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Asymmetric epoxidation of cinnamic acid derivatives by in situ generated dioxiranes of chloroacetones: scope and limitations

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ABSTRACT

Efficient epoxidation of chiral cinnamic acid derivatives has been achieved by in situ generated dioxiranes of chloroacetones with moderate to good diastereoselectivity (dr up to 90:10) in high yields. Reactivity of cinnamic acid derivatives containing different chiral auxiliaries versus chloroacetones–monochloroacetone **3** (MCA), 1,1-dichloroacetone **4** (DCA) and 1,1,1-trichloroacetone **5** (TCA) and Oxone™ loading was studied. Both Oxone™ loading and reaction time reduce with an increase of chlorine atoms in the acetone. The use of 1.1 equiv of TCA was found to be effective for the epoxidation of cinnamate substrates and enhances the reaction up to 4–10-fold compared to acetone and that also decreases the Oxone™ loading. This method provided methyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate (−)-**2**, a key intermediate for the synthesis of diltiazem hydrochloride, with >99% of enantiomeric purity.

1. Introduction

α,β-Epoxy carbonyls are key building blocks in organic synthesis, as these versatile functionalities are readily and stereoselectively transformed by ring opening into a variety of oxyfunctionalized compounds.[1] The development of an efficient stereocontrolled method for the synthesis of chiral α,β-epoxy carbonyls is still of considerable interest. Though much progress has been made, the asymmetric epoxidation of allylic alcohols and olefins, chiral auxiliary based asymmetric epoxidation of α,β-unsaturated acid derivatives is also an important strategy in organic synthesis. Peracids[2] and dioxiranes[3] such as dimethyl dioxirane (DMD) are the popular oxidizing agents for the epoxidaton of alkenes. Adam et al. reported the opposite π-face selective epoxidation of chiral tiglic amides using dimethyl dioxirane (DMD) and *m*-chloroperbenzoic acid (*m*-CPBA).[4] To avoid preparation and storing of DMD,[5] it is more convenient to epoxidize the alkenes by in situ generated dioxirane. As dioxiranes are electrophilic in nature, epoxidation of electron-deficient alkenes using in situ generated dioxiranes is usually very slow, when normal ketones such as acetone,[6] 2-butanone[6] and hexanones[6] are used. Yang et al.[7] described the enhanced rate of epoxidation by in situ generated methyl(trifluoromethyl) dioxirane from 1,1,1-trifluoroacetone and Oxone™, where the high electronegativity of fluorine makes it a stronger epoxidizing agent. Later Chen et al. demonstrated[8] the asymmetric epoxidation of various camphor derived *N*- and *O*-enones by in situ generated dioxirane using a large excess of the costly trifluoroacetone (33–47 equiv) and Oxone™ (4–11 equiv). This might be due to the low boiling point (22 °C) and high volatility of 1,1,1-trifluoroacetone. This prompted us to consider that cheaper and easily synthesizable chloroacetones could be an alternative to fluoroacetones. As electronegativity of chlorine is close to flurorine, dioxirane of chloroacetones might have similar reactivity. More important, the high boiling point of chloroacetones might reduce the ketone as well as Oxone™ loadings.

We are interested in the asymmetric epoxidation of chiral cinnamic acid derivatives because chiral epoxy cinnamoyl compounds are important building blocks for the synthesis of many biologically active compounds for example, methyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate (−)-**2**, a key intermediate for the synthesis of diltiazem hydrochloride **1** that is one of the most potent calcium antagonists and has been used as a drug for the treatment of angina and hypertension (Fig. 1). Thus, we report an efficient

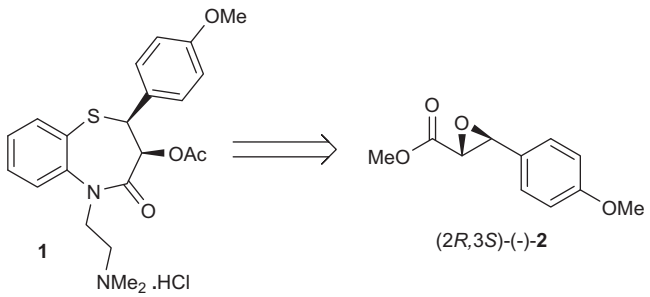

Figure 1.

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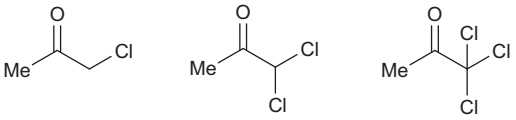
epoxidation of cinnamic acid derivatives containing different chiral auxiliaries by in situ generated dioxiranes using 1.1 equiv of 1,1,1-trichloroacetone **5** (Fig. 2) and Oxone™ (1.5–5.0 equiv) that provides moderate to good diastereoselectivities (up to 90:10) in high yields and the study on the reactivity of in situ generated dioxiranes of different chloroacetones **3–5** towardchiral cinnamic acid derivatives versus Oxone™ loading.



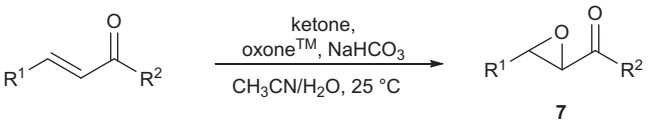
3 4 5

Figure 2.

