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N-Heterocyclic carbene: a highly efficient catalyst in the reactions of aziridines with silylated nucleophiles

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Abstract—Ring-opening of aziridines with silylated nucleophiles catalyzed by *N*-heterocyclic carbene (NHC) afforded the corresponding products in excellent yields under mild reaction conditions.

N-Heterocyclic carbenes (NHCs) have received considerable attention in recent years. They have been successfully employed as ligands in a wide range of transition-metal catalyzed processes,[1] as well as substrates in multi-component reactions.[2] And also, they have been served as versatile catalysts in various organic transformations[3] such as nucleophilic substitutions,[4] umpolung reactions,[5] trifluoromethylation reaction,[6] and transesterification reactions.[7] Louie also demonstrated that NHCs were effective catalysts for trimerization of isocyanates.[8] In the course of our ongoing studies on novel methods for the aziridine transformations, we were attracted to use readily available *N*-heterocyclic carbenes (NHCs) as catalysts for ring-opening reactions of aziridines.

It is well-known that aziridine is a versatile building block for the syntheses of many nitrogen-containing biologically active molecules.[9] The reactivity of aziridines toward ring opening and expansion is dependent upon their extremely strained ring structures. Among the procedures of ring opening of aziridines, a nucleophilic ring-opening reaction is one of the major routes to highly functionalized compounds.[9] Ring-opening reactions of aziridines have been developed using silylated nucleophiles.[10] Most of these methods are limited to the use of heavy and/or expensive metal-based catalysts such as a Lewis acid and frequently result in the formation of mixtures of regioisomers. We also found that TBAF and DMF could promote the ring-opening reactions of aziridines and silylated nucleophiles.[10k,l] However, the non-activated aziridines are inert to these conditions. Recently, small organic molecules, such as phosphine, amine, and nitrile, were utilized as catalysts or mediates to effect this transformation.[10m] For example, very recently, Minakata[10m] reported the ring opening of *N*-tosylaziridines with trimethylsilylated nucleophiles, catalyzed by *N*,*N*,*N*′,*N*′-tetramethyl-ethylenediamine (20 mol %), led to the production of β-functionalized sulfonamides in good yields. However, the catalyst loading was high (20 mol %) and reactions usually needed 24–100 h for completion. On the other hand, although this amine-catalyzed reaction of aziridines with TMSX (X = CN, N_3, Br, and I), was readily opened by cyanide, azide, bromide, and iodide in the presence of a catalytic amount of TMEDA to give the desired compounds in good yields, strangely, ring opening of aziridines with the silyl chloride under the conditions did not proceed at all to recover the starting material. Again, only activated aziridines (with electron-withdrawing group attached on the nitrogen of aziridine ring) were suitable for this reaction. Inspired by the recent advances of *N*-heterocyclic carbene catalysts, we envisioned that we could exploit the strong σ-donating property of NHCs to effect reactions between silylated nucleophiles and aziridines. Herein, we would like to disclose our preliminary results for this transformation.

Our studies commenced with the ring-opening reaction of aziridine **1a** with trimethylsilyl azide catalyzed by

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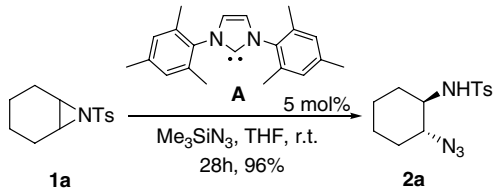


Scheme 1.

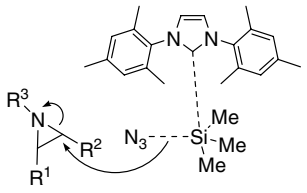


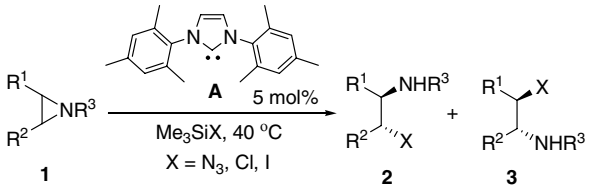
Figure 1.

