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Asymmetric epoxidation of α,β-unsaturated ketones using α,α-diarylprolinols as catalysts

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Asymmetric epoxidation of α,β-unsaturated ketones has been extensively studied and several important procedures have been developed in the last decade. This review addresses the most significant advances in asymmetric epoxidation of α,β-unsaturated ketones using proline-derived α,α-diarylprolinols as catalysts. Special attention has been paid to the enantioselective epoxidation of chalcones, α,β-unsaturated trifluoromethyl, trichloromethyl ketones and β,γ-unsaturated α-keto esters based on the reseach of our group.

epoxidation, electron-deficient olefins, organocatalysis, ketone, prolinol

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Optically active epoxides are highly useful intermediates and building blocks for the synthesis of biologically active compounds. Various effective systems have been developed over the years for the preparation of chiral epoxides [1]. Among the many powerful methods for the enantioselective epoxidation of olefins, metal-catalyzed epoxidation of allylic alcohols with chiral titanium catalysts [2], epoxidation of allylic [3] and homoallylic [4] alcohols using chiral vanadium catalysts and epoxidation of unfunctionalized olefins using chiral manganese [5] or iron [6] catalysts have proven to be powerful approaches. In recent years, significant progress has been made by Shi [7] on asymmetric epoxidation of various types of olefins catalyzed by chiral ketonesand iminium salts [8], and Shibasaki has developed the epoxidation of electron-deficient olefins catalyzed by La-BINOL-Ph_3As=O complex which gave a better result [9].

Development of new methodologies, characterized by operational simplicity and use of easily available catalysts, is the main target of modern organic synthesis. Asymmetric organocatalysis offers most of these advantages, since metal-free and environmentally friendly conditions have been accomplished for many transformations using small organic molecules as chiral promoters. Since the epoxidation of electron-deficient carbonyl compounds [10] using alkaline H_2O_2 was reported by Weitz-Scheffer, much progress has been made towards the development of an asymmetric variant. Phase-transfer catalysts investigated by Wynberg et al. [11] and polyamino acids developed by Juliá and coworkers [12] for the asymmetric epoxidation of α,β-unsaturated ketones meant a breakthrough for this type of reactions. Recently, the use of chiral prolinols as organocatalysts has been reported as a new methodology for asymmetric epoxidation of electron-deficient olefins [13,14]. This review describes the progress in this area.

1 Asymmetric epoxidation of α,β-unsaturated ketones

1.1 Epoxidation of chalcones

In 2005, Lattanzi [13] reported that the commercially avail-

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able α,α-*L*-diphenyl prolinol **1** is an effective catalyst, at substoichiometric loadings, in the enantioselective epoxidation of *trans*-chalcone in hexane at room temperature with *t*-butyl hydroperoxide (TBHP) as oxygen donor (Scheme 1).

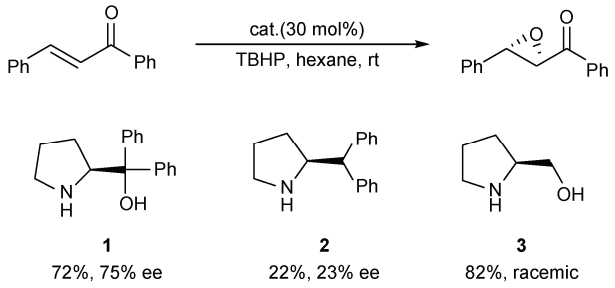
The *L*-prolinol **3** was the most active catalyst but completely unselective, while catalyst **2**, devoid of the hydroxy group, afforded the epoxide in low yield and ee. The asymmetric epoxidation of *trans*-chalcones using organocatalyst **1** gave the corresponding epoxy ketones in good yield. Complete diastereoselectivity for the *trans*-epoxide and moderate to good ee were obtained when substituted chalcones or alkyl α,β-enones were investigated. Study on the nonlinear effects suggests that one molecule of catalyst **1** was involved in the enantio-differentiating step.

Under similar conditions, we reported the enantioselective epoxidation of enones using the polyether dendritic chiral pyrrolidinylmethanol derivatives and TBHP as an oxidant in carbon tetrachloride [14].

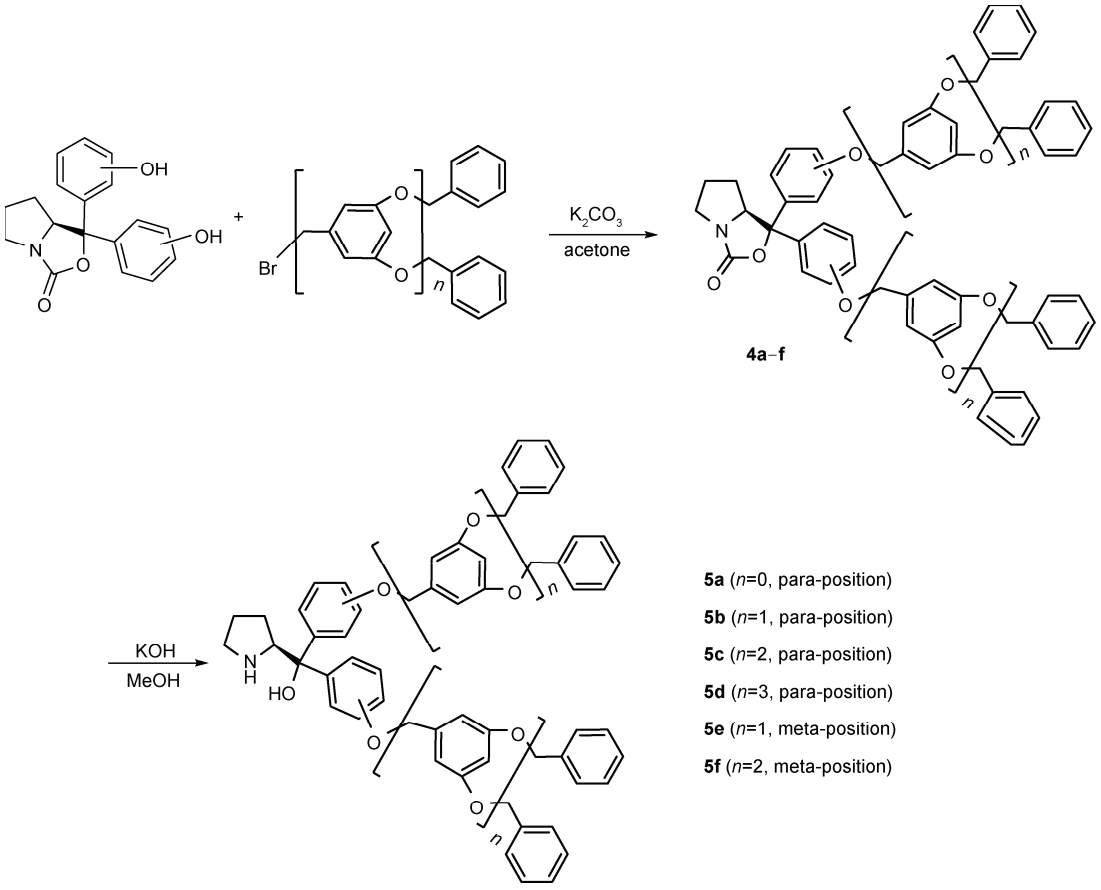
Dendrimers are well-defined macromolecules with controllable structures. Their applications in catalysis have attracted increasing attention, since dendritic catalysts have the advantages of complete solubility and can be analyzed with routine spectroscopic techniques [15]. Moreover, the globular shapes of higher generation dendritic catalysts are suitable for membrane filtration [16] or selective precipitation under specific conditions [17].