2. Results and discussion

To outline suitable reaction conditions, initially the epoxidation of achiral cinnamoyl substrates **6** was studied under different conditions. Initially 50% aqueous acetonitrile was found to be an effective solvent, as either lower or higher percentages of water retard the reaction. When a solution of methyl 4-methoxycinnamate **6a** in 50% aqueous acetonitrile and acetone (water/acetonitrile/acetone 2:1:1) was reacted with 1.5 equiv of Oxone™, where acetone functions as a ketone source as well as co-solvent, it showed 45% conversion after 3 h (Table 1; entry 1). Epoxidation of **6a** with 1.1 equiv of monochloroacetone **3** (MCA) and dichloroacetone **4** (DCA) under similar conditions provided very good conversion of 67% and 95% after 3 h, respectively (entries 2 and 3); compared to the reaction with acetone (entry 1). DCA mediated epoxidation could even attend 100% conversion, within 2 h, when a small excess of Oxone™ (2.0 equiv) was used (entry 4). As presumed, the reactivity of oxirane further increases in the case of 1,1,1-trichloroacetone **5** (TCA) and showed 100% conversion within 1 h (entry 5). Even 1.2 equiv of Oxone™ loading was found to be sufficient for TCA (entry 6). There was no appreciable change in the rate and conversion of the reaction with higher equivalents of DCA and TCA. Thus, 1.1 equiv of chloroacetones were found to be optimum for this epoxidation reaction. The reactivity of other α,β-unsaturated carbonyls such as ester **6b** and chalcones **6c** and **6d** (Table 1) were also studied. Unsubstituted methyl cinnamate **6b** is more electron-deficient than **6a**; so it is expected to be less reactive toward in situ generated dioxirane. It provided only 28% conversion with acetone and 30% for MCA after 15 h (entries 7 and 8) and DCA mediated epoxidation of **6b** showed little improvement (entry 9). Epoxidation of **6b** with TCA and 1.5 equiv of Oxone™ could not achieve 100% conversion even after 15 h (entry 10) and that required excess of Oxone™ (3.5 equiv; entry 11). A similar trend was also observed for chalcone **6c** (entries 12–16) and it was found to be more reactive than the corresponding ester **6b**. TCA mediated epoxidation of **6c** led to 100% conversion after 1.5 h (entry 15) and the reaction time further decreased to 0.5 h, when 4.0 equiv of Oxone™ was used (entry 16). It seems the electron-donating resonance (+R) effect of a phenyl group in chalcone **6c** reduces the electron-withdrawing effect of the carbonyl group and in turn increases the reactivity toward electrophilic dioxirane. Similarly electron rich chalcone, 3-(4-methoxyphenyl)-1-phenylpropenone **6d** showed a similar trend as of 4-methoxy cinnamate **6a** and with better reactivity. It showed 75% conversion with acetone after 3 h (entry 17), and under the similar reaction conditions TCA showed 100% conversion within 15 min (entry 21) and DCA mediated reaction took 45 min (entry 20). A similar conversion could also be achieved by MCA after 2 h when 2.0 equiv of Oxone™ was used

Table 1
Epoxidation of **4** in the presence of different chloroacetones



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6a: R^1 = 4-$MeOC_6H_4$, R^2 =OMe
6b: R^1 = Ph, R^2 = OMe
6c: R^1 = Ph, R^2 = Ph
6d: R^1 = 4-$MeOC_6H_4$, R^2 = Ph
6e: R^1 = Me, R^2 = OMe
6f: R^1, R^2 = -$(CH_2)_3$-

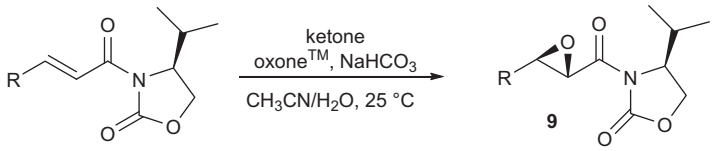
Entry	Substrate	Ketone	Oxone™ (equiv)	Base (equiv)	*t* (h)	Conv.[a] (%)	Yield[a] (%)
1	**6a**	Acetone	1.5	3.5	3	45	—
2	**6a**	**3**	1.5	3.5	3	67	55
3	**6a**	**4**	1.5	3.5	3	95	81
4	**6a**	**4**	2.0	4.5	2	100	90
5	**6a**	**5**	1.5	3.5	0.8	100	85
6	**6a**	**5**	1.2	3.0	0.8	100	90
7	**6b**	Acetone	1.5	3.5	15	28	28
8	**6b**	**3**	1.5	3.5	15	30	30
9	**6b**	**4**	1.5	3.5	15	41	41
10	**6b**	**5**	1.5	3.5	15	68	68
11	**6b**	**5**	3.5	8.5	9	100	>99 (92)
12	**6c**	Acetone	1.5	3.5	15	46	46
13	**6c**	**3**	1.5	3.5	15	50	50
14	**6c**	**4**	1.5	3.5	15	60	60
15	**6c**	**5**	1.5	3.5	1.5	100	>99 (93)
16	**6c**	**5**	4.0	9.5	0.5	100	>99
17	**6d**	Acetone	1.5	3.5	3	75	70
18	**6d**	**3**	1.5	3.5	3	85	75
19	**6d**	**3**	2.0	3.5	2	100	90
20	**6d**	**4**	1.5	3.5	0.7	100	90
21	**6d**	**5**	1.2	3.0	0.2	100	>99 (93)
22	**6e**	**3/4/5**	1.5–4	3.5–10	12	No reaction	
23	**6f**	**3/4/5**	1.5–4	3.5–10	12	No reaction	

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture with succinimide as an internal standard. Yields in the parentheses refer to the isolated yields after column chromatography.

