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Catalytic, Enantioselective *Syn*-Oxyamination of Alkenes

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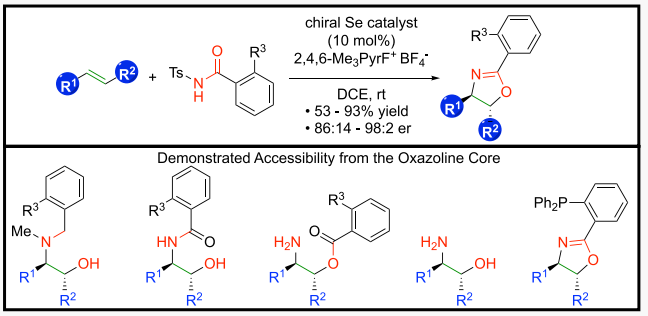
ABSTRACT: The chemo-, regio-, diastereo-, and enantioselective 1,2-oxyamination of alkenes using selenium(II/IV) catalysis with a chiral diselenide catalyst is reported. This method uses *N*-tosylamides to generate oxazoline products that are useful both as protected 1,2-amino alcohol motifs and as chiral ligands. The reaction proceeds in good yields with excellent enantio- and diastereoselectivity for a variety of alkenes and pendant functional groups such as sulfonamides, alkyl halides, and glycol-protected ketones. Furthermore, the rapid generation of oxazoline products is demonstrated in the expeditious assembly of chiral PHOX ligands as well as diversely protected amino alcohols.



INTRODUCTION

Enantiomerically pure 1,2-amino alcohols and their derivatives, including oxazolines, oxazolidinones, and oxazolidines, represent a ubiquitous motif in natural products,[1] bioactive molecules,[1a,b] organocatalysts,[2] chiral auxiliaries,[3] and chiral ligands (Figure 1).[4]

Given the importance of enantioenriched 1,2-amino alcohols, versatile and modular strategies to access these motifs are of great synthetic interest. Accordingly, a number of approaches have been developed for the assembly of enantioenriched 1,2-amino alcohols from a diverse array of starting materials, such as alcohols, aldehydes, ketones, amino acids, and amino esters.[5] Although these multistep syntheses provide good yields and enantioselectivities, a one-step protocol would offer the distinct advantage of a more efficient construction for more rapid generation of molecular complexity. Alkene difunctionalization, and more specifically alkene 1,2-oxyamination, offers a potentially modular approach to the assembly of 1,2-amino alcohols and has garnered considerable recent interest.[6] Furthermore, the broad availability of feedstock alkenes provides an accessible platform for rapid access to enantioenriched 1,2-amino alcohols.

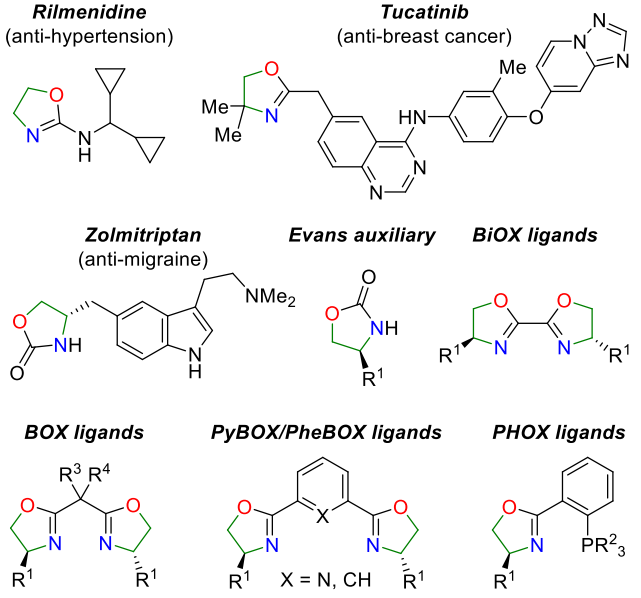


Figure 1. Important 1,2-amino alcohol derivatives in pharmaceuticals and ligands.

BACKGROUND

The seminal example of alkene 1,2-difunctionalization for accessing 1,2-amino alcohols was reported by Sharpless and co-workers in 1996 (Scheme 1a).[7] Following an initial report using stoichiometric amounts of osmium(VIII) to furnish racemic products,[8] the authors devised a catalytic and enantioselective method using chiral phthalazinediyl (PHAL) ligands with osmium(VIII) and Chloramine-T. Although this method gives respectable yields and enantioselectivities, it necessitates the use of symmetrical and electronically biased internal alkenes owing to deficiencies in the regioselectivity of unsymmetrical alkenes.[9] This shortcoming in regioselectivity was partially solved by Donohoe and co-workers using

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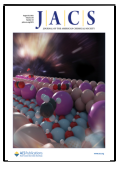

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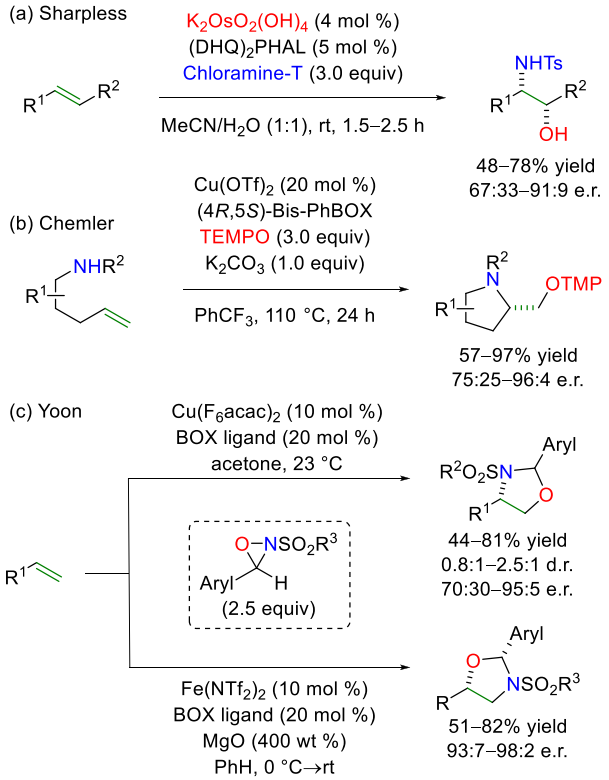
enantioenriched, amino-tethered alkenes to form an in situ generated imido osmium intermediate and promote an intramolecular 1,2-oxyamination.[10] In 2008, Chemler and co-workers disclosed an enantioselective, intramolecular 1,2-oxyamination of alkenes, combining unsaturated sulfonamides with copper(II) catalysts, chiral bisoxazoline (BOX) ligands, and TEMPO (Scheme 1b).[11] This method displays good to excellent yields and enantioselectivities in which the regioselectivity is controlled by intramolecularity. Follow-up studies demonstrate that either enantiomer can be accessed by this method through a judicious choice of the chiral BOX ligand.

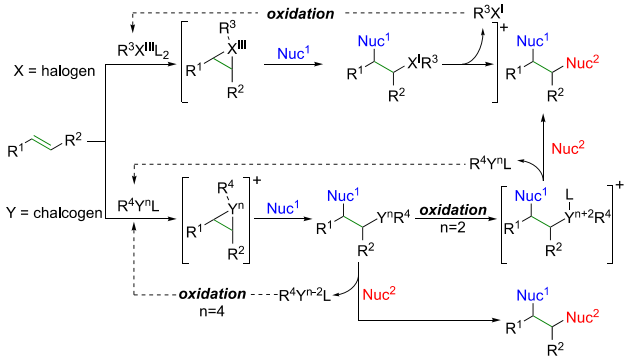
Scheme 1. Foundational Examples of Enantioselective 1,2-Oxyamination of Alkenes



Shortly thereafter, Yoon and co-workers discovered a pair of complementary methods for the enantioselective formation of oxazolidines from oxaziridines (Scheme 1c).[12] In this strategy, terminal olefins are functionalized enantioselectively using chiral BOX ligands to provide access to either constitutional isomer, depending on the choice of copper or iron as the catalyst. Good yields and enantioselectivities are observed in both cases, with excellent *cis*/*trans* diastereomeric selectivity in the iron catalysis system. Additional enantioselective alkene 1,2-oxyamination methods have been developed using (1) stoichiometric amounts of manganese,[13] (2) catalytic processes that employ copper,[14] palladium,[15] and iridium complexes,[16] and (3) bioenzymatic catalysis.[17]

Another promising strategy that has been employed for stereoselective 1,2-oxyamination of alkenes is the use of a redox-active catalyst that can form a highly electrophilic -iranium ion when combined with an alkene substrate. Chalcogens and halogens in rows 3−5 are often used for vicinal alkene difunctionalizations via -iranium ions, and their use as potential redox-active catalysts is of considerable interest (Scheme 2). Upon initial opening of the -iranium ion with a nucleophile, a secondary nucleophile can displace the catalyst, allowing for the 1,2-difunctionalization and regeneration of the catalyst. However, an oxidative step is necessary to turn over the redox process. Halogen(I/III)-based catalysts are released in a lower oxidation state than is required for -iranium formation and must be reoxidized to promote the -iranium formation. Iodine has been employed as a catalyst in this process to generate racemic oxazolines[18] and enantioenriched oxazolidinones[19] using chiral iodine reagents. In contrast, some chalcogen(II) catalysts must be oxidized to form a chalcogen(IV) leaving group for the second nucleophile addition. Alternatively, some Se(II) species can serve as a competent nucleofuge but then must be oxidized to the Se(IV) species to reenter the catalytic cycle. By comparison to the use of iodine as a redox catalyst to effect 1,2-oxyamination of alkenes, the use of chalcogens for this purpose remains underexplored.

