α'-Selective Selenium-catalyzed Allylic C-H Amination of Enol Derivatives

Alexander F. Dohoda,[a] Nicole Rishwain,[a] Y-Nhi Tran,[a] Forrest E. Michael,*[a]

[a] A. F. Dohoda, N. Rishwain, Y. -N. Tran, Prof. F. E. Michael
Department of Chemistry
University of Washington
Box 351700
E-mail: fmichael@uw.edu

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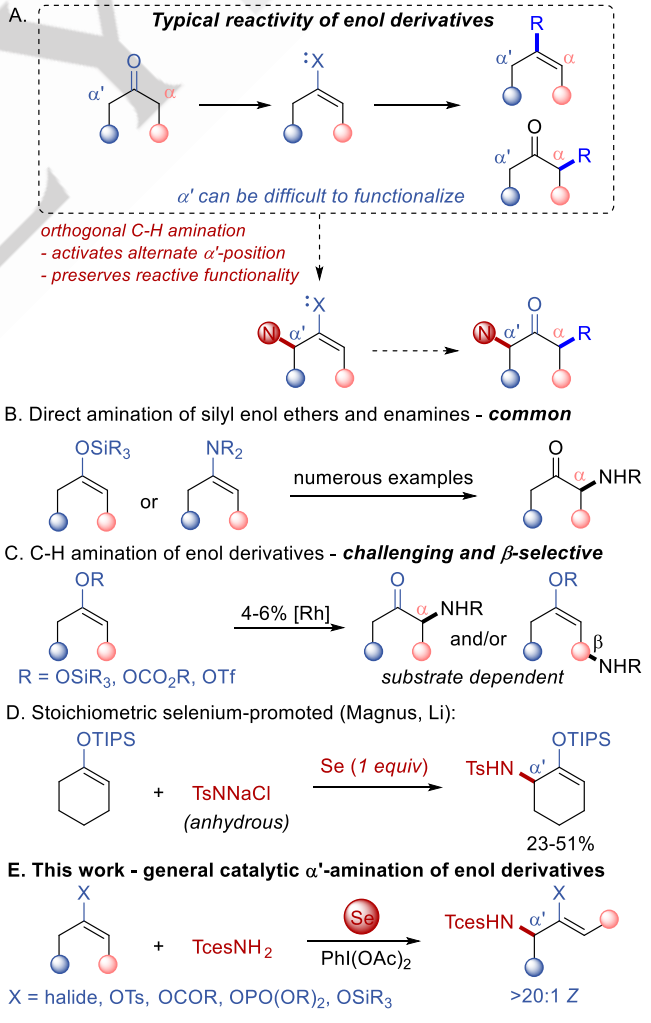
Abstract: A transition metal-free Se-catalyzed C-H amination protocol for α'-amination of enol derivatives has been developed. This reaction can be used to functionalize a wide variety of oxygen- and halogen-substituted alkenes spanning a vast range of nucleophilicities, giving α'-aminated enol derivatives with high regioselectivity. Amination of *E*/*Z* mixtures of alkenes proceeds stereoconvergently to give the (*Z*)-enol derivatives exclusively. Mechanistic studies revealed that the relative reactivity and α'-regioselectivity of these transformations is determined by substantial resonance donation to the heteroatom-bound carbon in the transition state. These products participate in traditional reactions of enol derivatives, allowing for efficient functionalization of both α- and α'-positions from a single enol derivative with high diastereocontrol.

Functionalization of ketones via enol derivatives has long been a powerful strategy in organic synthesis. Removal of the proton at one of the α-positions and installation of an electronegative substituent can generate diverse neutral organic intermediates that enable a variety of useful transformations (Scheme 1). One advantage to this approach is that the nature of the heteroatomic X substituent on the alkene has a profound influence on the reactivity and stability of these reagents. Alkenes bearing electron-releasing substituents, such as acyloxy and silyloxy groups, can serve as nucleophilic enolate equivalents in additions to a wide range of electrophiles.[1-3] Alternately, nucleofugal substituents like phosphates, sulfonates, and halides can serve as convenient handles for transition metal catalyzed cross-coupling reactions.[4-7] Depending on the heteroatomic substituent, the nucleophilicities of the C=C bonds and nucleofugacities of the leaving group can be varied by more than 15 orders of magnitude.[8] In both of these types of transformations the enol derivative is consumed in the functionalization, either via the removal of the carbon-heteroatom bond or the π-system itself. Reactions that functionalize enol derivatives without consuming this key reactive moiety would be a powerful tool orthogonal to the native reactivity of these compounds.

