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The Darzens condensation of α,β-unsaturated aldehydes and ketones

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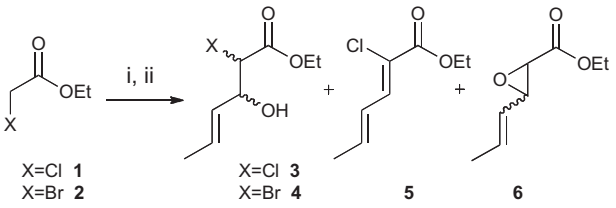
ABSTRACT

The one-pot Darzens condensation of α,β-unsaturated aldehydes and ketones with enolates of an α-bromo ester or ketone is described.

The reaction of α-halo esters with aldehydes and ketones under basic conditions to generate α,β-epoxy esters was first demonstrated in 1892 by Erlenmeyer.[1] However, it was the extensive study of the reaction by Darzens in the 1900's that resulted in the christening of the reaction.[2] The procedure is extremely useful for the preparation of functionalized molecules and as such, the transformation has found application in a number of syntheses. The reaction was fundamental to Schwartz's synthesis of the calcium channel blocker Diltiazem® and its analogues,[3] while Steel's synthesis of Epiasarinin also featured the aforementioned reaction as a key step.[4] More recently research has focused on improved asymmetric induction[5] and expansion of the reaction scope to encompass aziridine synthesis via the aza-Darzens reaction.[6] In the course of our studies we chose to utilize the Darzens reaction *en route* to a synthetic target.

On studying the literature it became evident that a number of aromatic and aliphatic aldehydes and ketones have been employed in the reaction, however, the use of unsaturated substrates is limited. Examples do exist, which involve the use of crotonaldehyde[7] and cinamaldehyde,[8] however, both are two-step procedures that pass through the isolated aldol product before further reaction with base at elevated temperatures to induce epoxide formation. Herein, we present examples of the successful application of α,β-unsaturated substrates in the one-pot Darzens condensation and provide further evidence regarding the mechanism involved in these transformations.

In terms of substrate scope both α-chloro and α-bromo esters are primarily used. Literature procedures currently employ strong bases for enolate generation such as LDA,[9] LiHMDS[10] and KHMDS,[9] with pre-formation of the α-halo ester enolate generally affording a more efficient reaction. As a consequence we initially attempted the reaction with ethyl chloroacetate and ethyl bromoacetate with enolate generation through low temperature treatment with LiHMDS[10] followed by reaction with crotonaldehyde. The reaction appeared capricious and depending on the reaction conditions employed, a range of products was observed (Eq. 1). In addition to the desired epoxide **6**, the aldol products **3** or **4**, the condensation product **5** and starting materials **1** or **2** were all obtained. A number of reactions



(1)

i) LiHMDS (1.0 equiv.), THF, -78 °C, 15 min.
ii) Crotonaldehyde (1.0 equiv.), T °C, 2 h.

were performed to identify the optimum conditions to achieve the desired transformation (Table 1). At reduced temperatures (Table 1, entries 1 and 2) reaction of ethyl chloroacetate resulted, in addition to the starting ester, in the formation of only the aldol product; no epoxide formation was observed. This is likely due to the poor leaving group ability of the chloride anion. This was further demonstrated when carrying out the reaction at 25 °C (Table 1, entry 3) where the increased temperature favored elimination of the hydroxyl group to form the condensation product **5** over epoxide

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Table 1
Optimization of reaction conditions (Eq. (1))

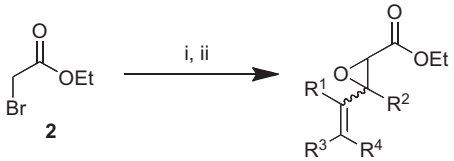
Entry	Ester	T (°C)	Product distribution[a]				Epoxide **6** *Cis*:*trans*[a]
			1/2	**3/4**	**5**	**6**	
1	**1**	−78	1	3.2	—	—	—
2	**1**	−25	1	8.1	—	—	—
3	**1**	25	1	1.9	1.1	0.3	0:100
4	**2**	−78	1	3.2	—	—	—
5	**2**	−25	1	0.7	—	1	41:59
6	**2**	25	1	—	—	2.9	43:57

[a] Determined from the ^{1}H NMR spectrum of the crude reaction mixture.

formation. The β-elimination of hydroxide to form the enone has been observed as a side reaction in previous studies, and is particularly prevalent in the case of chloride as the leaving group.[11,12] Although only minimal epoxide formation was observed, complete selectivity for the thermodynamically more stable *trans*-isomer was obtained.

