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Journal:	*ChemComm*
Manuscript ID	CC-COM-02-2022-000686.R1
Article Type:	Communication

COMMUNICATION

Synthesis of N-Tosylaziridines from Substituted Alkenes via Zirconooxaziridine Catalysis

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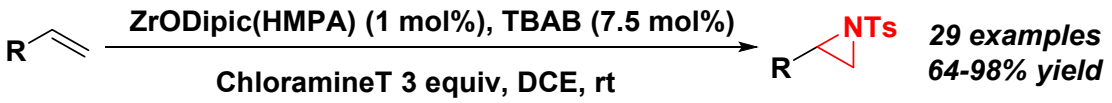
Received 00th January 20xx,
Accepted 00th January 20xx

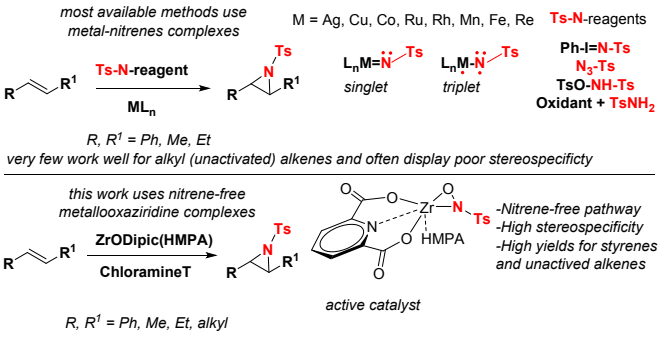
DOI: 10.1039/x0xx00000x



Herein we report the zirconooxaziridine promoted aziridination of alkenes using chloramine T as the quantitative source of N. The reaction works with high yields, diastereoselectivities and stereospecificity for a wide variety of substituted alkenes. A potential mechanism involving the formation of a zirconooxaziridine complex as the active catalyst has been proposed and initial mechanistic data would indicate that a highly associative mechanism is the predominant pathway for this transformation.

Aziridines are coveted building blocks in synthesis, as well as important synthetic targets.[1,2] The importance of synthetic methodologies for the preparation of aziridine systems has increased due to the interest in their biological properties, mainly as antitumor agents, which are displayed among many natural products.[3,4] As chemical templates, several useful scaffolds can be obtained through a variety of chemical reactions (amines, amino acids, amino alcohols, nitrogen-containing heterocycles).[5-9] Aziridines for the most part, are synthesized by reacting alkenes with a *N*-transfer reagent or nitrene equivalent.[10] After Evans' and Jacobsen's pivotal work using *Cu(I)* and sulfonylimino iodinanes as the metal–nitrene source, stereoselective aziridination has become a very active research area.[11-13] Many different scientists have developed methods around the same reaction principle of combining transition metals (*Ag, Co, Ru, Rh, Mn, Fe, Re*) and nitrene precursors.[14-20] On the other hand, Sharpless discovered that chloramines in the presence of Br_3^+ species promote the efficient aziridination of alkenes.[21] This reaction has been heavily investigated and despite its high productivity, it suffers from having poor stereospecificity and stereoselectivity.[22] Efforts to develop other transition-metal mediated versions of this reaction have led to the discovery that *Cu(I)* and *Fe(II)* complexes are efficient at promoting this reaction, but continue to have low stereoselectivities with poor substrate scope.[23,24] Most available methods rely on the formation of metal-nitrene complexes (some lack stereospecificity) and unactivated alkenes continue to be underrepresented as suitable substrates (**Figure 1**). Thus, developing reactions that have better generality and that do not suffer from poor stereoselectivity due to metal-nitrene pathways for the synthesis of aziridines continues to be of great significance in the field of organic chemistry.

