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Unexpected Ring-Opening Reactions of Aziridines with Aldehydes Catalyzed by Nucleophilic Carbenes under Aerobic Conditions

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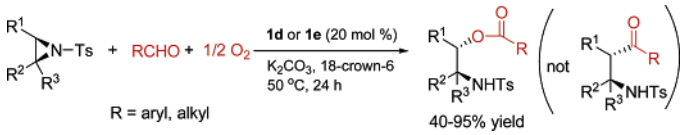
ABSTRACT



The chemoselective ring opening of *N*-tosyl aziridines with aldehydes catalyzed by an *N*-heterocyclic carbene was investigated under aerobic conditions. Unexpected carboxylates of 1,2-amino alcohols from the corresponding aldehydes, rather than the acyl anion ring-opened *β*-amino ketones, were exclusively obtained. A plausible mechanism for this unprecedented carbene-mediated reaction was also proposed.

The discovery of novel catalytic methods for chemoselective transformation is important to the development of synthetic organic chemistry. In addition to the well-established reactions involving enolates, the umpolung of the classic functional group opens up an avenue to various new reactions.[1] Following the concept of polarity of reversal, considerable efforts have been directed to the chemistry of acyl anions, readily prepared in situ from electrophilic aldehydes through covalent activating with catalytic cyanide or nucleophilic carbene.[2] A variety of electrophiles, aldehydes (benzoin condensation),[3] aldimine derivatives,[4] and polarized olefins (Stetter reaction)[5] as well as asymmetric patterns[6] have been studied extensively in the past decades; indeed, other electrophilic functionalities have not been thoroughly explored as possible substrates.[7] In addition, much of the fundamental chemistry of the electron-rich enaminol intermediate, formed by the addition of carbene to an aldehyde group,[2] remains to be studied. To address this deficiency, here we would like to present the first report on the highly

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chemoselective ring-opening reactions of aziridines with aldehydes promoted by a nucleophilic carbene catalyst under aerobic conditions.

The aziridines are widely recognized as valuable building blocks for functional group transformations. The nucleophilic ring opening of aziridines has been extensively investigated,[8] whereas most of these methods are limited to the use of metal-based catalysts such as Lewis acids. On the other hand, abundant nucleophiles, alkyl or aryl anions, enolates, olefins, and various heteroatoms have been applied in this chemistry. It would be intriguing to consider that the highly active *N*-tosyl aziridines would be selectively attacked by aldehydes mediated by a suitable organic carbene catalyst,[9,10] in competition with the self-benzoin condensation.

Encouraged by this idea, we first investigated the reaction of *N*-tosyl bicyclic aziridine **2a** and *p*-chlorobenzaldehyde **3a** in THF in the presence of catalytic thiazolium salt **1a** (Figure 1) and DBU *without exclusion of air*. After stirring

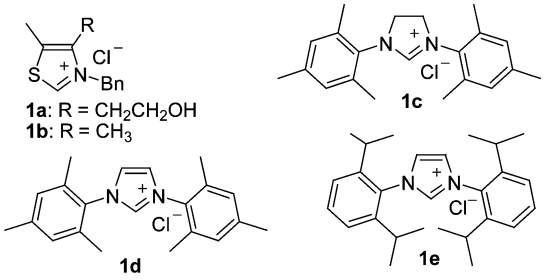
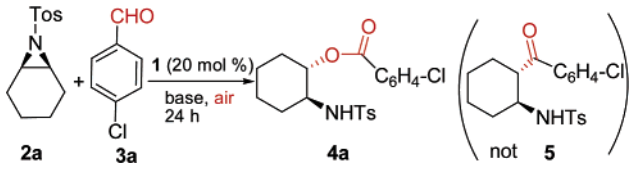


Figure 1. Structures of *N*-heterocyclic carbene precursors.

