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Convenient Preparation of Chiral α,β-Epoxy Ketones *via* Claisen–Schmidt Condensation-Epoxidation Sequence

Yongcan Wang,[a] Jinxing Ye,[b,*] and Xinmiao Liang[a,b,*]

[a] Dalian Institute of Chemical Physics, Chinese Academy of Science, 457 Zhongshan Road, Dalian 116023, People's Republic of China
Phone: (+86)-411-8437-9519; fax: (+86)-411-8437-9539; e-mail: liangxm@dicp.ac.cn
[b] School of Pharmacy, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, People's Republic of China
Phone/Fax: (+86)-21-6425-1830

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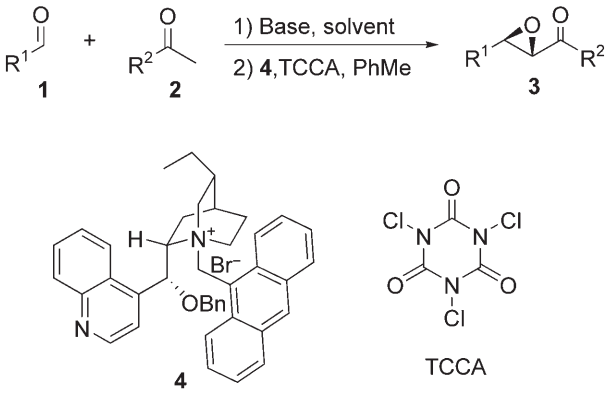
Abstract: A novel Clasisen–Schmidt condensation-epoxidation sequence of aldehydes and ketones was developed to produce a series of chiral α,β-epoxy ketones under asymmetric phase-transfer catalytic conditions. The organocatalytic method reported here can afford chiral α,β-epoxy ketones under mild conditions with moderate to good yields and up to 96% *ee*.

Keywords: aldehydes; asymmetric catalysis; condensation; epoxidation; ketones; one-pot

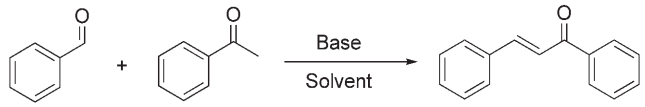
Chiral epoxides are important intermediates and precursors for further chemical transformations.[1] In recent years, a clean and efficient asymmetric phase-transfer catalytic epoxidation access to chiral α,β-epoxy ketones has become particularly attractive in the development of asymmetric processes.[2–9] A series of chiral quaternary ammonium salts such as *Cinchona* alkaloid derivatives and *N*-spiro C_2-symmetric binaphthyl derivatives have shown high catalytic efficiency and remarkable asymmetric control. In these bi- or triphase catalytic systems, a variety of oxidants such as hydrogen peroxide, sodium or potassium hypochlorite have demonstrated different reaction activities and selectivities under different reaction conditions. Recently, we have reported that a novel oxidation system, trichloroisocyanuric acid (TCCA) with an inorganic base such as potassium hydroxide, could serve as an efficient alternative for these oxidants in the epoxidation of enones with high activity and enantioselectivity under chiral phase-transfer conditions.[10]

It is well known that the Claisen–Schmidt condensation (CSC) is a convenient method for the synthesis of enones. The reaction of a ketone and an aldehyde can occur under aqueous or alcoholic alkaline conditions. Since a base is needed in both condensation and epoxidation, we envisioned that it would be possible to combine the two reactions into a one-pot sequential process. We hoped that the CSC products could be directly converted to epoxy ketones through asymmetric phase-transfer catalytic epoxidation without any isolation. Such a one-pot reaction sequence is a highly efficient and economic method in organic synthesis. To the best of our knowledge, this combination of condensation and epoxidation process has not been reported before. We herein present our results on the one-pot CSC-asymmetric epoxidation reaction to access chiral α,β-epoxy ketones. The aldehyde and ketone were treated with aqueous potassium hydroxide to yield the enone. TCCA and chiral quaternary ammonium salt were then added to this mixture to afford the corresponding α,β-epoxy ketone with moderate to high yield and satisfactory enantioselectivity (Scheme 1).



Scheme 1. Claisen–Schmidt condensation-epoxidation sequence for the preparation of chiral α,β-epoxy ketones.

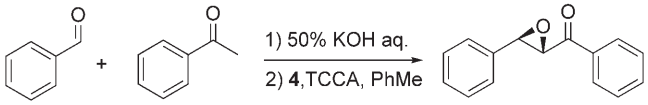
Table 1. Condensation of benzaldehyde and acetophenone.



Entry	Conditions	Time [h]	Conversion [%][a]
1	toluene/10% KOH aq./**4** (5% mol)	24	15
2	toluene/50% KOH aq./**4** (5% mol)	24	86
3	10% KOH aq.	24	96
4	20% KOH aq.	24	94
5	40% KOH aq.	6	97
6	50% KOH aq.	2	98

[a] The values of conversion were obtained by GC analysis base on acetophenone.

Table 2. One-pot condensation-epoxidation of benzaldehyde and acetophenone.



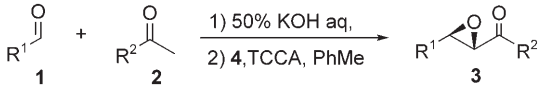
Entry	KOH [equivs.]	TCCA [equivs.]	Catalyst %	Time [h][a]	Conversion [%][b]	*ee* [%][c]
1	3.0	0.67	10	24	>99	85
2	3.0	0.67	5	24	88	84
3	6.0	1.0	10	8	>99	87
4	6.0	1.0	5	8	>99	87
5	6.0	1.0	1	24	72	86
6	12.0	2.0	1	24	77	87

[a] The epoxidation time.
[b] The values of conversion were obtained by HPLC analysis based on chalcone.
[c] Determined by HPLC using a Chiralpak® OD-H column.

