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Synthesis of aminoalcohols from substituted alkenes via tungstenooxaziridine catalysis†

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Herein we report the $\text{WO}_2\text{Dipic}(\text{H}_2\text{O})$ promoted oxyamination of alkenes using sulfonamides as the quantitative source of *N*. The reaction works for activated and unactivated alkenes in high yields, diastereoselectivities, and stereospecificity. A catalytic cycle involving the formation of tungstenooxaziridine complex **1** as the active catalyst and hydrolysis of tungstenooxazolidine intermediate **A** as the rate-determining-step has been proposed. Initial kinetic and competition experiments provide evidence for the proposed mechanism.

Introduction

The stereoselective oxyamination of alkenes for the synthesis of aminoalcohols and derivatives remains as one of the most fundamental transformations in organic chemistry to this date.¹ Much progress has been achieved towards the stereoselective difunctionalization of alkenes, however there are very few methods that are able to achieve direct oxyamination with high chemo-, regio-, and stereoselectivities.² This structural motif is prevalent in natural products and commercially available drugs with very important pharmacological profiles³ but also across a large array of chiral ligands, auxiliaries and organocatalysts.⁴ Therefore, the continuous development of novel methods for the systematic synthesis of aminoalcohols has great significance.⁵ Since the pioneering work by Sharpless in asymmetric aminohydroxylation,^{2b} multiple strategies have been developed to access aminoalcohols.⁶ Unfortunately, most suffer from poor regioselectivity or rely on intramolecular methods that require further functional group manipulations. Thus, direct stereoselective oxyamination methods continue to receive much attention in the field of organic chemistry (Fig. 1). Ground-breaking work by Yoon discovered that *N*-EWG oxaziridines can trigger oxyamination pathways by careful exposure to very specific transition-metal environments.⁷ Terminal alkenes, when using a copper catalyst, undergo oxyamination with high regioselectivity for

oxygen on the least substituted carbon and when using an iron catalyst, oxyamination occurs with high regioselectivity for oxygen on the more substituted carbon.⁸

Other efforts have found other transition metals also achieve oxyamination outcomes with general success (Mn, Pd, Ir, Cu, and Se).⁹ Moreover, efforts in visible-light photocatalysis have also demonstrated synthetically useful efficiencies and generality.¹⁰ This new generation of methods offers a large array of catalysts with unique properties, but regioselectivity

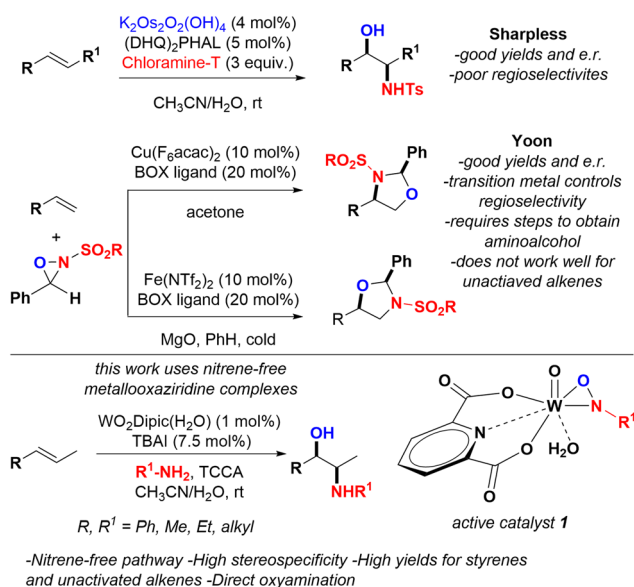


Fig. 1 Advances in stereoselective oxyamination.

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and poor reactivity across unactivated alkenes remains a problem.

Metallooxaziridines can be obtained from reacting metal-oxides and *amino*-containing reagents.¹¹ Their chemical properties are analogous to peroxy-complexes that transfer *O* atoms across alkenes and are comparable to metal oxide complexes known to achieve oxyamination reactions.¹² The chemistry of these metallooxaziridines has not been fully exploited; however, we recently reported that zirconooxaziridines are suitable catalysts for the highly stereoselective and stereospecific aziridination of unactivated alkenes.¹³ Early work by Sharpless provided some insights into the unique properties of these complexes as he found that *Mo* and *W* oxaziridines were able to activate π -systems.¹⁴

The Moura-Letts laboratory is focused on developing novel methods for the synthesis of complex nitrogen-containing molecules.¹⁵ Thus, we envisioned creating a well-defined catalytic system for the oxyamination of alkenes *via* the formation of metallooxaziridines as the active catalyst for the reaction. To the best of our knowledge, this would be the first report for such a catalytic process.

