syn-elimination of

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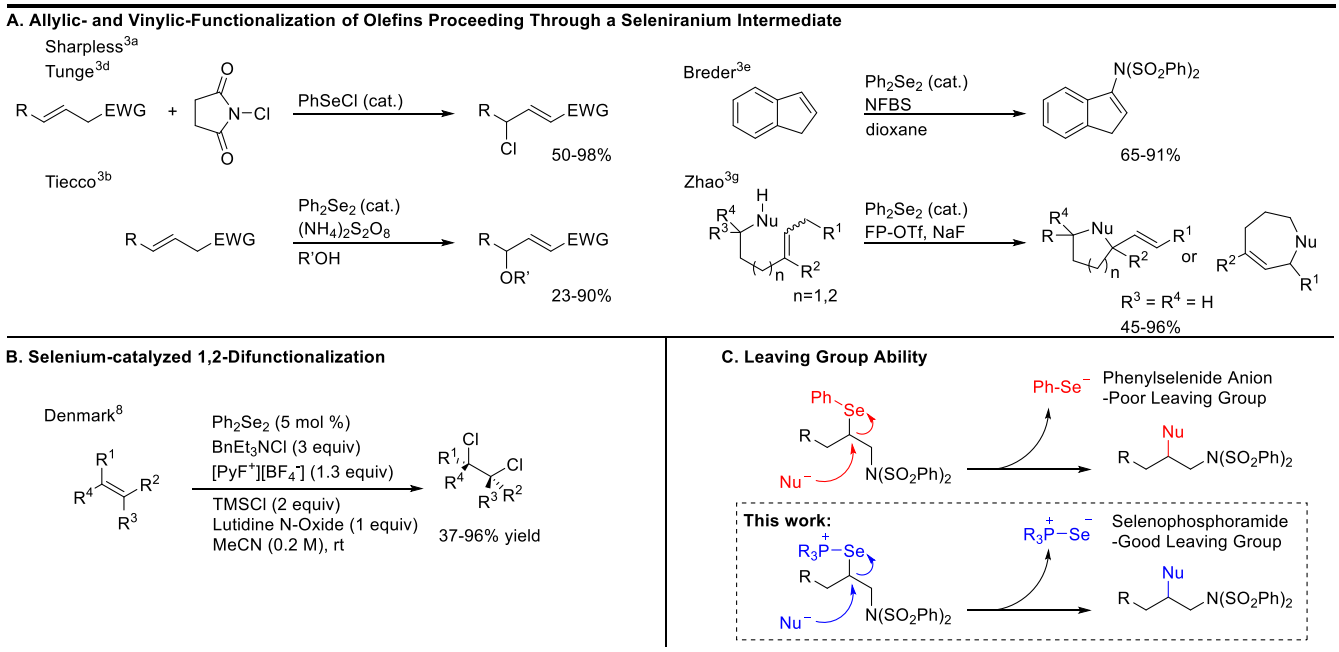
Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x



Scheme 2 Elimination vs. Substitution Pathways

the selenium-fluorine bond of intermediate **I** to give the vinyl amine product (Scheme 1C, pathway a). This step is isoeletronic to the well-known selenoxide elimination.[5] If, instead of undergoing elimination, intermediate **I** were intercepted by nucleophilic attack, the result would be a 1,2-difunctionalization of the alkene (Scheme 1C, pathway b). The major obstacle to this goal is the propensity for organoselenium intermediates to undergo a fast *intra*molecular elimination rather than the relatively slower *inter*molecular substitution. This is evident from the fact that the vast majority of organoselenium-promoted transformations end with this elimination step[1-4] (Scheme 2A), whereas selenium-promoted 1,2-difunctionalization has remained highly elusive. There are two known methods for promoting stoichiometric substitution of organoselenides: halogenation with Cl_2 or Br_2[6] and activation with PhSeOTf.[7] To our knowledge, only the syn-dichlorination of alkenes reported by Denmark *et al.*[8] has successfully employed this strategy in a catalytic reaction (Scheme 2B).[9] If a more general route to substitution by non-halide nucleophiles could be realized, it would greatly expand the utility of selenium catalysis by opening up an avenue to many new classes of products.

