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$Sc(OTf)_3$-Catalyzed [3+2]-cycloaddition of aziridines with nitriles under solvent-free conditions

Jie Wu,[a,b,*] Xiaoyu Sun[a] and Hong-Guang Xia[a]

[a]*Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China*
[b]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China*

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Abstract—[3+2]-Cycloaddition of aziridines with various nitriles in the absence of organic solvent catalyzed by $Sc(OTf)_3$ afforded the corresponding imidazolines in good to excellent yields under extremely mild reaction conditions.

The use of Lewis acids in organic synthesis, especially in catalysis has been one of the most rapidly developing fields in synthetic organic chemistry.[1] Among them, lanthanide triflates have attracted much attentions in the last decade due to their versatilities and water-stability.[1] Aziridine is a versatile building block for the syntheses of many nitrogen-containing biologically active molecules.[2] It reacts with various nucleophiles, and its ability to undergo regioselective ring-opening contributes largely to its high synthetic value.[2–6] In the course of our ongoing studies on novel methods for the aziridine ring-opening reactions, we were attracted to readily available lanthanide triflates as catalysts for ring-opening reactions of aziridines with carbon nucleophiles. During our studies for the reaction of *N*-tosyl-2-phenylaziridine with ethyl cyanoformate catalyzed by lanthanide triflates and other Lewis acids, we found that, the initial attempts to effect this transformation led to a surprising result when the reactions were performed in acetonitrile. No desired product was detected, while [3+2]-cycloaddition of *N*-tosyl-2-phenylaziridine with acetonitrile in the presence of lanthanide triflates occurred.

The cycloaddition reaction of aziridine with dipolarophiles, in particular, is a useful method for the syntheses of nitrogen-containing five- and six-ring molecules.[7,9,10] In most cases of this area, alkenes, and alkynes were involved as dipolarophiles for the [3+2]-cycloaddition of aziridines.[7] Although most nitriles are known to be poor dipolarophiles for intermolecular [3+2]-cycloaddition reactions,[8] utilization of nitriles as dipolarophiles for [3+2]-cycloaddition with aziridines[9,10] is promising since imidazoline would be generated during the process. It is well-known that imidazolines exhibit a wide range of pharmacological activities, such as anti-hyperglycemic, anti-inflammatory, antinociceptive, immunomodulating, anti-oxidant, antitumor, and anti-cancer activities.[11,12] However, the methods developed[9,10] usually suffered from harsh reaction conditions, stoichiometric amounts of Lewis acids promoter, low yields, and side reactions. For example, stoichiometric amounts of $BF_3{\cdot}Et_2O$[10a,b] or ZnX_2[10c] have to be utilized as promoter for the [3+2]-cycloaddition of aziridines with nitriles in order to achieve the respectable yields. However, only low to moderate yields could be obtained. And also, these Lewis acids employed are moisture sensitive. Moreover, under these conditions the side reactions are inevitable since halide anion from the promoter would act as a nucleophile to attack the aziridine ring. These drawbacks have prompted us to develop a simple, efficient, and catalytic protocol for synthesis of imidazolines utilizing [3+2]-cycloaddition of aziridines with nitriles based on the observations above. We now disclose our efforts on this area, which represent the first catalytic protocol for synthesis of imidazolines utilizing $Sc(OTf)_3$ as catalyst in the [3+2]-cycloaddition of aziridines with nitriles.

Initial studies were aimed at finding the optimal reaction conditions for this [3+2]-cycloaddition reactions. Our

* Corresponding author. Tel.: +86 2155 664619; fax: +86 2165 102412; e-mail: jie_wu@fudan.edu.cn

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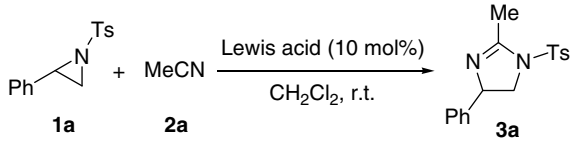
Table 1. Reaction of *N*-tosylaziridine **1** with nitrile **2** catalyzed by $Sc(OTf)_3$



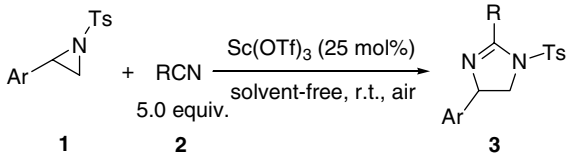
Entry	Lewis acid	Yield (%)[a]
1	$Sc(OTf)_3$	61
2	$Yb(OTf)_3$	11
3	$Dy(OTf)_3$	11
4	AgOTf	15
5	$Zn(OTf)_2$	34
6	$In(OTf)_3$	51

