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Regioselective Metal-Free Aza-Heck Reactions of Terminal Alkenes Catalyzed by Phosphine Selenides

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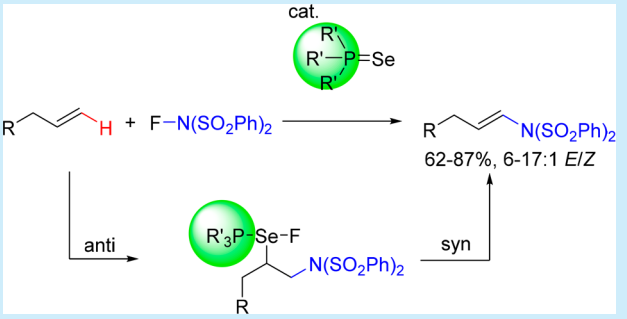
Supporting Information

ABSTRACT: Phosphine selenides are introduced as an alternate class of selenium-based catalysts for the aza-Heck reaction of alkenes. Using these catalysts, a range of terminal alkenes react with NFBS to give oxidative amination products. Judicious choice of phosphine ligand gives greater regio- and stereoselectivity than with diphenyl diselenide, enabling the selective formation of *E* terminal enimides in high yields. Isotope-labeling experiments and measurements of kinetic isotope effects reveal that the reaction occurs stereospecifically via irreversible anti addition, followed by rate-determining syn elimination.

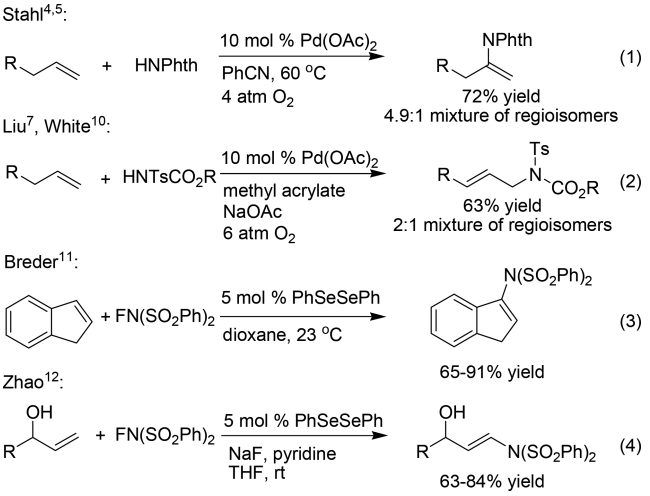


The aza-Heck[1] and aza-Wacker[2] reactions are powerful methods for the formation of new C−N bonds from alkenes. The vast majority of these reactions are catalyzed by palladium, proceeding via aminopalladation of the alkene, followed by *β*-hydride elimination. Though many intramolecular aza-Wacker and aza-Heck reactions have been reported, only a few intermolecular versions are known.[3−8] One of the major challenges in the development of an intermolecular aza-Wacker or aza-Heck reaction is the need to control the regioselectivity of both the aminopalladation and the *β*-hydride elimination steps. The combination of these steps can give up to four different isomeric products. This regioselectivity issue is further compounded by the propensity of palladium complexes to promote alkene isomerization reactions, resulting in even more isomeric products.[9] In addition to reducing the yield of the desired product, these isomers are often difficult to separate from it. Of the four potential products arising from unactivated terminal alkenes, only two have been reported to be accessed in reasonable selectivity. Stahl[5,6] has reported the selective formation of the internal enamide, and Liu[7] and White[10] have reported the selective formation of terminal allylamine (Scheme 1, eqs 1 and 2).

Recently, Breder[11] and Zhao[12] have shown that diphenyl diselenide can function as a promising alternative catalyst for the aza-Heck reaction of alkenes, presumably via a mechanism conceptually similar to palladium (eqs 3 and 4). The regioselectivity is high for styrenes and allylic alcohols and a few cyclic alkenes. However, control of regioselectivity was again a problem for simple terminal alkenes; complex mixtures of four regio- and stereoisomers were formed under both sets of conditions (see below). To date, understanding of the mechanistic details that control this selectivity is rather limited.