at room temperature for 24 h, unexpected *p*-chlorobenzoate of 1,2-amino alcohol **4a**,[11] rather than the *β*-amino ketone[12] compound **5** which was desired to be generated from the ring opening of aziridine by the normal acyl anion, was isolated in 15% yield, and a large amount of starting materials

Table 1. Optimization of Reaction Conditions for the Ring Opening of Aziridine **2a** with *p*-Chlorobenzaldehyde **3a**[a]



entry	catalyst **1**	base	solvent	*t* (°C)	yield[b] of **4a** (%)
1	**1a**	DBU	THF	25	15
2	**1a**	DBU	toluene	25	35
3	**1a**	DBU	DCM	25	
4	**1a**	DBU	*t*-butanol	25	
5	**1a**	DBU	toluene	50	40
6[c]	**1a**	K_2CO_3	toluene	50	40
7[c]	**1b**	K_2CO_3	toluene	50	45
8[c]	**1c**	K_2CO_3	toluene	50	50
9[d]	**1c**	K_2CO_3	toluene	50	65
10[d]	**1d**	K_2CO_3	toluene	50	90
11[d]	**1e**	K_2CO_3	toluene	50	90

[a] **2a**/**3a**/**1**/base = 1:1.2:0.2:0.18, at 0.2 mmol scale in 1 mL of solvent. [b] Isolated yield. [c] Adding 5 mol % of TBAB. [d] Adding 5 mol % of 18-crown-6.

remained (Table 1, entry 1). Only a very trace amount of benzoin product was detected in the reaction. *Notably, the presence of oxygen was crucial for this type of transformation because benzoin condensation was the dominant reaction at Ar atmosphere.* Inspired by this interesting finding, we screened various reaction conditions and catalytic systems to improve the efficiency of the novel transformation. The yield was improved to 35% when the reaction was conducted in toluene (entry 2), but complicated mixtures were obtained using DCM or *tert*-butyl alcohol as the solvent (entries 3 and 4). Similar results were given at 50 °C employing the K_2CO_3 and TBAB (tetrabutylammonium bromide) systems; however, a generally cleaner reaction was observed compared with what was gained employing DBU as the base (entries 5 and 6). The results were also not satisfactory using **1b** as the carbene precursor (entry 7). Subsequently, we were pleased to find that the yields could be elevated when bulky imidazolinium salt **1c** was applied (entry 8), and a better result was received using 18-crown-6 as the phase-transfer catalyst (entry 9). Furthermore, high isolated yields were achieved catalyzed by bulky imidazolium salts **1d** or **1e** (entries 10 and 11). On the other hand, it should be noted that the benzoin product was also the major one when the free carbene[13] previously prepared from **1d** was applied in air, and the expected **4a** was isolated in less than 10% yield.

With these results in hand, we next examined the reaction scopes of aldehydes under the established optimal conditions.

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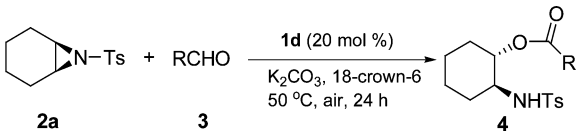
Table 2. Reaction Scopes of Aldehydes **3** in the Ring Opening of Aziridine **2a**[a]