Results and discussion

Since the discovery of zirconooxaziridine catalysis for the aziridination of alkenes, some results indicated that other chemical pathways could be optimized upon changing the transition-metal in the metallooxaziridine centre. The high chemoselectivity observed for LZrON-Ts was in part due to the group IV transition-metal nature of *Zr* and the geometry of the

respective LUMO across the *Zr*–*N* bond. Thus, analogous to Cu^{II} and Fe^{III} -promoted chemo- and regioselective diversity in oxyaminations,⁸ it was hypothesized that high-oxidation state group VI transition metal complexes (LMO_2NTs) would provide LUMO's leading to different chemo- and regioselective outcomes. Fortunately, it was discovered that while LWO_2NTs provided aziridine in very low yield, it provided aminoalcohol **3a** with high selectivity. As observed for Fe^{III} oxyaminations, the reaction chemoselectivity allows the transformation to occur across the *N*–*O* bond and, regioselective addition of *N*-Ts to the least substituted side of the alkene.¹⁶

The basic premise behind this study was to develop a simple and efficient oxyamination process with high stereoselectivity and stereospecificity for unactivated and activated alkenes (Table 1). Although our efforts for the aziridination of alkenes relied on chloramine T as the source of *N*, we discovered that further diversification could be introduced with sulfonamides and trichloroisocyanuric acid (TCCA) as an activator/oxidant to provide *in situ* RSO_2NHCl (RSO_2 -chloramine).¹⁷ Initial results using 1-hexene, indicated that metal oxides at 5 mol%, phase-transfer catalyst (PTC) at 7.5 mol%, and excess *p*-toluenesulfonamide/TCCA in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (10/1) promoted oxyamination in low yields, with a clear indication that *W* was able to provide the expected product with synthetically useful selectivities (entry 3). It was anticipated that dipicolinic acid (Dipic) would provide a more stable complex and it was found that $\text{WO}_2\text{Dipic}(\text{H}_2\text{O})$ improved the reaction yield to 48% and 10 : 1 : 1 **3a** : **4a** : **5a** product ratio (entry 5); *V* or *Mo* were not as successful at improving the reaction yield (entries 6 and 7). The nature of the PTC was tested, and it was found that TBAI provided a small increase in reaction performance (62% yield,

Table 1 Reaction optimization

Entry ^{a,b}	Metal catalyst	PTC	Solvent	Temp	Yield (%)	3a : 4a : 5a
1	MoO_3^c	CTAB	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	rt	5	1 : 1 : 1
2	V_2O_5^c	CTAB	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	rt	4	1 : 1 : 0
3	WO_3^c	CTAB	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	rt	24	4 : 1 : 0
4	ZrO_2^c	CTAB	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	rt	6	1 : 0 : 5
5	$\text{WO}_2\text{Dipic}^{c,d}$	CTAB	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	rt	48	10 : 1 : 1
6	$\text{V}_2\text{O}_3\text{Dipic}^{c,d}$	CTAB	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	rt	10	2 : 1 : 1
7	$\text{MoO}_2\text{Dipic}^{c,d}$	CTAB	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	rt	8	2 : 1 : 0
8	$\text{WO}_2\text{Dipic}^{c,d}$	TBAB	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	rt	38	10 : 1 : 0.5
9	$\text{WO}_2\text{Dipic}^{c,d}$	TBAI	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	rt	62	12 : 1 : 0.5
10	$\text{WO}_2\text{Dipic}^{c,d}$	TBACl	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	rt	44	10 : 1 : 1
11	$\text{WO}_2\text{Dipic}^{c,d}$	CTAI	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	rt	39	10 : 1 : 1
12	$\text{WO}_2\text{Dipic}^d(10 \text{ mol}\%)$	TBAI ^e	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	rt	58	10 : 2 : 3
13	$\text{WO}_2\text{Dipic}^d(1 \text{ mol}\%)$	TBAI	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	rt	88	16 : 0.5 : 1
14	$\text{WO}_2\text{Dipic}^d(1 \text{ mol}\%)$	TBAI	DCE/ H_2O	rt	73	16 : 1 : 1
15	$\text{WO}_2\text{Dipic}^d(1 \text{ mol}\%)$	TBAI	$\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$	rt	35	16 : 1 : 1
16	$\text{WO}_2\text{Dipic}^d(1 \text{ mol}\%)$	TBAI	DMF/ H_2O	rt	53	15 : 1 : 2
17	$\text{WO}_2\text{Dipic}^d(1 \text{ mol}\%)$	TBAI	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	0 °C	48	16 : 1 : 1
18	$\text{WO}_2\text{Dipic}^d(1 \text{ mol}\%)$	TBAI	$\text{CH}_3\text{CN}/\text{H}_2\text{O}$	60 °C	32	8 : 1 : 2

