Pergamon

Tetrahedron Letters 39 (1998) 2997–3000

TETRAHEDRON LETTERS

Catalytic Asymmetric Horner-Wadsworth-Emmons Reaction Under Phase-Transfer-Catalyzed Conditions

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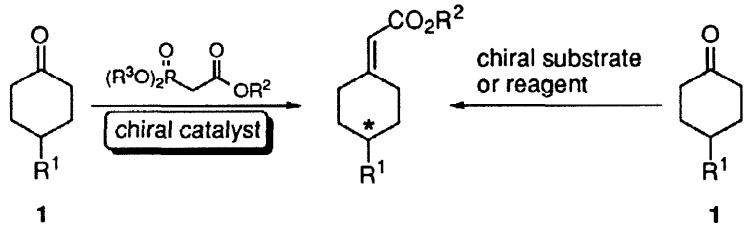
Received 22 December 1997; revised 19 February 1998; accepted 20 February 1998

Abstract: The catalytic asymmetric Horner-Wadsworth-Emmons reaction promoted by quaternary ammonium salts derived from cinchonine as a phase-transfer catalyst is described. Treatment of the prochiral ketone **1** with phosphonates under mild reaction conditions afforded the corresponding desired products in moderate enantiomeric excess.

Keywords: Asymmetric reactions; Catalysts; Olefination; Phase transfer.

The Horner-Wadsworth-Emmons (HWE) reaction is a potential method for the preparation of carbon-carbon double bonds, and optically active condensation products will be obtained using prochiral ketones such as **1** with catalytic or stoichiometric reagents (Scheme 1). All examples reported so far have required a stoichiometric amount of a chiral source to obtain the desired product as an optically active form.[1-3] However, a catalytic cycle may be established using a catalytic amount of a chiral quaternary ammonium salt as a phase-transfer catalyst (PTC) with an inorganic base because of the easy transformation of the ammonium phosphonate generated as an intermediate into the corresponding halide. In this communication, we report the first example of the catalytic asymmetric HWE reaction promoted by a chiral quaternary ammonium salt as a phase-transfer catalyst (PTC) derived from cinchonine, which gives optically active α,β-unsaturated esters.

Scheme 1



At the outset, we attempted the HWE reaction using the ketone **1a** with various phosphonates under phase-transfer-catalyzed conditions. We discovered that the reaction carried out in benzene[4] smoothly proceeded at room temperature in the presence of a strong base such as KOH with a catalytic amount of a chiral quaternary ammonium salt as a PTC to give condensation products (Scheme 2). The desired condensation products **3a** and **3b** were obtained using the methyl or ethyl phosphonate **2a** and **2b** in the presence of a catalytic amount (20 mol %) of (*N*-benzyl)cinchoninium chloride (PTC A)[5] or bromide (PTC

0040-4039/98/$19.00
PII: S0040-4039(98)00442-0

B) as the PTC with 43 and 38% ee, respectively, though chemical yields were not satisfactory (Table 1, runs 1 and 2). On the other hand, chemical yields were much better though the enantiomeric excess was very low, when the phosphonates involving *n*-propyl, isopropyl and *tert*-butyl carboxylate **2c-2e** were used as subatrates (Table 1, runs 3,4 and 5).[6] In run 4, PTC C[5] was used instead of PTC **B**. These results are summarized in Table 1.

Scheme 2. The Asymmetric Horner-Wadsworth-Emmons Reaction under Phase-Transfer-Catalyzed Conditions[a]