Scheme 2. General Flow for a Redox-Active Halogen/Chalcogen Catalysis



Although chalcogens have seen prior use in the dual opening of -iranium ions to effect 1,2-oxyamination of alkenes, this has historically been conducted using stoichiometric amounts of the chalcogen-based reagent. This strategy was first demonstrated in 1988 by Ogura and co-workers using benzenetellurinyl trifluoroacetate to form the telluriranium ion, with opening by the nitrile solvent in a Ritter-type process that ultimately displaces the tellurium through an invertive process that reduces the tellurium reagent (Scheme 3a).[20] Shortly thereafter, Tiecco and co-workers demonstrated that stoichiometric amounts of diphenyl diselenide, in the presence of an oxidant, can react with alkenes to form a seleniranium ion that can be opened by a variety of nucleophiles to provide 1,2-amino alcohol scaffolds upon displacement of the selenium (Scheme 3b).[21] This reaction platform generates 1,2-azido ethers, oxazolines, and oxazolidinones. Although this reaction was initially conducted as a two-step process with the alkyl selenide as an intermediate, subsequent studies by these authors found that the use of phenylselenenyl sulfate as the selenium source allows for a one-pot protocol for the formation of oxazolines.[22] The authors propose that the formation of a cationic diselenide from the alkyl selenide intermediate promotes the second nucleophilic attack and loss of the selenide.

A recent report from our laboratories demonstrated that a chiral diselenide can be used catalytically to effect enantioselective formation of oxazolidinones from alkenes and a carbamate in the presence of a mild oxidant to promote catalytic turnover (Scheme 3c).[23,24] Drawing on knowledge

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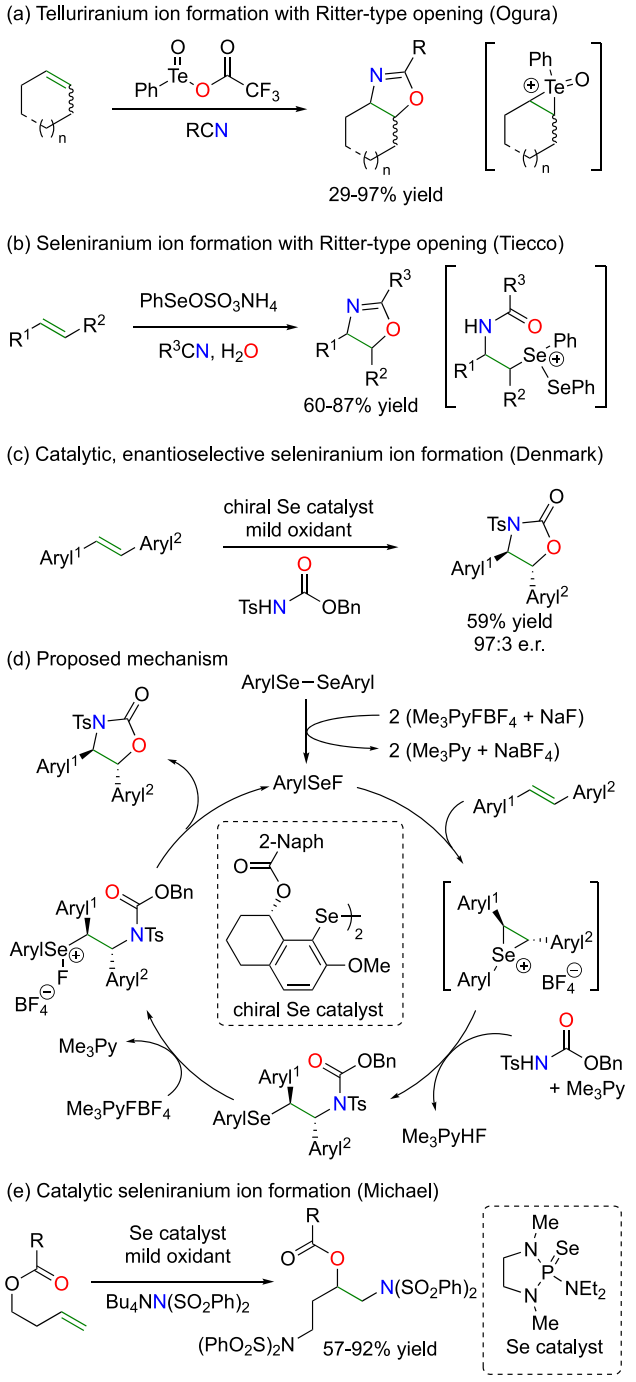
Scheme 3. Chalcogen−Iranium Ion Formation for the 1,2-Amino Oxygenation of Alkenes



gleaned from previous efforts in Se(II/IV) catalysis,[25] this process begins with a symmetrical diselenide Se(I) catalyst, which is oxidized to the active Se(II) catalyst (Scheme 3d). This species then forms a seleniranium ion, which can be opened enantioselectively through intermolecular attack by the carbamate. The resulting Se(II) species is oxidized to Se(IV) to create a leaving group for intramolecular closure by the carbamate and concomitant regeneration of the active Se(II) catalyst. Although this was but a single example within the context of an alkene diamination method, it nevertheless demonstrated the viability of this approach for catalytic, chiral selenium catalysis. Additionally, this marked the first example of a chemo-, regio-, diastereo-, and enantioselective 1,2-oxyamination of alkenes.

In addition, Michael and co-workers found that a selenophosphoramide can generate a seleniranium ion catalytically, while also acting as a good leaving group for a secondary nucleophilic addition (Scheme 3e).[26] This method comprises several examples using unsaturated esters and sulfonimides for the formation of racemic 1,2-amino alcohol precursors in fair to good yields. Interestingly, this method was disclosed as a serendipitous discovery within the context of an alkene diamination investigation.

Although significant progress has been made in the area of 1,2-oxyamination of alkenes, currently, few methods are available for simultaneous control of the chemo-, regio-, diastereo-, and enantioselectivity.[18b] The success of using the chiral diselenide catalyst with bifunctional nucleophiles to generate enantioenriched 1,2-difunctionalized alkenes (Scheme 3c) provided encouragement that a similar approach could be formulated with other bifunctional nucleophiles. Accordingly, a research program for the development of a general protocol for 1,2-oxyamination of alkenes that would provide useful scaffolds to access 1,2-amino alcohols was formulated.

RESEARCH PLAN

The alkene 1,2-diamination report disclosed a preliminary protocol for the use of selenium redox to accomplish 1,2-oxyamination of alkenes to oxazolidinones using carbamate nucleophiles.[23] However, further investigation of this approach identified a severe alkene substrate limitation, as only a narrow range of stilbene partners were viable. Accordingly, it was decided that a new class of bifunctional nucleophiles should be investigated for their compatibility with a broader range of alkenes. From the success of the *N*-tosyl urea nucleophiles, it was decided that *N*-tosyl amides would offer a close analogy for the nitrogen-centered nucleophile. Whereas both nucleophiles rely on the nucleophilicity of the carbonyl oxygen, it should be noted that the use of *N*-tosyl amides would require loss of the *N*-tosyl group as tosyl fluoride to create a stable product, whereas the previous protocol necessitated the loss of benzyl fluoride.