^a Isolated yields. ^b TsNH_2 (1.5 equiv.) is mixed with TCCA (0.5 equiv.) in CH_2Cl_2 at 0 °C for 30 min then solvent removed and $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ 0.125M (10 : 1), metal oxide, additive and alkene are added. ^c 5 mol% of metal and 7.5 mol% of PTC. ^d $\text{WO}_2\text{Dipic}(\text{H}_2\text{O})$, Dipic = dipicolinic acid.

^e 15 mol%. CTA = cetrimonium, TBA = tetrabutyl n-butylammonium.

entry 9). The different catalytic steps in this reaction take place in different phases in the reaction mixture. Thus, efficient PTCs are crucial to achieve conversion due to poorly soluble $\text{WO}_2\text{Dipic}(\text{H}_2\text{O})$ and *in situ* formed chloramine. Other catalysts failed to improve the reaction yield beyond the efficiency obtained with TBAI (entries 8, 10 and 11).

To further improve the reaction performance, catalyst loading was increased to 10 mol% but a complex mixture and lowered chemo- and regioselectivity due to catalyst decomposition was observed (entry 12); however, when loading was reduced to 1 mol% the yield and product ratio increased to 88% and 16 : 0.5 : 1 respectively (entry 13). The reaction solvent was also examined, and $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ remained to be optimal. Coordinating solvents (CH_3CN) are known to accelerate *N*-Ts transfer reactions and the role of H_2O as a ligand in the proposed process was anticipated. The reaction at different temperatures also failed to provide similarly high yields and selectivities (entries 17 and 18).

Given the results observed for the oxyamination of 1-hexene, this study focused on addressing the generality across different types of unactivated alkenes (Table 2).¹⁸ 1-Octene provided the corresponding aminoalcohol in equally high yield and similar observable rate (91% and 16 h, entry 2). Activation of alkenes, depending upon the nature of the *N*-transfer reagent, often suffers from poor diastereospecificity due to the formation of nitrene reactive intermediates that lead to stereochemical erosion.¹⁹ Analogous to the aziridination reaction, high stereospecificity was expected due to the fast formation of metalloheterocyclic intermediates (intermediate **A**) through a biradical transition state.

Thus, we tested 1,2-disubstituted alkenes and we found that (*E*)-2-octene, and symmetric (*E*)-4-octene reacted to produce the corresponding aminoalcohols in high yields and diastereoselectivities without visible stereochemical erosion (entries 3 and 4). Correspondingly, (*Z*)-4-octene provided the product in good yield, high diastereoselectivity and a comparable observable rate (88% and 18 h, entry 5). These results provide indication of a highly stereospecific delivery of both groups across the alkene, the high *syn*-selectivity correlates well with a tungstenoxaziridine *syn*-addition across the *N*-O bond. Further exploration of the scope revealed that cyclohexene, 1-methylcyclohexene, cyclooctene, and indene provided the corresponding aminoalcohols in high yields and slightly slower rates despite the increased substitution (18–22 h, entries 6–9).²⁰ The reaction proved to be successful across a variety of unactivated alkenes with high stereoselectivity and stereospecificity. The focus then turned towards addressing the generality across styrenes with activating and deactivating substituents (Table 3).

