DABCO: An Efficient Organocatalyst in the Ring-Opening Reactions of Aziridines with Amines or Thiols

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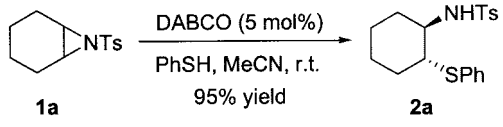
Efficient ring-opening of aziridines with various amines or thiols catalyzed by DABCO afforded the corresponding products in good to excellent yields under mild reaction conditions.

The interest in the field of organocatalysis has increased spectacularly in the last few years as result of both the novelty of the concept and, more importantly, the fact that the efficiency and selectivity of many organocatalytic reactions meet the standards of established organic reactions. The diverse examples show that in recent years organocatalysis has developed within organic chemistry into its own subdiscipline, whose "Golden Age" has already dawned.[1] The pinpointing of "privileged" catalyst classes (such as L-proline in aldol and Mannich reactions) showing general superiority for many reaction types is undoubtedly one of the most intriguing aspects and may have a considerable impact on the development of new catalytic systems.[2,3] Catalysts of the same class may promote similar reactions or less closely related reactions. For example, chiral thiourea derivatives and their analogues catalyze the hydrocyanation of imines (Strecker reaction) as well as asymmetric Mannich reactions.[4] Tertiary amines are another example of a privileged catalyst class. They are able to mediate an astonishingly wide variety of transformations.[5,6] For instance, DABCO and its analogues show high efficiency in Morita-Baylis–Hillman reactions[6] as well as cyanation of ketones.[7] Recently, we found that it was also efficient as catalyst in the ring-opening reactions of aziridines with various nucleophiles, such as amines or thiols, which is disclosed herein.

Ring-opening reactions of aziridines with nucleophiles provide a useful protocol in organic synthesis, and many reagents have recently been developed to realize the opening of the aziridine ring.[8] However, most of these suffered from the fact that a Lewis acid or strong base was necessary to effect the reaction.[9] Moreover, varied reaction conditions were needed for various aziridines because of the different reactivity of substrates and reagents, as well as the complexity of the structure of aziridines.[10–12] Recently, Hou developed nonmetallic catalyzed ring-opening reactions of aziridines with nucleophiles by utilizing tributylphosphane as catalyst, which opens the way to a variety of 1,2-bifunctional products.[13] However, the catalyst, Bu_3P, is not stable and easy to be oxidized in the air. Furthermore, high loading catalyst (at least 10%) had to be utilized in order to achieve the respective yields. The yield and rate was dramatically decreased if catalyst loading was reduced. For example, in the reaction of aziridine **1a** with thiophenol in acetonitrile, 95% yield of the corresponding product was obtained after 4 hours at room temperature when 1.0 equivalent of catalyst was employed. However, the reaction was retarded if catalyst loading was reduced (10 mol-% of Bu_3P, 36 hours, 90% yield; 2 mol-% of Bu_3P, 56 hours, 30% yield).[13]

In view of the stability and nucleophilic similarity, DABCO should be a very attractive alternative due to its unique characteristics. Initial studies were performed by using DABCO (5 mol-%) as catalyst in the reaction of compound **1a** with thiophenol in different solvents (THF, toluene, MeCN, CH_2Cl_2, DMF) at room temperature. To our delight, we observed the formation of the corresponding product **2a**. Complete conversion and 95% isolated yield was obtained after 3 hours when the reaction was performed in MeCN. (Scheme 1) Further study showed that 1 mol-% of catalyst was also efficient in this reaction at the



Scheme 1. Reaction of **1a** with thiopenol catalyzed by DABCO (5 mol-%).

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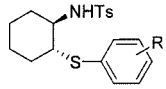
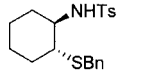
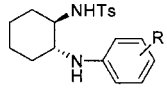
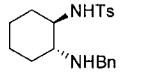
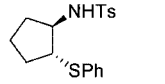
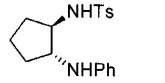
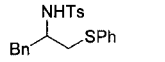
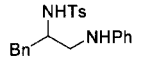
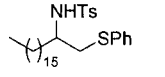
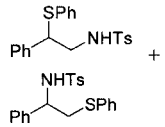
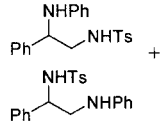
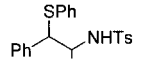
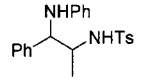
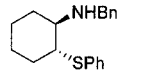
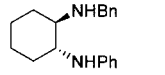
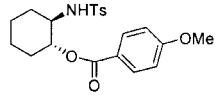
Table 1. Ring-opening reactions of aziridines with nucleophiles catalyzed by DABCO.