RESULTS

1. Orienting Experiments and Optimization. The initial investigation commenced by mimicking the conditions in the alkene 1,2-diamination report.[23] Thus, *N*-tosyl-3-methoxybenzamide was combined with (*E*)-2-methylstyrene in the presence of a diphenyl diselenide catalyst, *N*-fluorocollidinium fluoroborate,[27] and sodium fluoride (Table 1). Initial evaluation with acetonitrile, the solvent from the diamination protocol, resulted in no conversion to the desired product (entry 1). However, upon switching to dichloromethane, a moderate yield of product was observed (entry 2). In surveying a range of halogenated solvents, 1,2-dichloroethane (DCE) afforded an elevated yield (entry 3), but other solvents such as chloroform, chlorobenzene, and α,α,α-trifluorotoluene delivered only trace amounts of the desired product (entries 4−6). Varying the concentration of the reaction only decreased the product yield (entries 7 and 8). Use of the chiral diselenide catalyst (**3a**), afforded a 71% isolated yield of the desired product with a 93:7 er as a single diastereomer (entry 9).

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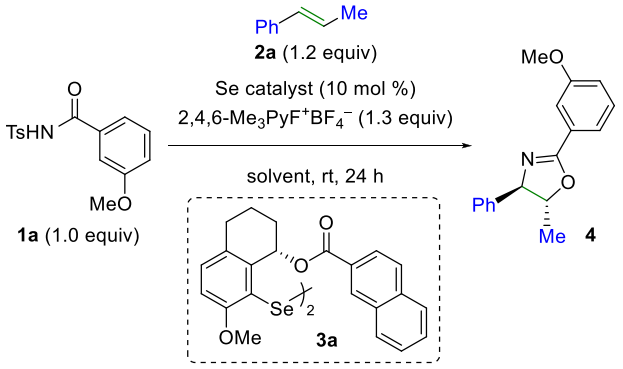
Table 1. Survey of Solvents for the 1,2-Oxyamination of Alkenes[a]



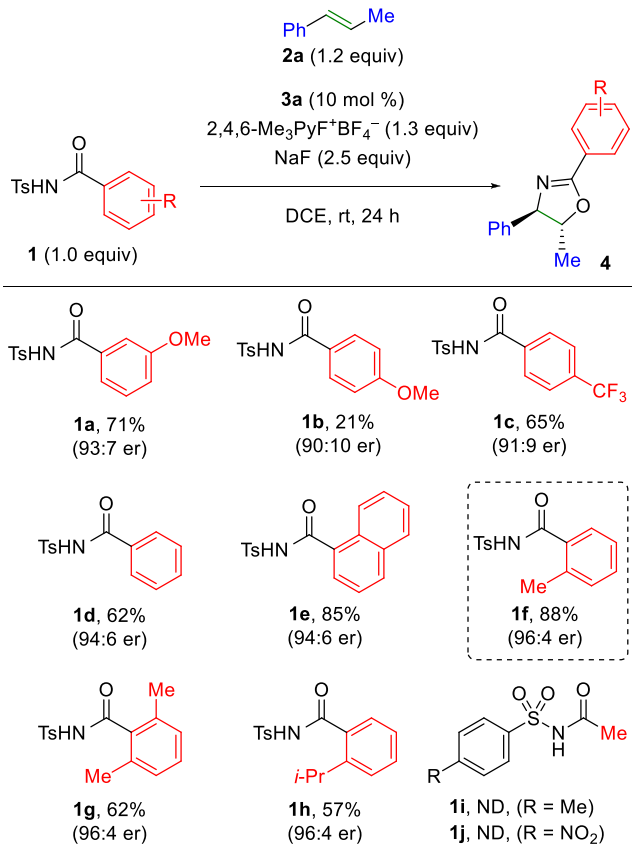
entry	Se catalyst	solvent	conc (M)	yield 4[b] (%)
1	Ph_2Se_2	MeCN	0.2	0
2	Ph_2Se_2	CH_2Cl_2	0.2	33
3	Ph_2Se_2	DCE	0.2	43 (35)[c]
4	Ph_2Se_2	$CHCl_3$	0.2	<5
5	Ph_2Se_2	PhCl	0.2	<5
6	Ph_2Se_2	$PhCF_3$	0.2	<5
7	Ph_2Se_2	DCE	0.1	24
8	Ph_2Se_2	DCE	0.4	37
9	**3a**	**DCE**	**0.2**	**87 (71)**[c,d]

[a]All reactions were performed on a 0.2 mmol scale. [b]Yields obtained from quantitative ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard. [c]Yield in parentheses is an isolated yield. [d]Enantiomeric ratio of 93:7 determined by CSP-HPLC. See the Supporting Information for details.

2. Identification of the Optimal Oxyamination Reagent. With initial conditions in hand, a survey of *N*-sulfonamide benzamides was conducted with (*E*)-2-methylstyrene to ascertain the optimal reagent for achieving both high yield and enantioselectivity (Table 2). In contrast to the original *N*-tosyl-3-methoxybenzamide (**1a**), the 4-methoxy analog (**1b**) resulted in a substantial decrease in yield with a slightly decreased enantioselectivity, whereas the 4-trifluoromethyl analog (**1c**) displayed slightly lower yield and enantioselectivity. Both the unsubstituted phenyl- (**1d**) and 1-naphthylbenzamides (**1e**) exhibited enantioselectivities comparable to that of **1a**, and **1e** also led to a higher yield. Appending a 2-methyl group on the benzamide (**1f**) resulted in an increase in both yield and enantioselectivity, whereas appending 2,6-dimethyl (**1g**) or 2-isopropyl groups on the benzamide (**1h**) showed similar enantioselectivities, but with a substantial decrease in yield. Finally, attempts to employ aliphatic *N*-tosylamides were unsuccessful; either *N*-tosyl- (**1i**) or *N*-nosylacetamides (**1j**) were unreactive. Accordingly, on the basis of yield and enantioselectivity, the 2-methylbenzamide was chosen as the optimal reagent for further studies.

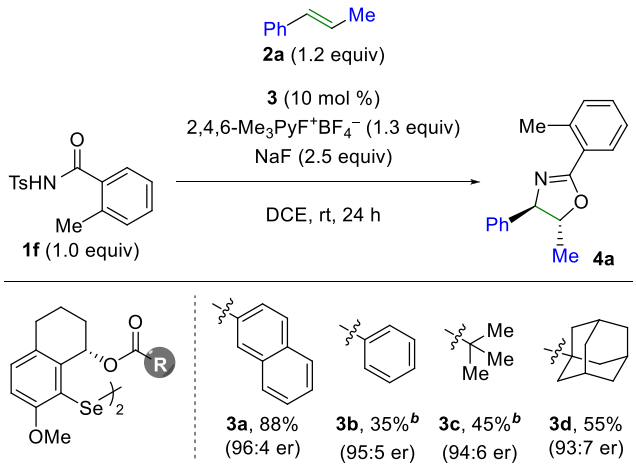
3. Identification of Optimal Catalyst. Several chiral diselenide catalysts were surveyed for yield and enantioselectivity that varied the ester group of the (*S*)-7-methoxy-1,2,3,4-tetrahydronaphthalene-8-diselenyl scaffold (Table 3). Upon changing the 2-naphthoate ester to a benzoate ester (**3b**), comparable enantioselectivity was observed, but with significantly reduced yield. Alkyl esters such as *tert*-butanoyl (**3c**) or 2-adamantoyl (**3d**) afforded poor yields with similar enantioselectivities. Clearly, the 2-naphthoyl catalyst offered the best results for both product yield and enantioselectivity.

Table 2. Survey of *N*-Sulfonamide Benzamides for 1,2-Oxyamination of (*E*)-2-Methylstyrene[a]



[a]All reactions were performed on a 0.2 mmol scale. Yields are of isolated, purified products. Enantiomeric ratios were determined after chromatographic purification by CSP-HPLC. See the Supporting Information for details.

Table 3. Survey of Chiral Diselenide Catalysts for Optimal Yield and Enantioselectivity[a]



[a]All reactions were performed on a 0.2 mmol scale. Yields are of isolated material. Enantiomeric ratios were determined after chromatographic purification by CSP-HPLC. See the Supporting Information for details. [b]Performed on a 0.05 mmol scale.

To determine the relative and absolute configurations of the oxazoline products, oxazoline **4a** derived from (*E*)-2-

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methylstyrene and benzamide **1f** (96:4 er) was hydrolyzed to the corresponding 1,2-amino alcohol with strong acid. The optical rotation recorded for 1-amino-1-phenylpropan-2-ol hydrochloride matched the reported literature value for an absolute configuration of 1*R*,2*R*,[28] which unsurprisingly matched the absolute configuration observed in the alkene 1,2-diamination using the same chiral diselenide catalyst (see the Supporting Information for details).