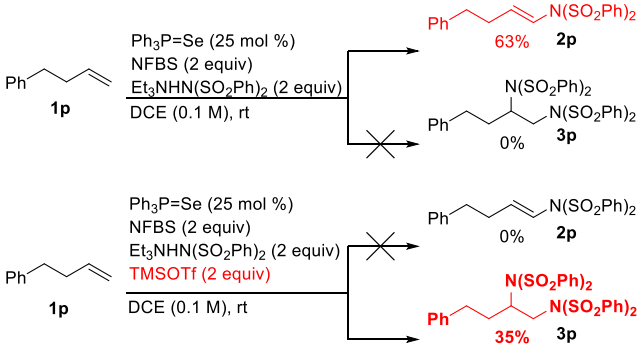
As a first demonstration of this principle, we imagined displacing intermediate **I** with a benzenesulfonimide anion, yielding a 1,2-diamination product. 1,2-Diamines are present in natural products and have widespread use in medicinal chemistry, agrochemistry, as ligands in chemical synthesis, and in many other areas.[10] While several protocols exist for synthesizing 1,2-diamines from alkenes, most suffer from a limited and/or highly engineered substrate scope.[11,12] There are comparatively few general and broadly applicable fully intermolecular 1,2-diamination methods.[14]

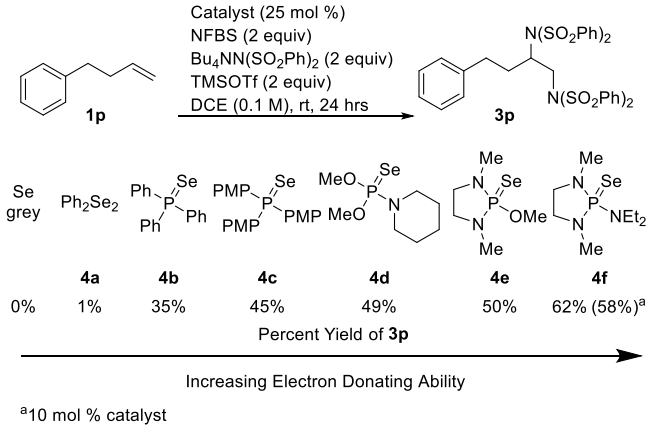
Analysis of the key substitution step reveals that using phosphine selenide catalysts in place of diphenyl diselenide should accelerate the desired reactivity (Scheme 2C). Instead of displacement of a phenylselenide anion, a relatively poor leaving group, substitution of the same intermediate in the phosphine selenide catalyzed system should be more facile because the phosphine selenide is a much better leaving group. However, our previous results made clear that in addition to accelerating the substitution step, the syn elimination must also somehow be inhibited.

Results and discussion

We hypothesized that the introduction of a fluoride scavenger would prevent the syn-elimination pathway by sequestering the fluoride on intermediate **I**, thereby allowing substitution to take place. To test this hypothesis, 4-phenyl-1-butene (**1p**) was subjected to catalytic phosphine selenide in presence of N-fluorobenzenesulfonimide (NFBS) and added benzenesulfonimide nucleophile (Scheme 3). As we

Scheme 3 Fluoride Scavenger Changes Reactivity





Scheme 4 Catalyst Screen

observed previously, only elimination products were formed. However, performing the same reaction in the presence of two equivalents of trimethylsilyl trifluoromethanesulfonate (TMSOTf) suppressed the elimination, gratifyingly giving a 35% yield of the desired diamination product **3p**.[15]

In an effort to increase the yield, a variety of sterically and electronically diverse catalysts were screened under these reaction conditions (Scheme 4). We observed a systematic trend: increasing the electron donating ability of the ligand led to higher yields of the desired product. It is important to note that neither diphenyl diselenide (Ph_2Se_2), the most commonly used organoselenium catalyst, nor commercially available grey selenium, gave meaningful amounts of the desired product (see Supporting Information for more details), even in the presence of fluoride scavenger, illustrating the key role the phosphine ligand plays in promoting this new reactivity. Ultimately, selenophosphoramide catalyst **4f** provided the highest yield of 62% and was chosen as the optimal catalyst. The catalyst loading could be further reduced to 10 mol % with little impact on the yield. With the optimized conditions in hand, control experiments individually omitting each component of the reaction were performed and no desired product was observed, thus confirming the necessity of each of the reagents.