Reaction of ethyl bromoacetate at −78 °C (Table 1, entry 4) provided an identical result to that of the chloride (Table 1, entry 1). However, the superior leaving group ability of the bromide resulted in epoxide formation at −25 °C albeit with little selectivity in geometry (Table 1, entry 5). Increasing the reaction temperature further to 25 °C (Table 1, entry 6) enhanced epoxide formation but with no discernible effect on the geometrical ratio. This was judged to be the optimum temperature as higher temperatures resulted in a large amount of decomposition. Extension of the reaction times resulted in the formation of additional by-products affording the epoxide in reduced quantities but with increased *trans* selectivity. This changing ratio is most likely due to the preferential decomposition of the less stable *cis*-epoxide than selective formation of the *trans*-form. Employing more dilute conditions was also found to be detrimental, leading to a more complex reaction mixture. Finally we examined the effect of altering the ratio of bromoacetate to crotonaldehyde on the yield. However, neither an excess of bromoacetate or crotonaldehyde lead to an improvement in the extent of conversion to the epoxide. It should also be noted that no 1,4-addition products were observed under any of the reaction conditions examined.

The optimal reaction conditions (Table 1, entry 6) were applied to a range of α,β-unsaturated aldehydes and ketones with varying substitution patterns (Table 2, Eq. 2) to test the generality of the procedure.[13] It was hoped that any observed differences arising from altering the alkene substituents would provide insight into the mechanistic intricacies of the transformation.

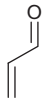
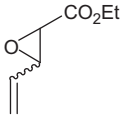
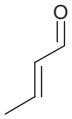
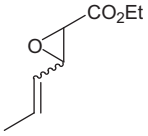
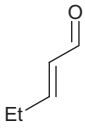
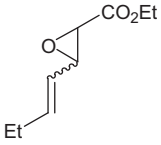
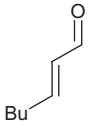
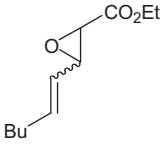
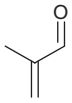
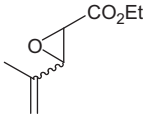
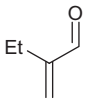
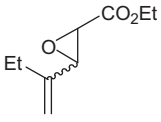
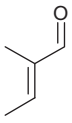
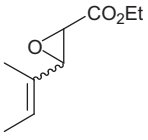
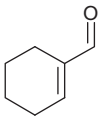
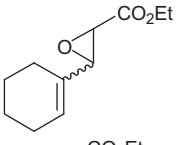
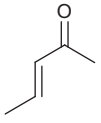
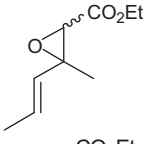
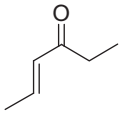
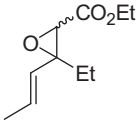
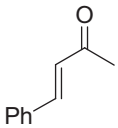
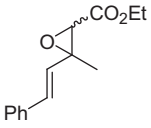


(2)