The chiral dendrimers were synthesized as shown in Scheme 2. The pyrrolidinylmethanol ligands **4a–f** were first synthesized according to the published method in acetone under basic conditions [18]. Hydrolysis of the ester moieties with KOH afforded the corresponding prolinols **5a–f** in 61%–96% yields.

Investigation of the dendritic catalysts **5a–f** shows that corresponding optically active epoxide could be obtained in good yields. The enantioselectivities were moderate to good (41%–71%). Among all the dendritic chiral catalysts evalu-



Scheme 1 Asymmetric epoxidation of *trans*-chalcone mediated by *L*-proline derivatives.



Scheme 2 Synthesis of chiral dendritic prolinols.

ated in this reaction, the second-generation ligand **5f** was the best one in terms of yield and ee. A slightly higher enantioselectivity and substantial improvement in the yield could be observed when the reaction was carried out in the presence of 4 Å molecular sieves.

The scope and potential for the organocatalytic epoxidation are shown in Table 1. A series of different substituted enones were reacted with TBHP at room temperature in the presence of **5f** (30 mol%) as the catalyst. Almost all reactions proceeded with reasonable reaction time at room temperature and diastereoisomerically pure *trans*-(2*R*,3*S*)-epoxides were obtained with moderate enantioselectivities. It was found that 4-nitro chalcone could be transformed to the epoxide in 93% yield with 73% ee in a relatively short time, which promoted us to investigate the epoxidation of α,β-unsaturated trifluoromethyl, trichloromethyl ketones and β,γ-unsaturated α-keto esters subsequently.

After the reaction was completed, dry methanol was added to the reaction mixture, and catalyst **5f** was almost quantitatively precipitated and recovered *via* filtration. The recovered catalyst was reused for the epoxidation of chalcone at least five times with little or no loss of activity and enantioselectivity (Table 2).

A possible mechanism for this epoxidation of enones was proposed according to the catalytic cycle by Lattanzi (Scheme 3) [13]. Catalyst **5** activated the nucleophile by deprotonation of TBHP, thus generating *t*-butyl hydroperoxide anion, which attacked the hydroxyl-activated chalcones to give the epoxide and eliminate the *t*-butoxy anion. Finally, the *t*-butoxy anion regenerated catalyst **5**.

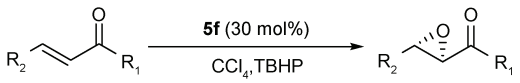
An improvement of the protocol shows that electron-donating groups in the phenyl ring of catalyst **1** enhanced the activity and a significant effect on the enantioselectivity was observed when methyl groups were placed at meta positions (Figure 1). An improved procedure for the enantioselective epoxidation of α,β-enones was then developed employing novel organocatalyst **11** with 30 mol% loading at 0°C in carbon tetrachloride (Table 3). Similar results were also observed by Lattanzi [19].

Compared with the previously reported epoxidation catalyzed by **1**, significant improvements have been achieved: (1) the reaction time was reduced (72–144 h); (2) high yields and enantioselectivities (up to 99% ee) were obtained. The improvement may be attributed to the enlarged steric interaction between the 3,5-dimethylphenyl group of the catalyst and the phenyl group attached to the carbonyl group [19], which made **TS-2** the favored transition state. Attack on the *Re*-face of the C–C double bond by the *t*-butyl hydroperoxy anion would afford the (2*R*,3*S*)- epoxide predominantly, as experimentally observed (Figure 2).

More steric catalysts were also investigated in the epoxidation of chalcones by Lattanzi and Russo [20]. The catalyst **12** was used with 10 mol% loading at 4°C, but no improvement in yield and enantioselectivity was obtained compared with the result achieved by catalyst **11**. Longer time was needed for the reaction to get high yield. This reveals that more steric substituents on the phenyl ring of the catalyst were deleterious to the epoxidation. The reaction proceeded slowly and both yield and enantioselectivity were suppressed (Figure 3).