(entry 19). So, it was observed that both Oxone™ loading and reaction time decrease with the increase of chlorine atom in the acetone. However, under the same reaction conditions, methyl crotonate **6e** and cyclohexenone **6f** did not show any reaction even upon use of a large excess of Oxone™ (entries 22 and 23). It might be concluded that in situ generated methyl(trichloromethyl)dioxirane is not sufficiently reactive toward more electron-deficient alkenes such as crotonate and cyclohexenone.

Toward the development of an asymmetric epoxidation and to study the reactivity of the substrates along with diastereoselectivity, we carried out the epoxidation of α,β-unsaturated carboxylic acid derivatives containing different chiral auxiliaries such as Evans oxazolidinone (Table 2), oxazolidine, (Table 3) and Oppolzer's sultam (Table 4). We initially studied the epoxidation of chiral (4*S*)-*N*-(*p*-methoxycinnamoyl)-4-(1-methyl)-2-oxazolidinone **8a** (Table 2). As MCA mediated epoxidation showed a poor to moderate increase in reactivity, epoxidation of chiral cinnamoyl substrates with MCA was not included. However, epoxidation in the presence of acetone as a ketone source as well as co-solvent was studied in order to compare the reactivity with DCA and TCA. Epoxidation of **8a** with 1.5 equiv of Oxone™ in CH_3COCH_3/CH_3CN/H_2O (1:1:2) gave 65% conversion with a diastereomeric ratio (dr) of 55:45 (entry 1) after 10 h. The same reaction showed 100% conversion within half an hour, when TCA **5** (1.1 equiv) and Oxone™ (1.5 equiv) were used (entry 3) and for DCA **4** it took 1 h (entry 2). Also 0.5 equiv of TCA was also found to be effective for the 100% epoxidation of **8a** (entry 4). We also studied the epoxidation of other *N*-enoyl-2-oxazolidinone substrates (Table 2). Epoxi-

Table 2
Epoxidation of **8** in the presence of chloroacetones

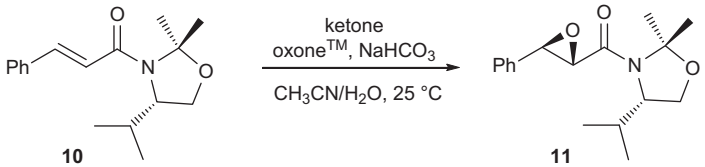


8a: R = 4-MeOC$_6$H$_4$, **8b**: R = Ph, **8c**: R = 4-ClC$_6$H$_4$, **8d**: R = Me

Entry	Substrate	Ketone	Oxone™ (equiv)	Base (equiv)	*t* (h)	dr[a]	Conv.[a] (%)
1	**8a**	Acetone	1.5	3.5	10	55:45	65
2	**8a**	**4**	1.5	3.5	1	56:44	100
3	**8a**	**5**	1.5	3.5	0.5	57:43	100 (90)
4	**8a**	**5**[b]	1.5	3.5	0.5	56:44	100
5	**8b**	Acetone	1.5	3.5	10	ND	35
6	**8b**	**4**	1.5	3.5	10	ND	65
7	**8b**	**4**	4.0	10	10	56:44	100 (93)
8	**8b**	**5**	1.5	3.5	10	ND	80[c]
9	**8b**	**5**	2.5	6.0	4	55:45	100
10	**8c**	Acetone	1.5	3.5	6	ND	20
11	**8c**	**4**	1.5	3.5	6	ND	55
12	**8c**	**4**	3.5	8.5	6	65:35	80 (75)
13	**8c**	**5**	1.5	3.5	6	63:37	85[c]
14	**8c**	**5**	3.0	7.0	6	62:38	94[c]
15	**8d**	**4**/**5**	1.5–4	3.5–10	12	No reaction	

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture with succinimide as an internal standard.
[b] Using 0.5 equiv of TCA.
[c] 10–15% epoxide decomposition compounds. Isolated yields after column chromatography are referred in the parentheses. ND: Not determined.

Table 3
Epoxidation of **10** in the presence of chloroacetones



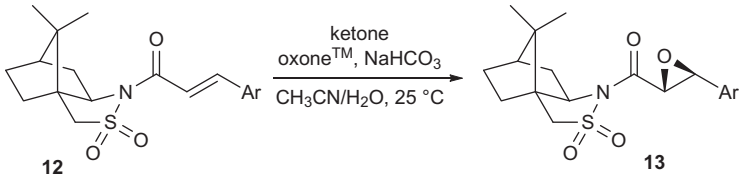
Entry	Ketone	Oxone™	Base (equiv)	*t* (h)	dr[a]	Conv.[a] (%)
1	Acetone	2.5	6.0	12	ND	35
2	**4**	2.5	6.0	5	87:13	89[b]
3	**5**	1.5	3.5	6	88:12	88[b]
4	**5**	2.5	6.0	2	90:10	100 (95)

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture with succinimide as an internal standard.
[b] Along with 10–24% epoxide decomposition products. Isolated yield after column chromatography is referred in the parenthesis. ND: Not determined.