Preliminary studies focused on the investigation of the condensation of benzaldehyde and acetophenone under phase-transfer catalytic conditions. The reaction condition was similar to the epoxidation that we had reported using chiral quaternary ammonium salt **4** as phase-transfer catalyst.[10a] But under the toluene/aqueous biphasic conditions, the reaction was time-consuming with a low conversion (Table 1, entries 1 and 2). Then we turned our interest to the CSC reaction under aqueous conditions. It has been reported that the CSC reaction could take place under aqueous conditions by using cetyltrimethylammonium bromide (CTMAB) as a surfactant.[11] Unfortunately, such a process was unsuitable in our CSC-asymmetric epoxidation sequence because the epoxidation of enones could be catalyzed by CTMAB as well,[12] which would cause low enantioselectivity. Our experiment indicated that the condensation of benzaldehyde and acetophenone could take place in 10% potassium hydroxide aqueous at room temperature without CTMAB, but the reaction rate was slow (Table 1, entry 3). Further experiments showed that the reaction rate increased with higher concentrations of aqueous potassium hydroxide. When a 50% potassium hydroxide solution was used, the condensation was completed (>98% conversion) in 2 h to yield the chalcone in 92% isolated yield. This encouraging result indicates that the direct conversion of benzaldehyde and acetophenone to a chiral epoxy chalcone under one-pot conditions is feasible.

Further studies show that this one-pot condensation-epoxidation sequence can be simply achieved. The condensation mixture was transferred to PTC epoxidation conditions similar to our reported procedure by adding toluene, TCCA and catalyst **4**, and the corresponding epoxide was obtained after 24 h with 85% *ee* (Table 2, entry 1). The epoxidation was incomplete using 0.67 equivalents of TCCA and 3.0 equivalents of potassium hydroxide with 5% mol of catalyst. However, the reaction was efficiently complete within 8 h with only 5% mol of catalyst using 1.0 equivalent of TCCA and 6.0 equivalents of 50% potassium hydroxide aqueous (Table 2, entries 2–4). We reasoned that the dichloroisocyanuric acid produced by TCCA with one molecule of potassium hydroxide is not an efficient reagent to produce the oxidant hypochlorite. While using 1.0 equivalent of TCCA, only highly active TCCA was involved in the

Table 3. One-pot condensation-epoxidation of aldehydes and ketones.



Entry	R^1	R^2	Time [h][a]	Yield [%]	*ee* [%][b9]
1	4-ClC_6H_4	Ph	10 (3)	68	75
2	4-BrC_6H_4	Ph	12 (4)	75	80
3	4-ClC_6H_4	4-ClC_6H_4	14 (6)	73	93
4	4-MeC_6H_4	Ph	10 (3)	82	84
5	2-ClC_6H_4	Ph	9 (4)	61	77
6	4-$NO_2C_6H_4$	Ph	12 (10)	68 [c]	96
7	Ph	4-$MeOC_6H_4$	24 (6)	66 [d,e]	91
8	1-Naphthyl	Ph	24 (10)	64 [e]	81

[a] The value in parentheses is the CSC reaction time.
[b] Determined by HPLC using a Chiralpak® OD-H column or a Chiralpak® OJ-H column.
[c] 10% KOH aqueous was used.
[d] The conversion of epoxidation is 81%.
[e] 10% mol of catalyst was used.

epoxidation. More experiments showed that the epoxidation was incomplete with 1 mol% catalyst even when using 2.0 equivalents of TCCA and 12.0 equivalents of 50% potassium hydroxide solution.

To test the generality of this procedure, a series of aldehydes and ketones was examined. As shown in Table 3, all of the benzaldehydes and acetophenones were converted to the corresponding chiral epoxy ketones with satisfactory yields and enantioselectivities up to 96% *ee*. The enantioselectivity of the one-pot condensation-epoxidation reactions was comparable to that of the previous asymmetric phase-transfer catalytic epoxidation of enones. Other kinds of aryl aldehyde, such as 2-naphthaldehyde, also gave good results, while alkyl ketones or alkyl aldehydes gave poor epoxidation results (not shown in Table 3).

In summary, a novel one-pot Claisen–Schmidt condensation-asymmetric phase-transfer catalytic epoxidation procedure was developed to prepare chiral α,β-epoxy ketones. The method reported here allows us to obtain chiral α,β-epoxy ketone simply from an aldehyde and a ketone under mild conditions with high enantioselectivity. It is a valuable alternative method for the synthesis of chiral α,β-epoxy ketones.

Experimental Section

General Procedure for the One-Pot Condensation-Epoxidation

A suspension of aldehyde (1.00 mmol) and ketone (1.00 mmol) in 50% KOH aqueous solution (0.67 g, 6.00 mmol KOH) was stirred at 25 °C until the reaction was complete (detected by GC). Toluene (3.0 mL) and catalyst **4** (0.05 mmol) were then added to the resulted mixture and cooled to 0 °C. TCCA was added in one portion and the reaction mixture was stirred at 0 °C until the enone disappeared (detected by TLC). To the resultant mixture was added water (3 mL) and the whole was extracted with ether (3 × 15 mL). The organic phase was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was purified on silica gel column with petroleum ether/ethyl acetate as eluent giving the corresponding epoxyketone. For more details, see Supporting Information.

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