Then the substituent on the 4-position of the catalyst was investigated [21]. With the same bis (3,5-dimethylphenyl) methanol substituted on the 2-position, 4-substituted-α,α-diaryl-prolinols **15** and **16** were synthesized in four steps from *trans*-4-hydroxyl-L-proline (Figure 4). A preliminary exploration was performed on the catalytic properties of these catalysts in the asymmetric organocatalytic epoxidation of α,β-enones with TBHP in different solvents. 1,3-diphenyl-propenone was selected as a model substrate to carry out this reaction using 30 mol% of catalysts at room temperature. When *trans*-4-benzyloxy-α,α-bis-(3,5-dimethylphenyl)-L-prolinol **15** was used as the catalyst in hexane, a more inferior result (76% yield, 85% ee) compared with that using catalyst **11** was obtained, which revealed that *trans*-configuration of the substituents on the 2- and 4-position was not favored for the reaction. On the other hand, the

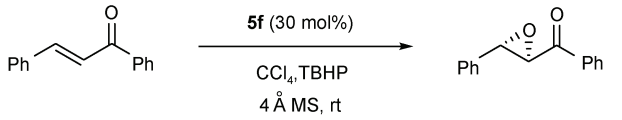
Table 1 Catalytic enantioselective epoxidation of enones promoted by **5f** and TBHP



Entry	R_1	R_2	*t* (h)	Yield (%)	ee (%)
1	Ph	Ph	144	84	74 (2*R*, 3*S*)
2	*p*-Cl-C_6H_4	Ph	144	90	73 (2*R*, 3*S*)
3	*p*-F-C_6H_4	Ph	144	92	74 (2*R*, 3*S*)
4	*p*-NO_2-C_6H_4	Ph	120	93	73 (2*R*, 3*S*)
5	*p*-Ph-C_6H_4	Ph	144	60	77 (2*R*, 3*S*)
6	Ph	*p*-Cl-C_6H_4	120	90	73 (2*R*, 3*S*)
7	*p*-F-C_6H_4	*p*-Cl-C_6H_4	120	90	78 (2*R*, 3*S*)
8	Ph	*p*-MeO-C_6H_4	200	trace	nd
9	Ph	*o*-Cl-C_6H_4	120	90	56 (2*R*, 3*S*)
10[a)]	Ph	*o*-Cl-C_6H_4	120	85	37 (2*R*, 3*S*)
11	CH_3	Ph	144	70	69 (2*R*, 3*S*)
12	*i*-Pr	Ph	120	trace	nd

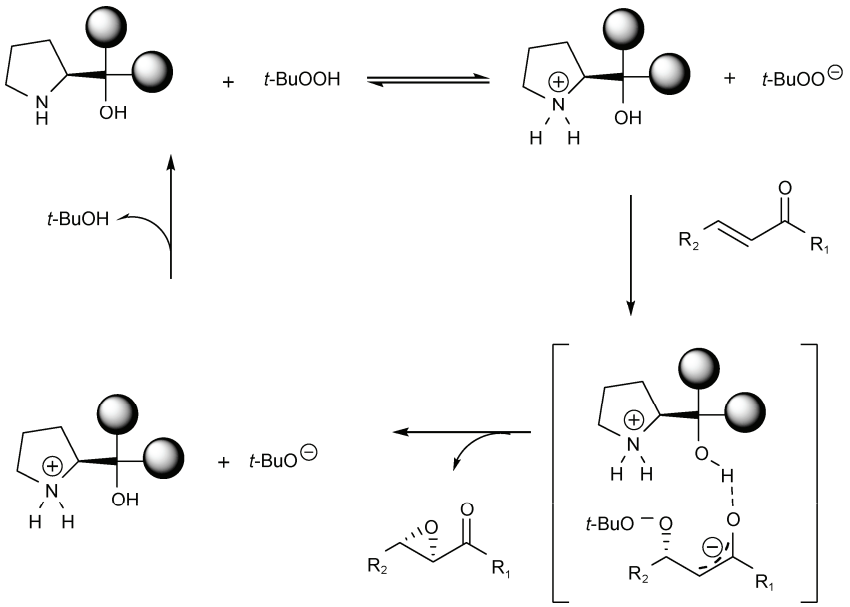
a) Using α,α-diphenyl-L-pyrrolidinemethanol as the bifunctional organocatalyst.

Table 2 Recycling use of dendritic catalyst in asymmetric epoxidation of chalcone



Entry	Catalyst	*t* (h)	Yield (%)	ee (%)
1	**5f**	144	84	74
2	**5f** (second)	144	84	73
3	**5f** (third)	144	80	72
4	**5f** (fourth)	144	81	73
5	**5f** (fifth)	144	83	72

reaction using **16b**, which has a sterically congested benzyloxy moiety at the *cis*-4-position, proceeded smoothly under similar conditions, giving the desired epoxide with excellent enantioselectivity (75% yield, 94% ee), which was a great improvement as compared with **15**'s result. Catalyst with a less bulky group (allyloxy at the *cis*-4-position) gave a similar result albeit with a little decrease in enantioselectivity (76% yield, 93% ee). Large substituents at *cis*-4-positions have a deleterious effect on the reaction. *cis*-4-Naphthalen-2-ylmethoxy-prolinol **16c** furnished an obviously slow reaction (144 h, 60% yield, 93% ee), while *p*-methoxyl-benzyloxy-substituted catalyst **16d** afforded a poor result both in yield and in enantioselectivity (32% yield, 80% ee).



Scheme 3 Proposed catalytic cycle.

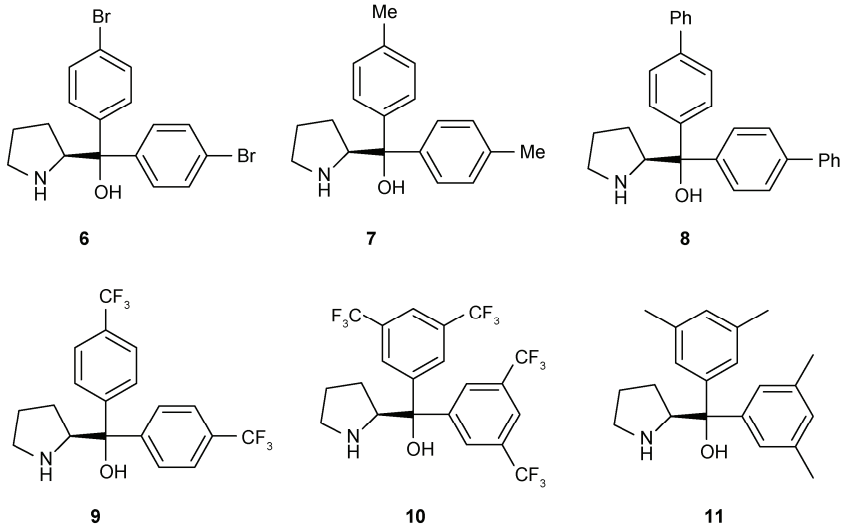
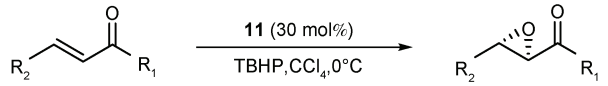


Figure 1 Catalysts with different substituents on the phenyl ring.

