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One-pot production of chiral α,β-epoxy ketones from benzaldehydes and acetophenones by recyclable poly(amino acid) catalysis

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ABSTRACT

An efficient one-pot, two-step process was disclosed for production of chiral α,β-epoxy ketones from benzaldehydes and acetophenones catalyzed by imidazolium-modified poly(L-leucine). Two effective reaction systems with complementary high enantioselectivities (up to 98% ee) or satisfactory yields (up to 89%) have been developed. Importantly, the poly(amino acid) catalyst can be easily recovered and recycled for ten times without losing its catalytic efficiency in terms of both enantioselectivity and yield.

1. Introduction

Asymmetric epoxidation is a remarkably powerful organic transformation, which can efficiently establish two stereogenic centers in one simple operation. In the past several decades, a broad spectrum of endeavors have been made to turn this fundamentally important strategy into many synthetically useful asymmetric epoxidation methods.[1–13] However, no universal method is available for highly enantioselective epoxidation of all classes of different alkene structures. Continuously exploring more effective and practical catalytic systems for asymmetric epoxidation of each specific class of alkene structures is currently still of great interest to organic chemists. Among a variety of olefin substrates, α,β-enones are particularly attractive since they can undergo the asymmetric epoxidation to provide a class of versatile building blocks, chiral epoxy ketones, with complementary reactivities of epoxide and carbonyl functional groups. These chiral multi-functionalized compounds have been extensively used in making valuable bioactive molecules and natural products in both synthetic organic laboratories and various chemical manufacturers, ranging from pharmaceutical to agriculture industries.[14] Therefore, development of highly efficient and reliable asymmetric epoxidation of α,β-enones has drawn great attention from both academia and industry. A variety of chiral catalytic systems have been developed for this purpose to date[3,15–17] and homo-oligopeptides were considered as the most powerful chiral catalysts.[17] However, almost all the successful asymmetric syntheses of chiral epoxy ketones are a two-step sequence: (1) synthesis of α,β-enones and (2) asymmetric epoxidation of α,β-enones. Few successful examples of one-pot synthesis of chiral α,β-epoxy ketones directly from an aldehyde and a ketone have been reported[18,19] by using these existing catalytic systems. The reason could be partially due to the deactivation of the chiral catalyst when it is exposed to the reaction mixture in the condensation reaction (first step). For instance, Choudary and co-workers developed a bifunctional nonocrystalline MgO catalyst for synthesizing chiral epoxy ketones. The synthesis began with the condensation of benzaldehydes with acetophenones to yield chalcones followed by asymmetric epoxidation to afford chiral epoxy ketones with moderate to good yields and moderate to high enantioselectivities (ees) in a two-pot reaction.[18] However, they failed to develop a similar efficient one-pot reaction with the same catalytic system and reasoned that as the poisoning effect of water, which was formed in situ in the condensation reaction and adsorbed on the catalyst. In 2007, Liang and co-workers reported the first example of a combination of condensation and epoxidation process for the synthesis of chiral epoxy ketones with an expensive alkaloid, *Cinchona*, as catalyst.[19] However, the enantionselectivities varied from moderate to high while the yields are generally just moderate, furthermore, the expensive chiral catalyst may be difficult to isolate from the reaction system and to be reused. More

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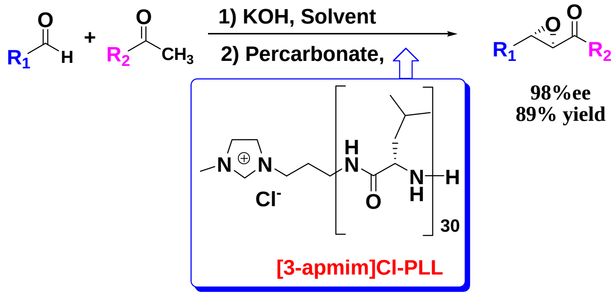
recently, Shi and Dai reported a one-pot way to synthesize α,β-epoxy ketones oxidized by hydrogen peroxide in methanol, but it is a non-chiral epoxidation process.[20]