In preparing these reagents, a regioselective deprotonation event determines which of the adjacent α-carbons becomes part of the new alkene, and the subsequent reactivity of these species is then determined by that event. For some ketones, differences in acidity can make one of the two positions much more difficult to activate, thus making it challenging to functionalize that site. Once one α-position is activated, the alternate α'-position is no longer easily functionalized without returning to the parent ketone. We imagined that a regioselective C-H allylic amination of heteroatom-substituted alkenes could allow functionalization of the alternate α'-carbon of enol derivatives while simultaneously preserving the key reactivity of the enol derivative. This orthogonality would allow these aminated products to be derivatized further by the vast array of transformations available to enol derivatives. In this manner, the latent reactivity of both ketone α-positions could be unlocked. Furthermore, existing methods for achieving regioselective synthesis of enol derivatives

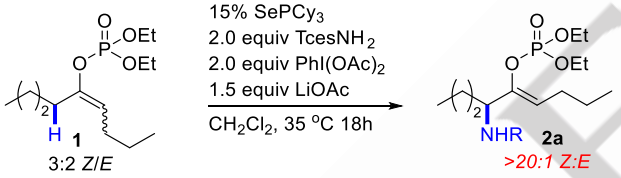


Scheme 1. C-H Amination of Enol Derivatives for Selective α'-Functionalization

could be leveraged to control amination regioselectivity in a counterintuitive fashion.

C-H amination has become a powerful tool to functionalize unreactive carbon-hydrogen bonds,[9-12] especially those adjacent to a π bond.[13-19] One limitation of these reactions, especially those that employ transition metals, is that this reactivity can be incompatible with reactive functional groups like enol derivatives. Consistent with their high reactivity, though many direct aminations of enol derivatives are known, only a few examples of selective C-H amination of these species have been reported (Scheme 1B,C).[20-30] Hashimoto and Dauban have successfully applied Rh-catalyzed C-H amination conditions to silyl enol ethers, vinyl carbonates, and vinyl triflates.[31-34] These reactions were found to be highly sensitive to both the overall substrate structure and the nature of the vinyl O-substituent, sometimes leading to competing or preferential enol amination. In these cases, C-H activation took place selectively at the β-position rather than the α'-position. The sole example of an α'-selective C-H amination was reported by Magnus,[35-38] who applied Sharpless' stoichiometric Se-promoted allylic amination to derivatize TIPS silyl enol ethers (Scheme 1D). This strategy was also used by Li in a recent synthesis of the daphnezomines, illustrating the potential utility of this approach.[39] However, this reaction suffers from prominent drawbacks; namely, it requires stoichiometric selenium and explosive anhydrous Chloramine-T, was limited to a small handful of silyl enol ethers, and gives mediocre yields.

Table 1. Initial studies and reaction optimization.