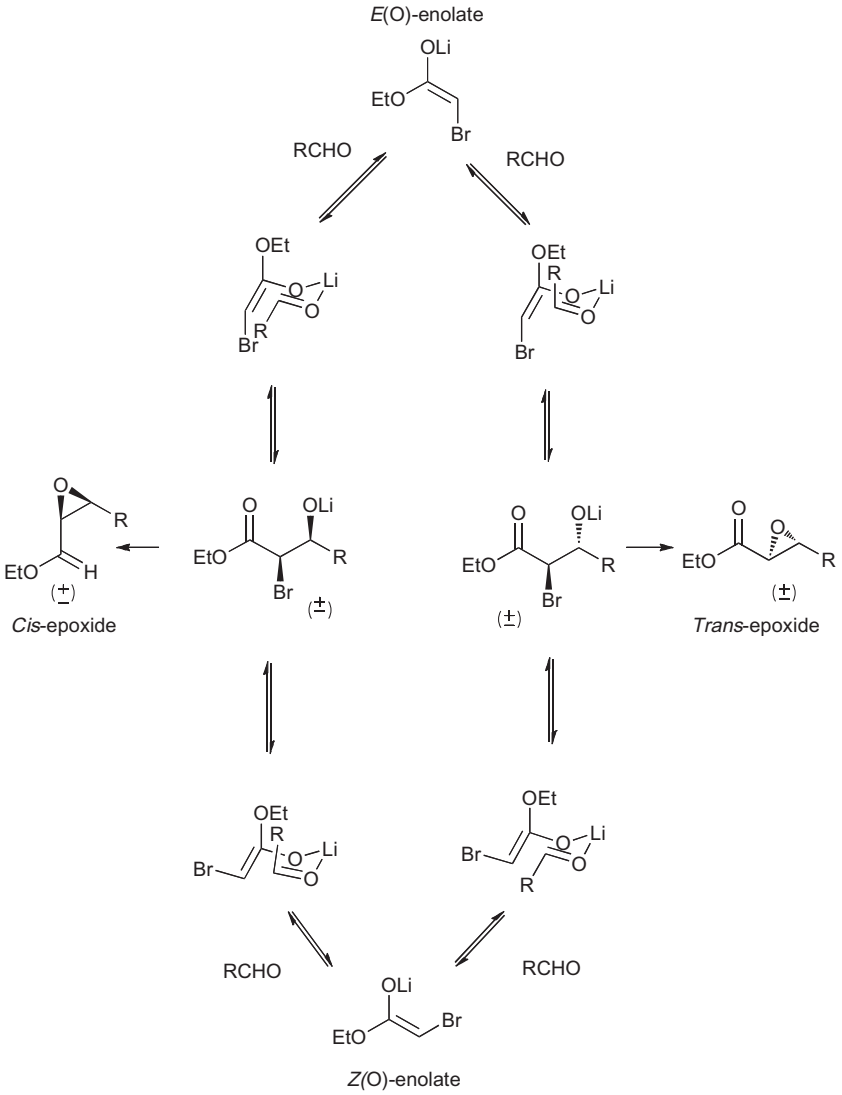
i) LiHMDS (1.0 equiv.), THF, -78 °C, 15 min.
ii) Electrophile (1.0 equiv.), 25 °C, 2 h.

The aldehydes possessed different substituents at the enone β-position (Table 2, entries 1–4), enone α-position (Table 2, entries 5 and 6) and both enone α- and β-positions (Table 2, entries 7 and 8). In all of these cases the optimized conditions afforded the desired epoxides in good yields with limited variation. In most cases the remainder of the mass balance was largely unreacted starting material. There appears a slight tendency for higher yields with an increase in the molecular weight of the epoxide, suggesting product volatility may be the cause. In terms of epoxide geometry there was surprisingly little selectivity through the variety of substrates tried, a 2:3 ratio of *cis*:*trans* was generally observed. Several α,β-unsaturated ketones were also examined (Table 2, entries 9–11). The reactions proceeded in a similar fashion to those of the aldehydes with comparable yields. There was still very little selectivity between the *cis* and *trans*-epoxide isomers except with an ethyl ketone (entry 10) where a 4:1 ratio favoring the cis isomer was obtained.

Table 2
Reaction scope (Eq. 2)

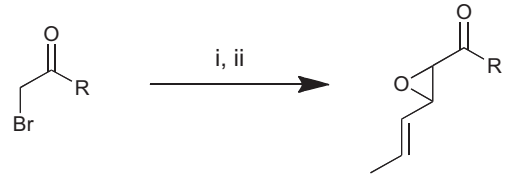
Entry	Electrophile	Epoxide	Yield[a] (%)	*Cis*:*trans*[b]
1			57	43:57
2			62	43:57
3			60	45:55
4			72	40:60
5			58	38:62
6			64	41:59
7			69	35:65
8			70	34:66
9			63	50:50
10			57	81:19[c]
11			44	50:50

[a] Isolated yield after purification by SiO_2 column chromatography.
[b] Determined from the ^{1}H NMR spectrum of the crude reaction mixture.
[c] Determined by ^{1}H NMR NOE spectroscopy.