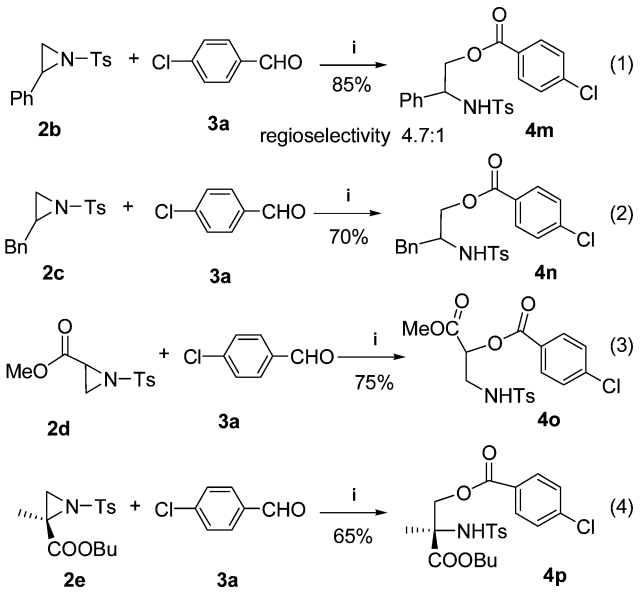


2a **3** **4**

entry	R	product	yield[b] (%)
1	*p*-Cl−Ph	**4a**	90
2	Ph	**4b**	70
3	*o*-Cl−Ph	**4c**	83
4	*p*-F−Ph	**4d**	70
5	*p*-CH_3O−Ph	**4e**	40
6	*m*-CH_3−Ph	**4f**	95
7	1-naphthyl	**4g**	50
8	2-furanyl	**4h**	90
9	*n*-propyl	**4i**	90
10	CH_3	**4j**	75
11	*i*-propyl	**4k**	65
12	cyclohexyl	**4l**	90
13[c]	CH_3CH=CH	**4i**	75

[a] **2a**/**3a**/**1d**/K_2CO_3 = 1:1.2:0.2:0.18, at 0.2 mmol scale in a 1 mL of toluene in the presence of 5 mol % of 18-crown-6. [b] Isolated yield. [c] The saturated butyrate **4i** was obtained.

Scheme 1. Regioselective Ring Opening of Unsymmetric Aziridines **2b**−**e**[a]



[a] Conditions: (i) **2**/**3a**/**1e**/K_2CO_3 = 1:1.2:0.2:0.18. The reaction was conducted at 0.2 mmol scale in 1 mL of toluene in the presence of 5 mol % of 18-crown-6 at 50 °C for 24 h.

As summarized in Table 2, various structured aryl aldehydes bearing electron-donoting or -withdrawing substituents (Table 2, entries 1−7), a heteroaryl aldehyde (entry 8), linear or branched aliphatic aldehydes (entries 9−12), and an α,*β*-unsaturated aldehyde (entry 13) could be successfully utilized as the donors in the reactions with aziridine **2a**. All reactions cleanly produced the corresponding carboxylates of 2-aminocyclohexanol. The result was not satisfying for *p*-methoxybenzaldehyde because of the easy oxidation of aldehyde functionality (entry 5). It should be noted that a 40% aqueous solution was applied in the case of acetaldehyde, and good yield was still received (entry 10). On the other hand, the corresponding saturated carboxylate **4i** was obtained when crotonaldehyde was applied (entry 13).[7k−o]

With an acceptable result for the ring opening of *meso*-*N*-tosyl aziridine **2a** in hand, the methodology was extended to a variety of unsymmetric aziridines using more bulky **1e**[14] as the catalyst precursor to investigate the regioselectivity, which was generally obtained as mixtures of regioisomers in the Lewis acid catalyzed ring-opening reactions.[8] In the case of phenyl aziridine **2b**, good regioselectivity (4.7:1) was obtained when *p*-chlorobenzaldehyde **3a** was applied, in the attacking at the less crowded ring carbon (Scheme 1, eq 1). For benzyl aziridine **2c**, a complete regioselective ring opening was observed (eq 2). Interestingly, the regioselectivity was completely changed to the more crowded carbon when functionalized aziridine **2d** was applied, probably because of the electron-withdrawing effects of the carboxylate group (eq 3). In contrast, for aziridine **2e** with a quaternary carbon, the ring-opened product was the α-methylated serine derivative **4p**, also in complete regioselectivity (eq 4).