Attracted by its simple experimental procedure and inexpensive operational cost, we are particularly interested in developing a novel one-pot synthesis of chiral α,β-epoxy ketones directly from an aldehyde and a ketone with a recyclable catalyst. We envisaged that these chiral compounds could be prepared by a Claisen–Schmidt condensation (CSC) followed by an asymmetric epoxidation. The key element to ensure the successful development of such a process with high enantioselectivity and good yield is the employment of a proper chiral catalyst. In our previous research, we discovered a new asymmetric catalyst, which could rapidly catalyze Juliá–Colonna epoxidation of chalcones within several minutes to produce the corresponding chiral epoxychalcones in satisfactory enantioselectivities and yields.[21] More importantly the modified poly(amino acid) catalyst could be quantitatively and repeatedly recycled and reused in the next batch of reaction without losing its catalytic activity. Herein, we wish to report a convenient and efficient one-pot process for production of chiral α,β-epoxy ketones directly from benzaldehydes and acetophenones with the recyclable poly(amino acid) as catalyst for the first time (Scheme 1).



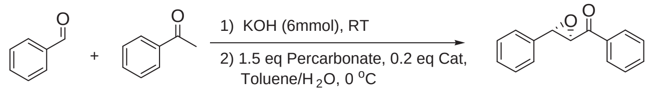
Scheme 1.

2. Results and discussion

We initiated our project with a Claisen–Schmidt condensation of benzaldehyde and acetophenone with 6 equiv of KOH in H_2O, followed by an asymmetric epoxidation in an added organic solvent in the presence of sodium percarbonate (1.5 equiv) and catalytic amount of [3-apmim]Cl-PLL (0.2 equiv). The CSC reaction with high concentrated KOH aqueous solution proceeded quickly into completion followed by the asymmetric epoxidation to afford the chiral epoxychalcone in 94% ee and 61% overall yield (Table 1, entry 1). The moderate overall yield could be caused due to the side reactions, such as Cannizzaro reaction of benzaldehyde and self-condensation of acetophenone incurring under the strong basic environment in the condensation reaction. Therefore, lower concentration of KOH aqueous solution was used to suppress these side reactions in order to increase the overall yield, although a decrease of reaction rate was observed. The optimal balance between selectivity and reactivity was achieved by using 10% w/w KOH aqueous solution as the CSC reaction solvent to afford the chiral epoxychalcone in 96% ee and 75% overall yield (Table 1, entry 3 vs entries 1 and 2). Change of the organic solvent for the asymmetric epoxidation from toluene to CH_2Cl_2 slightly decreased the overall yield although the enantioselectivity remained the same (Table 1, entry 3 vs entry 4).

Table 1

Optimization of the reaction conditions in heterogeneous solvent reaction system[a]



Entry	KOH (%)	Solvent	Time (h)[b]	Yield (%)	ee (%)
1	50	Toluene	2(8)	61	94
2	20	Toluene	24(12)	69	95
3	10	Toluene	24(12)	75	96
4	10	DCM	24(12)	70	96

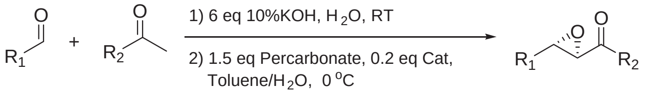
[a] Reaction conditions: benzaldehyde (1.0 mmol), acetophenone (1.0 mmol), KOH (6 mmol), H_2O (3 mL), room temperature (rt) then percarbonate (1.5 mmol), [3-apmim]Cl-PLL (0.2 mmol), solvent (3 mL), 0 °C.

[b] The value in parentheses is the epoxidation reaction time.

In order to examine the scope of this one-pot CSC-asymmetric epoxidation chemistry, a variety of aromatic benzaldehydes and acetophenones were subjected to the optimal reaction system. The results are demonstrated in Table 2. Almost all of the aromatic aldehydes and acetophenones bearing substituents with various electronic (both electronic rich and deficient) and steric properties at different (*meta*- and *para*-) positions on the aromatic rings underwent the one-pot CSC-asymmetric epoxidation smoothly to afford the corresponding substituted chiral epoxychalcone in good yields and excellent ees (Table 2, entries 1, 3–7, and 9–13). Only in two cases, while *o*-methoxy benzaldehyde/acetophenone (74% ee, Table 2, entry 2) and benzaldehyde/*m*-bromoacetophenone (80% ee, Table 2, entry 8) were used as condensation partners, the asymmetric epoxidation performed less selectively but still gave the final products in good ees. The enantioselectivity for the oxidation of chalcone was much higher than that of Liang's catalytic system (97% ee vs 87% ee).[19]