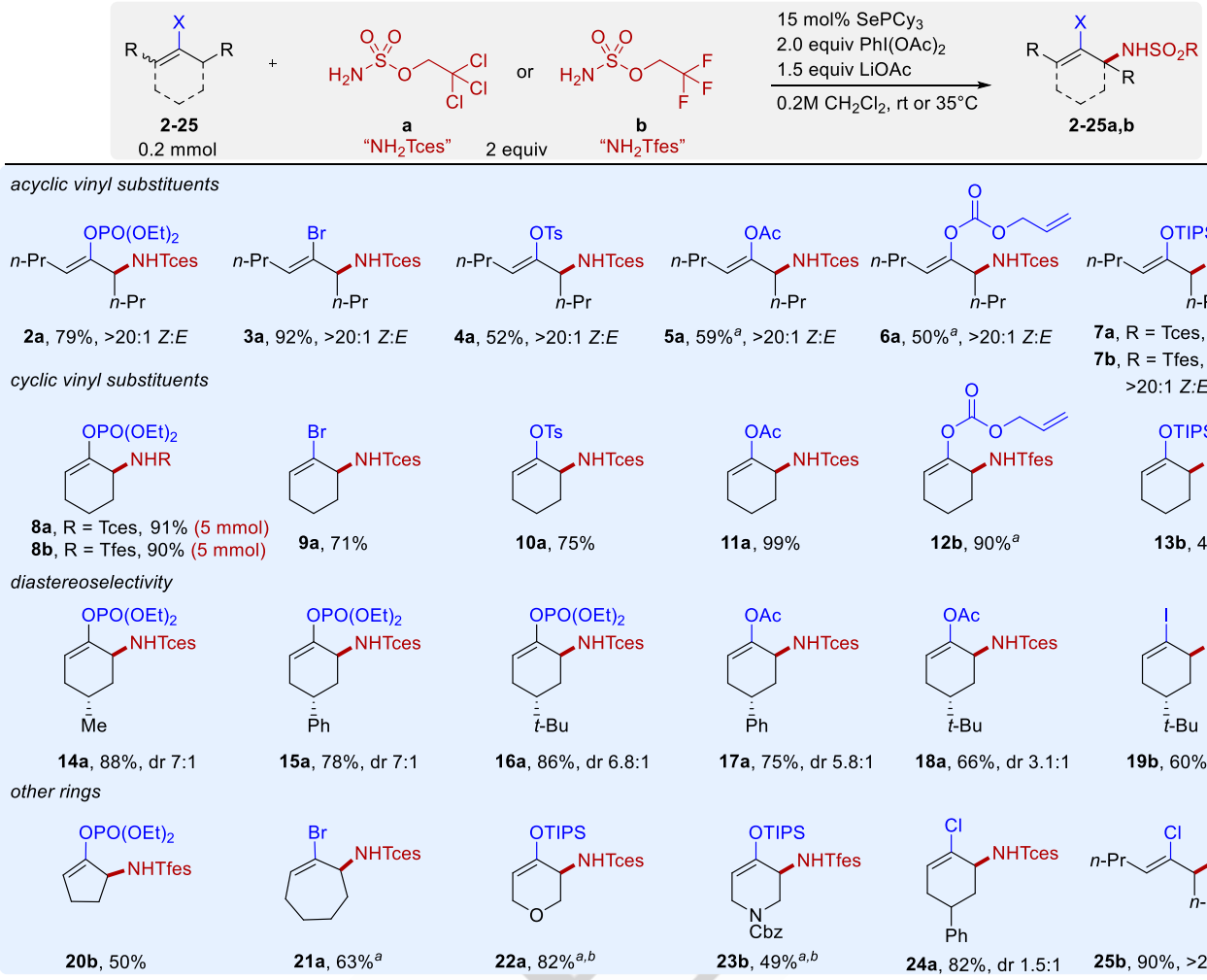


Entry	Deviation from Conditions	yield
1	none	79%
2	$NsNH_2$ instead of $TcesNH_2$, no base[40]	10%
3	$TfNH_2$ instead of $TcesNH_2$, no base	53%
4	SeIMe instead of $SePCy_3$	71%
5	$SePPh_3$ instead of $SePCy_3$	53%
6	$SePNp_3$ instead of $SePCy_3$	57%
7	CaO instead of LiOAc	64%
8	MgO instead of LiOAc	76%

