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DABCO-catalyzed ring opening of activated cyclopropanes and recyclization leading to γ-lactams with an all-carbon quaternary center†

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A novel and efficient method for the construction of γ-lactams with an all-carbon quaternary center is developed *via* a DABCO-catalyzed reaction of EWG-activated cyclopropanecarboxamides and electron-deficient alkenes. The process involves sequential ring-opening of activated cyclopropanes, intermolecular Michael addition and intramolecular aza-cyclization.

γ-Lactams (pyrrolidin-2-ones) are ubiquitous structural subunits in natural products and small molecules of pharmaceutical relevance.[1] Due to the biological importance and synthetic utility, a lot of methods for the construction of γ-lactams have been developed.[2] Despite the advances, the development of novel and efficient methods for the preparation of γ-lactams with various structural features and substitution patterns, especially those containing all-carbon quaternary center(s),[3] remains one of the hottest topics in synthetic chemistry.

Over the past few decades, Lewis acid catalyzed ring-opening of donor–acceptor cyclopropanes (which function as the source of 1,3-dipoles) has attracted great interest of organic chemists and has found a wide range of applications in the construction of various carbocycles and heterocycles.[4] However, to our knowledge, Lewis base-catalyzed ring-opening of activated cyclopropanes has been less reported till now (Fig. 1).[5] In our previous study on EWG-activated cyclopropanes, we developed an efficient cascade strategy toward aza/oxa-heterocycle construction, mainly based on the ring-opening and recyclization of activated cyclopropanes.[6] In the continued work, we explore the feasibility of Lewis base-catalyzed ring-opening of activated cyclopropanes, as well as the potential application (Scheme 1). As a result of this research, γ-lactams with a quaternary carbon center were efficiently synthesized *via* a DABCO-catalyzed reaction of EWG-activated cyclopropanecarboxamides **1** and appropriate electrophiles.

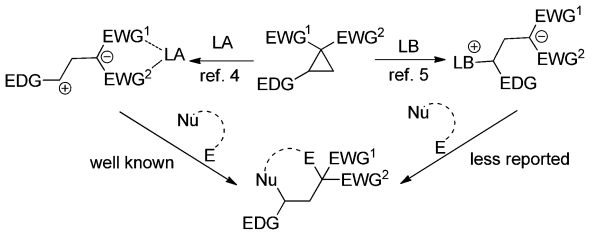
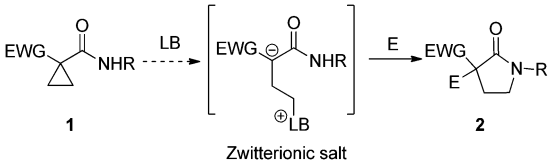


Fig. 1 Lewis acid *versus* Lewis base-catalyzed ring-opening model of activated cyclopropanes.

The initial investigation was performed with 1-acetyl-*N*-phenylcyclopropanecarboxamide **1a** (1 mmol) and acrylonitrile (1.1 equiv.) as the model substrates under the Lewis base conditions (Table 1). With DABCO as the Lewis base in DMSO at 60 °C, pleasingly, γ-lactam **2a** was formed in 61% yield (Table 1, entry 1). Other solvents such as DMF, THF, DCE, $MeNO_2$, 1,4-dioxane and MeCN were tested (Table 1, entries 2–7) and MeCN was demonstrated to be the best one, which afford **2a** in 93% yield (Table 1, entry 7). Under otherwise identical conditions, lowering the reaction temperature to 30 °C or cutting down the amount of DABCO to 0.1 equiv. led to decreased yields, even though the reaction time was prolonged to 24 h (Table 1, entries 8 and 9). Other Lewis bases were also examined. DMAP, Et_3N and DBU proved to be less effective and Ph_3P inert (Table 1, entries 10–13).

Having established the optimal conditions for the γ-lactam synthesis (Table 1, entry 7), a series of DABCO-catalyzed reactions of substrates **1** and acrylonitrile were carried out (Table 2).



Scheme 1 The working proposal.