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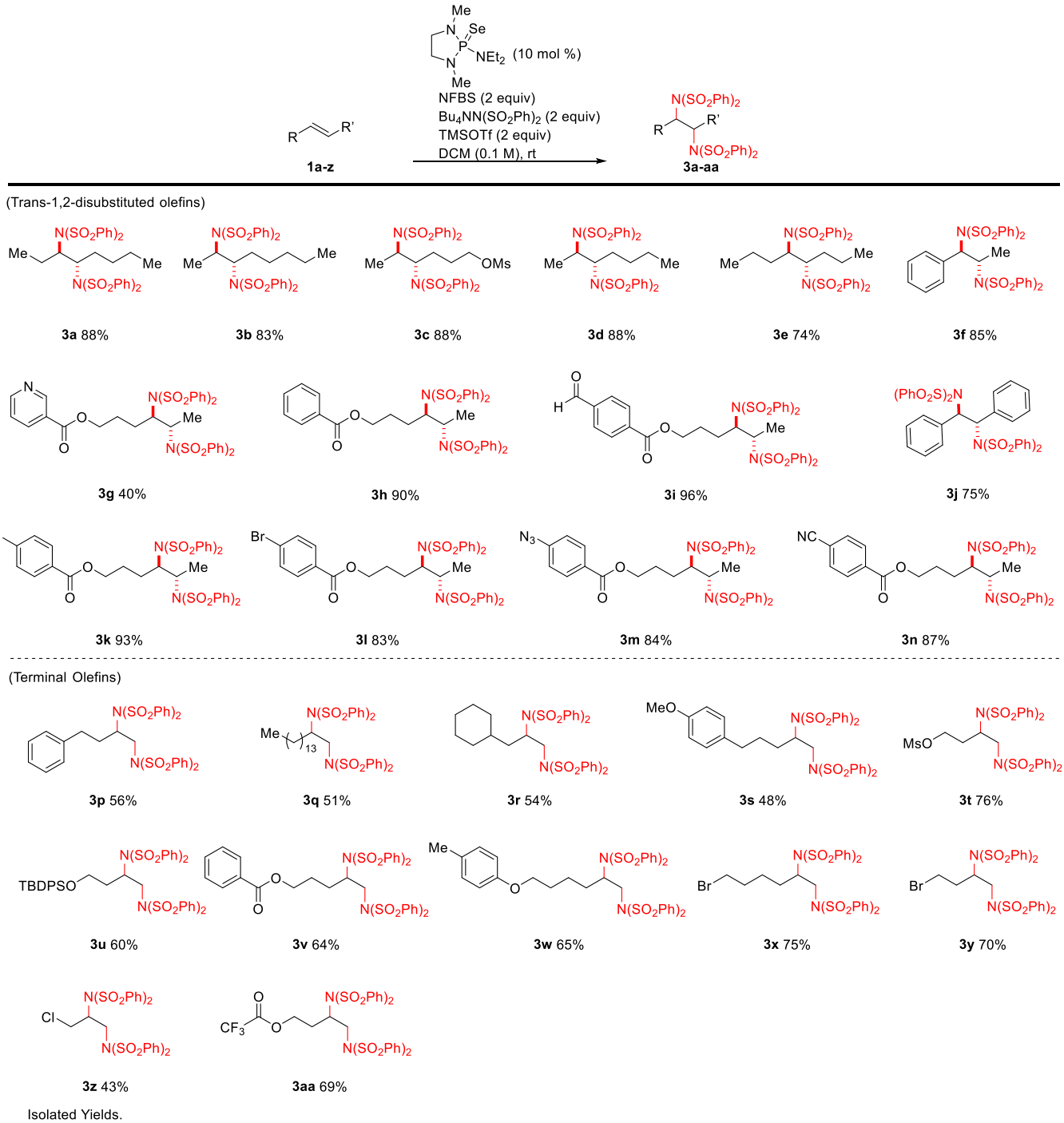
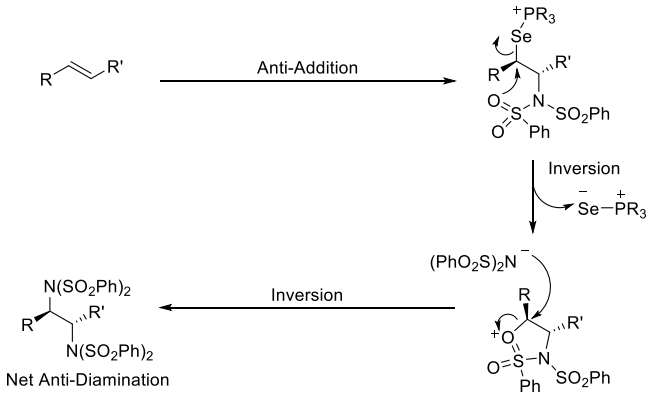


