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A general method for synthesis of *cis*-dicarbonyl epoxides through DBU/LiBr-cocatalyzed cyclization of α,β-dicarbonyl peroxides

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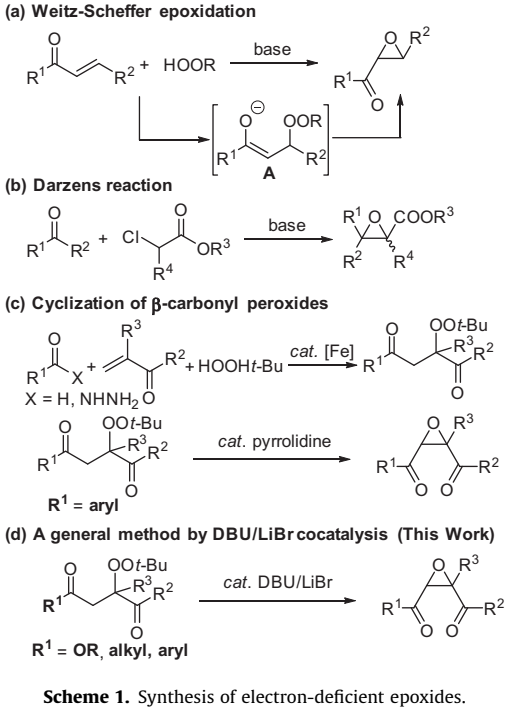
ABSTRACT

A general method for synthesis of *cis*-dicarbonyl epoxides is developed. The highly diastereoselective cyclization of α,β-dicarbonyl peroxides is achieved by DBU/LiBr cocatalysis. The coordination of lithium ion with two carbonyl groups is proposed for the control of *cis* selectivity.

Epoxides are highly useful intermediates and building blocks for synthesis of biologically active compounds and natural products.[1] Epoxidation of alkenes by activated oxygen source presents the most important method for synthesis of epoxides.[2] Great progresses have been achieved for epoxidation of electron-rich alkenes.[2,3] However, the successful strategies for the synthesis of electron-deficient epoxides such as carbonyl epoxides are still limited.[4] Weitz–Scheffer epoxidation of α,β-unsaturated ketones using hydroperoxides in the presence of base is one of useful methods for the preparation of α,β-epoxy ketones via the key peroxide enolate intermediate **A** (Scheme 1, a).[5] *trans*-Disubstituted epoxides were selectively formed due to the steric effect.[4a] Darzens reaction of aldehydes (or ketones) and α-halo esters under basic conditions presents a general method for the formation of α,β-epoxy esters (Scheme 1, b).[1a,6] Although multi-substituted epoxides could be achieved, a mixed diastereomers were obtained generally in Darzens reaction.[6a] Recently, we developed an iron-catalyzed three-component strategy for the synthesis of a variety of β-carbonyl peroxides,[7] which were envisioned as the precursors of the peroxide enolate intermediate **A** in Weitz–Scheffer epoxidation by base-catalyzed deprotonation. Accordingly, we developed an efficient pyrrolidine-catalyzed cyclization of α,β-dicarbonyl peroxides for selective synthesis of *cis*-dicarbonyl epoxides (Scheme 1, c).[8,9] The developed method was successfully applied for the selective



Scheme 1. Synthesis of electron-deficient epoxides.

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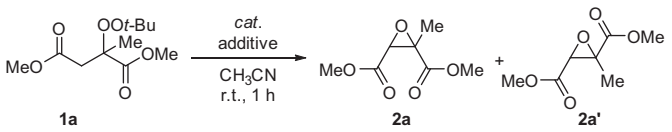
0040-4039/

Table 1
Optimization of the reaction conditions[a]