Table 3 Asymmetric epoxidation of chalcones catalyzed by **11**



Entry	R_1	R_2	*t* (h)	Yield (%)	ee%
1	Ph	Ph	96	85	95 (*2R*, *3S*)
2	*p*-CH_3O-C_6H_4	Ph	144	70	96 (*2R*, *3S*)
3	*p*-Cl-C_6H_4	Ph	96	90	95 (*2R*, *3S*)
4	*p*-F-C_6H_4	Ph	96	88	95 (*2R*, *3S*)
5	*p*-Br-C_6H_4	Ph	96	87	93 (*2R*, *3S*)
6	*p*-NO_2-C_6H_4	Ph	72	90	90 (*2R*, *3S*)
7	Ph	*p*-CH_3-C_6H_4	144	77	96 (*2R*, *3S*)
8	Ph	*p*- CH_3O-C_6H_4	144	55	96 (*2R*, *3S*)
9	Ph	*p*-Cl-C_6H_4	96	87	97 (*2R*, *3S*)
10	Ph	*p*-NO_2-C_6H_4	96	85	99 (*2R*, *3S*)
11	Ph	*o*-Cl-C_6H_4	120	40	82 (*2R*, *3S*)
12	*p*-Cl-C_6H_4	*p*-CH_3-C_6H_4	120	78	98 (*2R*, *3S*)
13	*p*-Cl-C_6H_4	*p*-CH_3O-C_6H_4	144	70	98 (*2R*, *3S*)
14	*p*-Cl-C_6H_4	*p*-Cl-C_6H_4	96	90	90 (*2R*, *3S*)
15	*p*-F-C_6H_4	*p*-Cl-C_6H_4	72	92	94 (*2R*, *3S*)
16[a)]	CH_3	Ph	144	40	99 (*3R*, *4S*)

a) 50 mol% of **11** was added.

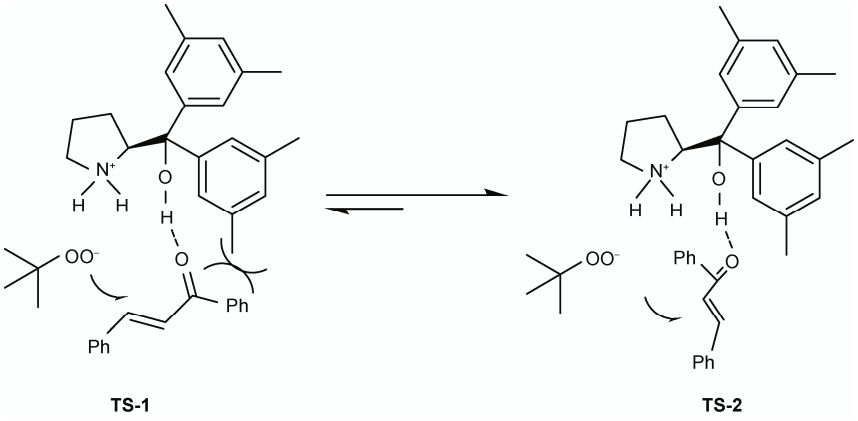


Figure 2 Postulated nuclephilic transition states.

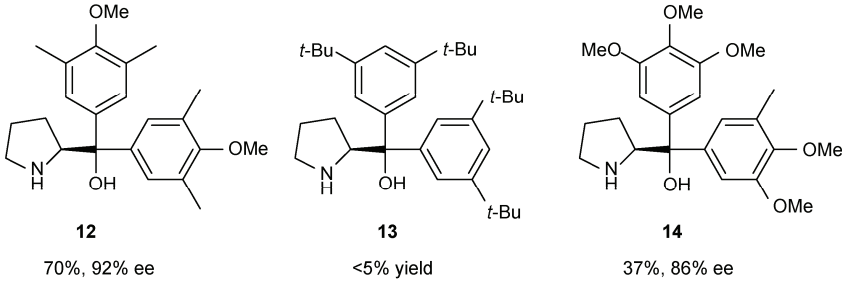


Figure 3 More steric catalysts used in the epoxidation.

Similar to the result obtained previously, using the catalyst **16b**, the epoxidation carried out in tetrachloromethane gave a result parallel to that obtained in hexane. Reactions in toluene gave a satisfying ee but with slow reaction rate. Polar solvent, such as tetrahydrofuran, was totally inert to the epoxidation in all the reaction system.

A series of different *trans*-α,β-unsaturated ketones were evaluated in the presence of catalyst **16b**. The results are summarized in Table 4. In most of the examples, diastereoisomerically pure *trans*-(2*S*,3*R*)-epoxides were obtained in 89%–96% ee. α,β-Enones with substituted groups of different electronic characters on the phenyl ring of the carbonyl side afforded satisfying results. Electron-donating groups decreased the reaction activity but increased the enantioselec-

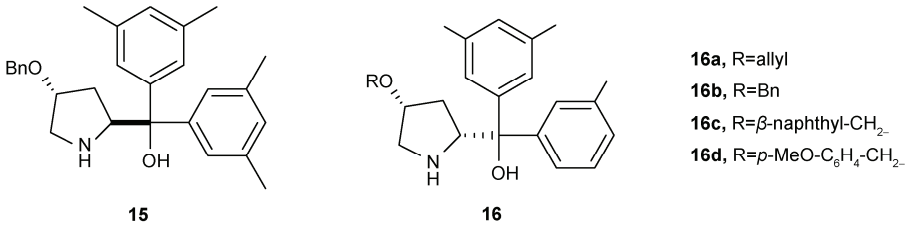
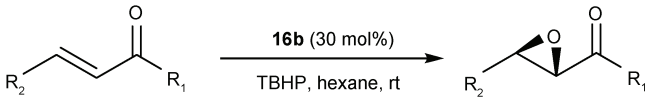


Figure 4 Catalysts with different substituents on the 4-position.

