Pergamon

Tetrahedron Letters 39 (1998) 2145–2148

TETRAHEDRON
LETTERS

Catalytic Asymmetric Darzens Condensation Under Phase-Transfer-Catalyzed Conditions

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Received 2 December 1997; revised 5 January 1998; accepted 6 January 1998

Abstract : The catalytic asymmetric Darzens condensation promoted by the quaternary ammonium salt (PTC A) derived from cinchonine as a phase-transfer catalyst is described. Treatment of phenacyl chloride with various aldehydes under mild reaction conditions afforded the corresponding desired product in good yield with good to moderate enantiomeric excess.

Development of catalytic asymmetric carbon-carbon bond forming reactions is one of the most challenging aspects of organic synthesis.[1] Many successful achievements involving molecular catalysts in which well-designed chiral ligands and transition metals have played an important role have been reported over the past two decades.[1,2] Thus, dramatic progress in catalytic asymmetric synthesis has been recognized. Industry usually requires the development of clean and efficient asymmetric processes involving high yields, selectivities, low cost, safety, operational simplicity, mild reaction conditions, and environmental consciousness. On the other hand, phase-transfer catalysts (PTC) have been recognized as a clean and mild reagent since their discovery.[3] Reactions promoted by PTC can be a direct methodology for practical synthesis. Many examples have been reported including the addition-elimination reaction,[4] C-C bond forming reaction,[5] oxidation,[6] and reduction.[7] Actually, several results have been very successful in industrial chemistry. For asymmetric syntheses, more than one hundred papers using chiral crown ethers,[8] polymers,[9] and quaternary ammonium salts[10] as PTC have been reported. However, enantiomeric excess observed in products is not always satisfactory when compared to the transition metal catalyzed asymmetric reactions. In this communication, we report an efficient catalytic asymmetric Darzens condensation[11] promoted by the chiral quaternary ammonium salt derived from cinchonine.

The Darzens condensation is one of the most potential methodologies for the preparation of α,β-epoxy carbonyl compounds with complete control of two stereogenic centers. In metal-promoted asymmetric processes, it is very difficult to establish a catalytic cycle in this reaction because of the generation of stable and less reactive inorganic salts such as metal halides from both metal catalysts and substrates. Therefore, a stoichiometric amount of metal reagents is needed in any Darzens condensation system. In fact, almost all reported procedures are *not catalytically enantioselective* but are diastereoselective Darzens condensations using a stoichiometric amount of chiral auxiliaries[12] in substrates or reagents.

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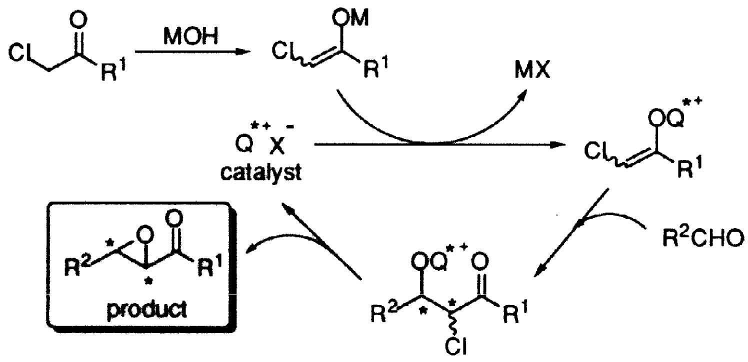
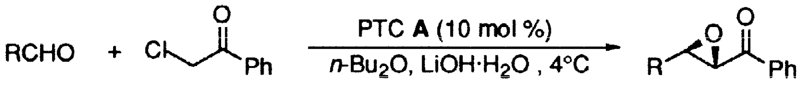
PII: S0040-4039(98)00081-1

Scheme 1. Proposed Catalytic Cycle for Asymmetric Darzens Condensation



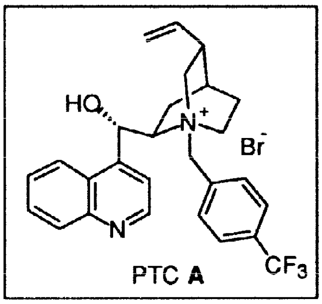
On the other hand, a chiral base generated *in situ* from an achiral inorganic base and a chiral quaternary ammonium halide under phase-transfer-catalyzed conditions reacts with a substrate and produces both a coupling product and ammonium halide, thus establishing a catalytic cycle (Scheme 1).[13] We envisioned that the catalytic asymmetric Darzens condensation promoted by chiral PTC would become a practical method for the preparation of optically active epoxy compounds. Initial work focused on the catalytic asymmetric Darzens condensation with α-chloroketones and various aldehydes (Table 1).