Table 1 Substrate Scope

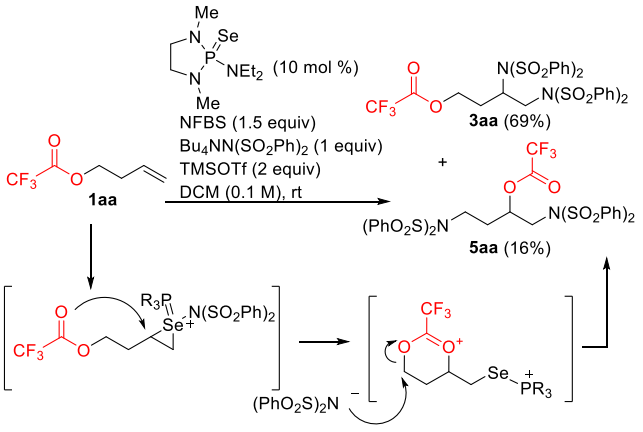
A variety of alkenes were subjected to the optimized conditions (Table 1). Both terminal- and 1,2-disubstituted olefins gave diamination products in good to excellent yields. The reaction is tolerant of silyl ethers, alkyl halides (including

allyl), aryl halides, electron-rich and electron-poor aromatics, esters, nitriles, azides, sulfonates, and aldehydes. Internal olefins performed particularly well, giving yields from 74-96%. Aryl iodide **3k** and heteroarene **3g** were noteworthy, as these substrates are not compatible with typical metal-catalyzed protocols. All products derived from internal alkenes were formed with high diastereoselectivity, giving anti-1,2-diamines with no detectable amounts of the syn diastereomers.[13] (*Z*)-1,2-disubstituted-olefins gave diamine products, but in poor diastereoselectivity. Tri- and tetrasubstituted olefins gave poor yields under these conditions.



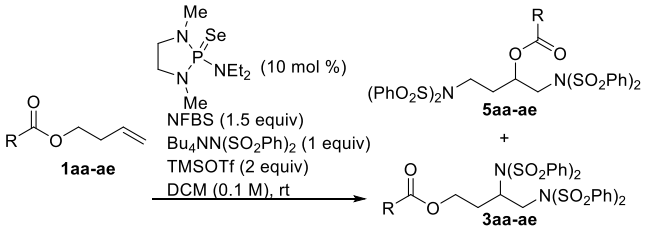
Scheme 5 Mechanistic Hypothesis for Observed Stereochemistry