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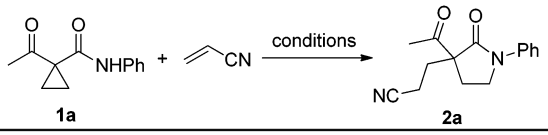
† Electronic supplementary information (ESI) available: Experimental details and characterization of all new compounds and crystal structure data. CCDC 1001190 (**2c**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc03392b

Table 1 Screening of the reaction conditions for the synthesis of **2a**[a]



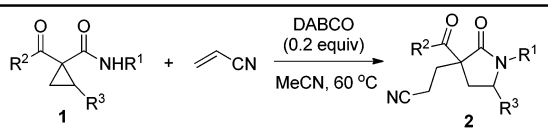
Entry	Catalyst (equiv.)	Solvent	T (°C)	Time (h)	Yield[b] (%)
1	DABCO (0.2)	DMSO	60	12	61
2	DABCO (0.2)	DMF	60	12	75
3	DABCO (0.2)	THF	60	12	56
4	DABCO (0.2)	DCE	60	12	13
5	DABCO (0.2)	$MeNO_2$	60	12	Trace
6	DABCO (0.2)	1,4-Dioxane	60	12	Trace
7	**DABCO (0.2)**	**MeCN**	**60**	**6**	**93**
8	DABCO (0.2)	MeCN	30	24	35
9	DABCO (0.1)	MeCN	60	24	78
10	DMAP (0.2)	MeCN	60	12	Trace
11	NEt_3 (0.2)	MeCN	60	12	12
12	DBU (0.2)	MeCN	60	12	Trace
13	PPh_3 (0.2)	MeCN	60	12	NR

[a] Reactions were carried out with **1a** (1.0 mmol), acrylonitrile (1.1 equiv.) and a Lewis base (0.1 or 0.2 equiv.) in solvent (2.0 mL). [b] Isolated yield.

It was observed that all the reactions of **1a–j** bearing varied electron-donating and electron-withdrawing aryl groups or hetero-aryl groups could proceed smoothly to afford the corresponding highly functionalized γ-lactams **2** in moderate to excellent yields (Table 2, entries 1–10). For *N*-alkyl counterpart **1k** (R^1 = Bn), an unidentified mixture was formed (Table 2, entry 11).[7] Neither 1-acetylcyclopropanecarboxamide (**1l**, R^1 = H) nor 1-benzoyl-*N*-phenylcyclopropanecarboxamide (**1m**, R^2 = Ph) gave satisfactory results (Table 2, entries 11 and 12). Substrate **1n** containing a methyl group on the cyclopropyl ring afforded merely trace amounts of desired product **2n** (Table 2, entry 13). The structure of **2c** was confirmed by X-ray single crystal diffraction (Fig. 2).

Reactions of *N*-phenylcyclopropanecarboxamides bearing different EWGs at the C1-position were conducted (Scheme 2).[8]

Table 2 Synthesis of γ-lactams **2** with a quaternary carbon center[a]



Entry	1	R^1	R^2	R^3	Time (h)	2	Yield[b] (%)
1	**1a**	Ph	Me	H	7	**2a**	93
2	**1b**	4-MeC_6H_4	Me	H	12	**2b**	90
3	**1c**	4-$MeOC_6H_4$	Me	H	10	**2c**	89
4	**1d**	2,4-$Me_2C_6H_3$	Me	H	10	**2d**	82
5	**1e**	4-ClC_6H_4	Me	H	12	**2e**	81
6	**1f**	2-ClC_6H_4	Me	H	12	**2f**	65
7	**1g**	2-Cl-5-$OMeC_6H_3$	Me	H	9	**2g**	61
8	**1h**	2-$NO_2C_6H_4$	Me	H	12	**2h**	79
9	**1i**	1-Naphthyl	Me	H	7	**2i**	87
10	**1j**	2-Py	Me	H	7	**2j**	95
11	**1k**	Bn	Me	H	12	**2k**	—[c]
12	**1l**	H	Me	H	12	**2l**	NR
13	**1m**	Ph	Ph	H	12	**2m**	Complex
14	**1n**	Ph	Me	Me	12	**2n**	Trace

[a] Reactions were carried out with **1a** (1.0 mmol), acrylonitrile (1.1 equiv.) and DABCO (0.2 equiv.) in MeCN (2.0 mL) at 60 °C. [b] Isolated yield. [c] Unidentified mixture.