Table 4 Asymmetric epoxidation of α,β-enones catalyzed by **16b**



Entry	R_1	R_2	t (h)	Yield (%)	ee (%)
1	Ph	Ph	144	75	94 (2*S*, 3*R*)
2	*p*-CH_3O-C_6H_4	Ph	144	70	96 (2*S*, 3*R*)
3	*p*-Cl-C_6H_4	Ph	96	80	90 (2*S*, 3*R*)
4	*p*-F-C_6H_4	Ph	100	82	89 (2*S*, 3*R*)
5	*p*-NO_2-C_6H_4	Ph	120	86	91 (2*S*, 3*R*)
6	Ph	*p*-CH_3-C_6H_4	122	72	94 (2*S*, 3*R*)
7	Ph	*p*-Cl-C_6H_4	105	76	96 (2*S*, 3*R*)
8	Ph	*p*-NO_2-C_6H_4	96	90	94 (2*S*, 3*R*)
9	*p*-CH_3O-C_6H_4	*p*-Cl-C_6H_4	144	66	94 (2*S*, 3*R*)
10	*p*-Cl-C_6H_4	*p*-CH_3-C_6H_4	144	70	92 (2*S*, 3*R*)
11	CH_3	Ph	144	49	94 (2*S*, 3*R*)
12	*i*-Pr	Ph	120	trace	nd
13	furan-2-yl	Ph	120	78	95 (2*S*, 3*R*)
14	CH_3	$CH_3(CH_2)_4$	120	61	72 (3*S*, 4*R*)

tivity, while the electron-withdrawing ones had the opposite effects. Substitution on the β-phenyl ring of the enones by *p*-Me, *p*-Cl, and *p*-NO_2 groups did not change the enantioselectivity; the ee values were within the experimental error. Yet, a definite trend to higher yields was displayed by these *para* substituents in the order *p*-NO_2 > *p*-Cl > *p*-Me; specifically, when the enone bearing a strong electron-withdrawing nitro-group in β-phenyl ring was used as the substrate, epoxides were obtained in an excellent yield (90%). However, the reaction failed when R_1 was isopropyl, which may be ascribed to its bulkiness. Enones with aromatic heterocycle substituted on the carbonyl side, such as 1-furan-2-yl-3- phenyl-propenone, afforded an excellent enantioselectivity with high yield. The aliphatic enone, which was considered as a more challenging substrate, was selectively epoxidized with moderate enantioselectivity (Table 4, entry 14).

1.2 Epoxidation of α,β-unsaturated trifluoromethyl ketones

In the epoxidation of chalcones, when an electron-withdrawing substituent, such as the nitro group, was on the phenyl ring of the carbonyl side, the rate of the reaction was accelerated slightly. Thus we speculated that if the phenyl ring of the chalcone on the carbonyl side was changed to trifluoromethyl, trichloromethyl or ester group, the reaction would be promoted largely [22].

With the catalysts used in the epoxidation of chalcones, a model reaction was carried out with (*E*)-1,1,1-trifluoro-4-phenylbut-3-en-2-one in hexane with 10 mol% of the catalyst at 0°C. *Cis*-4-Benzyloxy-α,α-bis-(3,5-dimethylphenyl)-*L*-prolinol **16b**, which gave the better enantiomeric excess in the asymmetric epoxidation of chalcones, afforded the corresponding epoxide in 78% yield and 72% ee in only 10 h. As expected, the introduction of trifluoromethyl group into the enones largely improved the reaction activity of the substrates and hence the corresponding epoxides were obtained in short time. The resulting epoxides quickly transformed to its hydrated modality with a molecule of water in the process of subsequent disposal (Figure 5).

When catalyst **16a** with a less bulky allyloxy group at the *cis*-4-position was used, a comparative yield was obtained albeit with a decrease in enantioselectivity (8 h, 76% yield, 60% ee). Large substituent at *cis*-4-position has a deleterious effect on the reaction. *Cis*-4-naphthalen-2-ylmethoxy-prolinol **16c** furnished an obviously slow reaction and a large decrease in enantioselectivity (18 h, 72% yield, 51% ee). The dendrimer-supported catalyst **5f** afforded the desired epoxide lower in yield and enantiomeric excess (8 h, 72% yield, and 57% ee). The catalyst **11**, which improved the reactivity and enantioselectivity in our and Lattanzi's work for the asymmetric epoxidation of chalcones, however, gave the corresponding product with only 52% ee (8 h, 80% yield). Surprisingly, when 20 mol% or 30 mol% of catalyst

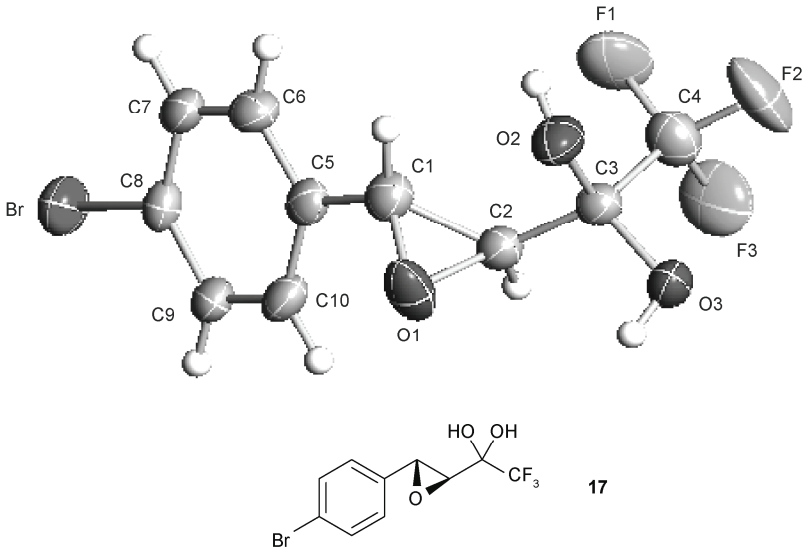


Figure 5 X-ray structure of hydrated modality of the product.

16b was used, lower enantioselectivities were obtained. This was possibly due to the high activity of the trifluoromethyl substrate which was converted to the epoxide too quickly to interact with the catalyst. This could be supported by that when the reaction catalyzed by **16b** in hexane was carried out at 0°C, 96% ee was obtained without loss of the yield and the reaction completed within 18 h.

