Phase-transfer catalyzed asymmetric Darzens reaction of cyclic α-chloro ketones

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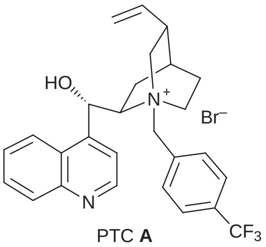
Catalytic asymmetric Darzens reaction using cyclic α-chloro ketones promoted by chiral quaternary ammonium salts as a phase-transfer catalyst proceeded smoothly under mild reaction conditions to afford the desired products with reasonable enantioselectivities at room temperature.

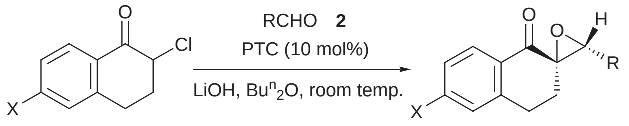
The Darzens reaction, which allows the generatation of new stereocenters with complete diastereocontrol, is one of the most powerful methodologies for the synthesis of α,β-epoxy carbonyl and related compounds, and therefore has been recognized as one of the most significant C–C bond forming processes in synthetic organic chemistry. Although many trials have been performed aimed at developing an asymmetric equivalent in recent decades, many of them require a stoichiometric amount of chiral source[1] and few examples which proceed catalytically are known.[2] We have previously reported an effective catalytic asymmetric Darzens reaction promoted by a chiral quaternary ammonium salt acting as a phase-transfer catalyst (PTC).[3a] According to this procedure, the desired products were obtained with reasonable enantioselectivities in a stereoselective fashion under mild reaction conditions. Here we report recent results for a new system utilizing cyclic α-chloro ketones in the catalytic asymmetric Darzens reaction.

At the outset, we investigated the reaction of the easily prepared cyclic α-chloro ketones **1**[4] as the carbon nucleophile with various aldehydes **2** in the presence of a catalytic amount of the commercially available chiral quaternary ammonium salt PTC **A**, derived from cinchonine under mild reaction conditions. In this system, chiral quaternary carbons which are commonly considered to be difficult to create *via* direct carbon–carbon bond forming reactions, can be formed by the use of α-substituted chloro ketones. The reaction of isobutyraldehyde **2a** with α-chloro ketone **1a** *via* the use of a stoichiometric amount of LiOH in the presence of chiral PTC **A** (10 mol%) in Bu_2O proceeded smoothly to give the desired epoxide **3aa** in good yield at room temperature. The diastereoselectivity of the reaction was perfect and its enantioselectivity was found to be 69% ee *via* HPLC analysis,[5] as shown in Table 1. Next, we attempted to use as PTCs other easily prepared quaternary salts derived from cinchonine involving *O*-protected or substituted benzyl moieties. In spite of our efforts, higher enantioselectivities were not realized in the formation of **3aa** *via* use of a catalytic amount of these analogous PTCs.[6] Although the role of the 4-trifluoromethyl group on the phenyl ring is not clear in this asymmetric induction at present, we believe that the electron-deficiency of the phenyl group in the PTC skeleton plays an important role because the 4-methylated PTC, which is sterically equivalent to the 4-trifluoromethylated derivative (PTC **A**), afforded **3aa** with 0% ee. Also the unsuccessful results obtained by use of the hydroxy-protected PTC in this reaction system support the possibility that the hydrogen bonding, based upon the hydroxy group, between a catalyst and a substrate is a significant interaction in the asymmetric induction, similar to the known related reaction systems.[7] Herein, we have found that 4-trifluoromethylated quaternary salt PTC **A** derived from cinchonine appears to act as an efficient PTC in asymmetric Darzens reactions utilizing cyclic ketones.[8] Encouraged by this result, other aliphatic aldehydes such as **2be** were applied using similar reaction conditions with **1a**, revealing that the reaction with **1** proceeded smoothly to give the corresponding coupling adducts **3**. In particular, treatment of **1a** with **2d** or **2e** afforded the corresponding compounds **3ad** or **3ae** in good yield with 84 and 86% ee, respectively (entries 4 and 5). The reaction of other substrates such as **1b** with aldehydes **2b** or **2e** also gave the corresponding products with moderate ee (entries 6 and 7). The relative configurations of the coupling adducts were determined by both X-ray crystallographic analysis† using the coupling product **3ba** obtained from **1b** with **2a** and comparison of ^{1}H NMR analyses. The ORTEP figure shown in Fig. 1 reveals that it was the *trans* isomer, and other analogous products were determined



PTC **A**

Table 1 Catalytic asymmetric Darzens reaction under PTC conditions



1a X = H
b X = OMe

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Entry	Ketone	Aldehyde	*t*/h	Product	Yield (%)	Ee (%)
1	**1a**	2a R = Pr^i	61	**3aa**	99	69
2	**1a**	2b R = Bu^i	63	**3ab**	86	74
3	**1a**	2c R = *c*-Hex	62	**3ac**	80	69
4	**1a**	2d R = Et_2CH	252	**3ad**	67	84
5	**1a**	2e R = Bu^tCH_2	84	**3ae**	86	86[a]
6	**1b**	2b R = Bu^i	48	**3bb**	65	50
7	**1b**	2e R = Bu^tCH_2	63	**3be**	90	75

[a] 85% de.