Table 2

Synthesis of chiral epoxides with [3-apmim]Cl-PLL in heterogeneous solvent reaction system[a]



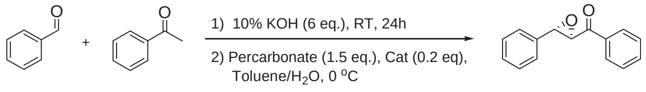
Entry	R_1	R_2	Yield (%)	ee (%)
1	Ph	Ph	75	97
2	*o*-MeOC$_6$H$_4$	Ph	55	74
3	*m*-MeOC$_6$H$_4$	PH	68	97
4[b]	*p*-ClC$_6$H$_4$	Ph	67	96
5[b]	*p*-BrC$_6$H$_4$	Ph	68	90
6	*m*-BrC$_6$H$_4$	Ph	72	90
7	*p*-MeC$_6$H$_4$	Ph	74	90
8	Ph	*m*-BrC$_6$H$_4$	64	80
9[b]	Ph	p-BrC$_6$H$_4$	62	98
10	Ph	*p*-ClC$_6$H$_4$	66	96
11	Ph	*m*-MeC$_6$H$_4$	74	96
12	Ph	*p*-MeC$_6$H$_4$	76	95
13[b]	Ph	*p*-MeOC$_6$H$_4$	75	96

[a] Reaction conditions: aldehyde (1.0 mmol), ketone (1.0 mmol), KOH (6 mmol), H_2O (3 mL), rt; then percarbonate (1.5 mmol), [3-apmim]Cl-PLL (0.2 mmol), toluene (3 mL), 0 °C.

[b] Aqueous KOH (50%) was used.

As we demonstrated in our previous publication, the imidazolium-modified PLL catalysts are generally powdery solids, which are insoluble in either water or organic solvents. This important physical property plus their high catalytic efficiency make the imidazolium-modified PLLs excellent candidate catalysts for recycle and reuse in asymmetric epoxidation chemistry. Hence, we investigated the reusability of [3-apmim]Cl-PLL catalyst used in this research and the results are summarized in Table 3. According to the experimental data, it clearly demonstrates that [3-apmim]Cl-PLL catalyst is a valuable catalyst for this one-pot CSC-asymmetric epoxidation since it can be almost quantitatively recycled and successfully reused for 10 cycles without deterioration in catalytic efficiency. Noteworthy, the recycle of this insoluble, powdery catalyst can be easily achieved by a simple filtration after the reaction has completed.

Table 3
PLL catalyst recycle and reuse[a]

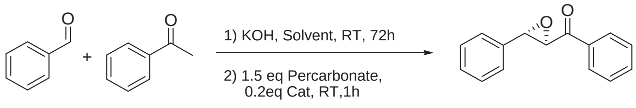


Entry	Catalyst recovery (%)	Yield (%)	ee (%)
1	> 99	70	97
2	>99	74	96
3	>99	73	97
4	>99	73	95
5	99	74	96
6	98	72	96
7	97	73	96
8	98	71	96
9	97	69	95
10	96	64	93

[a] Reaction conditions: aldehyde (2.0 mmol), Ketone (2.0 mmol), KOH (12 mmol), H_2O (6 mL), rt; then percarbonate (3.0 mmol), [3-apmim]Cl-PLL (0.4 mmol), toluene (6 mL), 0 °C.