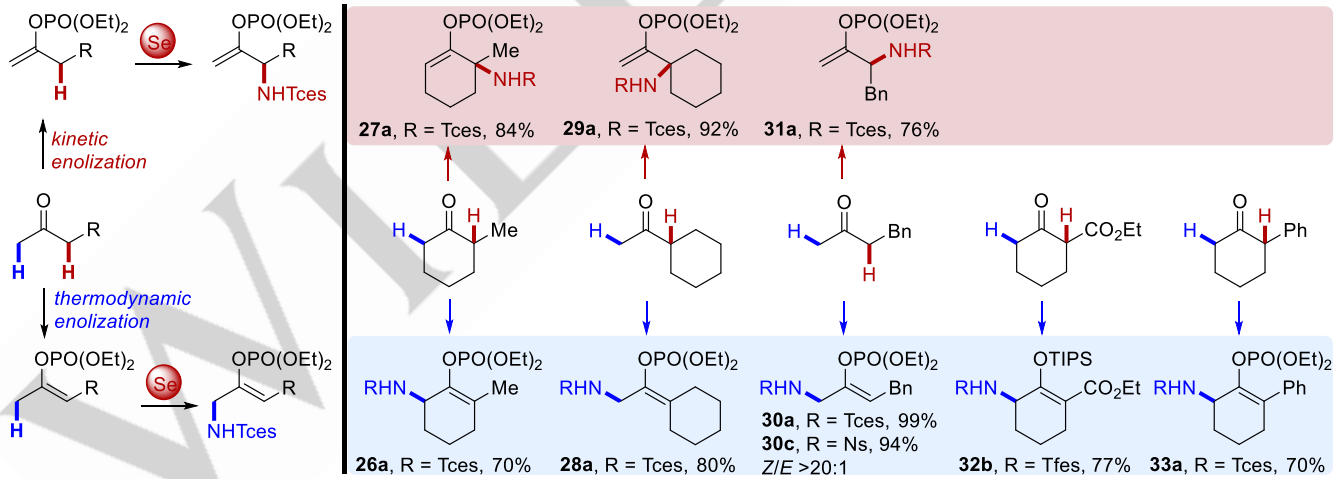
We have previously reported a Se-catalyzed allylic C-H amination method that tolerates a wide range of functional groups.[40-42] In particular, we demonstrated that vinyl boronates and silanes could be used as substrates without disturbing that potentially cross-reactive functionality.[43] From this precedent, we imagined that our Se-catalyzed allylic amination protocol could address previous limitations and aminate a much wider variety of enol derivatives in the α'-position while preserving the alkenyl functional group for future transformation. For our initial investigation, we chose nonanone-derived vinyl phosphate **1** as our model substrate (Table 1). Vinyl phosphates had not been previously used as allylic amination substrates, and the choice of an acyclic substrate offered the chance to assess the *E*/*Z* selectivity of our reaction. Notably, preparation of stereopure acyclic vinyl phosphates can be challenging, and so we employed a 3:2 *Z*/*E* mixture of compound **1**.[5] Our original amination conditions[40] gave a disappointing 10% yield after 24 hours, accompanied by 20% overoxidation to the α,β-unsaturated imine.[35] A screen of sulfonamides and sulfamates found that sulfonamides routinely gave overoxidation to imines while more electron-poor sulfamates gave solely the desired C-H amination product. $SePCy_3$ performed optimally as a catalyst with SeIMe also functioning comparably well. Other phosphine selenides gave worse mass recovery. We carried forward with $SePCy_3$ and SeIMe as precatalysts and trichloroethylsulfamate ($TcesNH_2$) and trifluoroethylsulfamate ($TfesNH_2$) as nitrogen sources for further optimization. Hydrolysis of the alkenyl phosphate was observed, which we hypothesized could arise from acid generated in the course of the reaction. A screen of bases found that addition of MgO, LiOAc, CaO, and Li_2CO_3 all increased mass balance, but also gave slower reaction rates. Mild heating to 35 ºC restored the reactivity and with these optimized conditions, allylic amination product **2a** was formed in 79% yield.

Notably, product **2a** was formed exclusively as a single alkene stereoisomer, which was established to have the *Z* configuration by NOESY (see SI). As has previously been seen for other Se-catalyzed allylic aminations,[42,43] migration of the alkene during the initial ene reaction destroys the starting alkene geometry, allowing both *E* and *Z* isomers to converge to a single product. The final stereochemistry is then set during the subsequent [2,3]-sigmatropic rearrangement and is governed by the balance between $A_{1,2}$ and $A_{1,3}$-strain in the 5-membered ring transition state. In contrast to the reactions of vinylsilanes and boronates, where the alkyl substituent ended up *trans* to the Si or B, here the alkyl substituent prefers the sterically favored *cis* position. Given the challenges in preparing isomerically pure ketone enol derivatives, this stereoconvergent protocol offers a powerful means of rectifying poor stereocontrol in the enolization step.