dation of **8b** with 1.5 equiv of Oxone™ and acetone as a ketone gave only 35% conversion after 10 h (entry 5), and DCA showed 65% conversion (entry 6). Under the same reaction condition, TCA gave 80% conversion along with 15% of undesired compounds (entry 8). When the reaction was carried out with an excess of Oxone™ and NaHCO$_3$ in portions, it provided an improved conversion (entries 7 and 9). DCA mediated epoxidation of **8b** using 4.0 equiv of Oxone™, NaHCO$_3$ (10 equiv) afforded 100% conversion after 10 h (entry 7), and for TCA **5**, 2.5 equiv of Oxone™ and 4 h was found to be sufficient (entry 9). Epoxidation of cinnamoyl substrate **8c** with different acetones was also studied. Among these, DCA was found to be a more efficient ketone source, which gave a clean epoxidation with 80% conversion and moderate diastereoselectivity (65:35; entry 12). TCA also showed good conversion (94%) along with the formation of 15% epoxide decomposition compounds (entry 14). Acetone showed only 20% conversion (entry 10). Similar to methyl crotonate, alkenoyl substrate **8d** did not respond to this epoxidation under different reaction conditions (entry 15). Thus, epoxidation of cinnamoyl substrates containing an Evans oxazolidinone chiral auxiliary by the in situ generated dioxiranes of acetone/chloroacetones showed poor to moderate diastereoselectivity and the rate enhanced on increasing the chlorine atom in acetone that also lowered the Oxone™-loading.

Again, asymmetric epoxidation of *N*-cinnamoyl oxazolidine **10** was performed under similar conditions. It was observed that the reaction of **10** with 2.5 equiv of Oxone™ gave only 35% of conversion after 12 h when acetone was used as a ketone source (Table 3, entry 1). Under the similar reaction condition that is, use of 2.5 equiv of Oxone™, DCA **4** (1.1 equiv) mediated epoxidation of **10** provided improved conversions; however the formation of an appreciable amount of by-products was an additional problem (entry 2). Shorter reaction time (3 h) using TCA **5** (1.1 equiv) as a ketone afforded a clean reaction with 100% conversion and good diastereoselectivity (90:10) (entry 4). It was found that under similar reaction conditions cinnamoyl substrate **10** containing oxazolidine chiral auxiliary underwent faster reaction with high diastereoselectivity (Table 3; entry 4) compared to the substrate **8b** containing oxazolidinone chiral auxiliary (Table 2; entries 8 and 9). It is to be noted that *N*-(4-methoxycinnamoyl) oxazolidine

Table 4
Epoxidation of **12** in the presence of chloroacetones



12a: Ar = 4-MeOC$_6$H$_4$, **12b**: Ar = Ph

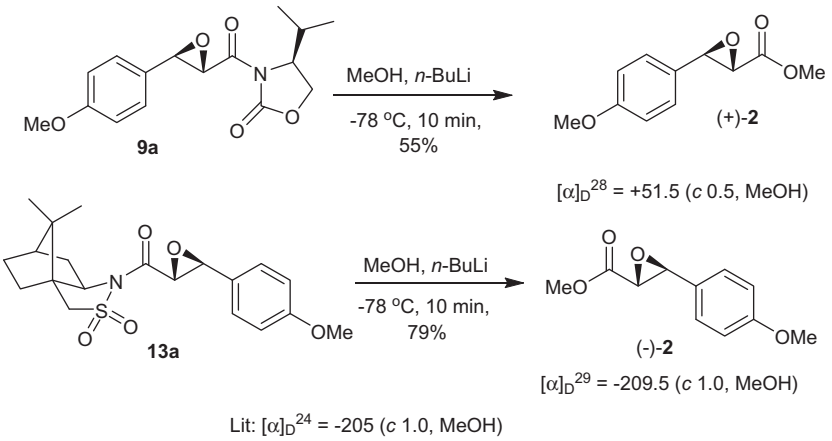
Entry	Substrate	Ketone	Oxone™ (equiv)	Base (equiv)	*t* (h)	dr[a]	Conv.[a] (%)
1	**12a**	Acetone	1.5	3.5	4	ND	20
2	**12a**	**4**	1.5	3.5	3	ND	54
3	**12a**	**4**	2.5	6.0	3	85:15	82
4	**12a**	**5**	1.5	3.5	2	ND	85[b]
5	**12a**	**5**	2.5	4.7	2	ND	100[b]
6	**12a**	**5**	2.5	11	2	84:16	100[c] (92)
7	**12b**	Acetone	1.5	3.5	12	ND	<10
8	**12b**	Acetone	5.0	12	12	ND	18
9	**12b**	**4**	1.5	3.5	12	ND	27
10	**12b**	**4**	5.0	12	12	ND	30
11	**12b**	**5**	1.5	3.5	12	ND	36
12	**12b**	**5**	5.0	12	12	82:18	55 (51)

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture with succinimide as an internal standard.
[b] Along with 18–20% epoxide decomposition products.
[c] Along with 8% epoxide decomposition products. Isolated yields after column chromatography are referred in the parentheses. ND: Not determined.

could not be prepared in pure form, because it decomposed on silica gel.