Figure 1. Advances in stereoselective aziridination



Metallooxaziridines are organometallic complexes that are derived from reacting metal-oxides and *N*-transfer reagents.[25] They are analogous to metal peroxo compounds known to transfer *O* atoms across alkenes.[26] The chemistry of these metallooxaziridines has not been fully exploited; however, V(V) peroxo complexes are widely known to efficiently transfer *O* atoms across activated alkenes.[27] Studies on group 6 metallooxaziridines as suitable N-transfer reagents have proven somehow succesful, thus potentially more stable group 4 (Zr) metallooxaziridines are poised to become ideal catalysts for N-transfer reactions across π-systems.[28]

The Moura-Letts laboratory is focused on developing novel methods for the synthesis of complex nitrogen-containing heterocycles.[29] Recent efforts towards novel *N*-transfer reagents allowed the discovery that chloramine T in the presence of metal oxides and tridentate ligands reacts with alkenes to provide aziridines as the major product. Moreover, the combination of high oxidation state metal oxides, tridentate ligands and phenyl hydroxylamines are

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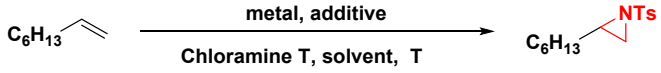
Electronic Supplementary Information (ESI) available: [Characterization data for zirconooxaziridine and known and unknown aziridines is included]. See DOI: 10.1039/x0xx00000x

known to provide metallooxaziridines and in some examples as reactive intermediates for *N*-transfer reactions. Thus, we envisioned creating a well-defined catalytic system for the aziridination of alkenes via the formation of a metallooxaziridines as the active catalyst for *N*-transfer reactions. To the best of our knowledge, this would be the first report for such catalytic process.

Table 1. Reaction optimization.



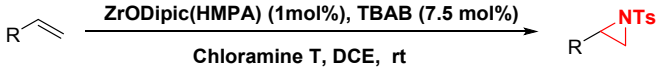
Entr	Metal	Additiv	Solv	Temperat	Yield
1	MoO_3[c]	CTAB	CH_3CN	rt	12
2	V_2O_3[c]	CTAB	CH_3CN	rt	16
3	WO_3[c]	CTAB	CH_3CN	rt	35
4	ZrO_2[c]	CTAB	CH_3CN	rt	28
5	ZrODipic[c]	CTAB	CH_3CN	rt	60
6	WO_2Dipic[c]	CTAB	CH_3CN	rt	50
7	MoO_2Dipic[c]	CTAB	CH_3CN	rt	49
8	ZrODipic[c,d]	BTMACl	CH_3CN	rt	38
9	ZrODipic[c,d]	BTAB	CH_3CN	rt	64
10	ZrODipic[c,d]	BTACl	CH_3CN	rt	48
11	ZrODipic[c,d]	BTAI	CH_3CN	rt	57
12	ZrODipic[c] (10 mol%)	BTAB[e]	CH_3CN	rt	62
13	ZrODipic[c] (1 mol%)	BTAB[e]	CH_3CN	rt	88
14	ZrODipic[c] (1 mol%)	BTAB[e]	DCE	rt	93
15	ZrODipic[c] (1 mol%)	BTAB[e]	CH_2Cl_2	rt	24
16	ZrODipic[c] (1 mol%)	BTAB[e]	DMF	rt	53
17	ZrODipic[c] (1 mol%)	BTAB[e]	DCE	0 °C	48
18	ZrO	BTAB[e]	DCE	60 °C	51

a. Isolated yields. b. Metal oxide is added to alkene in solvent and additive and chloramine T are then added. c. 5 mol% of metal and 7.5 mol% of additive. d. MO2Dipic(HMPA),Dipic = dipicolinic acid. e.15 mol%. f. 1.5 mol%.