Scheme 1.

In an attempt to influence the cis/trans selectivity of the reaction through steric effects we performed the reaction with the *t*-butyl ester **7** (Eq. 3). However, the *t*-butyl group appeared to have little influence over the geometrical product ratio, undoubtedly owing to its distance from the bond-forming site. Alternatively, using α-bromopinacolone **8** we aimed to bring the steric bulk of the *t*-butyl group closer to the reaction site. The reaction proceeded as expected in a yield that was consistent with those obtained previously. However, much greater *trans* selectivity in the epoxide product **10** (*cis*:*trans*, 10:90) was demonstrated thus allowing exclusive isolation of the *trans*-isomer.



(3)

7 R=O*t*Bu
8 R=*t*Bu

9 R=O*t*Bu, 50%, 40:60 *cis:trans*
10 R=*t*Bu, 56%, 10:90 *cis:trans*

i) LiHMDS (1.0 equiv.), THF, -78 °C, 15 min.
ii) Crotonaldehyde (1.0 equiv.), 25 °C, 2 h.

With regard to the mechanism in operation for the reaction, previous studies on the formation of α,β-epoxy ketones from α-halo ketones invoked a dynamic equilibrium, which favors the formation of the more thermodynamically stable *trans*-epoxide.[13–15] It was shown that the treatment of the isolated aldol products with base at ambient temperature afforded, in addition to the desired epoxide, the α-halo ester and aldehyde retro-aldol products, and that the *anti*-aldol diastereoisomer cyclized to afford the *trans*-epoxide via an *anti*-periplanar displacement of the halide. However, in certain instances the *syn*-aldol product also generated the *trans*-epoxide. Cyclization to generate the *cis*-epoxide can be sufficiently hindered that the substrate undergoes the *retro*-aldol before reforming the *anti*-isomer and eliminating to form the *trans*-epoxide. Thus, the kinetic resolution process is fundamentally more important than the relative stereochemistry of the initial aldol process.

Our results suggest that this dynamic equilibrium may be in operation under the reaction conditions, exemplified by the consistent isolation of starting materials (Tables 1 and 2, Scheme 1). However, the relatively low selectivity observed for the reaction of ethyl bromoacetate suggests that the transition state for cyclization from the *anti*-aldol product to form the *trans*-epoxide is not significantly lower in energy than cyclization from the *syn*-aldol

to form the *cis*-epoxide. This indicates there is a minimal steric interaction between the alkoxyl group of the ester and the alkene substituents as the *cis*-epoxide is still formed under the reaction conditions. The presence of the *tert*-butyl group, in the reaction of α-bromopinacolone, increases this steric interaction resulting in much greater selectivity for the more thermodynamically stable *trans*-epoxide in the halide displacement step. Thus the geometrical outcome of epoxide formation is strongly influenced by the steric nature of the enolate partner, substitution on the unsaturated carbonyl electrophile has minimal impact.

In conclusion we have successfully developed the reaction conditions for the Darzens condensation of α,β-unsaturated aldehyde and ketone electrophiles, which can be applied to a range of substrates to afford the desired epoxide in good yields. Where α-bromo esters were employed, little selectivity for the *cis* or *trans*-epoxide was observed, however, it was possible to bias the reaction to give predominantly the *trans* -form when a *t*-butyl ketone was employed.

Acknowledgments

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13. *General procedure*: A solution of LiHMDS (1.0 equiv, 2 mmol., 2 mL–1.0 M soln in THF) was cooled to −78 °C under a positive pressure of argon before the drop wise addition of ethyl bromoacetate (1.0 equiv, 2 mmol, 0.22 mL). After 15 min the electrophile (1.0 equiv, 2 mmol) was added drop wise over 5 min and the reaction allowed to warm to 25 °C where it was stirred for 2 h. The reaction was quenched through the addition of 10% HCl (0.4 mL) before dilution with Et_2O (5 mL) and washing of the organic phase with 10% HCl (1.6 mL), H_2O (2 mL) and brine (2 mL). Drying ($MgSO_4$) and solvent removal afforded the crude product as orange oil. Purification was performed by silica column chromatography (Hexane/EtOAc, 10:1, $R_f \sim 0.4$).
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