Although aromatic aldehydes and ketones undergo this one-pot CSC-asymmetric epoxidation chemistry can generally achieve high enantioselectivities when they are performed in H_2O/toluene heterogeneous solvent reaction system, the yields were only in the range of moderate to good (55–76%, Table 2, entries 1–13). Therefore, we decided to explore the possibility of increasing the yields and maintaining the high enantioselectivities at the same time. Thus, we developed a homogeneous solvent reaction system for this purpose. The syntheses started with a Claisen–Schmidt condensation of benzaldehyde and acetophenone with KOH in EtOH/H_2O solvent mixture, which was followed by an asymmetric epoxidation in the presence of sodium percarbonate (1.5 equiv) and catalytic amount of [3-apmim]Cl-PLL (0.2 equiv). This one-pot reaction sequence afforded the chiral epoxychalcone in 71% yield and 35%ee (Table 4, entry 1). A number of different solvent mixtures have been investigated in order to increase both of the yield and enantioselectivity of the asymmetric epoxidation. The THF/H_2O solvent system turned out to be the best solvent system for this reaction (Table 4, entry 5 vs entries 1–4). Efforts to further improve the yield and enantioselectivity by adjusting the ratio of THF/H_2O homogeneous binary solvent mixture and equivalent of base (KOH) loading successfully revealed the optimized reaction condition (Table 4, entry 10 vs entries 5–10). Generally, the stereoselectivity of the asymmetric epoxidation is temperature dependence, and performing the epoxidation reaction at lower temperature usually enhances the enantioselectivity. Thus, 84% yield and 95% ee were achieved by carrying out the reaction in THF/H_2O (1:3) homogeneous binary solvent system, and with 0.5 equiv KOH at 0 °C (entry 11).

Table 4
Optimization of reaction conditions in homogeneous solvent reaction system[a]



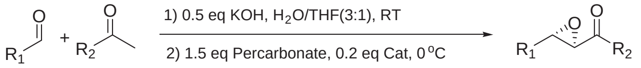
Entry	Solvent (v:v)	Base (equiv)	Yield (%)	ee (%)
1	EtOH/H_2O (1:1)	1.0	71	35
2	MeOH/H_2O (1:1)	1.0	78	51
3	DME/H_2O (1:1)	1.0	69	92
4	MeCN/H_2O (1:1)	1.0	64	82
5	THF/H_2O (1:1)	1.0	78	92
6	THF/H_2O (1:1)	0.5	80	92
7	THF/H_2O (1:1)	1.5	78	88
8	THF/H_2O (1:1)	5.0	79	85
9	THF/H_2O (3:1)	0.5	72	87
10	THF/H_2O (1:3)	0.5	84	92
11[b]	THF/H_2O (1:3)	0.5	84	95

[a] Reaction conditions: benzaldehyde (3.0 mmol), acetophenone (3.0 mmol), KOH (1.5–15 mmol), mixed solvent (45 mL), rt, 72 h; then percarbonate (4.5 mmol), [3-apmim]Cl-PLL (0.6 mmol), rt, 1 h.

[b] The epoxidation was performed at 0 °C.

The generality of this alternative reaction system has been investigated and the results are shown in Table 5. A series of condensation partners bearing substituents with various electronic (both electronic rich and deficient) and steric properties at different (*ortho*-, *meta*-, and *para*-) positions on the aromatic rings were subjected to this homogenous solvent reaction system and all afforded the chiral epoxychalcones in satisfactory yields and good to excellent ees. In general, the yields in this homogenous solvent reaction system are significantly higher (up to 22% higher) than those in the heterogeneous solvent one with no or slight enantioselectivity decreasing (Table 5 vs Table 2). For the substrate benzaldehyde, *p*-chlorobenzaldehyde, and *p*-bromobenzaldehyde, the yields were 20–30% higher than that of Shi's method.[20] One exception is noteworthy, the condensation partner *para*-bromo benzaldehyde/acetophenone achieved both higher yield and ee when the reaction was performed in this homogenous solvent reaction system compared to the data from the heterogeneous solvent one (83% yield and 93% ee, Table 5, entry 4 vs 68% yield and 90% ee, Table 2, entry 5). According to these experimental results, we concluded that these two reaction systems have complementary high yields or enantioselectivities as their merits. Therefore, they both should be considered as effective reaction systems for one-pot CSC-asymmetric epoxidation chemistry in terms of high enantioselectivities and satisfactory yields. Most importantly, both of these two reaction systems are superior to the previously reported one for several identical substrates in terms of ee and yield.