Interestingly, rather than a syn addition of the nitrogen nucleophiles as might be predicted by our mechanism and Denmark's dichlorination results, we observed selective formation of anti-diamines from (*E*)-alkenes. This indicates that an intramolecular substitution of the selenium species precedes intermolecular attack by the second benzenesulfonimide. We propose this occurs via the sulfonimide oxygen, as detailed in Scheme 5. A similar anti stereoselectivity and explanation thereof has been previously proposed by Muñiz *et al* in their stoichiometric iodine(III) promoted diamination of alkenes.[14a]



Scheme 6 Ester Rearrangement Mechanism

In the course of our studies, we noticed that small amounts of an isomeric side product were consistently observed in the reaction of trifluoroacetate **1aa**. We determined its structure to be rearrangement product **5aa** (Scheme 6). We propose that this product is formed by attack of the ester on the initially-formed seleniranium ion, followed by ring-opening with benzenesulfonimide.



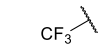
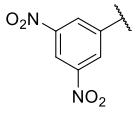
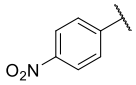
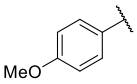
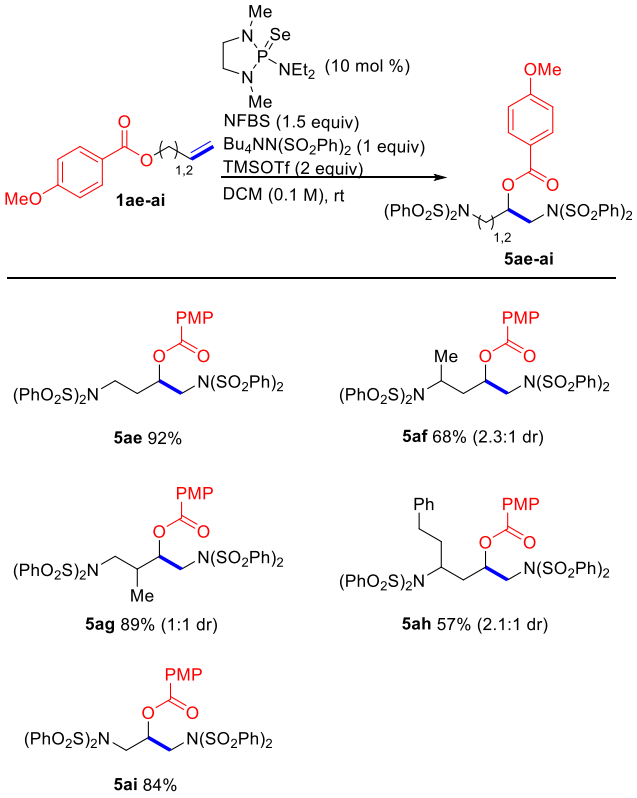
Starting Material	R =	Diaddition (**3**)	Rearrangement (**5**)
1aa		69%	16%
1ab		45%	25%
1ac		40%	50%
1ad		15%	66%
1ae		-	100%

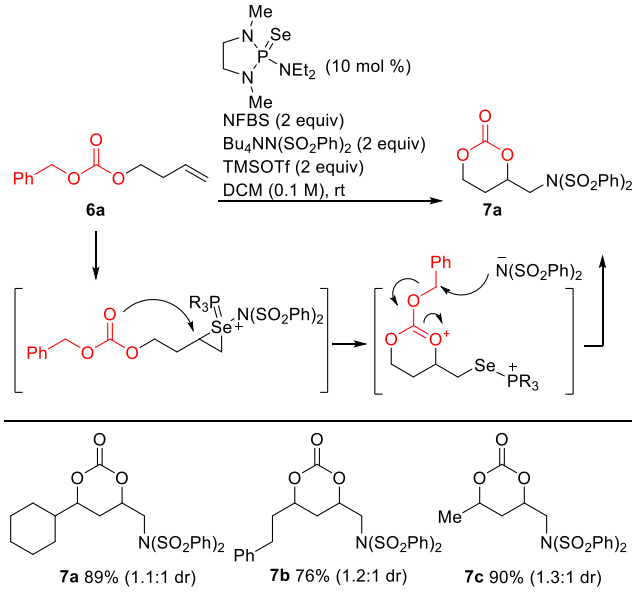
Table 2 Electron-Rich Esters Rearrange More Readily