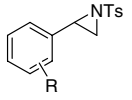
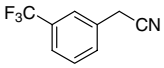
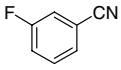
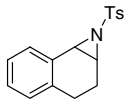
[a] Isolated yield based on aziridine **1a**.

investigation began with the reaction of *N*-tosyl-2-phenylaziridine **1a** and acetonitrile **2a** (1.2 equiv) in dichloromethane catalyzed by lanthanide triflates and other Lewis acids (10 mol %) (Table 1). Among the Lewis acids ($Sc(OTf)_3$, $Yb(OTf)_3$, $Dy(OTf)_3$, AgOTf, $Zn(OTf)_2$, $In(OTf)_3$) were screened, $Sc(OTf)_3$ was demonstrated as the best catalyst (61% yield, Table 1, entry 1). Further studies established showed that the reaction worked most efficiently in the absence of organic solvents (considering the ease of operation, 5 equiv of MeCN was used) among solvents investigation after 12 h. Reducing the amount of catalyst retarded the reaction. However, to our delight, the reaction went to completion in 20 min with 73% isolated yield when the amount of catalyst was increased to 25 mol %. No improvement was observed when the usage of catalyst kept increasing. Moreover, it is noteworthy that this reaction could be run under the air without loss of efficiency.

To demonstrate the generality of this method, we next investigated the scope of this reaction under the optimized conditions (in the absence of organic solvents, 25 mol % of $Sc(OTf)_3$, air, rt) and the results are summarized in Table 2. The operation was simple: nitrile (5.0 equiv) was added to a mixture of aziridine **1** (0.25 mmol) and $Sc(OTf)_3$ (25 mol %). The reaction mixture was stirred at room temperature for a period of time indicated in Table 2 under air atmosphere. After the reaction was completed monitored by TLC, the mixture was added to 5 mL of ethyl acetate, washed with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel afforded the corresponding product. As shown in Table 2, this method was equally effective for both *N*-tosyl-2-arylaziridines **1** and nitriles **2**. Various substituted *N*-tosyl-2-arylaziridines **1a–d** reacted smoothly with nitriles **2** to produce a range of imidazoline derivatives. Complete conversion and good to excellent isolated yields were observed for most of the substrates employed. However, when other aziridines, such as 7-tosyl-7-aza-bicyclo[4.1.0]heptane or *N*-tosyl-2-butylaziridine, reacted with nitriles, the starting materials could not be consumed even after 24 h and side products were observed (results not shown in Table 2).

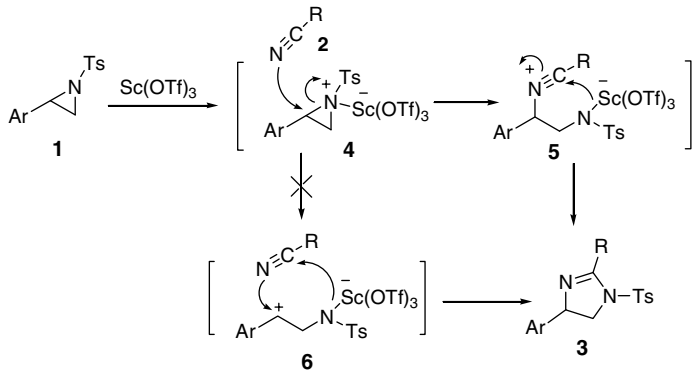
Table 2. Reaction of *N*-tosylaziridine **1** with nitrile **2** catalyzed by $Sc(OTf)_3$ under solvent-free condition at air atmosphere[a,14]



Entry	Aziridine **1**	Nitrile **2**	Time (min)	Product **3**	Yield (%)[b]
1	 R = H: **1a**	MeCN **2a**	20	**3a**	73
2	**1a**	^{n}PrCN **2b**	25	**3b**	84
3	**1a**	PhCN **2c**	20	**3c**	90
4	**1a**	BnCN **2d**	25	**3d**	83
5	**1a**	 **2e**	20	**3e**	53
6	**1a**	 **2f**	15	**3f**	51
7	**1a**	 **2g**	15	**3g**	76
8	R = 4-Cl: **1b**	**2a**	20	**3h**	94
9	**1b**	**2b**	15	**3i**	79
10	**1b**	**2c**	25	**3j**	70
11	**1b**	**2d**	15	**3k**	67
12	**1b**	**2f**	15	**3l**	66
13	**1b**	**2g**	15	**3m**	56
14	R = 4-Me: **1c**	**2a**	15	**3n**	87
15	**1c**	**2b**	10	**3o**	70
16	**1c**	**2c**	20	**3p**	77
17	**1c**	**2d**	12	**3q**	68
18	**1c**	**2f**	20	**3r**	67
19	 **1d**	**2a**	30	**3s**	54
20	**1d**	**2c**	120	**3t**	62