We then tested the range of vinyl substituents that could be tolerated in our C-H amination protocol (Scheme 2). We found that enol phosphates, tosylates, acetates, carbonates and silyl enol ethers all performed well under our reaction conditions, despite the wide range of electron-donating abilities and alkene nucleophilicities (**2a**-**7a**). Despite using *E*/*Z* mixtures of varying ratios of the starting alkenes for each of these acyclic substrates, all converged to a single *Z* isomeric product in good yields. TIPS enol ethers gave higher yields than analogs with smaller silyl substituents, which were prone to hydrolysis. Alkenyl chlorides (**24b**, **25a**), bromides (**3a**, **9a**, **21a**), and iodides (**19b**) also afforded products in good yields. This same diverse set of functional groups also gave high yields for cyclic substrates (**8a**-**13b**). As previously observed for TIPS enol ethers,[35-38] aminations of substituted cyclohexenes were diastereoselective, via stereoelectronically preferred axial attack (**14a**-**19a**). This axial selectivity was generally high for oxygen substituents, but was reduced for halides, suggesting a correlation between steric size

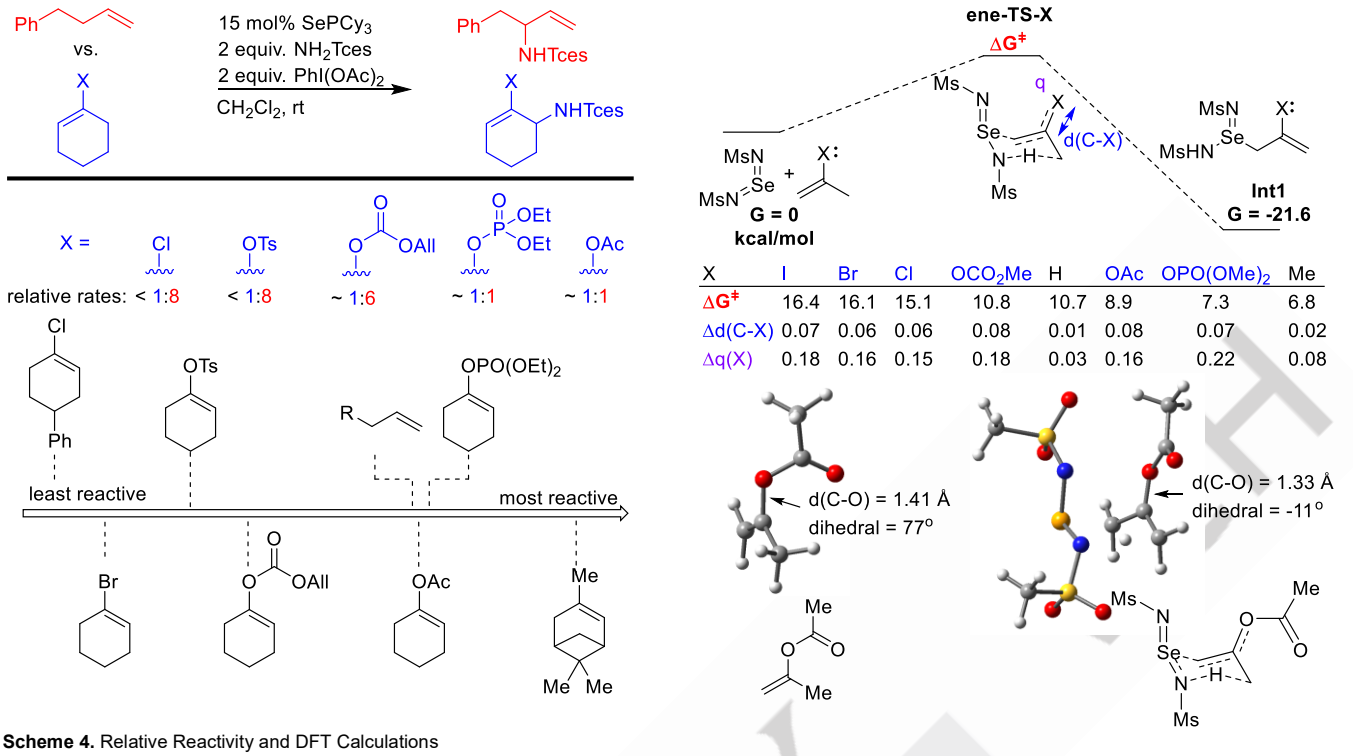


Scheme 2. Substrate Scope for Allylic C-H Amination of Enol Derivatives. [a]2.0 equiv. of MgO instead of LiOAc. [b]Toluene as solvent



Scheme 3. Regioselectivity Control by Enolization

and diastereoselectivity. Five-, six-, and seven-membered ring systems were aminated successfully under our conditions (**8a**-**24a**). *O*- and *N*-Heterocyclic enol phosphates failed to react, presumably due to deactivation of the alkene via induction, but upon switching to the more electron rich silyl enol ether, we were able to recover reactivity, affording heterocycles **22a** and **23b**. This illustrates the flexibility enabled by the broad tolerance of this allylic amination system, allowing a general strategy of tuning the reactivity of enol derivatives by adjusting the activating vinylic functional group. All substrates were highly selective for activation at the α'-position; neither γ-amination nor direct addition was ever observed. This reaction also performs well on a large scale, giving excellent