Styrene (entry 1) and styrenes with various alkyl electron-donating-groups (EDGs) were successful at providing the expected aminoalcohols in high yields and at faster observable rates (4–8 h, entries 2–6). Moreover, 4-methoxy styrene worked in similarly high yield and faster observable rate (3 h, entry 7). Other substitution patterns (biphenyl and naphthyl, entries 8 and 9) were also very productive for this transformation. The

Table 2 Reaction scope

$\text{R}-\text{CH}=\text{CH}_2 \xrightarrow[\text{CH}_3\text{CN}/\text{H}_2\text{O}, \text{rt}]{\text{Ts-NH}_2 (1.5 \text{ equiv}), \text{TCCA} (0.5 \text{ equiv}), \text{WO}_2\text{Dipic}(\text{H}_2\text{O}) (1 \text{ mol\%}), \text{TBAI} (7.5 \text{ mol\%})} \text{R}-\text{CH}(\text{OH})-\text{CH}_2\text{NHTs}$				
Entry	Alkene	Product ^c	Yield ^{a,b} (%)	d.r
1	2a	3a	88	—
2	2b	3b	91	—
3	2c	3c	82 ^d	18 : 1
4	2d	3d	84	20 : 1
5	2e	3e	88	20 : 1
6	2f	3f	93	20 : 1
7	2g	3g	91	18 : 1
8	2h	3h	95	20 : 1
9	2i	3i	92	19 : 1

^a Conditions: TsNH_2 (1.5 equiv.) is mixed with TCCA (0.5 equiv.) in CH_2Cl_2 at 0 °C for 30 min then solvent removed and $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ 0.125M (10 : 1), metal oxide, additive and alkene are added, and reaction stirred at rt for 16 h or until full conversion by TLC. ^b Isolated yields. ^c Reaction was purified by standard silica gel chromatography. ^d 6 : 1 mixture of **3c** and **4c**.

electronic properties around the ring were then changed; and 4-fluoro, 4-chloro, and 4-iodo provided aminoalcohol **3** in similar yields without apparent loss in observable reaction rates (4–8 h, entries 10–12). Moreover, 3-chloro, 2-chloro, 2,6-dichloro, and 4-trifluoromethyl worked in similar high yields but slower rates (12–14 h, entries 13–16). Surprisingly, 4-cyano and 4-nitro worked in slightly lower yields but there was no noticeable decrease in reaction rates (5 and 6 h, entries 17 and 18). The small differences in reaction efficiencies across styrenes with different substitution patterns support a concerted mechanism. We were also interested in addressing the reaction selectivity across disubstituted styrenes. It was discovered that α -methyl-styrene, α -methyl-toluene, and β -methyl-styrene provided aminoalcohol **3** in high yields and without activation of the allylic methyl group (entries 19–21).

Scope of sulfonamides would allow the introduction of more complex functionality across aminoalcohol **3** (Table 4). It was found that sulfonamides with different nitro groups around the ring reacted to form the respective *N*-transfer

Table 3 Reaction scope

$\text{Ar-CH=CH}_2 \xrightarrow[\text{CH}_3\text{CN/H}_2\text{O, rt}]{\text{Ts-NH}_2 \text{ (1.5 equiv), TCCA (0.5 equiv), WO}_2\text{Dipic(H}_2\text{O) (1 mol\%), TBAI (7.5 mol\%)}} \text{Ar-CH(OH)-CH}_2\text{NHTs}$			
Entry	Alkene	Product ^c	Yield ^{a,b} (%)
1	2j	3j	91
2	2k R = 4-methyl	3k R = 4-methyl	88
3	2l R = 3-methyl	3l R = 3-methyl	89
4	2m R = 2-methyl	3m R = 2-methyl	86
5	2n R = 4- <i>t</i> -butyl	3n R = 4- <i>t</i> -butyl	90
6	2o R = 2,4,6-trimethyl	3o R = 2,4,6-trimethyl	86
7	2p R = 4-methoxy	3p R = 4-methoxy	88
8	2q R = 4-phenyl	3q R = 4-phenyl	84
9	2r R = 2-naphthyl	3r R = 2-naphthyl	80
10	2s R = 4-fluoro	3s R = 4-fluoro	82
11	2t R = 4-chloro	3t R = 4-chloro	80
12	2u R = 4-iodo	3u R = 4-iodo	86
13	2v R = 3-chloro	3v R = 3-chloro	89
14	2w R = 2-chloro	3w R = 2-chloro	84
15	2x R = 2,6-dichloro	3x R = 2,6-dichloro	91
16	2y R = 4-trifluoromethyl	3y R = 4-trifluoromethyl	86
17	2z R = 4-cyano	2z R = 4-cyano	80
18	2aa R = 4-nitro	3aa R = 4-nitro	82
19	2ab	3ab	91
20	2ac	3ac	88
21	2ad	3ad	84 ^d