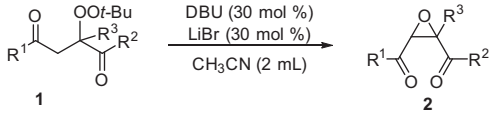
Entry	*cat.*	Additive	**2a** (%)[b]	**2a′** (%)[b]	d.r.
1	Pyrrolidine	—	—	—	—
2	DBN	—	5	4	55:45
3	DBU	—	14	11	55:45
4	DBU	LiBr	94	3	97:3
5	Pyrrolidine	LiBr	21	3	87:13
6	DBU	$MgCl_2$	<5	<5	—
7	DBU	$ZnCl_2$	<5	<5	—
8	DBU	KBr	11	10	52:48
9	DBU	NaCl	12	10	55:45
10	DBU	$CaCl_2$	6	5	55:45
11	DBU	LiCl	83	3	97:3
12	DBU	LiI	85	3	97:3
13	DBU[c]	LiBr	64	2	97:3

[a] Conditions: **1a** (0.5 mmol), *cat.* (0.15 mmol, 30 mol %), additive (0.15 mmol, 30 mol %), CH_3CN (2 mL), rt, 1 h, under N_2.
[b] NMR yield.
[c] DBU (0.05 mmol, 10 mol %).

construction of the desired epoxide unit in total synthesis of (±)-Clavilactones A, B, and proposed D.[10] However, pyrrolidine was ineffective for the cyclization of β-ester peroxides (R^1 = OR in Scheme 1, c) due to the weak basicity of pyrrolidine and the diastereoselectivity of the cyclization of β-carbonyl peroxides (R^1 = alkyl in Scheme 1, c) was not satisfied.[8] To overcome the limitations, we here report a general method for the synthesis of *cis*-dicarbonyl epoxides through DBU/LiBr-cocatalyzed cyclization of α,β-dicarbonyl peroxides under the mild reaction conditions (Scheme 1, d).

To initiate our studies, we chose dimethyl 2-(*tert*-butylperoxy)-2-methylsuccinate **1a** as the model substrate to establish the reaction conditions (Table 1). Pyrrolidine was failed to promote the intramolecular cyclization of **1a** due to the weak basicity of pyrrolidine (entry 1). When DBN and DBU were applied, the epoxides, **2a** and **2a′**, were obtained in low yields and poor diastereoselectivities (entries 2 and 3). A 94% yield of *cis*-dicarbonyl epoxide **2a** was achieved by the addition of LiBr into the reaction (entry 4). Notably, the cyclization occurred by the combination of pyrrolidine and LiBr, albeit in low efficiency (entry 5). These results indicated that (1) LiBr plays a role of Lewis acid to activate the acidity of α-H at the ester group (the efficiency); (2) the *cis* selectivity of the cyclization is most likely attributed to

Table 2
Scope of β-ester peroxides **1**[a]



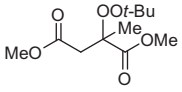
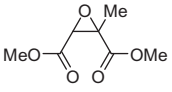
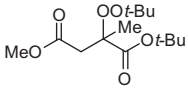
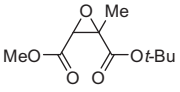
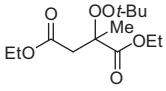
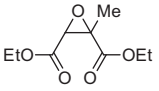
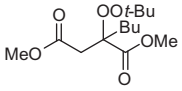
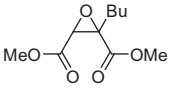
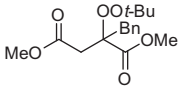
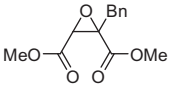
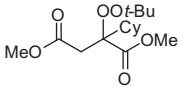
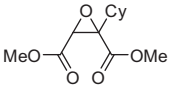
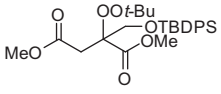
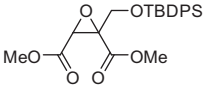
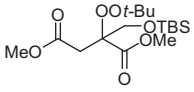
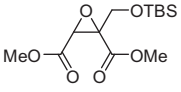
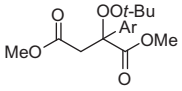
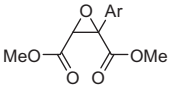
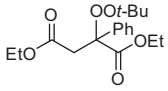
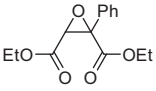
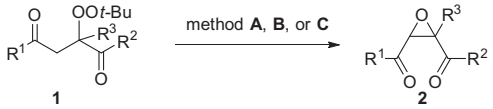
Entry	**1**		*T*/h	**2**		Yield (%)[b]
1		**1a**	rt/1 h		**2a**	97 (97:3) [90]
2		**1b**	rt/1 h		**2b**	92 (98:2) [85 (>99:1)]
3		**1c**	rt/1 h		**2c**	97 (98:2) [94 (>99:1)]
4		**1d**	rt/3 h		**2d**	87 (98:2) [90 (>99:1)]
5		**1e**	50 °C/2 h		**2e**	91 (97:3) [80 (>99:1)]
6		**1f**	50 °C/3 h		**2f**	82 (95:5) [80]
7		**1g**	rt/5 h		**2g**	80 (97:3) [65 (98:2)]
8		**1h**	rt/9 h		**2h**	80 (96:4) [74 (97:3)]
						