Entry	Aziridine	NuH	Time (h)	Product	Yield (%)[a]	Yield (%)[c][13]
1	**1a**	C_6H_5SH	3	 R = H	95 (**2a**)	15
2	**1a**	4-ClC_6H_4SH	7	R = 4-Cl	83 (**2b**)	
3	**1a**	4-$OMeC_6H_4SH$	5	R = 4-OMe	77 (**2c**)	
4[b]	**1a**	$C_6H_5CH_2SH$	24		68 (**2d**)	
5[b]	**1a**	$C_6H_5NH_2$	16	 R = H	84 (**2e**)	55
6[b]	**1a**	4-$FC_6H_4NH_2$	24	R = 4-F	74 (**2f**)	
7[b]	**1a**	4-$OMeC_6H_4NH_2$	24	R = 4-OMe	73 (**2g**)	
8[b]	**1a**	2,4,6-trimethylaniline	56	R = 2,4,6-trimethyl	41 (**2h**)	
9[b]	**1a**	$C_6H_5CH_2NH_2$	16		86 (**2i**)	50
10	**1b**	C_6H_5SH	6		73 (**2j**)	trace
11[b]	**1b**	$C_6H_5NH_2$	14		67 (**2k**)	
12	**1c**	C_6H_5SH	6		94 (**2l**)	
13[b]	**1c**	$C_6H_5NH_2$	24		71 (**2m**)	
14	**1d**	C_6H_5SH	6		87 (**2n**)	
15	**1e**	C_6H_5SH	6		87 (**2o**/**3o** = 1.1:1)	trace
16[b]	**1e**	$C_6H_5NH_2$	14		86 (**2p**/**3p** = 3.5:1)	
17	**1f**	C_6H_5SH	6		93 (**2q**)	
18[b]	**1f**	$C_6H_5NH_2$	14		74 (**2r**)	
19	**1g**	C_6H_5SH	16		95 (**2s**)	30
20[b]	**1g**	$C_6H_5NH_2$	16		86 (**2t**)	trace
21[b]	**1a**	C_6H_5OH	24		–	
22[b]	**1a**	EtOH	24		–	
23[b]	**1a**	$CH_2(COOMe)_2$	24		–	
24[b]	**1a**	4-$OMeC_6H_4CO_2H$	40		73 (**2u**)	

[a] Isolated yield based on aziridine. [b] Reaction was performed under reflux condition. [c] Absence of DABCO.

expense of reaction time (6 h, room temp., 94% yield). It is noteworthy that this reaction could be run under the air without loss of efficiency. The *anti*-stereochemistry of the product **2a** was confirmed by the coupling constant for two cyclic methine hydrogens at the *trans*-positions.[11e,12d] We also screened other tertiary amines (Et_3N, IPDEA, DBU, DMAP, and quinuclidine) as organocatalyst in the reaction of **1a** with thiophenol. It was found that DABCO was the best of choice.

To demonstrate the generality of this method, we next investigated the scope of this reaction and the results are summarized in Table 1. The operation is simple: thiol (1.1 equiv.) was added to a solution of substrate **1** (0.25 mmol) (Figure 1) and DABCO (5 mol-%) in MeCN (2.0 mL). The reaction mixture was stirred at room temperature for a period of time indicated in Table 1. After the reaction was completed monitored by TLC, the mixture was separated directly by flash chromatography column (silica gel) to afford the corresponding product (Scheme 2).

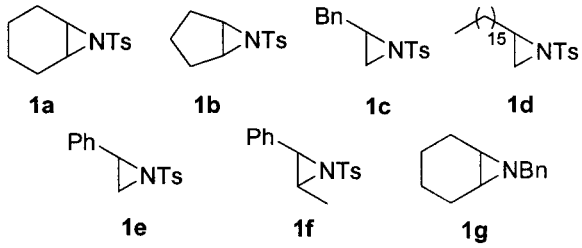
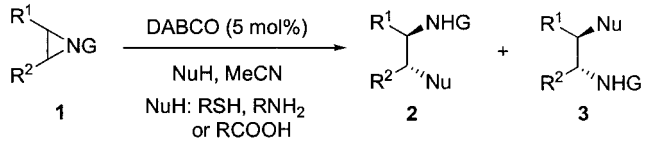


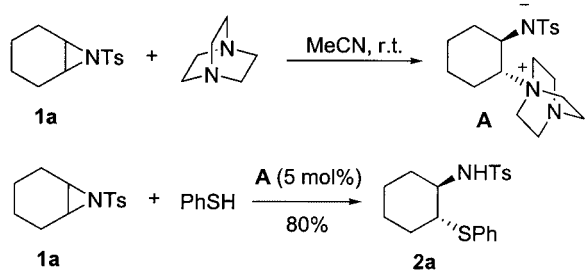
Figure 1. Aziridine substrates **1**.