Having presented the unexpected reactions of aldehydes mediated by carbene catalysts, we conducted more experiments to gain further insight with regard to the possible reaction mechanism, especially for the ones that might be involved in the ring opening of aziridines. Although it has been documented that aldehydes could be converted to carboxylic acids or esters in the presence of stoichiometric amounts of oxidizing agents such as flavin[15] or under electrochemical oxidative conditions[16] catalyzed by a thiazolium carbene, air oxidation of acyl anion entries has not been described and the efficient oxidation of aldehydes was not observed under our catalytic systems in the absence of aziridines. Moreover, no carboxylate ester could be detected after adding methanol, which verified that no active acylimidazolium intermediate was formed during the reaction.[7i−o,15,16] In addition, very low reactivity was observed when *p*-chlorobenzoic acid was directly applied in the reaction with **2a** under the same conditions. Therefore, it demonstrates that carboxylic acids might not be recognized as the intermediates involved in the ring opening of aziridines.

(14) Slightly better regioselectivity was obtained in the ring-opening reaction of aziridine **2b** and **3a** in comparison with what was received with **1d** (4.1:1).

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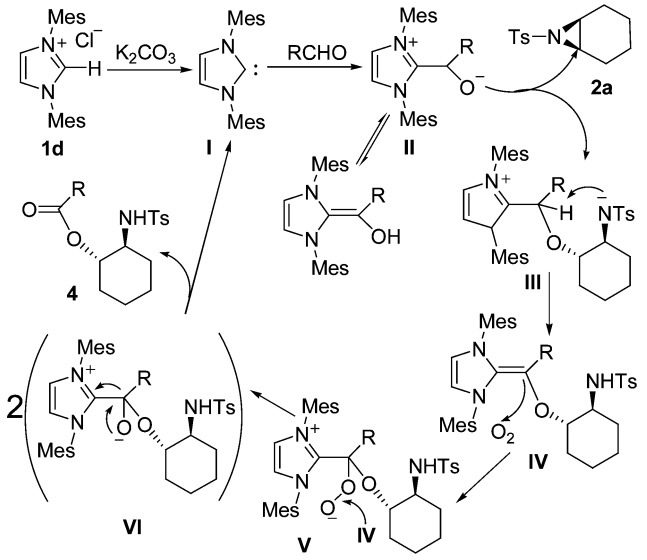
Scheme 2. Plausible Catalytic Cycle for Carbene-Catalyzed Ring Opening of Aziridine by Aldehyde under Aerobic Conditions



On the basis of these findings, a plausible mechanism for this novel transformation is proposed. As illustrated in Scheme 2, the initial event is the addition of in situ generated carbene **I** (or zwitterions) to the aldehyde to form an electron-rich intermediate **II**. Next, probably because of steric reasons, the harder oxygen anion[17] rather than the normal acyl anion attacks the aziridine, to give ring-opened intermediate **III**. After the proton transfer, the electron-rich enaminol ether[18] **IV** might react with electrophilic dioxygen to afford the hydroperoxide anion **V**.[19] Then, another enaminol ether **IV** might act as the reducing agent and react with intermediate **V** to generate two molecular **VI**, which subsequently eliminates the carbene catalyst **I** to furnish the carboxylate compound **4**. Nevertheless, the real reaction mechanism still remains to be investigated.[20]

In conclusion, we have disclosed a new reaction of aldehydes in the chemoselective ring opening of *N*-tosyl aziridines promoted by an organic *N*-heterocyclic carbene under aerobic conditions. Unexpected carboxylates of 1,2-amino alcohols, rather than the normal acyl anion ring-opened β-amino ketone products, were exclusively obtained under mild conditions. Moreover, excellent regioselectivity was observed in the ring opening of various unsymmetric aziridines. A plausible mechanism for this unprecedented reaction was given. We anticipated that this work would arouse more interest in the chemistry of *N*-heterocyclic carbenes. Further development of this reaction including asymmetric catalysis[21] and studies regarding the reaction mechanism and scopes are being pursued and will be reported in due course.

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Supporting Information Available: Experimental procedures, structural proofs, NMR and HRMS spectra of the products **4a**−**p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The phenomena have also been observed recently in the MCR reactions by Nair et al.; see ref 7f.

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