[a] Reaction conditions: aziridine (0.25 mmol), nitrile (5.0 equiv), $Sc(OTf)_3$ (25 mol %), room temperature.
[b] Isolated yield based on aziridine **1**.

The possible mechanism for formation of the cycloaddition product was rationalized in Scheme 1, where the aziridine nitrogen was coordinated to $Sc(OTf)_3$ generating a highly reactive intermediate **4**, which would then undergo a [3+2]-cycloaddition reaction with nitriles to provide the substituted imidazoline **3**. To support the mechanism, the ring-opening reaction of a chiral aziri-



Scheme 1.

dine, *R*-(−)-**1a** (>90 ee),[13] with acetonitrile was carried out under the same conditions shown in Table 1 and nonracemic imidazoline was produced ($[\alpha]^{20}$ −10.2 (*c* 0.38, $CHCl_3$)). Based on this observation, it was clear that the reaction proceeded through a cationic intermediate **4** (Scheme 1) instead of a stable benzylic carbocation intermediate **6** from which a racemic product could be expected.

In conclusion, we described $Sc(OTf)_3$ as a novel and efficient sub-catalyst in the [3+2]-cycloaddition of aziridines with nitriles under extremely mild reaction conditions, which provided a convenient way for the synthesis of imidazolines. The advantages of this method include: (1) employing easily available, water-stable $Sc(OTf)_3$ as sub-catalyst; (2) experimentally operational ease; (3) extremely mild conditions—room temperature under air atmosphere; and (4) in the absence of organic solvents.

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14. *General procedure*: Nitrile (5.0 equiv) was added to a mixture of aziridine **1** (0.25 mmol) and $Sc(OTf)_3$ (25 mol %). The reaction mixture was stirred at room temperature for a period of time indicated in Table 1 under air atmosphere. After the reaction was completed monitored by TLC, the mixture was added to 5 mL of ethyl acetate, washed with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography column on silica gel afforded the corresponding product. Selected examples: *2-Methyl-4-phenyl-1-tosyl-4,5-dihydro-1H-imidazole* **3a**:[10] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 2.46 (s, 3H), 3.64 (t, $J = 11.2$ Hz, 1H), 4.17 (t, $J = 10$ Hz, 1H), 4.98 (t, $J = 9.8$ Hz, 1H), 6.98–7.05 (m, 2H), 7.25–7.27 (m, 3H), 7.35 (d, $J = 8.32$ Hz, 2H), 7.75 (d, $J = 8.32$ Hz, 2H). *4-Phenyl-2-propyl-1-tosyl-4,5-dihydro-1H-imidazole* **3b**:[10] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00–1.04 (m, 3H), 1.79–1.80 (m, 2H), 2.43 (s, 3H), 2.72–2.73 (m, 2H), 3.60 (t, $J = 9.8$ Hz), 4.14 (t, $J = 9.8$, 1H), 4.96–5.00 (m, 1H), 7.02–7.03 (m, 2H), 7.23–7.30 (m, 3H), 7.33 (d, $J = 8.32$ Hz, 2H), 7.73 (d, $J = 8.32$ Hz, 2H). *2,4-Diphenyl-1-tosyl-4,5-dihydro-1H-imidazole* **3c**:[10] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.86 (dd, $J = 11.2$, 8.0 Hz, 1H), 4.44 (t, $J = 9.8$ Hz, 1H), 4.99 (t, $J = 9.8$ Hz, 1H), 6.97–6.98 (m, 2H), 7.20–7.22 (m, 5H), 7.39–7.41 (m, 4H), 7.51–7.56 (m, 1H), 7.77 (d, $J = 8.4$ Hz, 2H). *2-Benzyl-4-phenyl-1-tosyl-4,5-dihydro-1H-imidazole* **3d**:[10] ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.59 (t, $J = 8.0$ Hz, 1H), 4.13–4.18 (m, 3H), 5.01–5.06 (m, 1H), 6.97–7.01 (m, 2H), 7.19–7.40 (m, 12H).