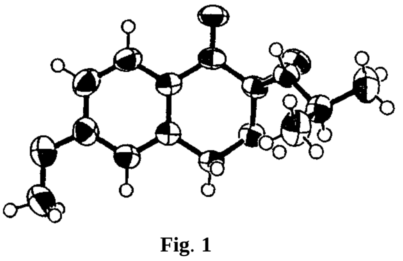
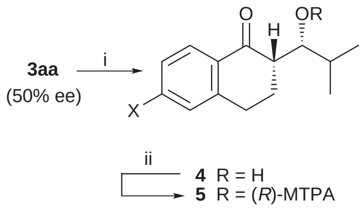


Fig. 1



Scheme 1 *Reagents and conditions*: i, SmI$_2$, 53%; ii, (*R*)-MTPACl, 85%.

by comparison of the coupling constants observed in their ^{1}H NMR spectra. To the best of our knowledge, this is the first example of the preparation of α,β-epoxy ketones *via* catalytic asymmetric Darzens reaction with more than 80% ee.

The absolute configuration of the coupling product **3aa** was determined by transformation to the corresponding (*R*)-MTPA ester. As shown Scheme 1, **3aa** (50% ee) was treated with SmI$_2$[9] in THF–MeOH to afford the corresponding β-hydroxy ketone **4** [$[\alpha]_D^{28}$ −13.8 (*c* 2.7, CHCl$_3$)] as a sole product without racemization, as shown by the HPLC analysis. The stereochemistry of **4** was determined as *syn* by comparison with the literature data.[10] The following esterification afforded **5** in 85% yield. Application of the product **5** to the Mosher method[11] revealed that **5** has the β*R* configuration.

In conclusion, we have demonstrated both the catalytic asymmetric Darzens reaction under PTC conditions utilizing cyclic α-chloro ketones and enantiocontrol for the formation of the quaternary carbons *via* direct C–C bond formation. This methodology is effective for producing α,β-epoxy ketones involving a chiral quaternary carbon in optically active form.

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Notes and references

† *Crystal data* for **3ba**: C$_{15}$H$_{18}$O$_3$, M = 246.31, colourless prismatic crystal, 0.80 × 0.20 × 0.60 mm, monoclinic, $P2_1/a$, a = 9.919(4), b = 12.587(5), c = 11.624(5) Å, β = 112.71(3)°, V = 1338.8(9) Å^3, T = 293 K, Z = 4, μ(Cu-Kα) = 6.80 cm^{-1}, 2441 reflections measured, 2294 independent reflections, 1878 reflections observed, R = 0.052, Rw = 0.211. CCDC 182/1075. The crystallographic data is available as a .cif file at http://www.rsc.org/suppdata/cc/1999/49

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5 Use of α-bromo ketones as substrate instead of chloro ketones gave **3aa** with significantly lower enantio- and diastereo-selectivities.

6 Easily prepared PTCs substituted at the 4-position on the phenyl ring with other electron-withdrawing groups such as NO$_2$ or CN, and electron-donating groups such as MeO or alkyl groups, gave **3aa** with lower ee (4-NO$_2$, 5% ee; 4-CN, 6% ee; 4-OMe, 0% ee; 4-Bu^t, 5% ee). The PTC involving both a methyl-protected hydroxy group and a 4-trifluoromethylbenzyl unit afforded **3aa** as racemate. Other types of PTC including 2- or 3-substituted benzyl moieties also gave **3aa** with lower ee [3-CF$_3$, 3% ee; 2,4-(CF$_3$)$_2$, 17% ee].

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8 A typical procedure for the catalytic asymmetric Darzens reaction is as follows: To a suspension of **1a** (53.0 mg, 0.3 mmol), PTC **A** (16.0 mg, 0.03 mmol) and aldehyde **2a** (0.06 ml, 0.6 mmol) in Bu$_2$O (1.5 ml) was added LiOH (28.4 mg, 1.2 mmol) at room temperature. After the mixture had been stirred for 45 h, more **2a** (0.06 ml, 0.6 mmol) was added, the mixture was stirred for an additional 16 h and the reaction mixture was quenched with 1 M HCl (3.0 ml), extracted with Et$_2$O (15 ml × 3), washed with brine and dried over Na$_2$SO$_4$. Removal of the solvent followed by flash column chromatography (silica gel, hexane–Et$_2$O, 5:1) gave the desired coupling adduct **3aa** as a colorless oil (64.2 mg, 99%, 69% ee): $[\alpha]_D^{25}$ +55 (*c* 2.1, CHCl$_3$). Ees were determined by HPLC analysis by use of DAICEL CHIRALCEL OD+OD, hexane–Pr^{i}OH, 20:1, retention time, 16.9 (major) and 18.6 min (minor).

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