$Sc(OTf)_3$-catalyzed condensation of 2-alkyl-*N*-tosylaziridine with aldehydes or ketones: an efficient synthesis of 5-alkyl-1,3-oxazolidines†

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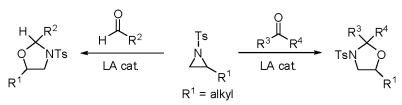
$Sc(OTf)_3$ effectively catalyzes the condensation of 2-alkyl-*N*-tosylaziridine with a wide variety of aldehydes and ketones, producing 5-alkyl-1,3-oxazolidines in good yields and excellent regioselectivity at catalyst loadings as low as 1 mol%.

The high ring strain of aziridines make them useful precursors to a wide range of functionalized nitrogen-containing compounds.[1,2] Among emerging reactions, the cycloaddition of aziridines to dipolarophiles provides a facile entry to heterocycles such as oxazolidinone,[3] oxazolidine,[4] iminooxazolidine,[5] and iminopyrrolidine.[6] In particular, 1,3-oxazolidines have found ever-expanding uses in the syntheses of both natural products[7,8] and designed medicinal agents (as prodrugs for 1,2-amino alcohols or carbonyl-containing pharmacophores).[9,10] However, traditional syntheses of 1,3-oxazolidines largely rely on the condensation of 1,2-amino alcohols with carbonyl substrates, which typically requires high temperatures, has limited scope, and can lead to many side products.[11,12]

Given the aforementioned impediments, the cycloaddition of aziridines to carbonyls in the presence of a Lewis acid (LA) is a more attractive strategy to 1,3-oxazolidine formation (Scheme 1). Surprisingly, very few reports have appeared on this method,[4,13,14] and with only modest scope and generality. For instance, because 2-alkyl-substituted aziridines are more resistant to LA-assisted ring-opening reactions, current reports are mostly limited to 2-aryl-substituted substrates.[13,14] In addition, catalytic examples for the synthesis of 1,3-oxazolidines are rare: the reported $Zn(OTf)_2$-catalyzed cycloaddition of 2-aryl-*N*-tosylaziridine to organic carbonyls[13] does not give consistent results (ESI†, Table S1); a stoichiometric amount of the Lewis acid (either $BF_3{\cdot}Et_2O$[4] or $Cu(OTf)_2$[14]) was often required to achieve good yields. Herein, we report an efficient and general Sc-catalyzed synthesis of 5-alkyl-1,3-oxazolidines from 2-alkyl-*N*-tosylaziridine and either aldehydes or ketones.



Scheme 1 The cycloaddition of 2-alkyl-*N*-tosylaziridine with either aldehydes or ketones catalyzed by Lewis acids.

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† Electronic Supplementary Information (ESI) available: General procedure for $Sc(OTf)_3$-catalyzed synthesis of 5-alkyl-1,3-oxazolidines and characterization data of all products; DFT calculations for model complexes and potential intermediates. See DOI: 10.1039/b902647a

When 2-methyl-*N*-tosylaziridine (**1**) was combined with 2 equiv. of *p*-nitrobenzaldehyde (**2e**) in CH_2Cl_2 at room temperature in the presence of several Lewis acids (10 mol%) (ESI†, Table S2), only $Sc(OTf)_3$ exhibited catalytic activity, providing the oxazolidine product **3e** in 32% yield after 18 h. While $Zn(OTf)_2$[13] and $Cu(OTf)_2$[14] have been reported to effect the cycloaddition of 2-aryl-*N*-tosylaziridine to aldehydes and ketones, in our hands $Cu(OTf)_2$ only afforded a trace conversion of **1** and $Zn(OTf)_2$ did not show any catalytic activity. Similarly, $SnCl_4$ and $TiCl_4$ only yielded a trace of **3e**. Indeed, while $Zn(OTf)_2$ can catalyze the cycloaddition of 2-phenyl-*N*-tosylaziridine to benzaldehyde (ESI†, Table S1, entry 8), it does not have any effect on the cycloaddition of 2-methyl-*N*-tosylaziridine to *p*-nitrobenzaldehyde, arguably a more activated carbonyl (ESI†, Table S2, entry 8). Thus, we selected $Sc(OTf)_3$ for further optimization.

Among the solvents evaluated (ESI†, Table S3), 1,2-dichloroethane and CH_2Cl_2, both polar and non-coordinating solvents, produced the best yield of the desired product **3e**. While high temperatures (80 °C) increase the rate of the reaction (ESI†, Table S3, entries 6–8), there is a significant amount of product decomposition, reducing the yield to a point that is only slightly higher than that obtained with CH_2Cl_2 at 40 °C. Coordinating solvents such as CH_3CN and THF gave a very poor yield of **3e**, most likely due to competitive solvent coordination at the Sc center,[15] which prevents aziridine complexation and catalyst turnover.