Based on this proposed mechanism, we hypothesized that we could selectively generate either one of the isomeric products by changing the nucleophilicity of the ester oxygen. A series of electronically varied homoallyl esters **(1aa-1ae)** were subjected to the standard conditions and we observed that electron-rich esters gave predominantly rearrangement while electron-poor esters favored diaddition (Table 2). This is consistent with our proposed mechanism, in which an electron-rich ester would be more likely to act as a nucleophile, participating in the intramolecular cyclization before intermolecular nucleophilic attack can happen. Since the *p*-methoxybenzoate ester gave exclusively rearrangement product, several other substrates bearing this ester were subjected to the reaction conditions. As shown in Scheme 7, several allyl- and homoallyl esters gave rearrangement products in moderate to high yields. We found that in addition to the electronic properties of the ester, the chain length of the alkene also played a role. Allyl and homoallyl esters readily participated in the rearrangement, whereas longer chains gave little to no rearrangement (Table 1, compound **3v**). These reactions are interesting because they afford 1,3-diamino-2-alcohols and 1,4-diamino-2-alcohols, both common structural units in HIV-protease inhibitors.[16,17]



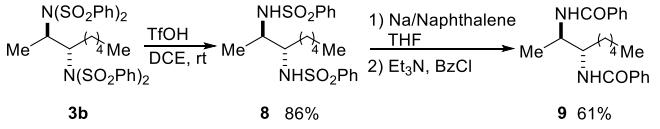
Scheme 7 Diamination/Rearrangement

Since intramolecular substitution with ester groups proceeded readily to give rearrangement products **5**, we envisioned that appropriately chosen carbonates could give cyclic products via a similar intramolecular attack, followed by dealkylation of the carbonate substituent (Scheme 8). Indeed, a brief screen of carbonates (Me, *t*-Bu, Bn) revealed that benzyl carbonates were optimal for this purpose, giving the desired cyclic carbonates in high yields.



Scheme 8 Carbonate Cyclization

A variety of procedures have been reported for the deprotection of sulfonimides and sulfonamides.[14a,18] To demonstrate the synthetic utility of the products, bis(sulfonimide) product **3b** was mono-deprotected to give bis(sulfonamide) product **8** in high yield (Scheme 9).[18d] Product **8** could then be fully deprotected to the free diamine, which was isolated as bis(benzamide) **9** for ease of purification.[18e]



Scheme 9 Selective sulfonamide deprotections

Conclusions

In summary, we have designed and implemented a new class of selenium-catalyzed 1,2-diaddition reactions of alkenes. This atypical mechanism was enabled by using a fluoride scavenger to shut down the typical syn-elimination pathway and by introducing a phosphine ligand on selenium to preferentially accelerate substitution reactions instead. The protocol is made successful by careful tuning of the phosphine ligand, revealing selenophosphoramides as the optimal catalysts. When an external benzenesulfonimide nucleophile was employed, 1,2-diamination of a range of terminal and 1,2-disubstituted alkenes was accomplished in high yields. The conditions tolerate a variety of functional groups. Additionally, substrates bearing appropriate internal nucleophiles, such as esters and carbonates, could be induced to undergo intramolecular substitution reactions, giving rearrangement and cyclization products. All told, the three types of diaddition reactions presented here (diamination, diamination/rearrangement, and oxyamination) allow access to a diverse set of products from simple alkene starting materials using a single set of conditions, demonstrating the utility of this new mode of catalysis. This allows access to a wide range of synthetically useful targets, including 1,2-diamines, 1,3-diamines, 1,4-diamines, and 1,2-aminocarbonates.[10,16]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the University of Washington and the National Science Foundation (CHE-1764450) for funding.

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