Scheme 2. Reactions of aziridine **1** with nucleophiles catalyzed by DABCO (5 mol-%).

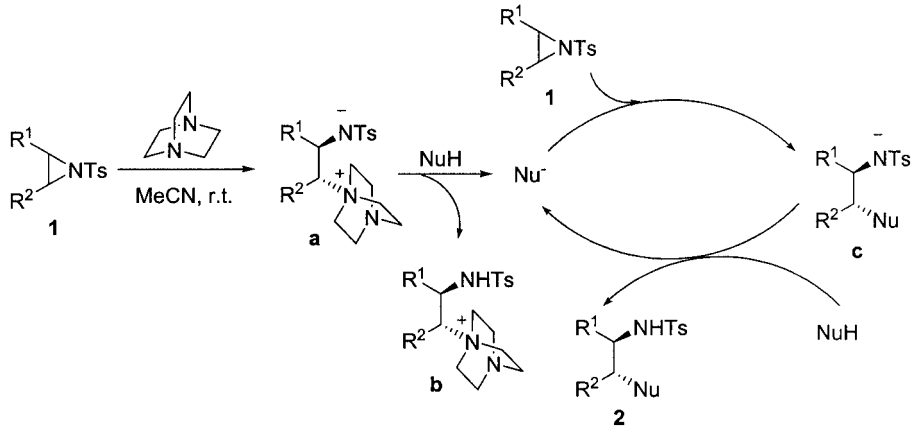
The conditions have proved to be useful for coupling a range of aziridines **1** with an array of thiols (Table 1). For reactions of compounds **1a**, various thiols are suitable substrates. Both electron-rich and electron-poor thiophenols gave similar yields. The reactions were very clean and the desired products were afforded in good yields. Aliphatic mercaptans were also good partners in this reaction. Usually, aromatic nucleophiles had higher reactivity than aliphatic ones. For example, reaction with thiophenol was finished in 3 hours (95% yield, entry 1). However, prolonged reaction time (24 h) and higher temperature (under reflux) were needed when benzyl mercaptan was used as nucleophile (68% yield, entry 4). In the case of unsymmetrically substituted aziridines **1c** and **1d**, completely regioselectivity with the attack of nucleophile on the less substituted aziridine carbon was observed. For the substrates **1f**, as previously reported, the attack of nucleophile was on the benzyl position due to electron effect. And also, it is reasonable that regioselectivity is not as specific as others when aziridine **1e** was employed as the substrate. Furthermore, The reactivity of aziridine was reduced according to the decreased electron-withdrawing ability of the substituent on the nitrogen atom of aziridine. When **1g** was employed in the reaction with thiophenol (entry 19), the reaction time was extended to 16 hours comparing to substrate **1a**. Further studies established showed that amines were also good nucleophiles by utilizing DABCO as catalyst although the reaction temperature should be elevated. (Table 1) In most of the cases, reactions of aziridines with aromatic and aliphatic amines were all performed smoothly to afford the corresponding product in good to excellent yields. Due to the steric effect, lower yield (41%) of product **2h** was obtained after 56 hours when 2,4,6-trimethylaniline was employed as substrate. (entry 8) Regioselectivities were similar to those described in the ring opening reaction with thiols. Other nucleophiles, such as phenol, alcohol, benzoic acid, dimethyl malonate, were also employed in the reaction of **1a** with expect to expand the scope of this reaction. However, only trace amount of product was detected even the reaction was performed at reflux condition when phenol, alcohol, or dimethyl malonate was used. (Table 1, entries 21–23) Reaction of *p*-methoxybenzoic acid with aziridine **1a** performed smoothly and 73% yield of the desired product was afforded (Table 1, entry 24).