Table 1. Catalytic Asymmetric Darzens Condensation under Phase-Transfer-Catalyzed Conditions[a, b]



1 2 3

run	aldehyde	time (h)	yield of **3** (%)	ee (%)
1	**1a** : *i*-Pr	60	**3a** : 80	53
2	**1b** : Et	117	**3b** : 32	79
3	**1c** : *n*-Pr	60	**3c** : 82	57
4	**1d** : *i*-Bu	134	**3d** : 73	69
5	**1e** : *t*-BuCH$_2$	91	**3e** : 50	62
6	**1f** : Et$_2$CHCH$_2$	117	**3f** : 76	58
7	**1g** : Ph(CH$_2$)$_2$	114	**3g** : 83	44
8	**1h** : *c*-Hex	61	**3h** : 47	63
9	**1i** : Ph	69	**3i** : 43	42



[a] All reactions were carried out in the presence of 2.0 eq of base.
[b] Absolute configuratuions of **3a**, **3b**, **3c** and **3i** were determined to be (α*S*,β*R*) by comparison of the optical rotation with literature data.[20, 21]

The use of both isobutyraldehyde **1a** and phenacyl chloride **2** as substrates was investigated. The reaction proceeded smoothly in the presence of a catalytic amount of PTC A[14] under phase-transfer-catalyzed conditions, and the desired product **3a** was obtained in high yield with complete diastereoselectivity. However, its enantiomeric excess was very low especially using a stoichiometric amount of a strong base such as NaOH or KOH in any of the usual solvents.[15]

It was recognized that the more reactive alkaline metal enolate generated from the strong base and the ketone reacted not with the chiral ammonium halide but smoothly with the aldehyde, and gave a condensation product with a low ee in this reaction system. On the other hand, treatment of **1a** and **2** in dibutyl ether[16] with the weaker LiOH[17] monohydrate base in the presence of a catalytic amount of PTC **A** (10 mol %) afforded **3a** in good yield with 53% ee.[18,19] Other substrates such as **1b**, **1d**, and **1i** gave the desired products with 79, 69, and 42% ee, respectively (Table 1, runs 2, 4, and 9). These results are summarized in Table 1.[20]

In summary, we have realized that the chiral quaternary ammonium salt PTC **A** is an effective catalyst in the asymmetric Darzens condensation. As shown in Table 1, PTC **A** appears to act as a useful phase-transfer catalyst to produce α,β-epoxyketones with good to modest enantiomeric excess. Although the catalyst turnover and enantioselectivity is not presently satisfactory, the results described here will lead to further progress.

Acknowledgments: One of the authors (S. A.) is grateful to the Sasakawa Scientific Research Grant for their financial support. This work was also supported by a Grant-in-Aid from the Ministry of Education, Science, Sports and Culture of Japan (to S. A.).

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13. The chiral ammonium hydroxide is difficult to generate because the equilibrium dramatically shifts to the ammonium halide. See : ref. 3 (b) Chapter 4.
14. PTC **A** was purchased from Aldrich Chemical Co., Ltd.
15. Solvents that are usually used under phase-transfer-catalyzed conditions such as toluene, benzene and CH_2Cl_2 were not effective in this reaction system.
16. The epoxyketone **3a** was obtained with a lower ee using other ether solvents such as THF, diethyl ether, diisopropyl ether, *t*-butyl methyl ether, and 1,4-dioxane.
17. In the case of the use of LiOH as a base, the reaction rate was much slower in the presence or absence of PTC than the use of NaOH or KOH in any solvents.
18. Other 4-substituted benzyl cinchoninium salts were not effective in this reaction system (4-CN : 3% ee, 4-Iodo : 16% ee, 4-NO_2 : 3% ee).
19. A typical procedure for the catalytic asymmetric Darzens condensation under phase-transfer-catalyzed conditions is as follows. To a solution of phenacyl chloride **2** (154 mg, 1.0 mmol) and isobutyraldehyde **1a** (0.14 mL, 1.5 mmol) in dibutyl ether (10 mL) was added *N*-(4-trifluoromethylbenzyl)cinchoninium bromide (PTC **A**) (53.3 mg, 0.1 mmol) at room temperature. After 20 min of stirring at 4℃, lithium hydroxide·monohydrate (84 mg, 2.0 mmol) was added and the reaction mixture was stirred for 72 h. The reaction mixture was quenched with 1*N* HCl (3.0 mL), extracted with diethyl ether (15 mL x 3), washed with brine and dried over Na_2SO_4. Removal of the solvent followed by flash column chromatography (silica gel, hexane:diethyl ether = 15:1) gave the desired product **3a** as a colorless oil (152.0 mg, 80 %, 53% ee), $[\alpha]_D^{19}$ -11.2 ° (*c* 2.6, $CHCl_3$). Enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALCEL OD, hexane:*i*-PrOH = 50:1. The retention time was 8.3 min for the (αS,βR)-isomer and 9.9 min for the (αR,βS)-isomer.
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