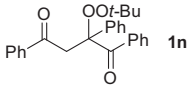
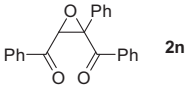
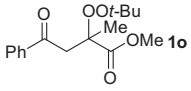
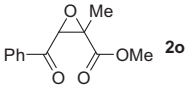
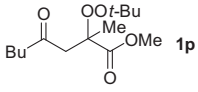
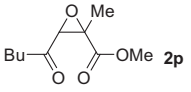
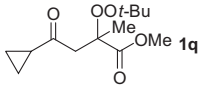
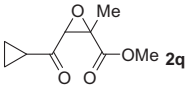
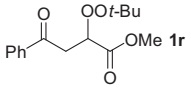
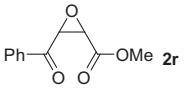
Table 2 (*continued*)

Entry	1		T/h	2		Yield (%)[b]
9	Ar = 4-OMeC$_6$H$_4$	**1i**	rt/3 h	Ar = 4-OMeC$_6$H$_4$	**2i**	79 (99:1) [65 (>99:1)]
10	4-MeC$_6$H$_4$	**1j**	rt/3 h	4-MeC$_6$H$_4$	**2j**	80 (99:1) [76 (99:1)]
11	Ph	**1k**	rt/3 h	Ph	**2k**	84 (98:2) [78 (98:2)]
12	4-ClC$_6$H$_4$	**1l**	rt/3 h	4-ClC$_6$H$_4$	**2l**	88 (90:10) [70 (91:9)]
13		**1m**	rt/5 h		**2m**	79 (>99:1) [76 (>99:1)]

[a] Conditions: **1** (0.5 mmol), DBU (0.15 mmol, 30 mol %), LiBr (0.15 mmol, 30 mol %), CH_3CN (2 mL), under N_2.
[b] The yields and ratios of **2** were determined by ^{1}H NMR; the isolated yields and the ratios of two diastereomers were given in square brackets.

Table 3
Scope of β-keto peroxides **1**[a]



Entry	1	Method	T/h	2	Yield (%)[b]
1	 **1n**	**A**	rt/1 h	 **2n**	88 (99:1) [77]
		B	rt/1 h		89 (72:28) [82 (73:27)]
		C	0 °C/1 h		95 (97:3) [93 (98:2)]
2	 **1o**	**A**	rt/1 h	 **2o**	93 (95:5) [86 (96:4)][c]
		B	rt/1 h		94 (75:25) [89 (76:24)]
		C	0 °C/1 h		97 (98:2) [90 (97:3)][d]
3	 **1p**	**A**	50 °C/3 h	 **2p**	61 (88:12) [45][c]
		B	rt/1 h		64 (60:40) [60 (58:42)]
		C	0 °C/1 h		82 (96:4) [75 (99:1)]
4	 **1q**	**A**	50 °C/3 h	 **2q**	89 (88:12) [78 (89:11)][c]
		B	rt/1 h		88 (66:34) [67 (63:37)]
		C	0 °C/1 h		95 (98:2) [81 (99:1)]
5	 **1r**	**A**	rt/2 h	 **2r**	62 (6:94) [52 (4:96)]
		B	0 °C/2 h		91(1:99) [88 (1:99)]
		C	0 °C/2 h		74 (43:57) [67 (44:56)]