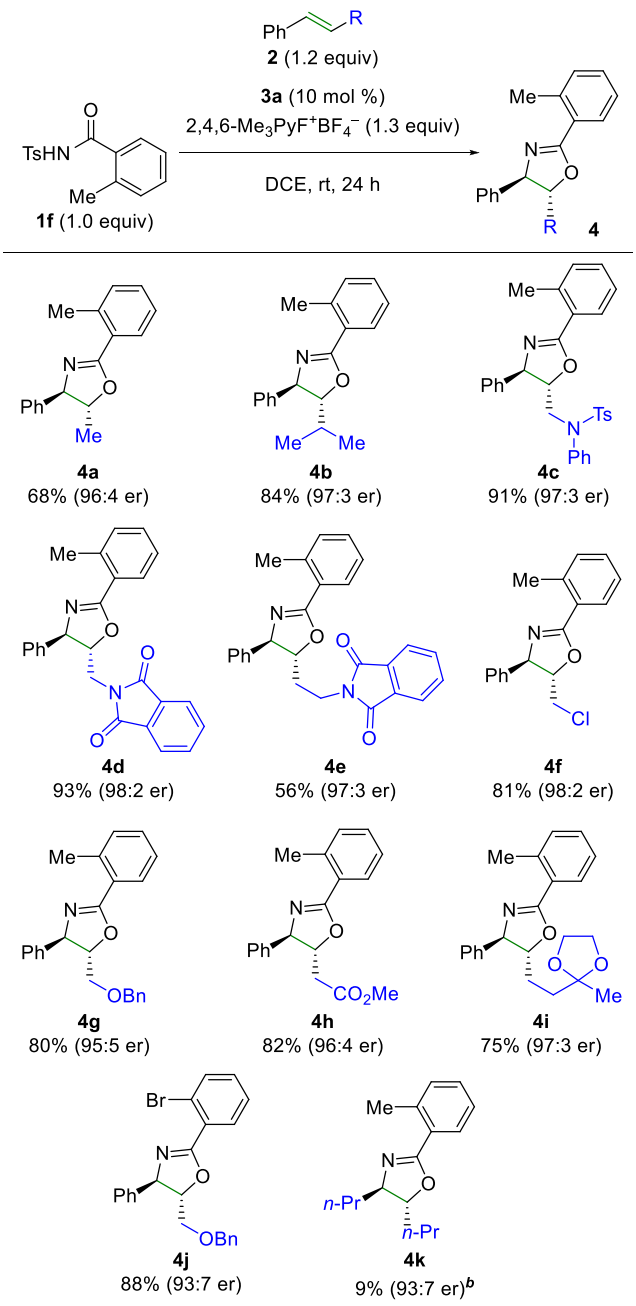
From these studies, it was also determined that sodium fluoride provided no constructive advantage and only led to increased heterogeneity. Accordingly, NaF was omitted from the final reaction conditions (see the Supporting Information for details).

4. Scope of Alkene Substrates. The scope of alkene substrates began with an investigation of the compatibility of various functional groups (Table 4). As a baseline, 2-alkyl-substituted alkenes such as (*E*)-2-methylstyrene and (*E*)-2-isopropylstyrene provided **4a** and **4b** in good yields with high levels of enantioselectivity. Substrates bearing functional groups on the methyl substituent such as *N*-tosylaniline and phthalimide led to **4c** and **4d** in high yields and excellent enantioselectivities. Furthermore, a phthalimide substrate bearing an additional methylene group afforded **4e** in modest yield, with negligible decrease in enantioselectivity. The presence of a primary alkyl chloride was compatible under the reaction conditions, producing **4f** in high yield and excellent enantioselectivity. Ether or ester functionalities were also compatible leading to **4g** and **4h** in high yields and high enantioselectivities. Similarly, a glycol-protected ketone was viable, illustrating further compatibility with protecting group strategies (**4i**). Changing the 2-methylbenzamide to a 2-bromobenzamide improved the yield slightly though the enantioselectivity decreased slightly (**4j**). Finally, as was the case for 1,2-diamination, aliphatic alkenes afforded very poor yields but high levels of enantioselectivity were conserved (**4k**). Although the poor yield for dialkyl alkenes was disappointing (and provides a critical direction for further investigation) the current iteration of this method displays compatibility with a wide range of functional groups.

Next, variation of the aromatic ring on the alkene substrate was examined (Table 5). Products bearing electron-withdrawing groups, in the case of 4-trifluoromethyl- (**4l**) or 2-bromophenyl (**4n**) groups, were formed in modest yields with good enantioselectivities. A substrate bearing a 4-methoxy group afforded **4m** in a comparable yield but with a notably lower enantioselectivity. The use of aromatic systems beyond substituted benzene rings was also explored; e.g., a 2-thienyl group led to a modest yield and good enantioselectivity (**4o**). A 2-naphthyl-substituted alkene afforded a good yield with good enantioselectivity (**4p**). A similar yield was observed for the product bearing a 1-naphthyl group (**4q**), but with lower enantioselectivity.

Stilbenes were also evaluated beginning with unsubstituted (*E*)-stilbene, which provided a good yield with excellent enantioselectivity (**4r**). Attachment of electron-donating 3-methoxy groups to the stilbene core afforded a noticeable drop in yield with a slight decrease in enantioselectivity (**4s**). The regioselectivity of addition was tested with an unsymmetrically substituted 4-methoxy-4′-trifluoromethylstilbene, which afforded a single diastereomer in excellent yield and enantioselectivity (**4t**). This connectivity was established through heteronuclear multiple bond correlation spectroscopy (HMBC), observing a correlation between the oxazoline HC(5) methine and the carbons on the trifluoromethyl aromatic ring.

Table 4. Alkene Substrate Scope for Functional Group Variation[a]



[a]All reactions were performed on a 1.0 mmol scale. Yields are of isolated, analytically pure material. Enantiomeric ratios were determined after chromatographic purification by CSP-HPLC. See the Supporting Information for details. [b]Performed on a 0.2 mmol scale.

Although this protocol was successfully applied to a wide range of alkene partners, a number of substrates provided less than satisfactory yields (Table 6). Both acetate (**2u**) and propargyl ether (**2v**) functionalities demonstrated only moderate compatibility with the reaction conditions. Additionally, it was known from **4n** that 2-substituted styrene derivatives gave lower yields. Accordingly, a 2-methoxyphenyl

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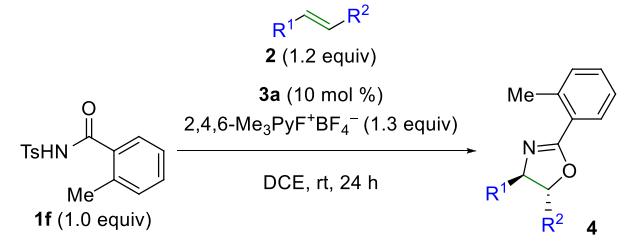
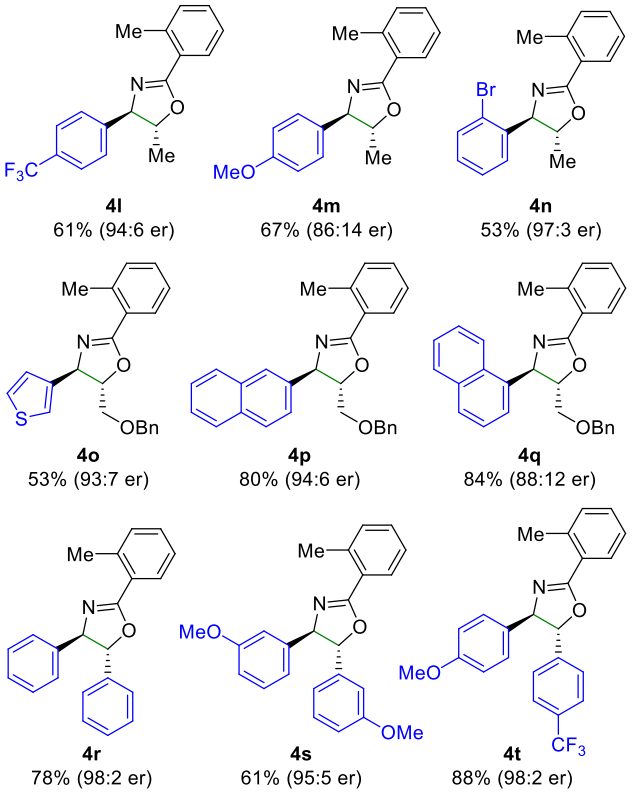
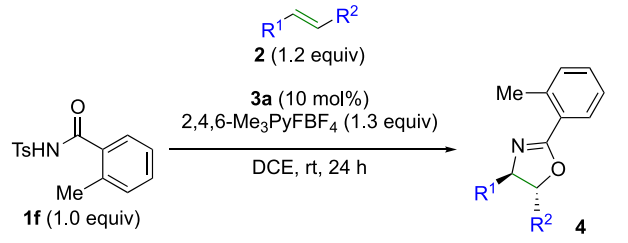
Table 5. Alkene Substrate Scope for Variation on the Aromatic Ring[a]