Similar to the substrates **8** and **10**, the rate of epoxidation of **12** containing camphorsultam chiral auxiliary also enhanced on increasing the chlorine atoms in the acetone and with lower rates. The sultam chiral auxiliary showed good diastereoselectivity (Table 4). Epoxidation of electron-rich substrate **12a** could not achieve 100% conversion with acetone, and DCA **4** even using excess Oxone™ (entries 1–3). Moreover, 100% conversion with good diastereoselectivity (dr: 84/16) could only be achieved with 2.5 equiv of Oxone™ by TCA **5** (entry 5). TCA-mediated reactions produced 20% of undesired epoxide decomposition compounds, which could be minimized by using an excess of $NaHCO_3$ (11 equiv) (entry 6). However, oxazolidinone substrate **8a** showed 100% conversion within half an hour with only 1.5 equiv of Oxone™ (Table 2, entries 3 and 4). Similarly substrate **12b** provided moderate conversion (55%) and good diastereoselectivity (82:18) when an excess of Oxone™ (5 equiv) was used (entry 12). This might be due to the presence of a strong electron-withdrawing sulfonyl group (–SO_2–) with cinnamoyl substrates **12** containing a sultam chiral auxiliary, which are less reactive towardelectrophilic dioxiranes compared to the substrates **8** and **10** containing oxazolidinone and oxazolidine chiral auxiliaries, respectively. However, substrates **12** were found to provide better selectivity than the oxazolidinone substrates **8**. It is to be noted that the solubility of compounds **12** in 50% aqueous CH_3CN was poor; that might be an additional reason for the low conversion. Stereochemistry of the major epoxide **13** was assigned by comparison with the literature data of epoxide **13b**.[8a]

The configurational assignment of the major epoxides **9** was confirmed by confirming the stereochemistry of **9a** (Scheme 1). The reaction of the non-separable mixture of diastereomers **9a** was reacted with MeOLi, prepared by reaction of *n*-BuLi and MeOH at −78 °C and produced (+)-methyl-3-(4-methoxyphenyl)glycidate (+)-**2**. The specific rotation of (+)-methyl glycidates (+)-**2** {$[\alpha]_D^{29} = +51.5$ (*c* 0.5, MeOH) was compared with the literature data {lit. $[\alpha]_D^{24} = -205$ (*c* 1.0, MeOH)}.[9] This ascertained the stereochemistry of major epoxide **9**. Similarly pure **13a,** obtained after recrystallization from 30% ethyl acetate in hexane, was reacted with



Scheme 1. Configurational assignments of epoxides **9** and **13** and the synthesis of (−)-methyl glycidate (−)-**2**.

MeOLi at −78 °C and produced (−)-methyl-3-(4-methoxyphenyl)-glycidate (−)-**2** with specific rotation of $[\alpha]_D^{29} = -209.5$, (*c* 1.0, MeOH) {lit. $[\alpha]_D^{24} = -205$ (*c* 1.0, MeOH)}.[9] Thus it provided enantiomerically pure (>99% ee) (−)-methyl glycidate (−)-**2**, the key intermediate for the synthesis of many biologically active compounds, in particular, diltiazem **1**. The formation of glycidate (−)-**2** from epoxide **13a** further supports the stereochemistry of epoxide **13**. The configurational assignment of **11** was confirmed from single crystal X-ray analysis (Fig. 3).[10]

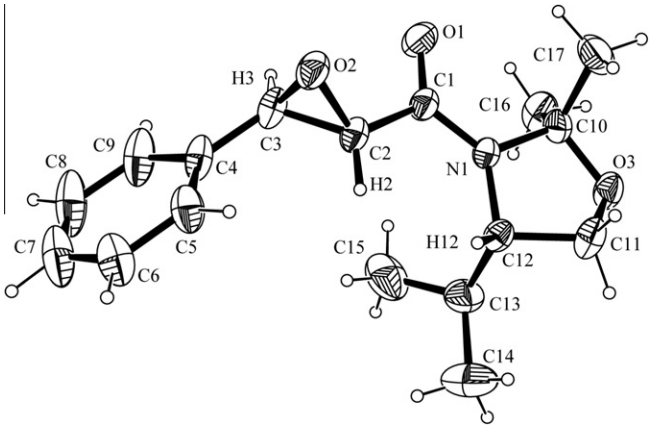


Figure 3. ORTEP diagram of compound **11** with thermal ellipsoid at 30% probability level.

Among the chiral auxiliaries, the sultam was found to provide better diastereoselectivity by in situ generated dixiranes of chloroacetones. It is known in the literature that for α-unsubstituted camphorsultam *N*-enones, the *s-cis* conformation **12** is energetically favoured over *s-trans* **12′** where the carbonyl group is oriented away from the sulfonyl moiety to avoid dipole–dipole interaction.[11] Thus, an attack of methyl(trichloromethyl)dioxirane from the top *Re* face of *s-cis* conformation of *N*-cinnamoyl camphorsultam **12** provides the desired major epoxide **13** (Scheme 2).