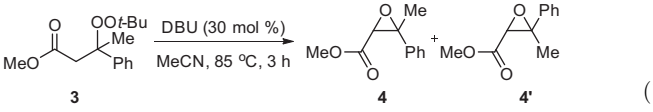
[a] Conditions: method **A**: **1** (0.5 mmol), pyrrolidine (0.25 mmol, 50 mol %), CH_3CN (2 mL), under N_2; method **B**: **1** (0.5 mmol), DBU (0.15 mmol, 30 mol %), CH_3CN (2 mL), under N_2; method **C**: **1** (0.5 mmol), DBU (0.15 mmol, 30 mol %), LiBr (0.15 mmol, 30 mol %), CH_3CN (2 mL), under N_2.
[b] Reported yields were based on **1** and determined by ^{1}H NMR using an internal standard; isolated yields were given in parentheses.
[c] Ref. 8.
[d] DBU (0.05 mmol, 10 mol %).

the coordination of lithium ion with two carbonyl groups of **1a** (the selectivity). Furthermore, other additives were investigated (entries 6–12). Mg, Zn, K, Na, and Ca ions were all ineffective for the present cyclization (entries 6–10), while LiCl and LiI gave the similar results as LiBr (entries 11 and 12). The results demonstrated that lithium ion plays a unique and important role for the cyclization. It should be noted that the efficiency of the reaction is reduced by a reducing amount of DBU (entry 13).

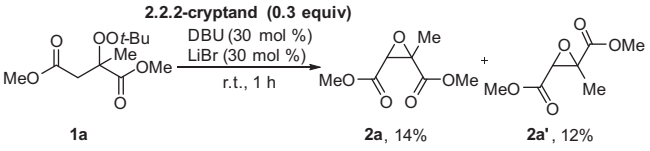
Subsequently, the scope of the substrates was investigated under the optimal reaction conditions (Tables 2 and 3). A variety of α,β-diester peroxides **1** were transformed smoothly into the desired *cis*-dicarbonyl epoxides **2** with excellent diastereoselectivities (Table 2). Ester groups showed no influence on the selectivity and reactivity of the cyclization (entries 1–3). The substrates bearing alkyl and aryl groups (R^3) were also applicable for the present cyclization (entries 4–13). Although the efficiency of the cyclization was not affected by the electronic effect of aryl groups (entries 9–12), an electron-withdrawing group such as Cl group on the phenyl ring dramatically reduced the diastereoselectivity to 9:1 (entry 12). We hypothesized that the coordinative ability of α-ester group with lithium ion was reduced by electron-withdrawing group R^3 and thus the cyclization lose the diastereoselectivity.

To demonstrate the generality of the present protocol in *cis*-dicarbonyl epoxide synthesis, the cyclization of various β-carbonyl peroxides were further investigated using pyrrolidine (method **A**), DBU (method **B**), and DBU/LiBr (method **C**) (Table 3). By comparing the results of the applied methods, we found that the method of DBU/LiBr cocatalysis (method **C**) could not only instead pyrrolidine catalysis (R^1 = aryl; entries 1 and 2)[8] but also successfully apply for alkyl (R^1) substrates (entries 3 and 4). As an extreme example, *trans*-dicarbonyl epoxide **2r′** was selectively obtained by methods **A** and **B** due to the steric effect, while the ratio of *cis*-/*trans*-isomers was improved to 44:56 by DBU/LiBr cocatalysis (entry 5). The results strongly supported that lithium ion plays a key role in the diastereoselective cyclization of α,β-dicarbonyl peroxides.