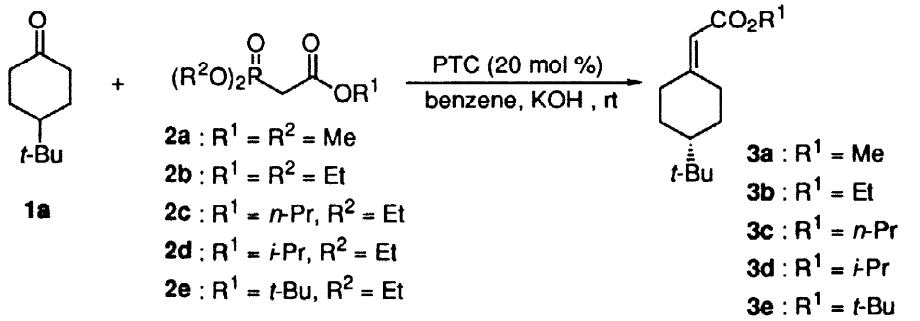
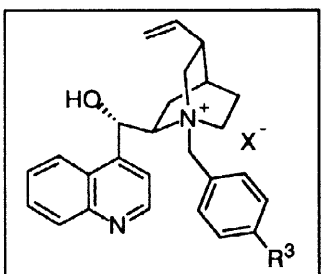


Table 1

run	phosphonate	PTC	time (h)	yield of **3** (%)	ee (%)[b,c]
1	**2a**	**A**	38	**3a** : 15	43
2	**2b**	**B**	42	**3b** : 24	38
3	**2c**	**B**	41	**3c** : 78	8
4	**2d**	**C**	65	**3d** : 86	19
5	**2e**	**B**	40	**3e** : 89	7

[a]All reactions were carried out in the presence of 5.0 eq of base except run 3 (3.0 eq). [b]Enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALCEL OD (hexane:*i*-PrOH = 20:1). [c]Absolute configurations of **3a** and **3b** were determined by comparison of the optical rotation with literature data.[1]



In order to obtain the desired products in high yield, we have tried to acidify the reaction system at the end of the reaction. Methyl and ethyl esters are easily hydrolyzed under basic conditions and give the corresponding alkaline metal salts of the carboxylic acids. Treatment of the salt with the corresponding alcohol and *conc* HCl at 60℃ afforded the desired products as an ester form which can be easily isolated in good yield.[7] Fortunately, its enatiomeric excess was not lost. Next, we aimed to prepare and examine a more effective PTC[8] derived from cinchonine for the development of the catalytic asymmetric HWE reaction.

The HWE reaction smoothly proceeded in the presence of a catalytic amount of the new cinchoninium bromide derivatives with RbOH[9] and gave **3b** with the acidification procedure[10] in modest enantiomeric excess. According to examination of the effect of the substituent groups on the phenyl ring in this reaction system, PTC alkylbenzyl functions seemed to give the best result.[11] Actually, a catalytic amount (20 mol %) of PTC involving the *tert*-butyl group at the 4-position afforded **3b** in 75 % yield with 55 % ee after the acidifidation procedure (Table 2, run 3). These results are summarized in Table 2.

In conclusion, we have developed the catalytic asymmetric HWE reaction promoted by quaternary ammonium salts using as PTC. As shown in Table 2, cinchonine derivatives are effective catalyst to produce the desired product with modest enantiomeric excess. Although catalytic turnover and enantiomeric excess are not presently satisfactory, the results described here will lead to further progress.

Scheme 3. The Catalytic Asymmetric Horner-Wadsworth-Emmons Reaction with Various PTCs[a]

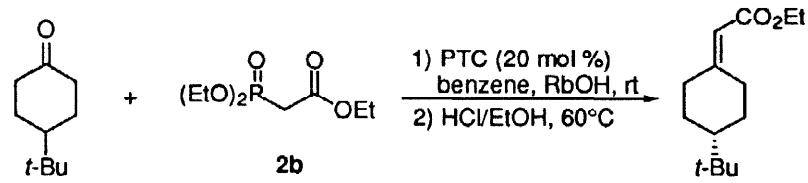
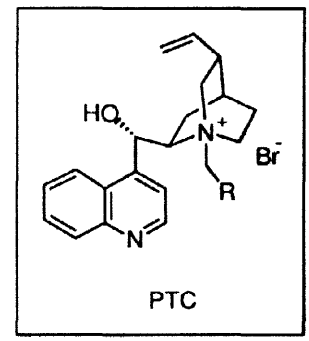