^a Conditions: TsNH₂ (1.5 equiv.) is mixed with TCCA (0.5 equiv.) in CH₂Cl₂ at 0 °C for 30 min then solvent removed and CH₃CN/H₂O 0.125M (10 : 1), metal oxide, additive and alkene are added, and reaction stirred at rt for 16 h or until full conversion by TLC. ^b Isolated yields. ^c Reaction was purified by standard silica gel chromatography. ^d 10 : 1 mixture of 3ad (22 : 1 d.r.) and 4ad.

reagent and then provided 3 in great yields (entries 1–3). Moreover, substituted heterocyclic sulfonamides reacted well and the respective aminoalcohols were also obtained in high yields (entries 4–6). Substituted benzenesulfonamides (4-Br, 4-F, 2-Me) and methylsulfonamide also provided 3 in great yields and optimal stereoselectivities (entries 7–10).

The foundational knowledge discovered for the zirconooxaziridine-mediated aziridination of alkenes along with the available studies on metal-oxide promoted alkene difunctionalization helped design the mechanistic studies for this reaction. The main questions to be addressed were the mode of *N*-Ts group transfer, competing pathways and the mode of OH transfer across the alkene and metal-centre.

Based on the observed chemoselectivity and high stereoselectivity, we anticipated a potentially fast tungstenooxaziridine addition across the alkene with formation of short-lived biradical species through homolytic cleavage of the *N*-O bond in the transition state.²¹ Experiments with deuterated sub-

Table 4 Reaction scope

$\text{tBu-CH=CH}_2 \xrightarrow[\text{CH}_3\text{CN/H}_2\text{O, rt}]{\text{R}^1\text{-NH}_2 \text{ (1.5 equiv), TCCA (0.5 equiv), WO}_2\text{Dipic(H}_2\text{O) (1 mol\%), TBAI (7.5 mol\%)}} \text{tBu-CH(OH)-CH}_2\text{NHR}^1$			
Entry	Sulfonamide	Product ^c	Yield ^{a,b} (%)
1		3ae	93
2		3af	89
3		3ag	84
4		3ah	82
5		3ai	86
6		3aj	88
7		3ak	80
8		3al	84
9		3am	91
10		3an	84

^a Conditions: RNH₂ (1.5 equiv.) is mixed with TCCA (0.5 equiv.) in CH₂Cl₂ at 0 °C for 30 min then solvent removed and CH₃CN/H₂O 0.125M (10 : 1), metal oxide, additive and *t*-butylstyrene are added and reaction stirred at rt for 16 h or until full conversion by TLC. ^b Isolated yields. ^c Reaction was purified by standard silica gel chromatography.

strates showed that 2j1-*d* and 2p1-*d* reacted to provide 3j1-*d* and 3p1-*d* without any deuterium scrambling, thus both experiments confirming that a highly concerted *syn*-addition is likely to be the predominant pathway. We also wanted to address if 3 formed through hydrolysis of aziridine 5 under the reaction conditions, and we found that 5j does not provide 3j under the reaction conditions. Other control experiments showed that WO₂Dipic(H₂O) is crucial for reaction conversion, thus no halogen-mediated activation pathway is taking place, and that the reaction can also work under stoichiometric amounts of 1 (low conversion, details on ESI†).

Thus, we propose a catalytic cycle in which 1 forms within minutes from reacting WO₂Dipic(H₂O) with Ts-chloramine, obtained *in-situ* from reacting *p*-toluenesulfonamide and TCCA (Fig. 2). Complex 1 can also be efficiently isolated by reacting WO₂Dipic(H₂O) and *p*-toluenesulfonamide/TCCA or chlora-