Table 5
Synthesis of chiral epoxides with [3-apmim]Cl-PLL as catalyst in homogeneous solvent reaction system[a]



Entry	R_1	R_2	Yield (%)	ee (%)
1	Ph	Ph	84	95
2	*o*-$MeOC_6H_4$	Ph	69	74
3	p-ClC_6H_4	Ph	89	94
4[b]	*p*-BrC_6H_4	Ph	83	93
5	*p*-FC_6H_4	Ph	76	88
6	*m*-FC_6H_4	Ph	81	80
7	Ph	*o*-BrC_6H_4	87	82
8	Ph	*m*-BrC_6H_4	76	72
9	Ph	*p*-BrC_6H_4	80	94
10	Ph	*p*-ClC_6H_4	81	97
11	Ph	*m*-MeC_6H_4	75	95
12	Ph	*p*-MeC_6H_4	75	95
13	Ph	*p*-$MeOC_6H_4$	83	97

[a] Reaction conditions: aldehyde (3.0 mmol), ketone (3.0 mmol), KOH (1.5 mmol), solvent mixture (45 mL), rt, 72 h; then percarbonate (4.5 mmol), [3-apmim]Cl-PLL (0.6 mmol), 0 °C, 1 h.

[b] H_2O/THF (1:1).

3. Conclusions

In this work, we have disclosed a convenient and efficient one-pot process for production of chiral α,β-epoxy ketones directly from benzaldehydes and acetophenones catalyzed by a chiral modified poly(amino acid). Two effective reaction systems with complementary high enantioselectivities or satisfactory yields have been developed for this purpose. Importantly, the chiral poly(amino acid) catalyst is insoluble in either water or common organic solvents, and it can be simply filtered and reused in the next batch of reaction. The recycled catalyst has been continuously reused and recycled for 10 times without losing its catalytic efficiency in terms of both enantioselectivity and yield.

4. Experimental

4.1. General methods

^{1}H NMR spectra were measured on a Bruker 400 MHz spectrometer at 25 °C in $CDCl_3$ with TMS as the internal standard. Chemical shifts are given in parts per million (δ-scale), and coupling constants and widths of multiplets are given in hertz. ^{13}C NMR spectra were measured on a spectrameter (^{13}C at 100 MHz). The imidazolium-modified PLL ([3-apmim]Cl-PLL) catalyst was synthesized according to the reported method.[21] HRMS were recorded on a Bruker micrOTOF II spectrometer (ESI ionization). The ee was determined by chiral-phase HPLC analysis on a Chiralpak AD column (eluent 10% *i*-PrOH in hexane, UV detection at 254 nm).

4.2. General procedure for the one-pot condensation–epoxidation in homogeneous solvent reaction system

Aldehyde (3 mmol), ketone (3 mmol) was dissolved in THF (22.5 mL) and water (22.5 mL), KOH(1.5 mmol) was added and the mixture was stirred at 25 °C for 72 h. Then percarbonate (1.5 mmol) and catalyst (20 mol %) were added, the reaction mixture was stirred at 0 °C until the enone disappeared (detected by TLC). The catalyst was recovered by rapid filtration and washed with ethyl acetate. The combined organic fractions were dried over anhydrous Na_2SO_4, and were then evaporated in vacuo and purified by silica gel column chromatography (AcOEt/petroleum 1:10–1:30) to afford the corresponding epoxide.

4.3. General procedure for the one-pot condensation–epoxidation in heterogeneous solvent reaction system

Aldehyde (1.0 mmol), ketone (1.0 mmol), and 50% KOH aqueous solution (0.7 g, 6.0 mmol) was stirred at 25 °C until the reaction was complete (detected by TLC). Then toluene (3.0 mL), water (3 mL), percarbonate (1.5 mmol), and catalyst (20 mol %) were added, the reaction mixture was stirred at 0 °C until the enone disappeared (detected by TLC). The catalyst was recovered by rapid filtration and washed with ethyl acetate. The product work-up procedure was the same as the above-mentioned method.

4.4. General procedure for PLL catalyst recycle and reuse

Aldehyde (2.0 mmol), ketone (2.0 mmol), and 50% KOH aqueous solution (1.4 g, 12.0 mmol) was stirred at 25 °C until the reaction was complete (detected by TLC). Then, toluene (6.0 mL), water (6.0 mL), percarbonate (3.0 mmol) and the recovered catalyst (20 mol %) were added, the reaction mixture was stirred at 0 °C until the enone disappeared (detected by TLC). The catalyst was recovered by rapid filtration and washed with ethyl acetate. The product work-up procedure was the same as the above-mentioned method.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.05.024.

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