Though promising, further development of catalysts based on diphenyl diselenide is hindered by the difficulty of rapidly synthesizing an electronically and sterically diverse library of diselenides. Although Breder proposes that the Se−Se bond is crucial for catalytic activity, we wondered whether monoselenides might also be effective catalysts. Along these lines, we hypothesized that the selectivity of this and other reactions catalyzed by selenium compounds could be improved by conceiving of the phenyl group as a ligand for selenium rather than a substituent (Scheme 2). Replacement of this group by common ligands such as phosphines and *N*-heterocyclic carbenes (NHC) would suggest that phosphine selenides and selenoureas might also function as catalysts for these transformations.[13] An advantage of this strategy is that

Scheme 1. Intermolecular Aza-Wacker/Aza-Heck Reactions



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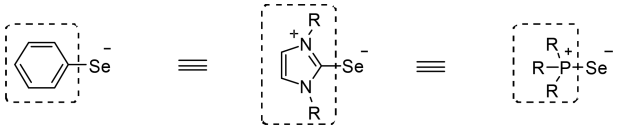
Scheme 2. Phosphine Selenides as Catalysts via Analogy to Aryl Selenides



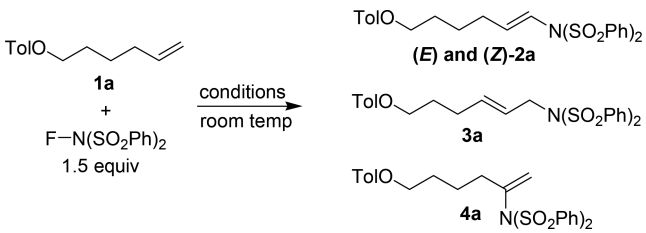
phosphine selenides and selenoureas are easily prepared in a single step from the corresponding phosphine[14] or NHC,[15] providing convenient access to a large library of sterically and electronically diverse catalysts that could enable more control over reactivity, regioselectivity, and stereoselectivity. Herein, we report that phosphine selenides indeed serve as active catalysts for the aza-Heck reaction of terminal alkenes and provide higher levels of regio- and stereoselectivity than diphenyl diselenide.

Treatment of terminal alkene **1a** under the conditions previously reported by Breder (Table 1, entry 1) and Zhao (entry 2) gave results similar to those reported by Zhao for 1-hexene; i.e., a mixture of four regio- and stereoisomers was formed in roughly equal amounts. When Ph_3PSe was used in place of diphenyl diselenide, the *E*/*Z* ratio improved slightly, but notably, the formation of internal regioisomer **4a** was suppressed (entry 3). A screen of other phosphine selenides revealed that a sterically hindered trialkylphosphine slightly improved the isomer ratios (entry 5). Ultimately, tri(*o*-tolyl)phosphine selenide was found to give the highest yield and selectivity for (*E*)-**2a** (entry 6). Unfortunately, the reactivity of the phosphine selenide catalysts under these conditions was substantially lower, giving only ~50% conversion after 65 h. A brief screen of reaction conditions revealed that simply adding 1 equiv of a benzenesulfonimide salt restored the reactivity, giving full conversion in 24 h (entry 7). As a final improvement to the procedure, we found that extending the reaction time for an additional 24 h further aminated all of the allyl sulfonamide isomer **3a** to bis-(sulfonimide) **5a**[16] (entry 8), without affecting the yield of **2a**. This allowed isolation of the desired terminal vinylamine product **2a** in 74% yield with only minor isomeric products. We also found that the phosphine selenide catalyst could be generated in situ by stirring Se powder with the phosphine for 3 h prior to addition of the remaining reagents (entry 9). Selenium powder in the absence of phosphine did not catalyze the reaction, emphasizing the need for a stabilizing ligand (entry 10).

These optimized conditions were applied to the amination of a variety of terminal alkenes (Scheme 3). Yields and *E*/*Z* selectivities were generally high. The reaction is compatible with esters, ethers, electron-rich aromatics, silyl ethers, sulfonamides, and nitriles. Notably, aliphatic and aromatic halides could also be successfully used as substrates (**2c**, **2d**, **2j**). The reaction of **1a** was performed under an ambient atmosphere on 4 mmol scale and gave **2a** with no significant loss of yield or selectivity.

To investigate the mechanism of this transformation further, the stereoisomeric deuterium-labeled substrates (*E*)-**1t**-*d* and