NHC **A** (5 mol %) in THF at room temperature (Scheme 1). To our delight, we observed the formation of the desired product **2a**. The isolated yield of 96% was obtained after 28 h. The anti-stereochemistry of the product **2a** was confirmed by the coupling constant for two cyclic methine hydrogens at the *trans*-positions. Further studies showed THF was the best choice of solvent among the solvents screened (CH_3CN, 28 h, 92% yield; CH_2Cl_2, 48 h, 65% yield; toluene, 72 h, 56% yield). When the temperature was elevated to 40 °C, the reaction shown in Scheme 1 was completed in 15 h and 99% yield of **2a** was obtained. Furthermore, 1 mol % of NHC **A** was found to be sufficient for catalysis although prolonged reaction time was needed for completion with slightly lower yield (1 mol % of NHC **A**, 40 °C, 36 h, 94% yield). Without catalyst, no reaction occurred at 40 °C in THF for 48 h. For the role of *N*-heterocyclic carbene catalyst in this reaction, according to the precedent reports for silyl reagents and the strong σ-donating property of NHC, we believed that *N*-heterocyclic carbene coordinated to trimethylsilyl azide to form hypervalent silicon compound,[11] which was active for further nucleophilic ring openings (Fig. 1).

To demonstrate the generality of this method, we then investigated the scope of this reaction under the optimized reaction conditions (NHC **A**: 5 mol %, THF, 40 °C) and the results were summarized in Table 1. The operation was simple: *N*-heterocyclic carbene **A** (5 mol %) was added to a solution of aziridine **1** (0.25 mmol) and silylated nucleophile (1.1 equiv) in THF (2.0 mL). The reaction mixture was stirred at 40 °C for a period of time indicated in Table 1. After the reaction was completed monitored by TLC, the mixture was washed with water, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel afforded the corresponding product.

This condition was proved to be useful for ring openings of a range of aziridines **1** (Table 1). In all the cases, reactions were very clean and afforded the desired products in excellent yields. Trimethylsilyl azide, as well as trimethylsilyl chloride and iodide were all suitable partners. In contrast of the report[10m] that trimethylsilyl chloride could not be employed in the ring-opening reaction of aziridine, the reactions of aziridine **1** with trimethylsilyl chloride were highly efficient and almost quantitative yields of the corresponding products were generated in 0.5–2.5 h (Table 1, entries 2, 5, 8, 10, 13, and 16). However, no product was detected at all when trimethyl(trifluoromethyl) silane reacted with aziridine **1a** (result not shown in Table 1). In the case of unsymmetrically

Table 1. Reaction of *N*-tosylaziridine **1** with silylated nucleophiles catalyzed by *N*-heterocyclic carbene[12,a]



1a: R^1, R^2 = -$(CH_2)_4$, R^3 = Ts; **1b**: R^1, R^2 = -$(CH_2)_3$, R^3 = Ts;
1c: R^1, R^2 = -$(CH_2)_4$, R^3 = Bn; **1d**: R^1 = Bn, R^2 = H, R^3 = Ts;
1e: R^1 = ^{n}Bu, R^2 = H, R^3 = Ts; **1f**: R^1 = Ph, R^2 = H, R^3 = Ts;
1g: R^1 = $^n C_8H_{17}$, R^2 = H, R^3 = Ts.

Entry	Aziridine **1**	TMSX	Time (h)	Product **2**	Yield (%)[b]
1	**1a**	$TMSN_3$	15	**2a**	99
2	**1a**	TMSCl	1	**2b**	97
3	**1a**	TMSI	0.5	**2c**	95
4	**1b**	$TMSN_3$	24	**2d**	91
5	**1b**	TMSCl	2.5	**2e**	98
6	**1b**	TMSI	0.5	**2f**	94
7	**1c**	$TMSN_3$	15	**2g**	96
8	**1d**	TMSCl	1.5	**2h**	89
9	**1e**	$TMSN_3$	11	**2i**	98
10	**1e**	TMSCl	0.5	**2j**	95
11	**1e**	TMSI	0.3	**2k**	98
12	**1f**	$TMSN_3$	12	**2l/3l** (1:1.4)[c]	95
13	**1f**	TMSCl	1	**2m/3m** (1:3.6)[c]	90
14	**1f**	TMSI	0.5	**2n/3n** (1:2.5)[c]	96
15	**1g**	$TMSN_3$	16	**2o**	98
16	**1g**	TMSCl	1	**2p**	99
17	**1g**	TMSI	0.3	**2q**	96