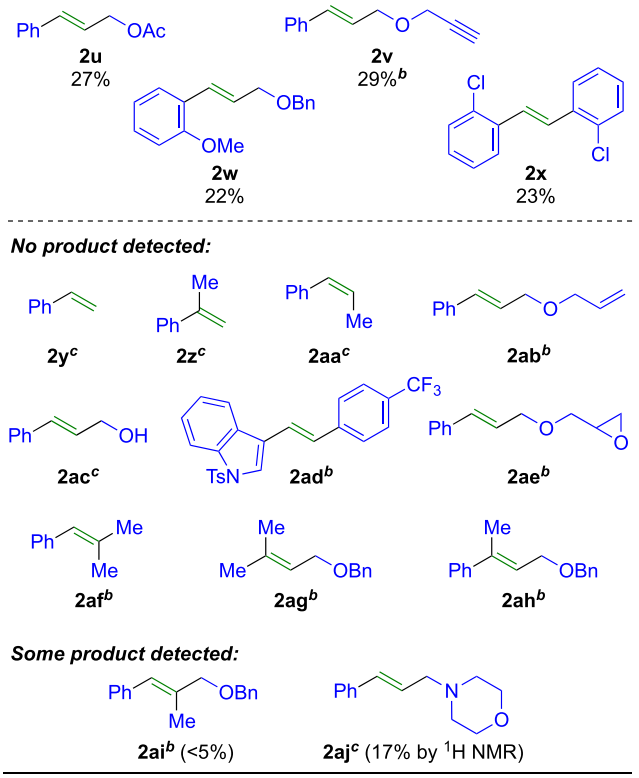




[a]All reactions were performed on a 1.0 mmol scale. Yields are of isolated, analytically pure material. Enantiomeric ratios were determined after chromatographic purification by CSP-HPLC. See the Supporting Information for details.

Table 6. Alkene Substrates Affording Poor or No Yields[a]





[a]All reactions were performed on a 0.2 mmol scale. Yields are of isolated purified material. See the Supporting Information for details. [b]Run with 40 mol % of di(2,4-dimethoxyphenyl) diselenide as the catalyst. [c]Run with 40 mol % of diphenyl diselenide as the catalyst.

alkene (**2w**) or 2,2′-dichlorostilbene (**2x**) afforded significantly diminished yield. Finally, a number of alkene substrates led to no productive conversion to the desired oxazoline products as reactions stalled quickly without alkene consumption. Styrene (**2y**), 1-methylstyrene (**2z**), and (*Z*)-2-methylstyrene (**2aa**) all exhibited this behavior. On the other hand, allyl cinnamyl ether (**2ab**) and cinnamyl alcohol (**2ac**) were completely consumed without product formation. Additionally, indole-bearing **2ad** did not display conversion, despite consumption of the alkene and its success in the diamination protocol. Attempts to generate product from epoxide-bearing **2ae** were also unsuccessful. Furthermore, trisubstituted alkenes were largely unsuccessful (**2af**–**ah**) and consumed the alkene without product generation, with the exception of **2ai**, which showed a trace (<5%) amount of product by ^{1}H NMR. Finally, an alkene with a pendant tertiary amine (**2aj**) resulted in poor conversion (17% by ^{1}H NMR) with a very messy crude reaction mixture.

5. Manipulation of Oxazoline Products. To demonstrate the synthetic utility of this transformation, derivatization of the oxazoline core was examined using product **4g** as a representative substrate (Scheme 4). First, conditions were established for partial and full hydrolysis of the imidate functionality to the corresponding 1,2-amino alcohol derivatives. Subjecting the oxazoline to acidic conditions in THF and methanol, followed by treatment with sodium bicarbonate, provided the *N*-benzoylated product (**5**) without compromising the enantiomeric composition. In contrast, careful treatment of the oxazoline under aqueous acidic conditions furnished the *O*-benzoylated product **6** as a stable hydrochloride salt in high yield. Applying the conditions used to furnish the 1,2-amino alcohol from (*E*)-2-methylstyrene for determination of the absolute configuration with oxazoline **4g** resulted in partial deprotection of the benzyl ether. Accordingly, a milder solution was investigated that would be applicable to the benzyl ether of **4g** as well as other sensitive functionalities. To produce the parent 1,2-amino alcohol, treatment of the *O*-benzoylated hydrochloride salt (**6**) with

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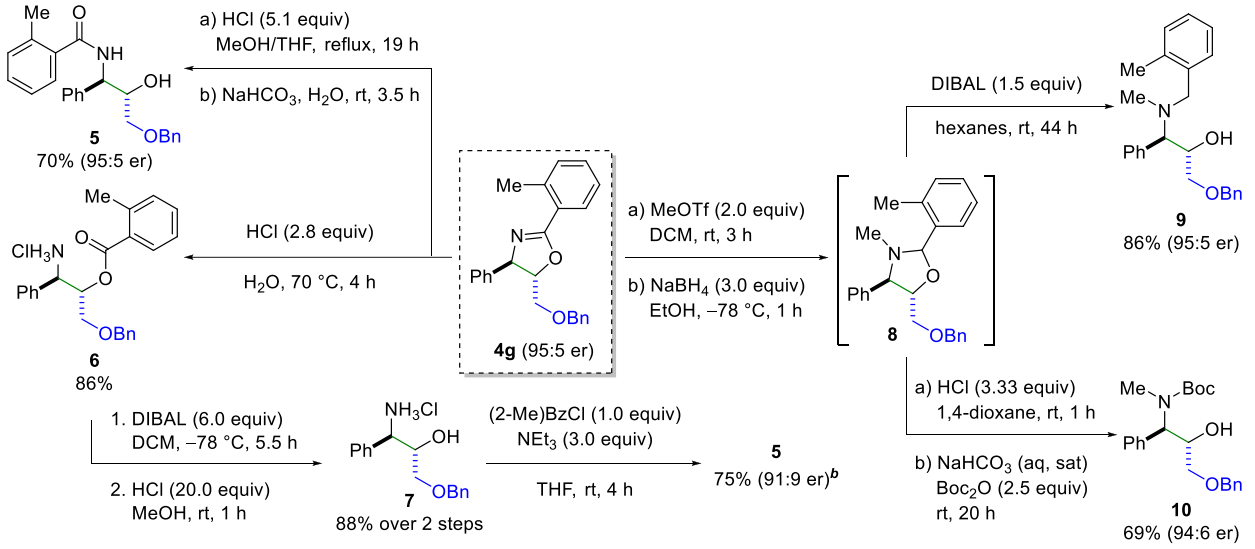
Scheme 4. Derivatization of the Oxazoline Core[a]



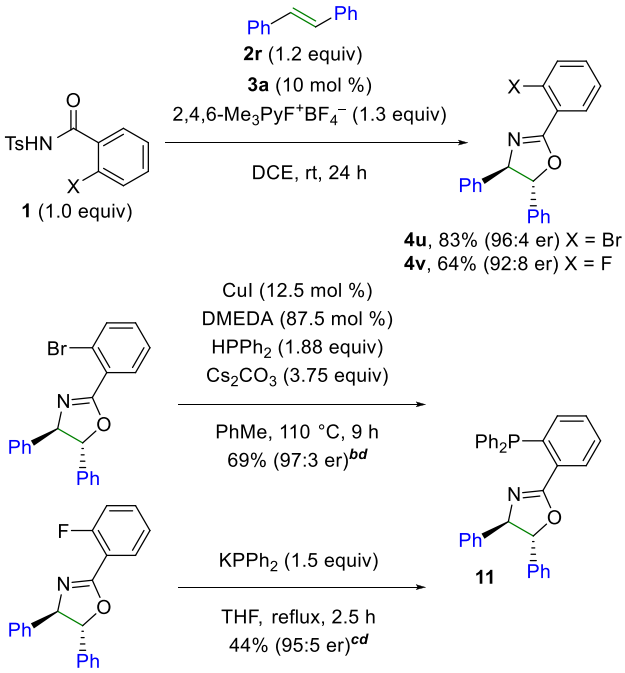
[a]Yields are of isolated, analytically pure material performed on a 1.0 mmol scale from racemic starting material. Enantiomeric ratios are of chromatographically purified material performed on ≤0.2 mmol scale from enantioenriched starting material, determined by chiral stationary phase HPLC. Refer to the Supporting Information for more details. [b]Yield and enantiomeric ratio are of chromatographically purified material performed on a 33.0 μmol scale from enantioenriched starting material.