yields at a 5 mmol scale, affording 2 grams of aminated product (**8a**, **8b**). Enamines and enamides were completely consumed under these conditions, but gave an intractable mixture of products. Enol triflates failed to react under our conditions and gave recovered starting material, consistent with their greater inductive withdrawing ability.



Scheme 4. Relative Reactivity and DFT Calculations

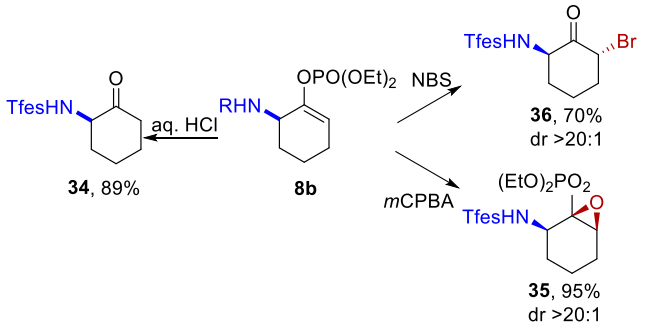
To illustrate that control over enolization site could be used to reliably direct amination to the opposite α'-position, we prepared regioisomeric pairs of enol phosphates from unsymmetrically substituted ketones and subjected them to our amination conditions (Scheme 3). We were pleased to see that our C-H amination method transformed each regioisomer smoothly and selectively and with no detectable isomerization of the alkene. The enol phosphate derived from the β-ketoester was unreactive to our catalytic system, likely due to deactivation from the ester. Again, switching to the TIPS enol ether restored reactivity, giving allylic amine **32b** in good yields. Importantly, in cases where preparation of one regioisomer is especially challenging due to large differences in C-H acidity (**32**, **33**), this α'-selective amination protocol allows C-N bond formation at a site that would be difficult to access due to difficulty in forming the corresponding kinetic enolate, illustrating that this C-H amination method is complimentary to existing C-H insertion and ketone α-amination methods.Å

We next examined the relative rates of amination of enol derivatives to probe the effects of the heteroatomic substituent on alkene reactivity (Scheme 4). In a series of intermolecular competition experiments, we found that the alkenyl phosphate and acetate both reacted at rates similar to an unfunctionalized monosubstituted alkene. The corresponding carbonate reacted about 6-fold slower, and the tosylate, chloride, and bromide all reacted at least an order of magnitude slower than this. All of these reactions were substantially slower than a substrate bearing a methyl substituent at that position. Further intermolecular competitions experiments established the order of reactivity (see SI).