To further examine the possible roles of lithium ion in the cyclization, control experiments were conducted (Eqs. 1 and 2). When β-ester peroxide **3**, without an α-ester group, was applied, the selectivity of the formation **4** and **4′** was dramatically dropped either with LiBr or without LiBr (Eq. 1). Furthermore, **2a** and **2a′** were obtained in 14% and 12% yields respectively when 2.2.2-cryptand, one of cationic trapping agents,[11] was added into the model reaction (Eq. 2). The result was the same as the entry 3 in Table 1, which clearly indicated that the high diastereoselectivity of the cyclization of α,β-dicarbonyl peroxides **1** to *cis*-dicarbonyl epoxides **2** by DBU/LiBr cocatalysis is most likely due to the coordination of lithium ion with two carbonyl groups of **1**.



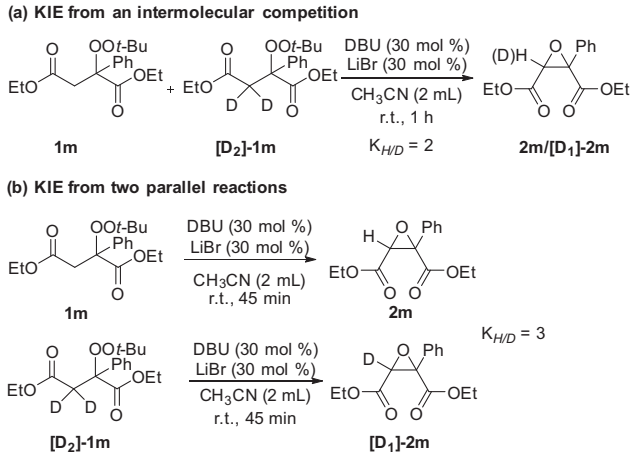
(1)



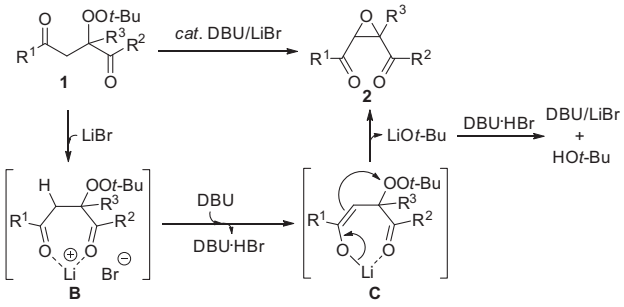
(2)

In addition, the kinetic isotope effect (KIE) experiments were conducted to probe the nature of the deprotonation step in the cyclization process (Scheme 2). Kinetic isotope effects ($k_{H/D} = 2$) were observed from intermolecular competition (Scheme 2, a). In addition, two parallel reactions give rise to a k_H/k_D value of 3 (Scheme 2, b). These results suggested that C–H cleavage of α-site of ester group is likely involved in the rate-determining step.

Based on our results and the literature's reports,[12] a tentative reaction pathway was proposed for DBU/LiBr cocatalyzed diastereoseletive cyclization of α,β-dicarbonyl peroxides **1** to *cis*-dicarbonyl epoxides **2** (Scheme 3). Initially, lithium ion coordinates with dicarbonyl groups of **1** to generate a key cyclic intermediate **B**, by which both the efficiency and diastereoselectivity of the cyclization were greatly enhanced as shown as entries 1–5 of Table 1. Deprotonation of **B** gives **C**, which subsequently undergoes intramolecular cyclization to form the final epoxide product **2**. DBU and LiBr are regenerated by the releasing of *tert*-butanol (HO*t*-Bu) as the sole byproduct of the cyclization.



Scheme 2. KIE experiments.



Scheme 3. A proposed mechanism.

In conclusion, we have demonstrated a general method for synthesis of *cis*-dicarbonyl epoxides by DBU/LiBr cocatalysis. A variety of multisubstituted epoxides were synthesized efficiently and selectively, which presents a practical alternative method for synthesis of electron-deficient epoxides. The lithium salt plays key roles for the efficiency and diastereoselectivity of the cyclization, in which the coordination of lithium ion with two carbonyl groups is proposed. Further studies on the mechanism and the applications are in progress.

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Supplementary data

Supplementary data (experimental procedures, spectrum data, and NMR spectra of the compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.07.034.

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