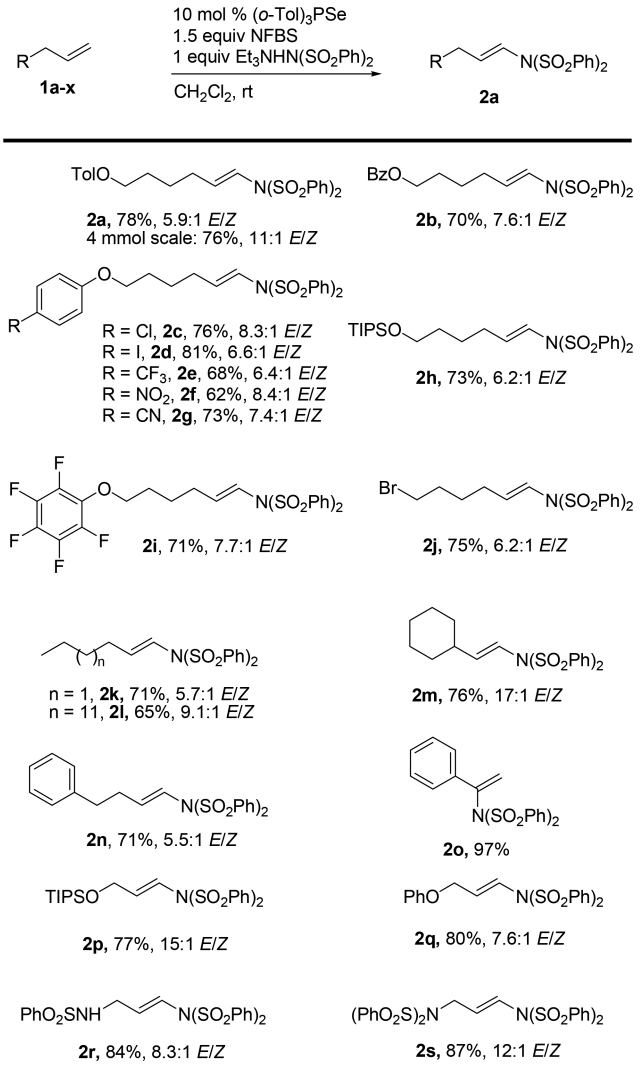
Table 1. Effects of Selenium Catalyst and Additives



entry	conditions	**2a** (%) (*E*/*Z*)[a]	**3a** (%)	**4a** (%)
1	5% PhSeSePh, THF (Breder, ref 11)	47 (1.8:1)	17	13
2	5% PhSeSePh, NaF, pyr, THF (Zhao, ref 12)	41 (1.9:1)	14	13
3	10% Ph_3PSe	18 (2.3:1)	7	tr
4	10% IPrSe	tr	tr	tr
5	10% Cy_3PSe	16 (2.6:1)	6	tr
6	10% (*o*-Tol)$_3$PSe	31 (4.1:1)	9	tr
7	10% (*o*-Tol)$_3$PSe, 1.0 equiv of $Et_3NHN(SO_2Ph)_2$, 48 h	74 (5.7:1)	12	4
8	10% (*o*-Tol)$_3$PSe, 1.0 equiv of $Et_3NHN(SO_2Ph)_2$, 48 h	**74 (5.7:1)**	tr	4
9	15% Se, 10% (*o*-Tol)$_3$P, 1.0 equiv, $Et_3NHN(SO_2Ph)_2$, 48 h	70 (4.8:1)	14	5
10	10% Se, 1.0 equiv of $Et_3NHN(SO_2Ph)_2$, 48 h	0	0	0

[a]NMR yields using 1,3-dinitrobenzene as internal standard. tr = trace.

Scheme 3. Alkene Scope[a]



[a]Isolated yields.

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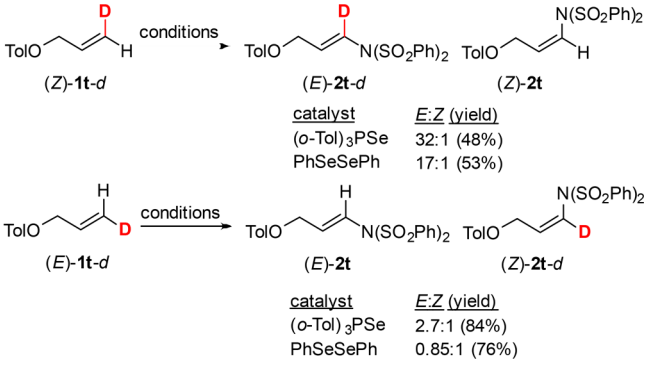
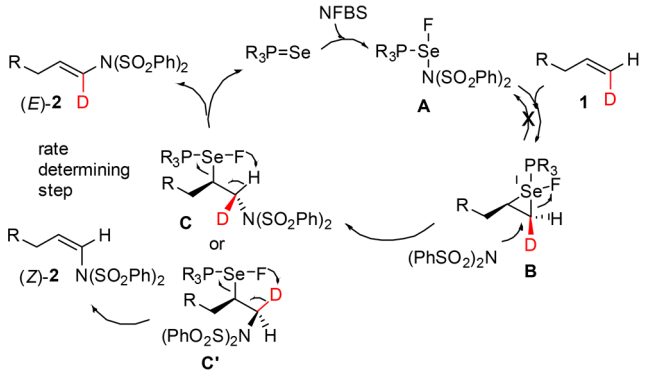
(*Z*)-**1t**-*d* were subjected to both our reaction conditions and the diphenyl diselenide-catalyzed conditions reported by Breder (Scheme 4). In all cases, we found that the hydrogen

Scheme 4. Deuterium-Labeling Experiment



at the terminal carbon atom was substituted stereospecifically, which is consistent with an anti addition followed by a syn elimination (see Scheme 5). Furthermore, we found that the