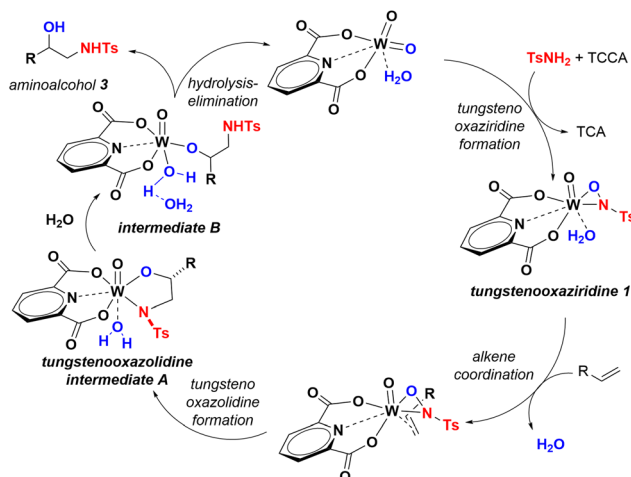


Fig. 2 Proposed catalytic cycle.

mine **T** in CHCl_3 or MeOH , and its presence can be detected in the catalytic reaction mixture spectroscopically.²² Ligand exchange allows for alkene coordination in such a way, so the HOMO of styrene is aligned with the $N\text{--}O$ bond α^* (LUMO) of complex **1**. This is then followed by fast *syn*-addition across the alkene to provide tungstenoxazolidine intermediate **A**. The intermediate then undergoes slow, rate-determining-step hydrolysis followed by incorporation of a second water molecule to provide intermediate **B**. The water molecule in **A** exchanges across the weakly coordinating $N\text{--}Ts$ group and the resulting intermediate **B** is then poised to trigger fast proton transfer to release **3** and regenerate precatalyst WO_2Dipic (H_2O).²³

Further analysis of the reaction kinetics revealed that hydrolysis of intermediate **A** is irreversible with a secondary kinetic solvent isotope effect (KSIE, $K_{\text{H}_2\text{O}}/K_{\text{D}_2\text{O}} = 0.83$, details in ESI†). The inverse KSIE obtained through pseudo-first-order kinetics validates a slow, rate-determining hydrolytic step. Experimental verification was obtained by further deuterium-labeling competition studies (Fig. 3). The results showed no secondary KIE when reacting a 1 : 1 mixture of **2j/2j2-d** ($k_{\text{H}}/k_{\text{D}} = 1.02$) and **2l/2j1-d** ($k_{\text{H}}/k_{\text{D}} = 1.01$). These results are in agreement with a fast, highly concerted tungstenoxaziridine addition across the alkene step and a slow hydrolytic rate-determining-step. The proposed catalytic cycle is in further agreement with a Hammett correlation study employing sub-

stituted styrenes (**2j,k,n,p,s,u**), which shows ρ -values of -1.87 for EDG-styrenes and 0.75 for EWG-styrenes. Concave Hammett plots are often observed on highly concerted cycloadditions with developing biradical characters in their transition-states, thus confirming the proposed catalytic cycle.

Conclusions

In summary, this work managed the discovery of a stereoselective tungstenoxaziridine-mediated catalytic oxyamination of alkenes. The reaction works with high efficiency and stereoselectivity for alkenes with diverse substitution patterns and for styrenes with a variety of functional groups. The proposed catalytic cycle involves the formation of active catalyst tungstenoxaziridine **1** that then delivers the $N\text{--}Ts$ and O groups through the formation of tungstenoxazolidine intermediate **A**, followed by rate-determining-step hydrolysis to provide aminoalcohol **3**. Further experiments to better understand and fully characterize all mechanism intermediates are ongoing and a follow up manuscript is in preparation.

Author contributions

R. M. and B. D. contributed equally for most of the experiments ($\sim 60\%$). E. L. D. (20%) and J. M. D. (10%) performed significant parts of the experiments as well. A. A. P and T. T made significant contributions at the discovery stage. D. A. R., A. M. H., J. L. S., D. A. M., S. J. F., A. N. S., and M. E. R. participated in compound characterization, and SI preparation. G. M. L. wrote the draft and supervised the research. All authors discussed the results and prepared the manuscript.

Conflicts of interest

There are no conflicts to declare.

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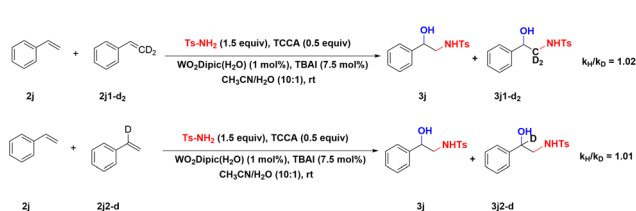


Fig. 3 Deuterium-labeling competition studies.

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