Early reports have demonstrated that metallooxaziridines can be obtained in the form of LMO_2N-Ar complexes.[30] However, efficient aziridination requires the delivery of N-EWG and chloramine T is an ideal source for the transient preparation of LMO_2N-Ts.[31] Therefore, this work aims to develop a simple and efficient metallooxaziridine-mediated aziridination process with high stereoselectivities and stereospecificity for unactivated alkenes (**Table 1**). Initial results using 1-hexene, indicated that metal oxides at 5 mol% with a phase-transfer catalyst (PTC, 7.5 mol%) and excess chloramine T promote aziridination in low yields (Entries 1-4). It was envisioned that tridentate ligands like dipicolinic acid (Dipic) would provide a more stable complex, thus potentially enhancing the reaction conversion.[32] It was found that the enhanced stability of Zr-complexes as in ZrODipic(HMPA) improved the reaction yield to 60% (entry 5), while W or Mo complexes were not as successful (entries 6 and 7). Due to the heterogeneous nature of this reaction, we tested different PTCs and found that TBAB provided a small increased in reaction performance (64% yield, entry 9). Other PTCs failed to improve the reaction yield (entries 8, 10 and 11) due to their low migration rates. To further improve the reaction performance, catalyst loading was increased to 10 mol% but no improvement was found (entry 12); however, when loading was reduced to 1 mol% the yield increased to 88% (entry 13). The reaction solvent was also examined, and despite not arriving at a homogeneous alternative, DCE showed slight improvement in yield (entry 14). The reaction at different temperatures also failed to provide similarly high yields (entries 17 and 18). Several reports have noted the apparent reactivity of alkenes with chloramine T in the presence of non-transition-metal promoters, thus several control experiments in the absence of ZrODipic were tested and no conversion to aziridine was observed. These experiments conclusively exclude those alternative pathways.

Given the success for the aziridination of 1-hexene, this study focused on addressing the generality across different types of alkyl alkenes (**Table 2**). 1-Octene provided the corresponding aziridine in equally high yields (Entry 2). 1,2-Disubstituted alkenes would allow to address the effect of steric hindrance on the reaction productivity and the stereospecificity of the transformation due to the inherited alkene stereochemistry. The aziridination of alkenes, depending upon the nature of the transfer reagent, often suffers from poor diastereospecifcity due to the formation of nitrene reactive intermediates.[33] Thus, addressing the scope of these alkenes would also provide evidence around the functioning mechanism for this reaction. The results indicated that *trans*-2-octene and *trans*-4-octene reacted to produce the corresponding *trans*-aziridines in good yields and good diastereoselectivities (entries 3 and 4). Correspondingly, *cis*-4-octene provided *cis*-aziridine in good yield and equally high diastereoselectivity (entry 5). These initial results highlight the high stereospecificity of the transformation for alkyl alkenes.[34]

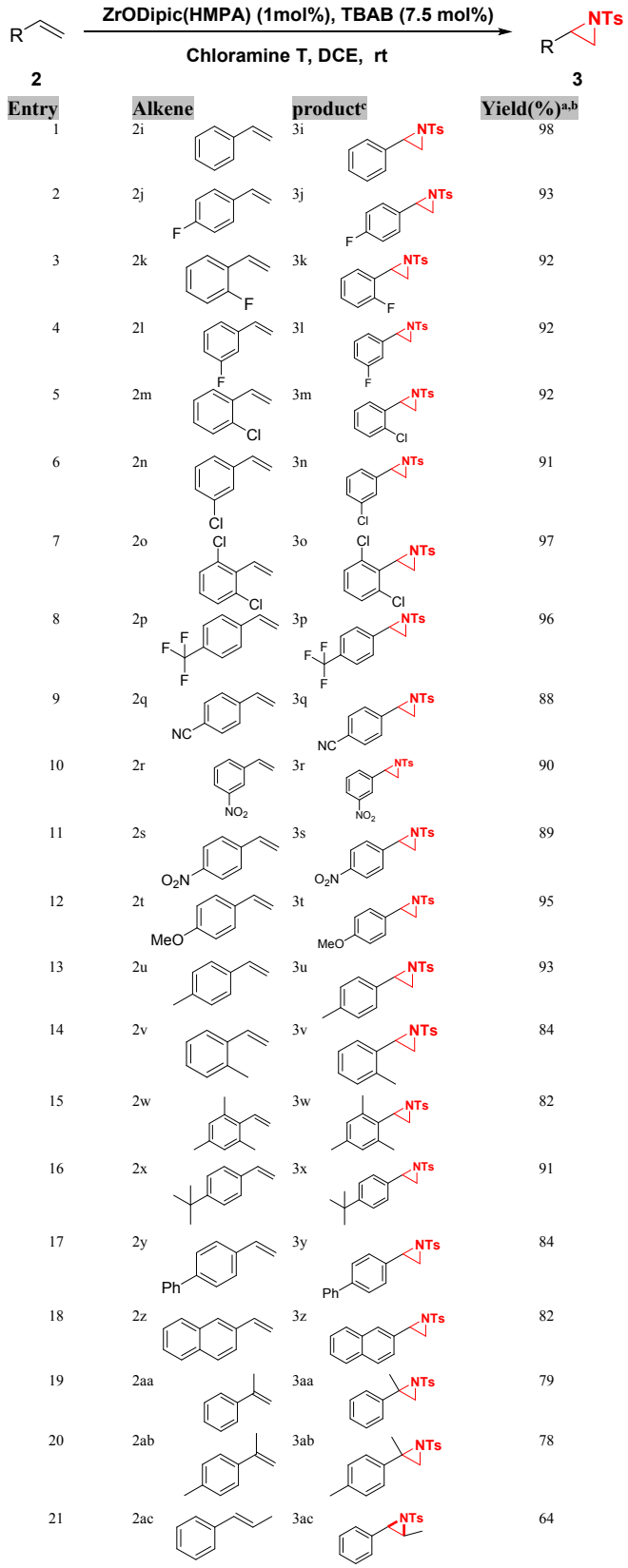
Table 2. Reaction scope.