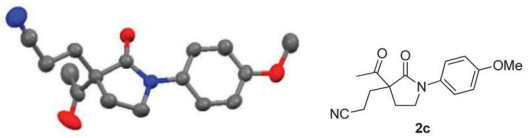
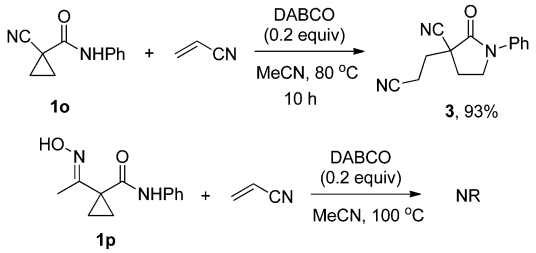


Fig. 2 ORTEP drawing of **2c**.



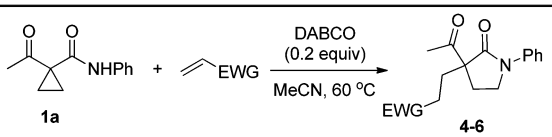
Scheme 2 Reactions of *N*-phenylcyclopropanecarboxamides bearing different EWGs at the C1-position.

1-Cyano-*N*-phenylcyclopropanecarboxamide (**1o**) afforded the desired product **3** in 93% yield in MeCN at 80 °C for 10 h, while 1-(1-(hydroxyimino)ethyl)-*N*-phenylcyclopropanecarboxamide (**1p**) was inefficient, with the substrate recoverable in quantitative yield.[9]

We next explored the reaction by expanding the scope of the external electrophiles. Electron-deficient olefins like acrylates and vinylsulfone proved to be suitable for this transformation, affording the corresponding products **4a–c** and **5** in excellent yields (Table 3, entries 1–4). *N*,*N*-dimethylacrylamide was less efficient, giving product **6** in only 35% yield (Table 3, entry 5). However, substituted olefins such as cinnamonitrile and ethyl cinnamate appeared to be unreactive under the standard reaction conditions,[10] presumably due to the effect of steric hindrance. All the above results indicated the efficiency, scope and limitations of the Lewis base activation protocol.

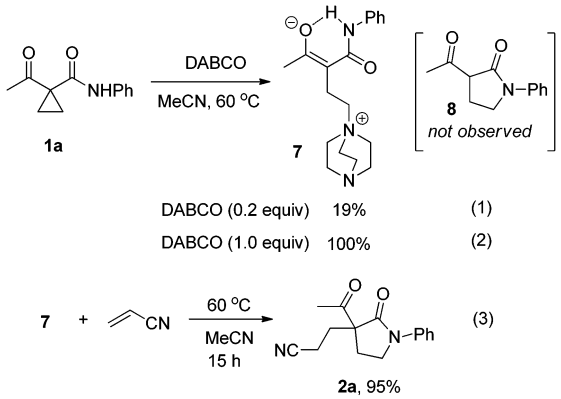
In order to elucidate the possible mechanism, some control experiments were conducted (Scheme 3). In the reaction of substrate **1a** and DABCO (0.2 equiv.) in MeCN at 60 °C (no external electrophile added), zwitterion **7** was observed (eqn (1)). When a stoichiometric amount of DABCO was used, compound **7** was isolated in quantitative yield by simple filtration

Table 3 The scope of external electrophiles[a]

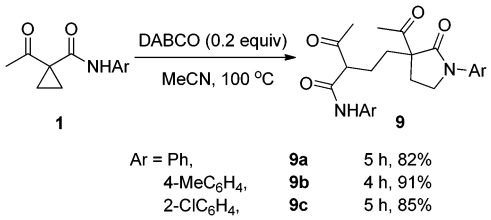


Entry	EWG	Time (h)	Product	Yield[b] (%)
1	CO_2Et	6	**4a**	95
2	CO_2n-Bu	5	**4b**	97
3	CO_2t-Bu	5	**4c**	94
4	SO_2Ph	6	**5**	98
5	$CONMe_2$	12	**6**	35

[a] Reactions were carried out with **1a** (1.0 mmol), electron-deficient olefin (1.1 equiv.) and DABCO (0.2 equiv.) in MeCN (2.0 mL) at 60 °C. [b] Isolated yield.



Scheme 3 Control experiments.

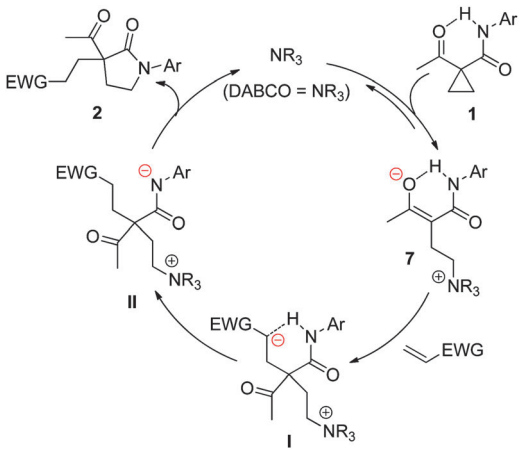


Scheme 4 Further work.