[a] Reaction conditions: aziridine (0.25 mmol), silylated nucleophile (1.1 equiv), *N*-heterocyclic carbene **A** (5 mol %), THF, 40 °C.
[b] Isolated yield based on aziridine **1**.
[c] Ratio was determined by ^{1}H NMR.

substituted aziridines **1d, 1e** and **1g**, completely regioselectivity with the attack of nucleophile on the less substituted aziridine carbon was observed. For the substrates **1f**, it was reasonable that regioselectivity was not as specific as others due to electronic effect. Non-activated aziridine **1c** was also suitable in the reaction of trimethylsilyl azide. The isolated yield of 96% of desired product **2g** was obtained after 15 h (Table 1, entry 7). However, NHC-catalyzed reaction of aziridine **1c** with trimethylsilyl chloride or trimethylsilyl iodide gave unstable product, which turned to be complicated during purification process (results not shown in Table 1).

In conclusion, we described *N*-heterocyclic carbene as a novel and efficient catalyst in the ring-opening reaction of aziridines with silylated nucleophile under mild reac-

tion conditions, which provided a convenient and alternative way for the synthesis of 1,2-difunctional compounds. The advantages of this method include: (1) employing easily available *N*-heterocyclic carbene as catalyst; (2) experimentally operational ease; (3) mild conditions; and (4) good substrates generality. Efforts to extend NHC catalysis to other organic transformations, including chiral *N*-heterocyclic carbenes-catalyzed desymmetrization of *meso*-aziridines with silylated nucleophiles are ongoing.

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12. General procedure for the reactions of aziridines **1** with silylated nucleophiles catalyzed by *N*-heterocyclic carbene: *N*-heterocyclic carbene **A** (5 mol %) was added to a solution of substrate **1** (0.25 mmol) and silylated nucleophile (1.1 equiv) in THF (2.0 mL). The reaction mixture was stirred at 40 °C for a period of time indicated in Table 1. After the reaction was completed monitored by TLC, the

mixture was washed with water, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel afforded the corresponding product. The data of products was identical with the literature reports.[10] Selected example: *N*-(2-Azidocyclohexyl)-4-methyl-benzenesulfonamide (**2a**).[10l] Colorless liquid. IR (film): 3273, 2940, 2863, 2100, 1599 cm^{-1}. ^1H NMR (400 M Hz, $CDCl_3$) δ (ppm): 1.10–1.45 (m, 4H), 1.60–1.80 (m, 2H), 1.95–2.15 (m, 2H), 2.45 (s, 3H), 2.90–3.00 (m, 1H), 3.00–3.10 (m, 1H), 4.80 (bd, *J* 6.0 Hz, 1H), 7.35 (d, *J* 8.0 Hz, 2H), 7.80 (d, *J* 8.0 Hz, 2H). MS: 295 (MH^+). HRMS: calcd for $C_{13}H_{18}NO_2S$ $(M-N_3)^+$: 252.1058. Found 252.1070. *N*-(2-Chlorocyclohexyl)-4-methylbenzenesulfon-amide (**2b**).[10l] White solid. Mp: 100–102 °C. IR (film): 3255, 2947, 2869, 1922, 1596 cm^{-1}. ^1H NMR (400 M Hz, $CDCl_3$) δ (ppm): 1.20–1.40 (m, 3H), 1.55–1.75 (m, 3H), 2.10–2.30 (m, 2H), 2.40 (s, 3H), 3.10–3.20 (m, 1H), 3.60–3.70 (m, 1H), 4.85 (br, 1H), 7.30 (d, *J* 8.0 Hz, 2H), 7.80 (d, *J* 8.2 Hz, 2H). MS: 289 (M^+, ^{37}Cl), 287 (M^+, ^{35}Cl). Anal. Calcd for $C_{13}H_{18}ClNO_2S$: C, 54.26; H, 6.26; N, 4.87. Found: C, 54.55; H, 6.26; N, 4.71. *N*-(-2-iodocyclohexyl)-4-methylbenzene-sulfonamide (**2c**).[10l] ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.26–1.32 (m, 3H), 1.61–1.71 (m, 3H), 2.16–2.27 (m, 2H), 2.43 (s, 3H), 3.24–3.27 (m, 1H), 3.99–4.01 (m, 1H), 5.01–5.02 (d, *J* 6.2 Hz, 1H), 7.26–7.31 (m, 2H), 7.8 (d, *J* 8.3 Hz, 2H).