Entry	alkene	product	Yield(%)[a,b]	d.r
1	2a C_4H_9	3a C_4H_9, NTs	93	-
2	2b C_6H_{13}	3b C_6H_{13}, NTs	89	-
3	2c C_5H_{11}	3c C_5H_{11}, NTs	84	16:1
4	2d C_3H_7, C_3H_7	3d C_3H_7, NTs, C_3H_7	79	16:1
5	2e C_3H_7, C_3H_7	3e C_3H_7, NTs, C_3H_7	86	18:1
6	2f	3f, NTs	88	-
7	2g	3g, NTs	75	-
8	2h	3h, NTs	84	-

a. Conditions: Alkene (1 mmol), ZrODipic(HMPA) (1 mol%), TBAB (7.5 mol%), chloramineT (3 mmol) in DCE (0.1M) at rt for 16h. b. Isolated yields. c. Reaction crude was purified by standard silica gel chromatography.

Table 3. Reaction scope.

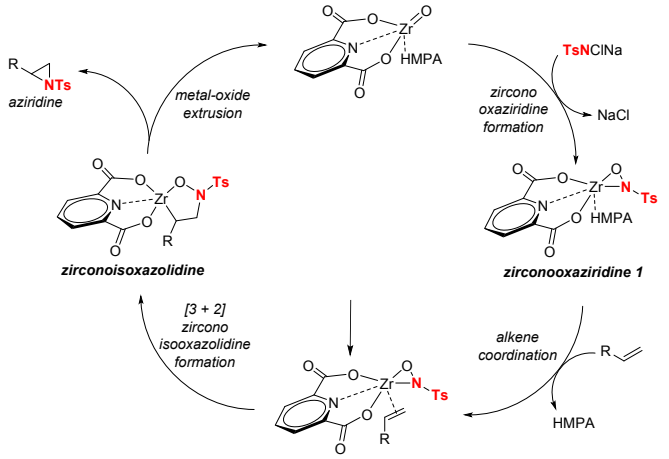


a. Conditions: Alkene (1 mmol), ZrODipic(HMPA) (1 mol%), TBAB (7.5 mol%), chloramineT (3 mmol) in DCE (0.1M) at rt for 16h. b. Isolated yields.
c. Reaction crude was purified by standard silica gel chromatography. d. 18:1 d.r.

Further exploration of the scope, revealed that cyclohexene, 1-methylcyclohexene and cyclooctene provided the corresponding aziridines in high yields despite the increased substitution (Entries 8-9).