3. Conclusions

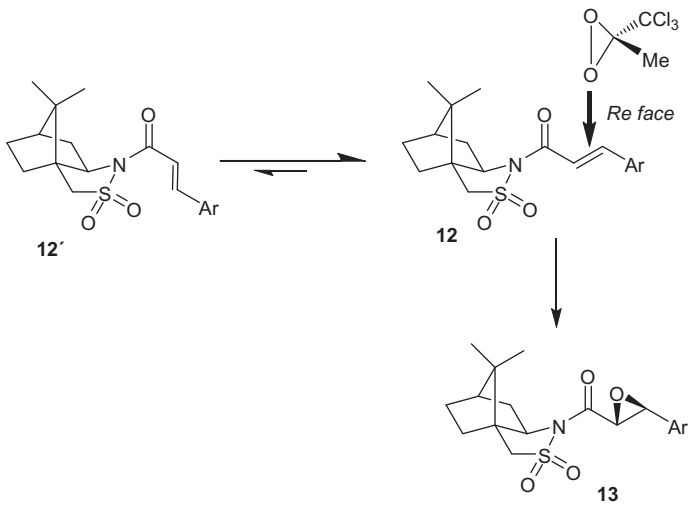
In conclusion, we have developed an efficient epoxidation of cinnamates and chalcones, in particular chiral α,β-unsaturated cinnamic acid derivatives by in situ generated dioxiranes using 1.1 equiv of chloroacetones and 1.5–5.0 equiv of Oxone™. As the number of chlorine atom increases in the acetone, the rate of epoxidation enhances and decreases the Oxone™ loading. Thus DCA **4** and TCA **5** were found to be efficient alternate ketones for the epoxidation of cinnamyl substrates. These enhanced the reaction up to 4–10-fold compared to acetone and also decreased the Oxone™ loading. A chiral auxiliary also plays an important role on reactivity and selectivity for the epoxidation by in situ generated dioxiranes. Cinnamoyl substrates containing an oxazolidinone chiral auxiliary smoothly underwent asymmetric epoxidation with moderate diastereoselectivity (up to 65:35) and substrates containing sultam chiral auxiliary underwent epoxidation slowly, but with good diastereoselectivity (up to 85:15). The reactivity of cinnamic acid derivatives decreases from the substrate containing oxazolidine to oxazolidinone and sultam chiral auxiliaries. This method could produce (−)-methyl-3-(4-methoxyphenyl)glycidate (−)-**2** with >99% of enantiomeric purity.

4. Experimental

4.1. General methods

All reactions were conducted with oven-dried glassware under an atmosphere of argon. Commercial grade reagents were used without further purification. Solvents were dried and distilled following usual protocols. Flash chromatography was carried out using Rankem Silica-gel (230–400 mesh) purchased from Ranbaxy, India. TLC was performed on aluminum-backed plates coated with Silica Gel 60 with F_{254} indicator (Merck).

The ^{1}H NMR spectra were measured on a Bruker-200 (200 MHz) and Bruker-400 (400 MHz) using $CDCl_3$ as a solvent. ^{13}C NMR spectra were measured with Bruker-200 (50 MHz) and Bruker-400 (100 MHz) using $CDCl_3$ as a solvent. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield to $CHCl_3$ ($\delta = 7.26$); ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to the central $CDCl_3$ resonance ($\delta = 77.0$). Coupling constants in ^{1}H NMR are expressed in Hertz. Specific optical rotations were measured with JASCO P-1020 Polarimeter. IR spectra were recorded using Perkin–Elmer Spectrum R×I FTIR Spectrometer. Elemental analyzes were carried out on a Perkin–Elmer 2400-II. Melting points were measured using Toshniwal (India) melting point apparatus.



Scheme 2. Proposed mechanism for the epoxidation of **12**.

4.2. General procedure for epoxidation

Epoxidation with acetone. To a stirred solution (0.03 M) of substrate in acetone/acetonitrile/water (1:1:2) were added Oxone™ and $NaHCO_3$ in portions at rt. The reaction was monitored by TLC and the resulting suspension was treated with water. The reaction mixture was extracted with Et_2O, washed with brine, dried over anhydrous Na_2SO_4, and evaporated to give the crude epoxide. Flash chromatography over silica-gel column gave pure epoxide.

Epoxidation with chloroacetones. Chloroacetone was added to a stirred solution (0.03 M) of substrate in 50% aqueous acetonitrile. A homogeneous mixture of Oxone™ and $NaHCO_3$ was added to the reaction mixture in portions. The reaction was monitored by TLC and the resulting suspension was treated with water. The reaction mixture was extracted with Et_2O, washed with brine, dried over anhydrous Na_2SO_4 ,and evaporated to give the crude epoxide. Flash chromatography over a silica-gel column afforded pure epoxide.

*Epoxidation of **8a** using trichloroacetone TCA **5***. Trichloroacetone **5** (0.089 g, 0.062 mL, 0.55 mmol) was added to a stirred solution of substrate **8a** (0.145 g, 0.5 mmol) in 17 mL of 50% aqueous acetonitrile. A homogeneous mixture of Oxone™ (0.369 g, 0.6 mmol) and $NaHCO_3$ (0.126 g, 1.5 mmol) was added to the reaction mixture in one portion at rt. The reaction was monitored by TLC and the resulting suspension was treated with water (10 mL) after 0.5 h. The reaction mixture was extracted with Et_2O (3×25 mL). The combined organic layers was washed with brine (15 mL), dried over anhydrous Na_2SO_4 ,and evaporated to give the crude epoxide. Flash chromatography over silica-gel (230–400 mesh) column eluting 25% of EtOAc in petroleum ether afforded pure epoxides **9a** (0.138 g) as a non-separable mixture of diastereomers in 90% yield.