Scheme 5. Proposed Catalytic Cycle

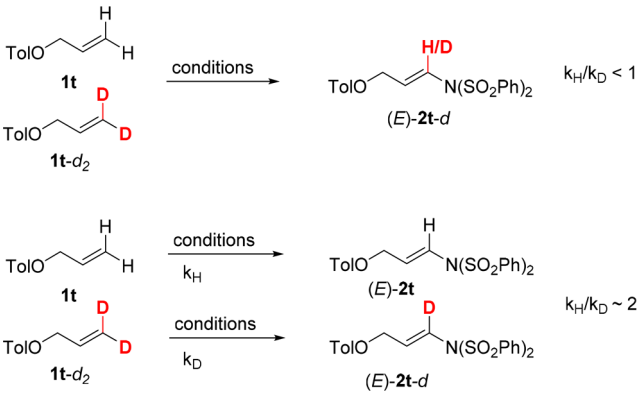


E/*Z* ratio of the products was strongly influenced by the geometry of the starting alkene, with the *Z* deuterated alkene giving substantially higher *E*/*Z* product ratios and the *E* deuterated alkene giving substantially lower *E*/*Z* ratios. By comparing these ratios with that of the closely related undeuterated substrate **1q** (7.6:1), it is apparent that the *E*/*Z* ratios increase by about a factor of 3 to 4 when using (*Z*)-**1t**-*d*, while they decrease by a roughly equivalent amount when using (*E*)-**1t**-*d*.

We propose the following mechanism based on these results (Scheme 5). The mechanistic experiments in Scheme 4 reveal that the basic mechanistic outline is the same for both diphenyl diselenide and phosphine selenide catalysts. Oxidative addition of NFBS to the phosphine selenide precatalyst gives selenium reagent **A**. Similar structures have been isolated and characterized by X-ray crystallography[17] and may be thought of as phosphine complexes of Se(II). Dissociation of benzenesulfonimide and addition to the alkene generate seleniranium ion **B**. Attack of benzenesulfonimide on this species gives the alkylselenium fluoride **C**, which can eliminate in a process that is isoelectronic to the well-known selenoxide elimination to give the product **2**. This anti addition/syn elimination would result in the deuterium-labeling patterns observed in the experiments in Scheme 4. Furthermore, the changes in *E*/*Z* ratios can be rationalized by a primary kinetic isotope effect in the elimination step ($k_H/k_D \sim 3-4$), which slows the formation of (*Z*)-**2** from the *Z* deuterated alkene (see structure **C′** in Scheme 5), and equivalently slows the formation of (*E*)-**2** from the *E* deuterated alkene. This isotope effect is comparable to that measured for the selenoxide elimination ($k_H/k_D = 5.2$).[18]

To learn more about the individual steps of the catalytic cycle, we measured the kinetic isotope effect (KIE) of deuterium substitution at the terminal position in two different ways (Scheme 6). First, we performed a competition

Scheme 6. Kinetic Isotope Effects



experiment between unlabeled compound **1t** and dideuterated **1t**-d_2. Under these conditions, we found a small inverse KIE ($k_H/k_D \sim 0.95$, see the Supporting Information for details). We also monitored the consumption of starting alkene in separate reactions of compound **1t** and compound **1t**-d_2. Under these conditions, the deuterated compound was consumed significantly more slowly, indicating a primary KIE ($k_H/k_D \sim 2$).[19] The inverse isotope effect in the competition experiment is typical for alkene addition reactions[20] and indicates that the product-determining step is the addition to the alkene; i.e., the initial addition of selenium to the alkene is irreversible. The primary isotope effect observed on the overall rate, however, indicates that the elimination of fluoroselenide **C** is the overall rate-determining step.

In summary, we have demonstrated that phosphine selenides may be used as a new class of catalysts in place of diaryl diselenide catalysts for the functionalization of alkenes. Proper choice of the phosphine allows enhanced regio- and stereoselectivity in the aza-Heck reaction of terminal unactivated alkenes with *N*-fluorobenzenesulfonimide. Mechanistic studies have revealed that the mechanism proceeds by an irreversible stereospecific anti addition, followed by a rate-determining syn elimination and that the syn elimination occurs with substantial C−H bond-breaking in the transition state.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03159.

Experimental details and characterization data (PDF)

Copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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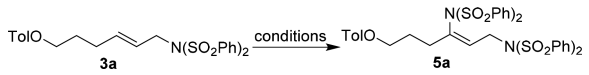

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(19) The isotope effect measured by the competition experiment in Scheme 5 is not exactly the same as that measured by labeling in Scheme 3 because neither experiment measures a pure single-step isotope effect for the elimination step. The labeling experiment incorporates a secondary isotope effect in the elimination of a proton, while the competition experiment may incorporate some of the secondary deuterium isotope effect from the addition steps.

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