DIBAL provided the free 1,2-amino alcohol, which was transformed to the hydrochloride salt (**7**) (for stability purposes) in excellent yield. The enantiomeric purity of this product was evaluated by *N*-acylation of the hydrochloride salt (**7**).[29]

Next, experiments were conducted for the direct conversion of the oxazoline core into functionalized 1,2-amino alcohols. Alkylation of **4g** with methyl triflate followed by reduction of the oxazolinium moiety produced the corresponding oxazolidine (**8**) quantitatively. From the crude oxazolidine, reduction with DIBAL produced the *N*,*N*-dialkylated product (**9**) in good yield with preservation of enantiopurity. Furthermore, telescoping treatment of the crude oxazolidine with acidic conditions followed by Boc protection of the amine furnished alcohol **10** in good yield again without erosion of enantiopurity. The diverse array of enantioenriched products formed from the oxazoline core demonstrates the utility of the alkene 1,2-oxyamination method.

Finally, in view of the ubiquitous presence of oxazolines in many ligand classes, the utility of this 1,2-oxyamination protocol was further demonstrated by synthesis of phosphinooxazoline (PHOX) ligands. For the assembly of the PHOX ligand (Scheme 5), 2-(bromophenyl) and 2-(fluorophenyl)-oxazoline derivatives were produced through the oxyamination protocol using (*E*)-stilbene as the substrate in good yields and enantioselectivities (**4u**–**v**). From **4u**, a copper-coupling method using diphenylphosphine, described by Stoltz and co-workers,[30] produced the targeted PHOX ligand (**11**) in 69% yield. Additionally, the canonical S_NAr attack on **4v** with potassium diphenylphosphide also produced the targeted PHOX ligand in 44% yield.

Scheme 5. Synthesis of PHOX and Ligands Using the Alkene 1,2-Oxyamination Method[a]



[a]All reactions were performed on a 1.0 mmol scale. Enantiomeric ratios were determined after chromatographic purification by CSP-HPLC. Yields are of isolated, analytically pure materials. See the Supporting Information for details. [b]Performed on 0.6 mmol scale. [c]Performed on 0.45 mmol scale. [d]Enantiomeric ratios were determined after chromatographic purification by CSP-SFC.

DISCUSSION

One of the distinguishing aspects of this alkene 1,2-oxyamination method when compared to the alkene 1,2-diamination method is the regioselectivity of the addition of the oxygen and nitrogen nucleophile. In the diamination case, the nucleophilic addition was degenerate, whereas the oxyamination results in two possible constitutional isomers. Foremost, the regioselectivity of this addition is largely dictated by the electronic character of the seleniranium ion intermediate (Figure 2a). In alkenes that contain an aryl and

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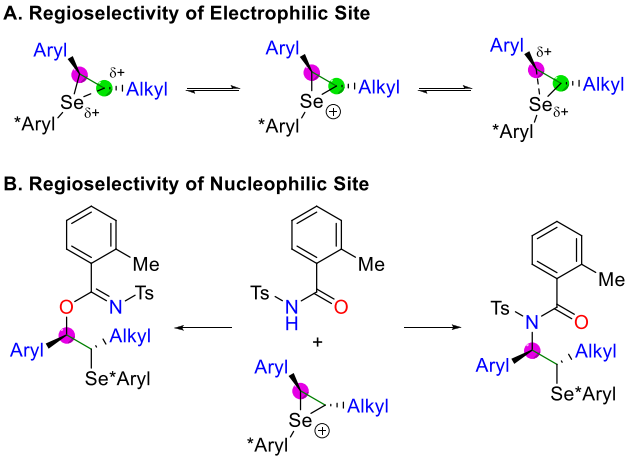

Figure 2. Regioselectivity of attack on the electrophilic sites in the seleniranium ion.

an alkyl substituent, the stabilization of the partial positive charge (pink) by the aryl substituent renders this site more electrophilic than the alkyl site (green). In the case of the unsymmetrical stilbene (**2t**), the electron donating nature of the 4-methoxy group enhances that stabilization more so than the 4-trifluoromethyl group and accordingly leads to product **4t** in which the nitrogen atom resides next to that substituent. Furthermore, when comparing the relative nucleophilicities of the oxygen and nitrogen nucleophiles on the *N*-tosyl benzamides (Figure 2b), the electron-withdrawing nature of the tosyl group would lower the propensity for delocalization of the nitrogen nonbonding electron pair to the carbonyl group. Second, the pK_a of the N−H bond is predicted to be ∼5, which would allow for it to be easily deprotonated by the 2,4,6-collidine, increasing its nucleophilicity. Accordingly, it follows that the nitrogen on the *N*-tosyl benzamide should act as the *first* nucleophile to attack the seleniranium ion at the site more capable of supporting positive charge. Finally, because the seleniranium ion formation is *syn* selective, the nucleophilic attack on the seleniranium ion takes place in an *anti* fashion, and the subsequent displacement of the Se(IV) intermediate by the carbonyl oxygen is invertive (see Scheme 3d), the overall stereochemical outcome can be predicted from the alkene geometry. Thus, an *E* alkene will result in a *trans* relationship for the 4,5-substitutents on the oxazoline, whereas a *Z* alkene would result in a *cis* relationship.

Although this alkene 1,2-oxyamination method provided high yields and enantioselectivities for a wide range of substrates, still many limitations provide opportunities for improvement. One notable aspect of the current protocol is the reduction in yield for styrenyl substrates bearing *ortho* substitutions. In the cases of a 2-methoxyphenyl alkene (**2w**) or 2,2-dichlorostilbene (**2x**), the yield was significantly diminished, potentially owing to the steric encumbrance of the alkene affecting either the seleniranium ion formation or the nucleophilic opening of the seleniranium ion, if formed. Furthermore, when a 1-naphthyl alkene was used (**2q**), the product conversion was good, but the enantioselectivity was attenuated compared to the 2-naphthyl substrate (**2p**). In this case, it appears that the increased steric bulk of the 1-naphthyl group interferes with the enantioinduction provided by the chiral selenium catalyst.

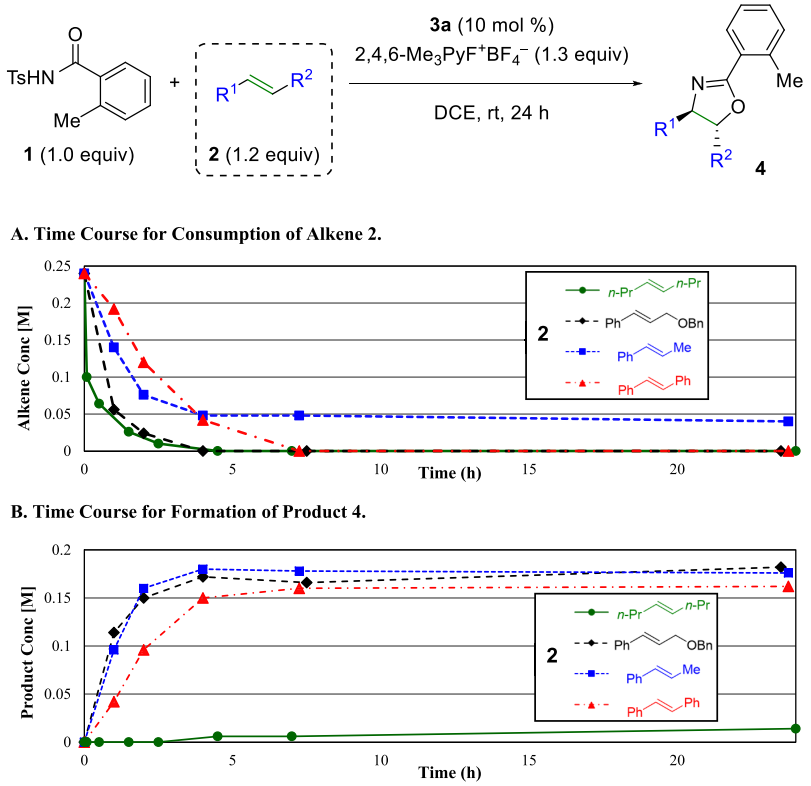

Figure 3. Kinetic plots for the alkene 1,2-oxyamination reaction. All reactions were performed on a 0.2 mmol scale with 0.2 mmol of 1,1,2,2-tetrachloroethane as an internal standard. Yields were determined through quantitative comparison of integrations. For (*E*)-4-octene, 25 mol % of catalyst was used.