Then, a series of different *trans*-α,β-unsaturated trifluoromethyl ketones were evaluated in the presence of catalyst **16b** (10 mol%) at 0°C to demonstrate the substrate scope and potential of the catalyst for the asymmetric epoxidation. The results are summarized in Table 5.

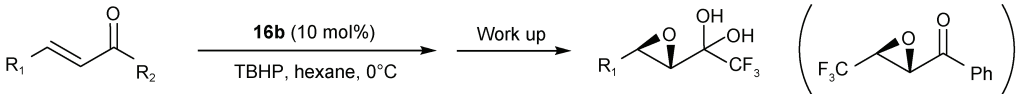
In most of the examples, *trans*-(2*S*, 3*R*)-epoxides were obtained in 89%–96% ee with high yields. α,β-Unsaturated trifluoromethyl ketones with substitents at the *p*-position of the β-phenyl ring afforded satisfying results (Table 5, entries 1–5) except the one with the ethyl group (Table 5, entry 6). Substituents at the *o*-position seemed to be deleterious for the epoxidation. With the substituent at the *m*-position of the β-phenyl ring, the enantioselectivity did not change largely with respect to entry 1 (Table 5, entry 8).

Hydrazinolysis of the trifluoromethyl epoxide **17** with phenyl hydrazine afforded the heterocyclic compound **18** with a trifluoromethyl substituted quaternary carbon centre in 85% yield [23]. These types of heterocyclic compounds are useful intermediates in the preparation of biologically interesting compounds [24] (Scheme 4).

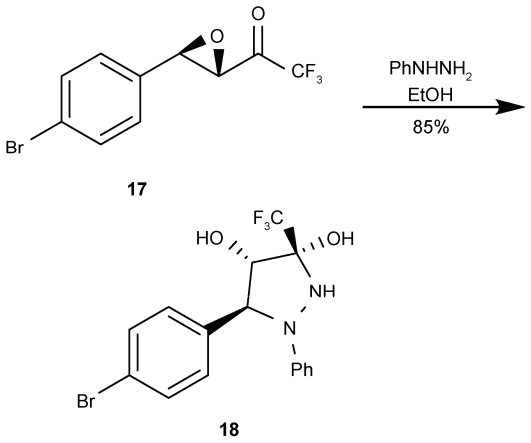
1.3 Epoxidation of α,β-unsaturated trichloromethyl ketones

Subsequently, the epoxidation of another useful type of α,β-enones, namely the α,β-unsaturated trichloromethyl ketones, was investigated [22]. It seemed that the sterically more demanding trichloromethyl group was inferior to the adjacent trifluoromethyl group for the present transforma-

Table 5 Asymmetric epoxidation of α,β-unsaturated trifluoromethyl ketones catalyzed by **16b**



Entry	R_1, R_2	*t* (h)	Yield (%)	ee (%)
1	Ph, CF_3	12	85	96
2	*p*-F-C_6H_4, CF_3	12	88	90
3	*p*-Cl-C_6H_4, CF_3	12	84	90
4	*p*-Br-C_6H_4, CF_3	12	82	95
5	*p*-CH3-C_6H_4, CF_3	18	80	95
6	*p*-Et-C_6H_4, CF_3	18	81	78
7	*o*-Cl-C_6H_4, CF_3	28	65	52
8	*m*-Cl-C_6H_4, CF_3	18	79	89
9	*o,p-di*-Cl-C_6H_4, CF_3	28	70	53
10	CF_3, Ph	48	9	74

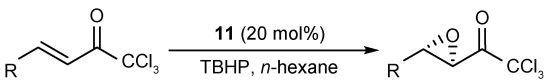


Scheme 4 Transformation of the product to a potential active compound.

tion: under the similar reaction conditions described above, the desired epoxides were generally obtained with diminished yields and enantioselectivities even with a slightly larger amount of the catalyst. However, acceleration in the reaction rates was still observed as expected and the reactions could complete within 7–36 h. When the reaction was conducted at a lower temperature, no improvement in the enantioselectivity was observed. With the best catalyst **11** screened, a series of substrates were investigated. Steric factors seemed to play a significant role in this system for the substrate bearing a substituent at the 2-position of the phenyl ring, giving the desired epoxide with both apparently lower yield and enantioselectivity (Table 6, entry 6). Notably, aliphatic ketone **3i** could also undergo the epoxidation to afford the desired product with moderate enantioselectivity and acceptable yield (Table 6, entry 9).

Conversions of the α,β-epoxy trichloromethyl ketones were more facile due to the good reactivity of the trichloromethyl group as a leaving group (Scheme 5). The amides **20**–**23** could be easily obtained in high yields by the reactions of **19** with corresponding amines in acetonitrile

Table 6 Asymmetric epoxidation of α,β-unsaturated trichloromethyl ketones



Entry	R	*t* (h)	Yield (%)	ee (%)
1	Ph	15	77	86
2	*p*-F-C_6H_4	10	82	81
3	*p*-Cl-C_6H_4	10	93	86
4	*p*-Br-C_6H_4	7	81	86
5	*m*-Cl-C_6H_4	10	83	84
6	*o*-Cl-C_6H_4	24	36	56
7	*p*-NO_2-C_6H_4	15	84	76
8	PhCH=CH	36	50	99
9	Me	36	43	75

without any catalyst [25]. The products **20** and **21** thus obtained are important intermediates in organic synthesis [26]. Furthermore, using an $Yb(OTf)_3$-catalyzed intramolecular ring-opening reaction of epoxide, a straightforward synthesis of chiral (–)-(5*S*, 6*R*)-balasubramide **23b** was achieved with good yield in two steps from **19**. This may be the most efficient method for the synthesis of this compound up to date (**14b**) [27]. By being heated in methanol in basic conditions for 0.5 h, the product **19** could be easily transformed to α-epoxy ester **24**.