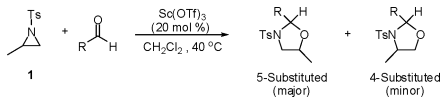
To confirm the aforementioned hypothesis, we investigated the ^{45}Sc NMR spectra of a [$Sc(OTf)_3$ + aziridine **1**] mixture in both CD_2Cl_2 and CD_3CN. While $Sc(OTf)_3$ itself is poorly soluble in CD_2Cl_2,[16] the [$Sc(OTf)_3$ + aziridine **1**] mixture becomes homogeneous in CD_2Cl_2 after 1 h, suggesting formation of an aziridine–Sc complex.[17] The ^{45}Sc NMR resonance of this mixture in CD_2Cl_2 appears as a broad signal that is significantly downfield (δ = 150 ppm) from the sharp singlet observed at δ = 0.4 ppm for the same mixture in CD_3CN.[18] As free $Sc(OTf)_3$ in CD_3CN also exhibits a sharp singlet at −2.5 ppm (ESI†, Fig. S1), it appears that **1** does not significantly influence the coordination environment of $Sc(OTf)_3$ in CD_3CN. Together, these data suggest that aziridine **1** can readily coordinate to $Sc(OTf)_3$ in a non-coordinating solvent such as CD_2Cl_2, but this coordination is weak and can be readily displaced by CD_3CN.

As expected, higher catalyst loadings and a higher excess of **2e** lead to faster conversions (ESI†, Table S4, entries 1–4). Under optimal conditions (20 mol% $Sc(OTf)_3$, 0.5 M or 1.0 M in **1**, 5 equiv. of **2e**, 2 h), **3e** can be formed in >90% yield. Longer reaction times can reduce the yield of **3e**, presumably due to the LA-catalyzed polymerization of aziridine **1**[19,20] and

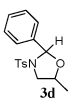
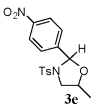
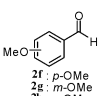
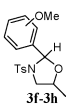
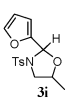
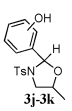
the instability of product **3e** in the presence of adventitious water (ESI†, Table S4, *cf.* entries 4 and 5).[21,22] For aldehydes that are more soluble, such as valeraldehyde (**2a**), the loading of $Sc(OTf)_3$ can be reduced to 1 mol% without significantly affecting the product yield, albeit with an increase in the reaction time (ESI†, Table S4, entries 7–9). To reduce the reaction time, neat substrate can be used in conjunction with low catalyst loading, affording oxazolidine product **3a** in 81% yield after 6 h (ESI†, Table S4, entry 10).

Table 1 outlines the scope of the $Sc(OTf)_3$-catalyzed condensation of 2-alkyl-substituted aziridines to aldehydes. Under our optimized reaction conditions, a wide range of 5-alkyl-1,3-oxazolidines are obtained with high regioselectivity and can be easily isolated in pure form *via* chromatography. Reactions with non-bulky aldehydes generally result in two diastereomeric products of approximately equal proportions (Table 1, entries 1–2 and 4–11). Interestingly, the diastereomeric ratio starts out high and degrades over time: for entry 5, the diastereomeric ratio at ~5% conversion was 2.6 : 1 (ESI†, Table S5).[23] Presumably, the kinetically formed *cis* product is isomerized to the *trans* isomer *via* Lewis acid-activated carbon–oxygen bond cleavage (Scheme 2, equilibrium shown on the lower left quadrant). This is indeed the case: a sample of *cis*-enriched **3e** (8.5 : 1) was readily isomerized to a 1.1 : 1 *cis* : *trans* mixture within 15 min in the presence of $Sc(OTf)_3$ (ESI†, Fig. S3).