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With regard to the substrates in Table 6 that provided poor/no product yield, the reaction profile for styrenes (**2y**/**2z**), as well as (*Z*)-2-methylstyrene (**2aa**), displayed stalling with only partial consumption of the alkene and no product conversion. Additionally, sensitive functionalities such as allyl (**2ab**) or epoxide groups (**2ae**) likely interfere with other reactive groups (including the possibility of intramolecular reactivity with the alkene) in the system before the alkene is able to affect the productive reaction. Trisubstituted alkenes (**2af**−**ai**), which were also a challenge for the 1,2-diamination chemistry, are likely too sterically encumbered for either seleniranium ion formation or the nucleophilic attack thereon. However, the observation of observable reactivity for **2ai** shows promise that tuning of the selenium catalyst and/or nucleophilic reagent could provide reactivity for this substrate class in the future. Finally, the diminished reactivity in the presence of a tertiary amine (**2aj**) likely arises from the coordinative effect of the nonconjugated electron lone pair on the nitrogen interfering with electrophilic species within the reaction system.

In addition to these problematic alkene classes, the most serious deficiency is the poor performance with aliphatic alkenes, such as (*E*)-4-octene, suggesting the need for an improved catalyst system. An initial hypothesis suggested that the aliphatic alkene sources were particularly unreactive. However, time course monitoring found them to be consumed extremely rapidly compared to a selection of different alkene types that led to productive reaction (Figure 3a). Correspondingly, although the productive conversion of other alkene partners was well-behaved, the reaction of (*E*)-4-octene showed no productive conversion early in the reaction and minimal productive conversion by 5 h, by which time the other alkene sources had achieved a productivity plateau (Figure 3b). This rapid consumption of the alkene, coupled with the sluggish conversion to product suggests the presence of a deleterious pathway, such as alkene polymerization, that outcompetes the productive oxyamination reaction. A number of remediations were attempted to overcome this deleterious pathway, such as slow addition of the alkene, use of a large excess of (*E*)-4-octene, and increasing/decreasing the diselenide catalyst loading; however, none of these efforts improved the reaction outcome. Moving forward, it is clear that a more tailored diselenide catalyst (potentially in concert with a more nucleophilic bifunctional nucleophile) will be needed to access this alkene class by outcompeting the off-cycle reactivity.

CONCLUSIONS AND FUTURE DIRECTIONS

In conclusion, a mild chemo-, regio-, diastereo-, and enantioselective alkene 1,2-oxyamination has been developed using *N*-tosylbenzamides and chiral selenium catalysis. This method displays tolerance for a wide range of conjugated internal alkenes bearing a variety of functional groups. The reaction proceeds in generally high yields with excellent enantioselectivities. Future investigations will involve a detailed study of the reaction mechanism to better understand the underpinnings of the poorly performing alkenes, with the aim of devising a more active catalyst for this vital alkene class.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c06750.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Sata, N. U.; Fusetani, N. Amaminols A and B, new bicyclic amino alcohols from an unidentified tunicate of the family Polyclinidae. *Tetrahedron Lett.* **2000**, *41*, 489−492. (b) Heravi, M. M.; Lashaki, T. B.; Fattahi, B.; Zadsirjan, V. Application of asymmetric Sharpless aminohydroxylation in total synthesis of natural products and some synthetic complex bio-active molecules. *RSC Adv.* **2018**, *8*, 6634−6659. (c) Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. Asymmetric synthesis of vicinal amino alcohols: xestoaminol C, sphinganine and sphingosine. *Org. Biomol. Chem.* **2008**, *6*, 1655. (d) Calder, E. D.; Zaed, A. M.; Sutherland, A. Preparation of anti-vicinal amino alcohols: asymmetric synthesis of d-erythro-sphinganine,(+)-spisulosine, and d-ribo-phytosphingosine. *J. Org. Chem.* **2013**, *78*, 7223−7233. (e) Park, J. N.; Ko, S. Y.; Koh, H. Y. Synthetic applications of the cyclic iminocarbonate rearrangement: enantioselective syntheses of chloramphenicol and 4-epi-cytoxazone. *Tetrahedron Lett.* **2000**, *41*, 5553−5556.

(2) Malkov, A. V.; Kabeshov, M. A.; Bella, M.; Kysilka, O.; Malyshev, D. A.; Pluháčková, K.; Kočovský, P. Vicinal amino alcohols as organocatalysts in asymmetric cross-aldol reaction of ketones: application in the synthesis of convolutamydine A. *Org. Lett.* **2007**, *9*, 5473−5476.

(3) (a) Wang, Z. Evans Aldol Reaction. *Comprehensive Organic Name Reactions and Reagents* **2010**, 1021−1025. (b) Heravi, M. M.; Zadsirjan, V.; Farajpour, B. Applications of oxazolidinones as chiral auxiliaries in the asymmetric alkylation reaction applied to total synthesis. *RSC Adv.* **2016**, *6*, 30498−30551.