4.2.1. (4*S*,2′*S*,3′*R*) and (4*S*,2′*R*,3′*S*)-3-[3′-(4-Methoxyphen yl)-oxiranecarbonyl]-4-(1-methylethyl)-2-oxazolidinone 9a

Non-separable mixture of diastereomers; white solid, mp 145–165 °C. IR (KBr, cm^{-1}): 574, 714, 776, 808, 836, 901, 975, 1030, 1055, 1112, 1176, 1210, 1253, 1303, 1373, 1386, 1410, 1438, 1519, 1615, 1709 (CO), 1782 (CO), 2968; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85–1.0 (m, 6H), 2.38–2.55 (m, 1H), 3.80 (s, 3H), 3.99 (d, J = 1.2 Hz, 0.57H), 4.03 (d, J = 1.6 Hz, 0.43H), 4.25–4.32 (m, 1H), 4.32–4.45 (m, 1H), 4.45–4.55 (m, 1H), 4.79 (d, J = 1.6 Hz, 1H), 6.85–6.95 (m, 2H), 7.25–7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (major isomer) 14.6, 17.8, 28.1, 55.3, 56.4, 58.3, 59.2, 64.1, 114.0 (2C), 126.6, 127.6 (2C), 154.0, 160.2, 167.6; ^{13}C NMR (100 MHz, $CDCl_3$): δ (minor isomer) 14.7, 17.9, 28.3, 55.3, 56.0, 58.7, 59.1, 64.4, 114.0 (2C), 126.6, 127.7 (2C), 154.1, 160.2, 167.4; Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.67; H, 6.44; N, 4.38.

4.2.2. (4*S*,2′*S*,3′*R*) and (4*S*,2′*R*,3′*S*)-3-(3′-Phenyl-oxiranecarbonyl)-4-(1-methylethyl)-2-oxazolidinone 9b

Non-separable mixture of diastereomers; white solid, mp 76–86 °C. IR (KBr, cm^{-1}): 697, 716, 772, 900, 912, 1022, 1057, 1095, 1109, 1202, 1216, 1265, 1296, 1307, 1353, 1373, 1383, 1390, 1400, 1422, 1460, 1712 (CO), 1780 (CO), 2970; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85–1.05 (m, 6H), 2.35–2.55 (m, 1H), 4.04 (d, J = 1.6 Hz, 0.56H), 4.08 (d, J = 1.6 Hz, 0.44H), 4.18–4.30 (m, 1H), 4.30–4.45 (m, 1H), 4.45–4.55 (m, 1H), 4.78 (d, J = 1.2 Hz, 1H), 7.27–7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (major isomer) 14.6, 17.9, 28.2, 56.6, 58.4, 59.3, 64.2, 126.2 (2C), 128.7 (2C), 129.1, 134.8, 154.1, 167.5; ^{13}C NMR (100 MHz, $CDCl_3$): δ (minor isomer) 14.8, 18.0, 28.4, 56.1, 58.8, 59.3, 64.5, 126.3 (2C), 128.7 (2C), 129.1, 134.8, 154.0, 167.4; Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.64; H, 6.01; N, 5.31.

4.2.3. (4*S*,2′*S*,3′*R*) and (4*S*,2′*R*,3′*S*)-3-[3′-(4-Chlorophenyl)-oxiranecarbonyl]-4-(1-methylethyl)-2-oxazolidinone 9c

Non-separable mixture of diastereomers; white solid, mp 145–165 °C; IR (KBr, cm^{-1}): 714, 796, 835, 901, 905, 1018, 1057, 1093, 1110, 1202, 1217, 1229, 1268, 1282, 1307, 1375, 1391, 1401, 1439, 1491, 1717 (CO), 1783 (CO), 2926, 2963; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80–0.90 (m, 6H), 2.32–2.45 (m, 1H), 3.95 (d, J = 1.6 Hz, 0.65H), 3.99 (d, J = 1.6 Hz, 0.35H), 4.18–4.26 (m, 1H), 4.26–4.37 (m, 1H), 4.37–4.50 (m, 1H), 4.64 (d, J = 1.6 Hz, 1H), 7.15–7.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (major isomer) 14.6, 17.8, 28.1, 56.7, 58.3, 58.5, 64.2, 127.5 (2C), 128.8 (2C), 133.3, 134.9, 154.1, 167.1; ^{13}C NMR (100 MHz, $CDCl_3$): δ (minor isomer) 14.7, 17.9, 28.3, 56.2, 58.4, 58.8, 64.5, 127.6 (2C), 128.8 (2C), 133.2, 134.9, 154.0, 167.0; Anal. Calcd for $C_{15}H_{16}ClNO_4$: C, 58.16; H, 5.21; N, 4.52. Found: C, 58.46; H, 5.35; N, 4.37.

4.2.4. (4*S*,2′*S*,3′*R*)-3-(3′-Phenyl-oxiranyl)-[4-(1-methylethyl)-2,2-dimethyl-oxazolidin-3-yl]-methanone 11

White solid, mp 96–97 °C; $[\alpha]_D^{26} = +64.3$ (c 0.5, $CHCl_3$); IR (KBr, cm^{-1}): 698, 755, 887, 1064, 1246, 1323, 1390, 1443, 1462, 1653 (CO), 2968, 3063; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (d, J = 7.2 Hz, 3H), 0.91 (d, J = 7.2 Hz, 3H), 1.58 (s, 3H), 1.70 (s, 3H), 1.80–1.95 (m, 1H), 3.48 (d, J = 1.2 Hz, 1H), 3.85–4.02 (m, 3H), 4.08 (d, J = 1.2 Hz, 1H), 7.20–7.45 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.4, 19.3, 22.9, 25.6, 31.8, 57.99, 58.09, 61.9, 64.9, 96.0, 125.5 (2C), 128.59 (2C), 128.69 (2C), 135.4, 163.8; Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.69; H, 7.83; N, 4.71.