Table 2

run	PTC : R	time (h)	yield of **3b** (%)	ee (%)
1	**A**[b]: C_6H_5	191	69	57
2[c]	**A**[b]: C_6H_5	98	24	37
3	**D** : 4-*tert*-Bu-C_6H_4	192	75	55
4	**D** : 4-*tert*-Bu-C_6H_4	161	61	43[d]
5	**E** : 2,4-Me_2-C_6H_3	187	77	48
6	**F** : Me_5-C_6	187	77	48
7	**G** : α-Naphthyl	190	69	39
8	**H** : β-Naphthyl	148	66	48
9	**I**[b]: 4-MeO-C_6H_4	165	86	46
10	**J** : 3,4,5-$(MeO)_3$-C_6H_2	191	73	54



[a]Other PTCs involving electron withdrawing groups on the phenyl ring gave lower ee. [b]Ammonium chloride was used. [c]**2a** was used as a substrate. [d]KOH was used as base.

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.

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cited therein.

2. The preparation of chiral esters via kinetic resolution was reported. See: (a) Narasaka, K.; Hidai, E.; Hayashi, Y.; Gras, J. -L. *J. Chem. Soc. Chem. Commun.*, **1993**, 102-104. (b) VanNieuwenhze, M. S.; Sharpless, K. B. *J. Am. Chem. Soc.*, **1993**, *115*, 7864-7865.
3. The preparation of chiral esters via asymmetric elimination was reported. See: (a) Komatsu, N.; Matsunaga, S.; Sugita, T.; Uemura, S. *J. Am. Chem. Soc.* **1993**, *115*, 5847-5848. (b) Solladié, G.; Zimmermann, R.; Bartsch, R. *Synthesis* **1985**, 662-665.
4. Other solvents such as Et_2O, THF, CH_2Cl_2, and toluene were not effective and gave the desired product with low ee.
5. PTC **A** and **C** were purchased from Aldrich Chemical and Fluka Co., Ltd., respectively.
6. Other substrates such as the cyano and ketophosphonate were not effective in this reaction system. Desired products were obtained in good yield with lower ee (cyanophosphonate: 72% yield, 0% ee, ketophosphonate: 78% yield, 1% ee, respectively).
7. The condensation product was easily hydrolyzed under these basic conditions and obtained in low yield from the asymmetric HWE reaction. We attempted to directly convert the carboxylate to the ester with acid in alcohol. This procedure is effective to obtain the desired product in the ester form in good yield. See ref. 10.
8. All PTCs except PTC **A** and **C** described here were prepared from cinchonine and a corresponding benzyl halide derivative under reflux in THF.
9. According to the investigation of the base effect for the asymmetric HWE reaction, RbOH was found to give the desired product with better enantiomeric excess.
10. A typical procedure for the catalytic asymmetric Horner-Wadsworth-Emmons reaction under phase-transfer-catalyzed conditions is as follows: To a solution of 4-*tert*-butylcyclohexanone **1** (100 mg, 0.65 mmol) in benzene (3.2 mL), triethyl phosphonoacetate **2b** (0.26 mL, 1.30 mmol) and *N*-(4-*tert*-butylbenzyl)cinchoninium bromide (PTC **D**, 68 mg, 0.13 mmol) were added at room temperature. After RbOH monohydrate (390.6 mg, 3.2 mmol) was added at room temperature, the reaction mixture was stirred for 192 h. The reaction mixture was acidified to ca. pH=3 with *conc.* HCl and then ethanol (10 mL) was added, and the reaction mixture was stirred for a further 96 h at 60℃. The reaction mixture was filtered and removal of the solvent followed by column chromatography (silica gel, hexane:diethyl ether = 2:1) gave the desired product **3b** as a colorless oil (109.2 mg, 75 %, 55% ee). Enantiomeric excess was determined by HPLC analysis (DAICEL CHIRALCEL OD, hexane:*i*-PrOH = 20:1, flow rate : 0.3 mL/min). The retention time was 13.1 min for the (*R*)-isomer and 14.1 min for the (*S*)-isomer.
11. The desired products were obtained with low ee in the case of using PTC involving an electron withdrawing group on the phenyl ring such as CN, F, Cl, Br, and NO_2 groups.