1.4 Epoxidation of β,γ-unsaturated α-keto esters

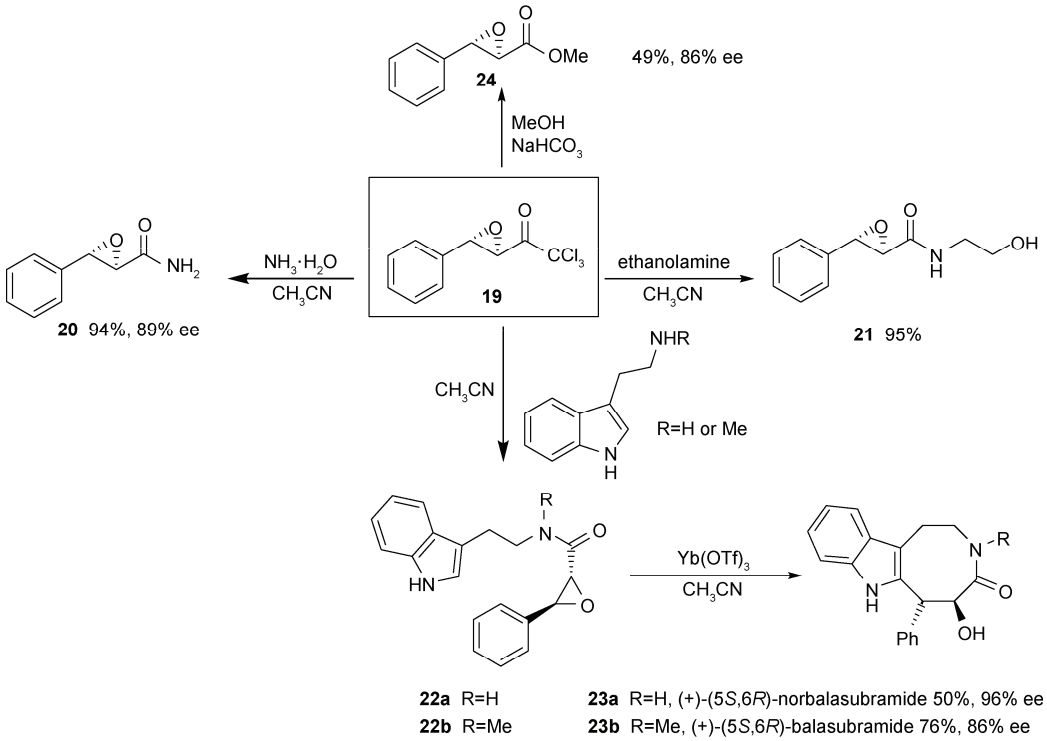
As expected, in comparison with the reactions of chalcones under similar reaction conditions, the reaction time was also significantly reduced for the epoxidation of (*E*)-methyl-2-oxo-4-phenylbut-3-enoate with moderate to excellent yields in the presence of 15 mol% of the catalysts **16a–16h** (Figures 4 and 6) and **11** using *n*-hexane as the solvent at room temperature [22]. Particularly, with the optimal catalyst **11**, the reaction could proceed to completion within 4 h affording the desired product in 94% yield and 90% ee. Furthermore, high enantioselectivity (91% ee) could still be achieved when the loading of **11** was lowered from 15 mol% to 10 mol%, albeit with a drop in the yield. Finally, the highest enantioselctivity was obtained (96% ee) with 83% yield when the reaction was conducted with 10 mol% of **11** at –10°C and this condition was adopted for subsequent study of the substrate scope.

The results of the epoxidation of a selected spectrum of α-keto esters under the above optimized reaction conditions are shown in Table 7. In general, most of the examined substrates with different substituents in both the ester moiety and phenyl ring could afford the desired products in good yields and with excellent enantioselectivities in 9–15 h, irrespective of the electronic nature or the steric hindrance of the substitutents.

Reduction of the β-epoxy α-keto esters **25** with sodium borohydride in the presence of anhydrous calcium chloride furnished the chiral diols **26** in excellent yield [28]. This compound could then be easily transformed to dihydroxyl tetrahydrofuran **27**, a structure that can be seen in many natural products [29], by refluxing in water for 3 h [30]. Alternatively, compound **26** could also be converted to another useful synthon epoxy aldehyde **28** (Scheme 6).

1.5 Epoxidation of α-benzylidene-β-keto esters

The product **29b** can be transformed to a series of useful building blocks [31] such as dihydroxyl compound and tertiary alcohol by ring-opening of the epoxy using aldehyde or other nucleophiles. The two electron-withdrawing groups attached to C–C double bond also enhance the activity of the substrate and hence an accessible way to the epoxidation of **29a** would be obtained (Scheme 7).



Scheme 5 Synthetic transformations of the chiral epoxide **19**.

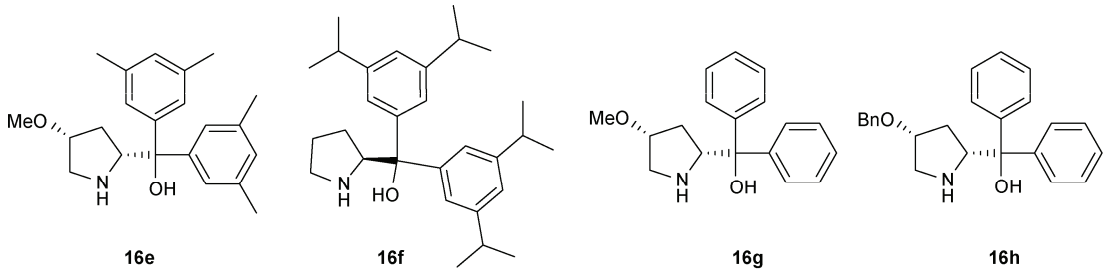
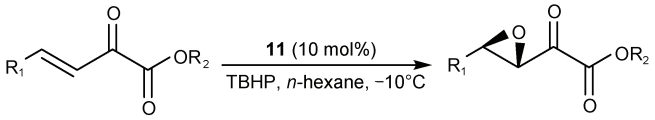


Figure 6 Catalysts used in the epoxidation.