4.2.5. (2*R*,2′*R*,3′*S*)-*N*-[3′-{(4-Methoxyphenyl) oxyranyl}methanone]bornanesultam 13a

Recrystallization from 30% ethyl acetate in hexane provided a pure diastereoisomer (dr >99:1) as a white solid, mp 131–132 °C; $[\alpha]_D^{29} = -167.8$ (c 0.5, $CHCl_3$); IR (KBr, cm^{-1}): 540, 759, 1031, 1067, 1139, 1169, 1227, 1243, 1255, 1275, 1336, 1412, 1518, 1616, 1690 (CO), 2961; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.97 (s, 3H), 1.19 (s, 3H), 1.30–1.50 (m, 2H), 1.75–2.00 (m, 3H), 2.00–2.25 (m, 2H), 3.41 (d, J = 13.6 Hz, 1H), 3.51 (d, J = 13.6 Hz, 1H), 3.79 (s, 3H), 3.82–4.00 (m, 1H), 4.01 (d, J = 1.6 Hz, 1H), 4.08 (d, J = 1.6 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.8, 20.8, 26.4, 32.8, 38.1, 44.7, 47.8, 49.3, 52.9, 55.2, 56.6, 59.3, 65.1, 114.0 (2C), 126.7, 127.4 (2C), 160.1, 166.5; Anal. Calcd for $C_{20}H_{25}NO_5S$: C, 61.36; H, 6.44; N, 3.58. Found: C, 61.56; H, 6.13; N, 3.29.

4.2.6. (2*R*,2′*R*,3′*S*) and (2*R*,2′*S*,3′*R*)-*N*-[(3′-Phenyl- oxiranyl)methanone]bornanesultam 13b

Non-separable mixture of diastereomers; white solid, mp 135–160 °C; IR (KBr, cm^{-1}): 536, 695, 760, 1070, 1138, 1167, 1225, 1241, 1278, 1332, 1420, 1458, 1560, 1654, 1689 (CO), 2928, 2968, 3014; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 3H), 1.19 (s, 3H), 1.30–1.46 (m, 2H), 1.85–2.0 (m, 3H), 2.05–2.25 (m, 2H), 3.43 (d, J = 13.6 Hz, 1H), 3.51 (d, J = 13.6 Hz, 1H), 3.90–4.0 (m, 1H,), 4.07 (d, J = 1.2 Hz, 0.82H), 4.09 (d, J = 1.2 Hz, 0.82H), 4.14 (s, 0.18H), 4.18 (s, 0.18H), 7.30–7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (major isomer) 19.8, 20.8, 26.4, 32.8, 38.1, 44.6, 47.8, 49.3, 52.9, 56.6, 59.3, 65.1, 125.9 (2C), 128.5 (2C), 128.8, 134.7, 166.5; Anal. Calcd for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.41; N, 3.88. Found: C, 62.85; H, 6.23; N, 3.71.

4.3. Synthesis of methyl-3-(4-methoxyphenyl)glycidate 2

Methanol (0.02 ml) was taken with 3 ml of dry Et_2O in a 25 ml two necked flask under an argon atmosphere. The flask was then placed in a low temperature bath (−78 °C) and *n*BuLi (0.16 ml, 1.6 M solution in hexane, 0.26 mmol) was added slowly. After 10 min a solution of epoxide (0.26 mmol) in dry Et_2O (5 mL) was

added dropwise and the reaction mixture was stirred for an additional 10 min at −78 °C. The reaction was quenched with saturated aqueous NH_4Cl solution (3 mL), extracted with Et_2O (3 × 10 mL), washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent and flash column chromatography over silica-gel affords pure epoxides.

4.3.1. Methyl-(2*R*,3*S*)-3-(4-methoxyphenyl)glycidate (−)-2[9]

Gummy liquid; $[\alpha]_D^{29} = -209.5$, (*c* 1.0, MeOH) {lit. $[\alpha]_D^{24} = -205$ (*c* 1.0, MeOH)}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.51 (d, J = 1.2 Hz, 1H), 3.81 (s, 3H), 3.82 (s, 3H), 4.05 (d, J = 1.2 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.5, 55.3, 56.5, 57.9, 114.1 (2C), 126.6, 127.2 (2C), 160.2, 168.8.

4.4. X-ray crystallographic analysis of 11

A single crystal of **6** was grown from 30% ethyl acetate/hexane; $C_{17}H_{23}NO_3$, Mr = 289.36, Monoclinic, space group *C*2, a = 19.92 97(6) Å, b = 7.2983(2) Å, c = 13.7430 (5) Å; V = 1715.38(9) Å^3, Z = 4, D_{calcd} = 1.120 Mg/m^3, X-ray crystallographic data were collected at 273 K with a Mo Kα radiation source (λ = 0.71073 Å) by using CCD diffractometer equipped with a graphite monochromator. The SMART software was used for data collection, for indexing the reflections and for determining the unit cell parameters; the collected data were integrated by using the SAINT software. The structures were solved by direct methods and refined by full matrix least-squares calculations (F^2) by using the SHELXL-97 software. The final R value is 0.0564 (R_W = 0.1687) for 4164 reflections [$I > 2\sigma(I)$]. Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 742654. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or email: deposit@ccdc.cam.ac.Uk).

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