(eqn (2)). No intramolecular aza-cyclization product of type **8** was observed.[11] It was thus concluded that intermolecular electrophilic addition takes place prior to the intramolecular aza-cyclization. The conclusion is also supported by the following reaction, *i.e.*, the separated zwitterion **7** may react with acrylonitrile (in the absence of a base) to give the target molecule **2a** in 95% yield (eqn (3)).

In further work, we found that, in the absence of external electron-deficient olefins and elevated temperature, unexpected γ-lactams **9a–c** were obtained in 82–91% yields *via* a formal bimolecular reaction of **1** (Scheme 4).

Based on all the results described above, a possible mechanism for the efficient one-pot transformation into functionalized γ-lactams **2** is proposed in Scheme 5. Initially, zwitterion **7** is generated *in situ via* DABCO-catalyzed ring-opening of



Scheme 5 Proposed mechanism for the formation of **2**.

activated cyclopropanes. We think that the hydrogen-bonding in substrate **1** is helpful for the ring-opening to occur.[12,13] Secondly, Michael addition between enolate **7** and electron-deficient alkenes takes place, giving intermediate I with a quaternary carbon center. Thirdly, an amide anion is generated *via* proton transfer. Finally, intramolecular aza-cyclization *via* nucleophilic substitution delivers product **2** with the elimination of DABCO to complete the catalytic cycle.[14] Product **9** could be generated in a similar way.[15]

In summary, a new and efficient organocatalyzed strategy for the synthesis of γ-lactams with an all-carbon quaternary center is developed. The process involves DABCO-catalyzed *in situ* zwitterionic salt formation, intermolecular Michael addition and intramolecular aza-cyclization. The organocatalyzed ring-opening of activated cyclopropanes appears to be intriguing.[16] Further work on exploring the scope of 1,3-dipole species catalyzed by a Lewis base and the cycloaddition reaction in the construction of various carbo/heterocycles is in progress in our laboratory.

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7 In the reaction of a stoichiometric amount of DABCO with *N*-benzylcyclopropanecarboxamide **1l** in MeCN at 100 °C, ring-opening of cyclopropane did not occur. The reason is currently unclear.

8 The cyclopropane substrates were prepared according to literature methods, see: D. Zhang, R. Zhang, D. Xiang, N. Zhang, Y. Liang and D. Dong, *Synthesis*, 2012, 705.

9 We found that the electron-withdrawing ability of EWG(s) on the cyclopropane, the presence of hydrogen bond or not, and temperature influence the reaction significantly.

10 Only ring-opening of the cyclopropane substrate **1a** to afford the corresponding zwitterion **7** takes place. Upon heating to 100 °C, compound **9a** was obtained. In all cases, the electrophile remains intact in the reaction system.

11 The reason for this may be due to (i) hydrogen bond binding, and (ii) more importantly, weak nucleophilic ability of *N*-arylamides.

12 Ring-opening reaction of 1-acetyl-*N*-methyl-*N*-phenylcyclopropanecarboxamide did not take place in MeCN at 100 °C for 10 h.

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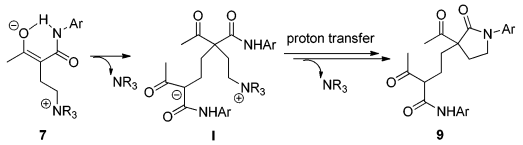
14 Actually the process involves organocatalyzed anion relay chemistry. Please refer to 6a–c.

15 The possible mechanism for the formation of **9** was given as follows



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16 Organocatalysis has attracted considerable attention and has been significantly developed. For reviews, see: (*a*) C. M. R. Volla, I. Atodiresei and M. Rueping, *Chem. Rev.*, 2014, **114**, 2390; (*b*) P. Renzi and M. Bella, *Chem. Commun.*, 2012, **48**, 6881; (*c*) J. G. Hernández and E. Juaristi, *Chem. Commun.*, 2012, **48**, 5396; (*d*) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178; (*e*) D. W. C. MacMillan, *Nature*, 2008, **455**, 304.