The much higher reactivity of the enol acetate vs. the vinyl halides is not consistent with their Hammett σ parameters (0.31 vs. 0.15, respectively). Instead, following the approach of Yukawa and Tsuno,[44] a simple average of σ and σ^+ parameters is better at recapitulating the observed reactivity order (0.06 vs. 0.17), hinting at a substantial role for resonance donation in determining relative rates. To probe this more deeply, we performed DFT calculations[45] on the ene reaction between a model selenium bis(imide) and a range of heteroatom-substituted propenes. The calculated activation barriers agreed qualitatively with the reactivity order established experimentally. All C-X bonds contracted substantially (Δd ~ 0.07 Å) in the calculated transition states, exhibiting bond distances that are nearly halfway in between the corresponding single and double bond lengths, consistent with an approximate C-X bond order of 1.5 in the transition state. Furthermore, while all vinyl-OR species preferred a perpendicular conformation in the ground state, they all rotated to a sterically disfavored coplanar conformation in the ene transition state, illustrating the importance of resonance donation in the transition state. Finally, calculated NBO charges revealed a substantial loss of electron density from the X group (Δq ~ +0.16 e) demonstrating that the substantial buildup of positive charge on the central carbon atom is significantly stabilized by resonance donation for all substrates. All these factors point to a resonance contribution of roughly half that of a full carbocation in the transition state, illustrating the asynchronicity of the ene reaction. For enol acetates and phosphates, this "half" resonance donation nearly cancels out their inductive withdrawing effect, resulting in a reaction rate similar to that of the unsubstituted alkene.

Typical reactions of enol phosphates were conducted on allylic amination product **8b**, demonstrating further functionalization and synthetic value (Scheme 5). Hydrolysis to afford the protected α-aminoketone **34** proceeded in high yield. Epoxidation with mCPBA gave epoxide **35** with excellent *cis* selectivity, directed via hydrogen bonding to the sulfamate.[46] Finally, bromination with NBS selectively affords the *trans* α-bromo-α'-aminoketone **36**. These reactions demonstrate not only that this allylic C-H amination method allows sequential

functionalization of both α-positions without the need for reactivation, but that the newly introduced sulfamate can afford high levels of stereocontrol.



Scheme 5. Diastereoselective Functionalization of Aminated Products

In summary, we have developed a transition-metal free Se-catalyzed C-H amination protocol that operates on enol derivatives. The reaction has broad scope, functionalizing allylic C-H bonds of enol derivatives bearing a wide range of oxygen and halogen substitutents. It is regioselective for C-H amination in the α'-position, allowing kinetic and thermodynamic enolate control to translate into regioselective C-H amination. We probed the relative rates of allylic amination for a variety of enol derivatives determining a hierarchy of reactivity with most enol derivatives being less reactive relative to the aliphatic alkenes. Finally, these products readily participate in traditional enol chemistry after amination, with the newly introduced sulfamate imparting high levels of diastereocontrol.

Supporting Information

Detailed experimental methods and characterization of all products is given in the Supporting Information. The authors have cited additional references within the Supporting Information.

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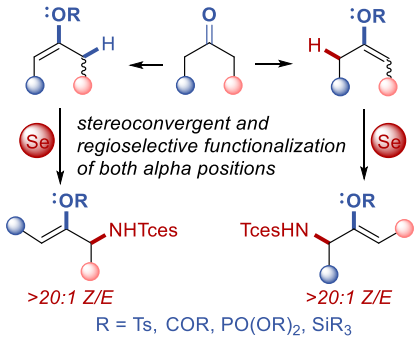

A selenium catalyst allows C-H amination of a wide range of potentially cross-reactive enol derivatives with unique selectivity for the α'-position, thereby unlocking the reactive potential of both ketone α-positions. Stereoconvergent formation of *Z* enol derivatives from *E*/*Z* mixtures eliminates the need for selective enolization methods. Resonance donation from the oxygen in the ene transition state is responsible for the high regioselectivity.

Institute and/or researcher Twitter usernames: Michael Group @othermichaellab