Table 1 The $Sc(OTf)_3$-catalyzed condensation of **1** with aldehydes[a]



(1)

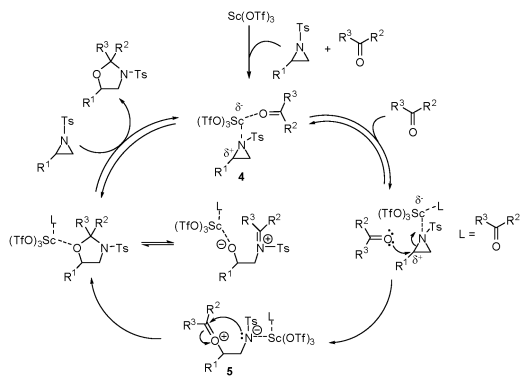
Entry	Aldehyde	Time/h	Isomer ratio[b]	Major product: Structure	*cis* : *trans*[c]	Conv. (%)[d]	Yield (%)[e]
1[f]	 **2a**	0.5	6.5 : 1	 **3a**	1.5 : 1	100	84
2[f]	 **2b**	0.5	5.5 : 1	 **3b**	1.5 : 1	100	82
3[f]	 **2c**	0.5	11 : 1	 **3c**	5.1 : 1	100	81
4	 **2d**	0.5	11 : 1	 **3d**	1.1 : 1	100	79
5	 **2e**	2	19 : 1	 **3e**	1.1 : 1	100	86
6	 **2f** : *p*-OMe **2g** : *m*-OMe **2h** : *o*-OMe	0.5	9.5 : 1 (**2f**)	 **3f-3h**	1.2 : 1	100	74
7			> 50 : 1 (**2g**)		1.2 : 1	100	n/a
8			9.4 : 1 (**2h**)		1 : 1.1	100	n/a
9	 **2i**	1	> 50 : 1	 **3i**	1 : 1.6	100	82
10	 **2j** : *p*-OH **2k** : *m*-OH **2l** : *o*-OH	0.5	11 : 1 (**2j**)	 **3j-3k**	1.1 : 1	100	n/a
11			20 : 1 (**2k**)		1 : 1.1	100	41
12			n/a[g] (**2l**)		—	—	—

[a] Reaction conditions: **1** (0.5 mmol), aldehyde (2.5 mmol, 5.0 equiv.), $Sc(OTf)_3$ (0.1 mmol, 20 mol%), CH_2Cl_2 (0.5 mL), 40 °C, ambient atmosphere. [b] Ratio of 5-substituted to 4-substituted isomers determined by GC analysis. [c] Confirmed by NOE experiments. [d] Conversion determined by GC analysis based on aziridine **1**. [e] Isolated yield of major product. [f] Reaction was carried out in neat aldehyde. [g] Complete consumption of **1** but there was no characterizable major product.

Our proposed mechanism for eqn (1) (Table 1) is shown in Scheme 2 (see ESI† for justification of the intermediates based on DFT calculations). The aziridine is first activated by coordination to the Lewis acidic Sc^{3+} metal center, generating intermediate **4** with differently polarized N–C bonds. Subsequent nucleophilic ring-opening of the coordinated aziridine by the oxygen atom of the carbonyl at the more substituted carbon results in the highly reactive intermediate **5**.[13,14] Cyclization finally leads to the formation of 1,3-oxazolidine product.

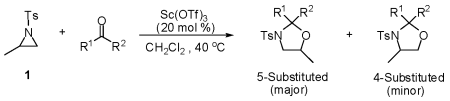
DFT calculations for a model Cl_3Sc(benzaldehyde)-(2-methylaziridine) complex (ESI†, Table S8) indeed suggest that coordination of the aziridine to the Lewis acidic Sc^{3+} center leads to increased differentiations in the partial charges present on the aziridine C^2 and C^3 carbons compared to that in free 2-methylaziridine. The increased electrophilic character of the C^2 carbon in the coordinated aziridine, coupled to an even larger increase in the nucleophilic character of the C^3 carbon (ESI†, Table S8), would result in higher selectivity for ring-opening at C^2. Consistent with this hypothesis, optically pure (*R*)-2-methyl-*N*-tosylaziridine is rapidly racemized in the presence of $Sc(OTf)_3$ in CH_2Cl_2 at 40 °C (ESI†, Fig. S6–S7).

Using the aforementioned model, the higher regioselectivity for **2e** over other *para*-substituted benzaldehydes (Table 1, *cf.* entries 4–6 and 10), can then be attributed to a reactivity–selectivity argument. Baldwin and co-workers have observed that compared to stronger Grignard nucleophiles, softer carbon nucleophiles such as cuprates preferentially attack 2-substituted *N*-tosylaziridine at the C^2 position,[24] which has a partial positive charge (ESI†, Table S8). In the same vein, we speculate that because the carbonyl oxygen of **2e** is less nucleophilic than those in other *para*-substituted benzaldehydes, it would preferentially ring-open the Sc-activated aziridine species **4** at the partially cationic C^2 over the partially anionic C^1 (ESI†, Table S8).

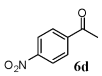
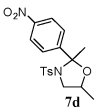
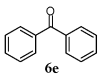


Scheme 2 A proposed mechanism for the $Sc(OTf)_3$-catalyzed condensation of 2-alkyl-*N*-tosylaziridine with aldehydes or ketones.