What is the role of DABCO in this reaction? When aziridine **1a** was mixed with 1.0 equiv. of DABCO in acetonitrile at room temperature, a white precipitate was formed after several hours. After isolation, the structure of this expected ammonium salt **A** was confirmed by ^1H and ^{13}C NMR spectroscopy. This revealed that DABCO played a role as nucleophile, and the attack of DABCO on aziridine to form a ammonium salt is most likely the first step of the reaction. When intermediate **A** was directly employed as catalyst in the reaction of **1a** and thiophenol, no displacement product *cis*-**2a** was observed and the desired product *trans*-**2a** was generated in 80% yield after 3 hours (Scheme 3).



Scheme 3. Reaction of **1a** with thiophenol triggered by intermediate **A**.

Moreover, Hou pointed out that deprotonated product of **2i**, can also catalyze the reaction of **1a** with BnSH.[13] According to these experimental facts, a possible mechanism can be proposed (Scheme 4). DABCO attacks the aziridine to form a ammonium intermediate **a**, which could deprotonate NuH to form intermediate **b** and Nu^-. Then Nu^- reacts with aziridine to give the ring-opened intermediate **c**, which reacts with another NuH to provide the product **2** and regenerate the Nu^- to complete the catalytic cycle. The



Scheme 4. Possible mechanism.

tertiary amine acts as a nucleophilic trigger to produce intermediate **a**, which serves as a base to deprotonate the nucleophile. Although the mechanism is not clear which need more evidences to support, the role of tertiary amine as base could not be excluded in this reaction. Details of the mechanism is investigated now.

In summary, we have discovered DABCO was an efficient catalyst in the reactions of aziridines with amines or thiols, which provided a general and convenient way to prepare a variety of 1,2-diamines and 1,2-aminothioethers. The advantages of this method include good substrate generality, the use of air-stable, inexpensive DABCO as catalyst under mild conditions, and experimentally operational ease. Mechanism studies and desymmetrization of *meso*-aziridines with various nucleophiles by using chiral tertiary amines as catalysts are under investigation in our laboratory.

Experimental Section

General Procedure for the Reaction of Aziridines 1 with Thiols or Amines: The thiol or amine (1.1 equiv.) was added to a solution of substrate **1** (0.25 mmol) and DABCO (5 mol-%) in MeCN (2.0 mL). The reaction mixture was stirred at room temperature (thiols) or under reflux (amines) for a period of time indicated in Table 1 After the reaction was completed monitored by TLC, the mixture was separated directly by flash chromatography column (silica gel) to afford the corresponding product; examples are described below.

4-Methyl-*N*-[2-(phenylthio)cyclohexyl]benzenesulfonamide (2a):[11e] Yield 95%, white solid; m.p. 130–131 °C. IR (film): $\tilde{\nu}_{max}$ = 3265 cm^{-1}. ^1H NMR (500 MHz, [D_6]DMSO): δ = 1.20–1.50 (m, 4 H), 1.50–1.75 (m, 2 H), 2.00–2.10 (m, 1 H), 2.20–2.30 (m, 1 H), 2.45 (s, 3 H), 3.00 (t, J = 11.4, 3.8 Hz, 1 H), 3.10 (dt, J = 11.1, 3.7 Hz, 1 H), 7.10–7.30 (m, 7 H), 7.63 (d, J = 8.2 Hz, 2 H), 7.80 ppm (d, J = 7.5 Hz, 1 H). EIMS: 361 (M^+); $C_{19}H_{23}NO_2S_2$ (361.5): calcd. C 63.13, H 6.41, N 3.87; found C 63.07, H 6.48, N 3.91%.

4-Methyl-*N*-[2-(phenylamino)cyclohexyl]benzenesulfonamide (2e):[13] Yield 84%, white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.02–1.07 (m, 1 H), 1.20–1.35 (m, 3 H), 1.64–1.78 (m, 2 H), 2.02–2.05 (m, 1 H), 2.15–2.18 (m, 1 H), 2.45 (s, 3 H), 2.92 (dt, J = 10.0, 3.7 Hz, 1 H), 3.07 (dt, J = 10.1, 3.7 Hz, 1 H), 5.03 (d, J = 5.5 Hz, 1 H), 6.48–6.50 (d, J = 7.8 Hz, 2 H), 6.71–6.73 (t, J = 7.3 Hz, 1 H), 7.14–7.20 (m, 2 H), 7.25–7.30 (m, 2 H), 7.75 ppm (d, J = 8.2 Hz, 2 H).

Acknowledgments

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