(4) Desimoni, G.; Faita, G.; Jørgensen, K. A. C 2-symmetric chiral bis (oxazoline) ligands in asymmetric catalysis. *Chem. Rev.* **2006**, *106*, 3561−3651.
(5) Shrestha, B.; Rose, B. T.; Olen, C. L.; Roth, A.; Kwong, A. C.; Wang, Y.; Denmark, S. E. A Unified Strategy for the Asymmetric Synthesis of Highly Substituted 1,2-Amino Alcohols Leading to Highly Substituted Bisoxazoline Ligands. *J. Org. Chem.* **2021**, *86*, 3490−3534. See also references cited therein.
(6) Hemric, B. N. Beyond osmium: progress in 1,2-amino oxygenation of alkenes, 1,3-dienes, alkynes, and allenes. *Org. Biomol. Chem.* **2021**, *19*, 46−81.
(7) Li, G.; Chang, H.-T.; Sharpless, K. B. Catalytic Asymmetric Aminohydroxylation (AA) of Olefins. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451−454.
(8) Sharpless, K. B.; Patrick, D. W.; Truesdale, L. K.; Biller, S. A. New reaction. Stereospecific vicinal oxyamination of olefins by alkyl imido osmium compounds. *J. Am. Chem. Soc.* **1975**, *97*, 2305−2307.
(9) Reviews on Sharpless AA: (a) O'Brien, P. Sharpless Asymmetric Aminohydroxylation: Scope, Limitations, and Use in Synthesis. *Angew. Chem., Int. Ed.* **1999**, *38*, 326−329. (b) Nilov, D.; Reiser, O. The Sharpless Asymmetric Aminohydroxylation -Scope and Limitation. *Adv. Synth. Catal.* **2002**, *344*, 1169−1173.
(10) (a) Donohoe, T. J.; Johnson, P. D.; Helliwell, M.; Keenan, M. The Regioselective Aminohydroxylation of Allylic Carbamates. *Chem. Commun.* **2001**, 2078−2079. (b) Donohoe, T. J.; Johnson, P. D.; Cowley, A.; Keenan, M. The Tethered Aminohydroxylation (TA) of Cyclic Allylic Carbamates. *J. Am. Chem. Soc.* **2002**, *124*, 12934−12935.
(11) (a) Fuller, P. H.; Kim, J.-W.; Chemler, S. R. Copper Catalyzed Enantioselective Intramolecular Aminooxygenation of Alkenes. *J. Am. Chem. Soc.* **2008**, *130*, 17638−17639. (b) Paderes, M. C.; Keister, J. B.; Chemler, S. R. Mechanistic Analysis and Optimization of the Copper-Catalyzed Enantioselective Intramolecular Alkene Aminooxygenation. *J. Org. Chem.* **2013**, *78*, 506−515.
(12) (a) Michaelis, D. J.; Williamson, K. S.; Yoon, T. P. Oxaziridine-mediated enantioselective aminohydroxylation of styrenes catalyzed by copper(II) bis(oxazoline) complexes. *Tetrahedron* **2009**, *65*, 5118−5124. (b) Williamson, K. S.; Yoon, T. P. Iron Catalyzed Asymmetric Oxyamination of Olefins. *J. Am. Chem. Soc.* **2012**, *134*, 12370−12373. (c) Racemic Cu: Michaelis, D. J.; Shaffer, C. J.; Yoon, T. P. Copper(II)-Catalyzed Aminohydroxylation of Olefins. *J. Am. Chem. Soc.* **2007**, *129*, 1866−1867. (d) Racemic Fe: Williamson, K. S.; Yoon, T. P. Iron-Catalyzed Aminohydroxylation of Olefins. *J. Am. Chem. Soc.* **2010**, *132*, 4570−4571.
(13) Nishimura, M.; Minakata, S.; Takahashi, T.; Oderaotoshi, Y.; Komatsu, M. Asymmetric N1 Unit Transfer to Olefins with a Chiral Nitridomanganese Complex: Novel Stereoselective Pathways to Aziridines and Oxazolines. *J. Org. Chem.* **2002**, *67*, 2101−2110.
(14) (a) Hajra, S.; Akhtar, S. M. S.; Aziz, S. M. Catalytic asymmetric aminolactonization of 1,2-disubstituted alkenoic acid esters Efficient construction of aminolactones with an all-carbon quaternary stereocentre. *Chem. Commun.* **2014**, *50*, 6913−6916. (b) Zhu, R.; Buchwald, S. L. Versatile Enantioselective Synthesis of Functionalized Lactones via Copper-Catalyzed Radical Oxyfunctionalization of Alkenes. *J. Am. Chem. Soc.* **2015**, *137*, 8069−8077.
(15) Shen, H.-C.; Wu, Y.-F.; Zhang, Y.; Fan, L.-F.; Han, Z.-Y.; Gong, L.-Z. Palladium-Catalyzed Asymmetric Aminohydroxylation of 1,3-Dienes. *Angew. Chem., Int. Ed.* **2018**, *57*, 2372−2376.
(16) Kim, S.; Kim, D.; Hong, S. Y.; Chang, S. Tuning Orbital Symmetry of Iridium Nitrenoid Enables Catalytic Diastereo- and Enantioselective Alkenes Difunctionalizations. *J. Am. Chem. Soc.* **2021**, *143*, 3993−4004.
(17) Cho, I.; Prier, C. K.; Jia, Z.-J.; Zhang, R. K.; Görbe, T.; Arnold, F. H. Enantioselective Aminohydroxylation of Styrenyl Olefins Catalyzed by an Engineered Hemoprotein. *Angew. Chem., Int. Ed.* **2019**, *58*, 3138−3142.
(18) (a) Wu, F.; Alom, N.-E.; Ariyarathna, J. P.; Naß, J.; Li, W. Regioselective Formal [3 + 2] Cycloadditions of Urea Substrates with Activated and Unactivated Olefins for Intermolecular Olefin Amino-oxygenation. *Angew. Chem., Int. Ed.* **2019**, *58*, 11676−11680. (b) Wu, F.; Kaur, N.; Alom, N.-E.; Li, W. Chiral Hypervalent Iodine Catalysis Enables an Unusual Regiodivergent Intermolecular Olefin Amino-oxygenation. *J. Am. Chem. Soc. Au* **2021**, *1*, 734−741.
(19) Wata, C.; Hashimoto, T. Organoiodine-Catalyzed Enantioselective Intermolecular Oxyamination of Alkenes. *J. Am. Chem. Soc.* **2021**, *143*, 1745−1751.
(20) (a) Hu, N. X.; Aso, Y.; Ogura, F. Tellurium-based organic synthesis: A novel one-pot formation of 2-oxazolines from alkenes induced by amidotellurinylation. *Tetrahedron Lett.* **1988**, *29*, 1049−1052. (b) Hu, N. X.; Aso, Y.; Otsubo, T.; Ogura, F. Amino-tellurinylation of Olefins and Its Utilization for Synthesis of 2-Oxazolidinones. *J. Org. Chem.* **1989**, *54*, 4398−4404.
(21) (a) Tingoli, M.; Tiecco, M.; Testaferri, L.; Temperini, A. Substituted azides from selenium-promoted deselenenylation of azido selenides. Glycosylation reactions of protected 2-azido-2-deoxy-1-selenoglycopyranoses. *J. Chem. Soc., Chem. Commun.* **1994**, 1883−1884. (b) Tingoli, M.; Testaferri, L.; Temperini, A.; Tiecco, M. Intramolecular Nucleophilic Deselenenylation Reactions Promoted by Benzeneselenyl Triflate. Stereospecific Synthesis of Vicinal Amino Alcohol Precursors. *J. Org. Chem.* **1996**, *61*, 7085−7091. (c) Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. Asymmetric Amidoselenenylation of Alkenes Promoted by Camphorselenenyl Sulfate: A Useful Synthetic Route to Enantiopure Oxazolines. *Eur. J. Org. Chem.* **2000**, 3451−3457.
(22) (a) Tiecco, M.; Testaferri, L.; Marini, F.; Temperini, A.; Bagnoli, L.; Santi, C. One-Pot Converstion of Alkenes into Oxazolines and Oxazolidin-2-ones Promoted by Diphenyl Diselenide. *Synth. Commun.* **1997**, *27*, 4131−4140. (b) Tiecco, M.; Testaferri, L.; Temperini, A.; Marini, F.; Bagnoli, L.; Santi, C. Selenium Promoted Stereospecific One-Pot Conversion of Cinnamyl Derivatives into Oxazoleses. A Simple Synthetic Route to Racemic Taxol Side Chain. *Synth. Commun.* **1999**, *29*, 1773−1778.
(23) Tao, Z.; Gilbert, B. B.; Denmark, S. E. Catalytic, Enantioselective *syn*-Diamination of Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 19161−19170.
(24) For recent reviews on the use of diselenides as catalysts in functionalization reactions, see: (a) Singh, F. V.; Wirth, T. Selenium reagents as catalysts. *Catal. Sci. Technol.* **2019**, *9*, 1073−1091. (b) Rathore, V.; Jose, C.; Kumar, S. Organoselenium small molecules as catalysts for the oxidative functionalization of organic molecules. *New J. Chem.* **2019**, *43*, 8852−8864.
(25) (a) Cresswell, A. J.; Eey, S. T. -C.; Denmark, S. E. Catalytic, stereospecific *syn* dichlorination of alkenes. *Nat. Chem.* **2015**, *7*, 146−152. (b) Gilbert, B. B.; Eey, S. T. -C.; Ryabchuk, P.; Garry, O.; Denmark, S. E. Organoselenium-catalyzed enantioselective *syn*-dichlorination of unbiased alkenes. *Tetrahedron* **2019**, *75*, 4086−4098.
(26) Tabor, J. R.; Obenschain, D. C.; Michael, F. E. Selenophosphoramide-catalyzed diamination and oxyamination of alkenes. *Chem. Sci.* **2020**, *11*, 1677−1682.
(27) A number of other oxidants, such as *N*-fluoropyridinium tetrafluoroborate, 2,6-dichloropyridium tetrafluoroborate, and Selectfluor, were tested early on in the reaction optimization process. None of these oxidants provided evidence of the desired product.
(28) (a) Yuste, F.; Ortiz, B.; Carrasco, A.; Peralta, M.; Quintero, L.; Sánchez-Obregón, R.; Walls, F.; García, J. L. Synthesis of enantiomerically pure 2-amino alcohols from amino acids mediated by sulfoxides. *Tetrahedron: Asymmetry* **2000**, *11*, 3079−3090. (b) Prelog, V.; Mutak, S. Stereoselectivity of 9,9′-Spirobifluorene Crown Ethers towards α-Amino Alcohols. *Helv. Chim. Acta* **1983**, *66* (7), 2274−2278.
(29) The erosion of the enantiomeric ratio is likely the result of the multiple manipulations performed on the material from the last measured enantiomeric ratio.
(30) (a) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. A Facile and Modular Synthesis of Phosphinooxazoline Ligands. *Org. Lett.* **2007**, *9*, 2529−2531. (b) Krout, M. R.; Mohr, J. T.; Stoltz, B. M. Preparation of (*S*)-*tert*-ButylPHOX. *Org. Synth.* **2009**, *86*, 181.