Table 2 The $Sc(OTf)_3$-catalyzed condensation of **1** with ketones[a]



(2)

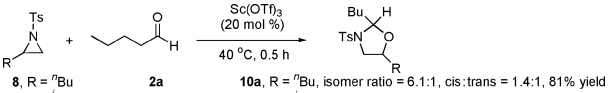
Entry	Ketone	Time/h	Isomer ratio[b]	Major product	Conv. (%)	Yield (%)[c]
1[d]	 **6a**	2	6.7 : 1	 **7a**	100	76
2[d]	 **6b**	4	13 : 1[e]	 **7b**	100	91[f]
3	 **6c**	2	10 : 1	 **7c**	100	78
4	 **6d**	1.5	41 : 1	 **7d**	100	73[g]
5[h]	 **6e**	1.5	13 : 1	 **7e**	100	68

[a] Reaction conditions: **1** (0.5 mmol), ketone (2.5 mmol, 5.0 equiv.), dried $Sc(OTf)_3$ (0.1 mmol, 20 mol %), CH_2Cl_2 (0.5 mL), 40 °C, N_2 atmosphere. [b] Ratio of 5-substituted to 4-substituted isomers determined by GC analysis. [c] Isolated yield of major product. [d] Reaction was carried out in neat ketone. [e] Determined by ^1H NMR. [f] Diastereomeric product, [(2*R*,5*S*)-**7b** + (2*S*,5*R*)-**7b**] : [(2*S*,5*S*)-**7b** + (2*R*,5*R*)-**7b**] = 1.3 : 1. [g] Diastereomeric product, [(2*R*,5*S*)-**7d** + (2*S*,5*R*)-**7d**] : [(2*S*,5*S*)-**7d** + (2*R*,5*R*)-**7d**] = 1 : 1.3. [h] The reaction was performed at 80 °C in 1,2-dichloroethane.

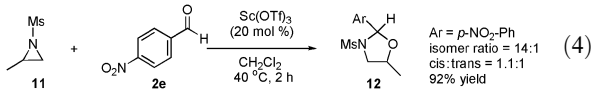
In an attempt to rationalize the high regioselectivity for 2-furaldehyde, *m*-methoxybenzaldehyde, and *m*-hydroxybenzaldehyde (Table 1, entries 7, 9, and 11), we hypothesize that these substrates may not coordinate to the $(OTf)_3Sc$(2-methylaziridine) intermediate through the carbonyl group. Instead, the coordination is *via* the secondary site of the aldehyde (furyl, methoxy, and hydroxy group, respectively), which favors an intramolecular delivery of the carbonyl oxygen to C^2 (ESI†, Scheme S1) over the intermolecular pathway shown in Scheme 2. DFT calculations for model Cl_3Sc(2-methylaziridine) complexes of 2-furaldehyde, *m*-methoxybenzaldehyde, and *o*-methoxybenzaldehyde (ESI†, Table S8) again reveal an increased differentiation in the partial charges present on the aziridine C^2 and C^3 carbons when compared to that in free 2-methylaziridine, with the biggest differences, and hence best selectivities, occurring for Sc(2-furaldehyde) and Sc(*m*-methoxybenzaldehyde).

While reactions of 2-methyl-*N*-tosylaziridine with ketones were slightly slower compared to those of aldehydes, the corresponding 2,2-disubstituted-1,3-oxazolidines can still be obtained in good yields (Table 2). Both acyclic and cyclic aliphatic ketones afforded the expected products in high yields, although bulkier substrates required longer reaction time (Table 2, *cf.* entries 1–3).

The reaction depicted in eqn (1) (Table 1) can be extended to other 2-alkyl-*N*-sulfonylaziridines. Oxazolidines **10a**, **10b**, and **12** can be obtained from 2-butyl-*N*-tosylaziridines, 2-isopropyl-*N*-tosylaziridines, and 2-methyl-*N*-mesylaziridines, respectively, in high yields (eqns (3)–(4)). Increasing the bulk of the alkyl group from Me to ^{i}Pr led to a slight decrease in regioselectivity (*cf.* Table 1, entry 1 and eqn (4)).



(3)



(4)

In conclusion, we have demonstrated a highly efficient and regioselective $Sc(OTf)_3$-catalyzed condensation of 2-alkyl-*N*-tosylaziridine with a variety of aldehydes and ketones. Excellent regioselectivity can be achieved if the aldehyde component possesses a secondary site that can coordinate to the catalyst and direct the carbonyl to the aziridine substrate.

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