Due to the success with alkyl alkenes, the focus then turned toward addressing the reaction productivity for substituted styrenes. These two types of alkenes often display opposing reactivity patterns in similar heteroatom transfer processes, thus the potential success of this reaction with substituted styrenes would further elevate the reaction value (**Table 3)**. We observed that styrene, 4-fluoro, 2-fluoro and 3-fluoro worked with great yields (Entries 1-4). 2-Chloro, 3-chloro and 2,6-dichloro were also very successful at providing the expected aziridine (entries 5-7). Moreover, 4-trifluoromethyl worked in similar high yields (entry 8).

Figure 2. Proposed mechanism.



The electronic properties around the ring were then changed; and 4-cyano, 3-nitro and 4-nitro styrene provided the respective aziridines in slightly lower yields (Entry 9-11). On the other hand, 4-methoxy accelerated the reaction performance to provide the aziridine in great yields (entry 12). Methylated styrenes with a variety of substitutions patterns also worked in high yields, but slightly slower than the fully activated substrates (entries 13-16). Other aromatic styrenes provided similar high yields for the transformation (entries 17 and 18). This study was also interested in addressing the stereospecificity across 1,1-dibustitited styrenes. It was discovered that α-methyl-styrene, α-methyl-(4-methyl)-styrene and trans-β-methylstyrene provided the corresponding aziridine in high yields and without activation of the allylic methyl groups (entries 19- 21). Despite some bulky and tetrasubstituted alkenes failing at providing aziridine in comparable yields (SI), this method provides a different alternative to available methods due the high conversion and stereoselectivity across unactivated alkenes and styrenes through a unique reaction pathway.

In order to elucidate the mechanism for this metal-mediated group transfer reaction, we have conducted kinetics and model reaction studies. These experiments attempt to address the central question of how the *N*-Ts group is transferred from the metal to the alkene (SI). Based on the observed results, it was apparent that the initial step in the catalytic reaction is the generation of **1** from reacting

ZrODipic with chloramine T (**Figure 2**). Thus, **1** forms within minutes and essentially quantitatively at rt when Chloramine T and ZrODipic are combined. **1** Can also be efficiently isolated by reacting ZrODipic and Chloramine T in $CHCl_3$ or MeOH, and its presence can be detected in the catalytic reaction mixture spectroscopically.[35] Moreover, the observation that the reaction of **1** with alkenes under optimized conditions works with considerably less efficiency below and above rt suggests that formation of **1** is very fast. We sought to determine whether the *N*-Ts group transfer step was dissociative or associative by examining the kinetics and formation of key intermediates for the reaction. Trapping experiments revealed the absence of radical intermediates (Ts-nitrene) thus demonstrating the absence of reactive nitrene species (SI). Kinetic experiments aimed at determining the role of ligand dissociation – alkene coordination as a potential rate-limiting step. The results indicated that in high excess of HMPA, reaction rate was significantly suppressed. This result indicates that ligand dissociation/coordination is most likely the rate-determining step. Based on these results an associative mechanism through the formation of **1**, followed by alkene coordination and then formation of a zirconoisoxazolidine intermediate has been proposed. The proposed intermediate then undergoes metal oxide extrusion to complete the catalytic cycle as outline in **Figure 1**. Zirconoisoxazolidine complexes have previously been reported, however efforts to isolate or characterize the formation of the proposed intermediate were not successful.[36]

Conclusions

In summary, a novel zirconooxaziridine-mediated catalytic aziridination of alkenes has been discovered. The reaction works with high efficiency and stereoselectivity for unactivated alkenes with diverse substitution patterns and for styrenes with a variety of functional groups. The proposed mechanism for the reaction involves the formation of a transient *N*-Ts zirconooxaziridine that then delivers *N*-Ts through a zirconoisoxazolidine intermediate followed by metal oxide extrusion to provide the aziridine. Further experiments to better understand and characterize the mechanism are undergoing and a follow up manuscript is in preparation.

There are no conflicts to declare.

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This material is based upon work supported by the National Science Foundation CAREER and MRI awards. Under grant numbers CHE-1752085 and CHE-1827938.

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