Table 7 Asymmetric epoxidation of β,γ-unsaturated α-keto esters



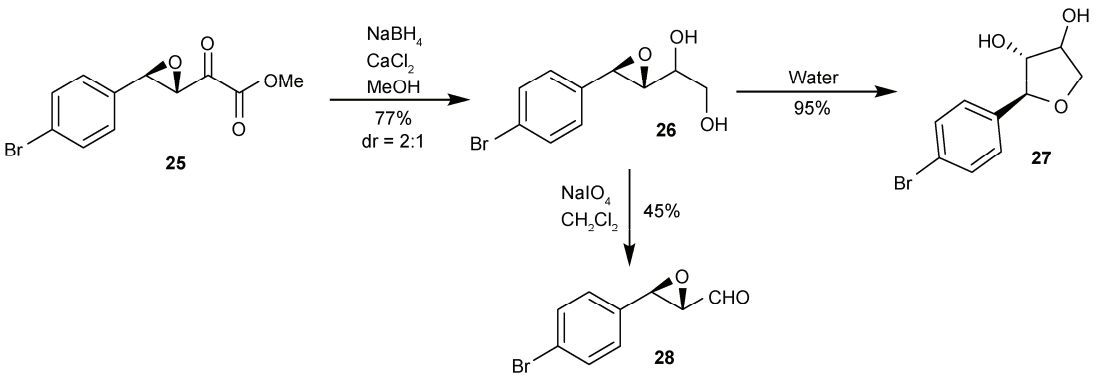
Entry	R_1, R_2	t (h)	Yield (%)	ee (%)
1	Ph, Me	11	83	96
2	Ph, Et	11	90	95
3	Ph, Allyl	11	91	94
4	Ph, *i*Pr	11	91	94
5	Ph, *t*Bu	9	92	96
6	Ph, Bn	14	96	94
7	*p*-F-C_6H_4, Me	9	90	96
8	*p*-Cl-C_6H_4, Me	15	87	98
9	*p*-Br-C_6H_4, Me	15	89	98
10	*o*-Br-C_6H_4, Me	15	88	94
11	*m*-Cl-C_6H_4, Me	10	87	97
12	*p*-NO_2-C_6H_4, Me	12	60	94
13	*p*-Me-C_6H_4, Me	24	52	92

Under similar conditions in the epoxidation of α,β-unsaturated trichloromethyl ketones, the most active catalysts **11** and **16b** were investigated in the reaction of (*Z*, *E*) -ethyl 2-benzoyl-3-phenylacrylate. However, the epoxide with high ee value was obtained as a minor product (87% yield, 90% ee, and 1:3 dr for **11** and 78% yield, 96% ee, and 1:1.7 dr for **16b**). Further screening of the catalysts (Figure 7) and oxidants revealed that a better dr for major products could be obtained with catalyst **30** using dicumyl peroxide (CMHP) as the oxidant (93% yield, 90% ee, 2.2:1) (Figure 8) .

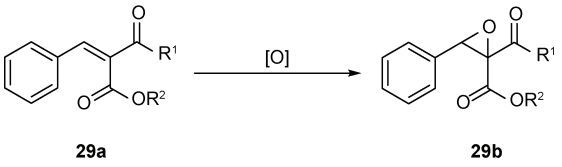
With the best conditions achieved above, other similar types of these substrates were also studied. The best result was obtained with the compound **37**. Further study on the epoxidation of α-benzylidene-β-keto esters is in progress.

2 Conclusions

Major progress in the area of asymmetric epoxidation of



Scheme 6 Transformation of the product **25**



Scheme 7 Epoxidation of α-benzylidene-β-keto ester.

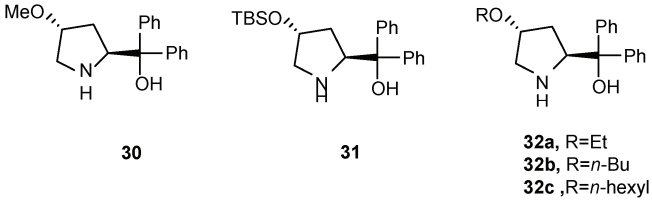


Figure 7 Evaluation of different substituents on the 4-position of the catalyst.

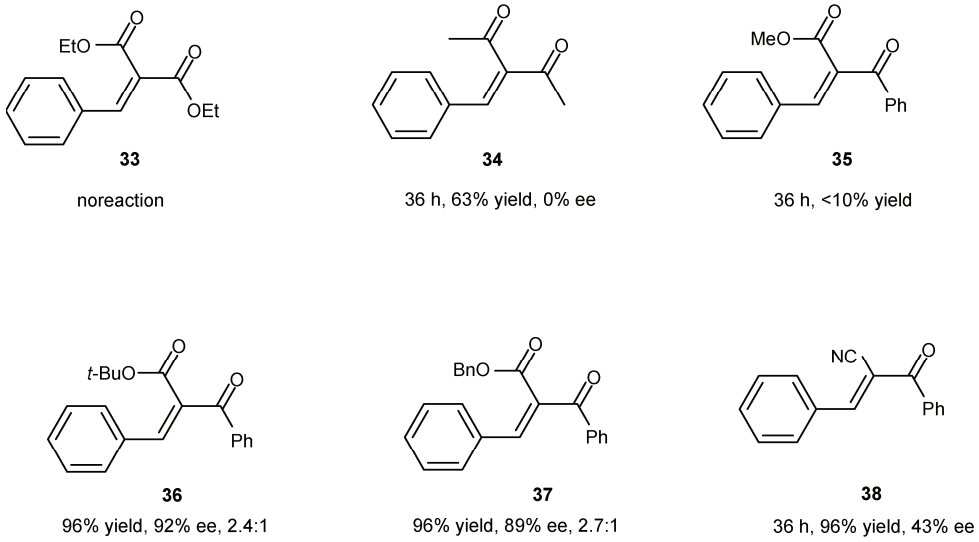


Figure 8 Epoxdation of similar types of substrates catalyzed by **30.**

α,β-unsaturated carbonyl compounds mediated by prolinols has been made in the last decade. Notable improvements have been achieved on the catalysts with different substituents at the 2- and 4-position and a broad range of substrates. Catalysts with electron-donating substituents, such as methyl group on the phenyl ring at the 2-position, were more active to the epoxidation, while substrates with electron-withdrawing groups, such as trifluoromethyl, trichloromethyl or ester group attached to the carbonyl, were also favored by the epoxdation, and the reaction was completed within a short time compared with the reaction of chalcones. This reaction largely expands the method for the synthesis of epoxides useful in a synthetic context.

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