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Phase-transfer-catalyzed asymmetric Michael reaction using newly-prepared chiral quaternary ammonium salts derived from L-tartrate

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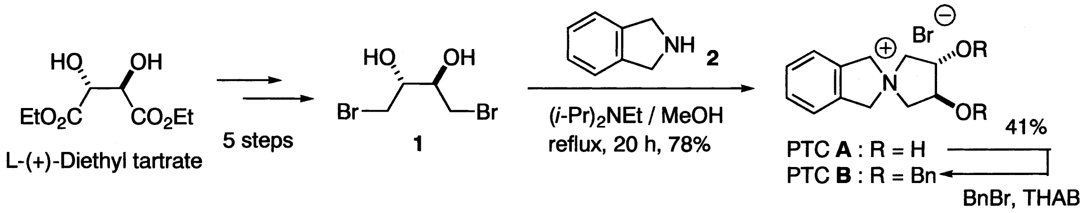
Abstract—The catalytic asymmetric Michael reaction of a glycine Schiff base was demonstrated using new PTCs and moderate to good ee's were achieved (up to 77% ee). © 2002 Elsevier Science Ltd. All rights reserved.

Since phase-transfer catalysis was reported in the 1960's, its application to transformations has attracted considerable interest because of its high cost performance, simplicity and safety and because it is environmentally benign. This methodology is still considered one of the most potent strategies for establishing green chemistry.[1,2] Ever since Dolling[3] and O'Donnell[4] independently reported their successful results in asymmetric phase-transfer chemistry, many quaternary ammonium salts derived from natural chiral amines such as cinchonine and cinchonidine have been examined as chiral PTCs. On the other hand, Maruoka,[5,6] Belokon[7] and Nagasawa[8] recently have reported the synthesis of non-natural PTCs which involves a highly efficient asymmetric chemical transformation. In this communication, we would like to report our results regarding a novel PTC derived from tartrate[9] and its application to the asymmetric Michael reaction[10,11] under PTC conditions.[12]

We interested in the PTC of less flexibility due to high symmetrical spiro structure. Initially, we prepared a novel PTC which has a spiro ammonium salt, as shown in Scheme 1. The alkylation of two hydroxy groups in PTC **A** produced a variety of ether derivatives. PTC **A**, which is a derivative of β-aminoalcohol, was prepared by reacting a highly nucleophilic amine, isoindoline **2**, with dibromide **1**, which is readily available from diethyl tartrate in five steps.[13] Quaternalization of these compounds was carried out under reflux conditions in MeOH to give the desired spiro ammonium bromide PTC **A** in good yield (Scheme 1).

As expected, PTC **A** promoted the Michael reaction of Schiff base **3** to **4** in the presence of base (Cs_2CO_3, 10 equiv.) under PTC conditions tested (Et_2O, 0°C), though the enantioselectivity was quite low under all of the conditions (Table 1, entry 1). Next, we sought out to prepare an *O*-protected ammonium salt such as PTC **B**. Treatment of PTC **A** with benzyl bromide under PTC conditions gave PTC **B** in moderate yield. This salt have enough solubility in organic solvent to proceed the reaction even at −40°C in 37% yield with low ee under similar conditions (entry 2). On the other



Scheme 1. Synthesis of PTCs **A** and **B**.

Keywords: asymmetric; catalysis; Michael reaction; phase-transfer.

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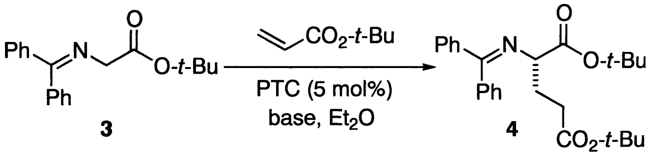
Table 1. Catalytic asymmetric Michael reaction using novel PTCs

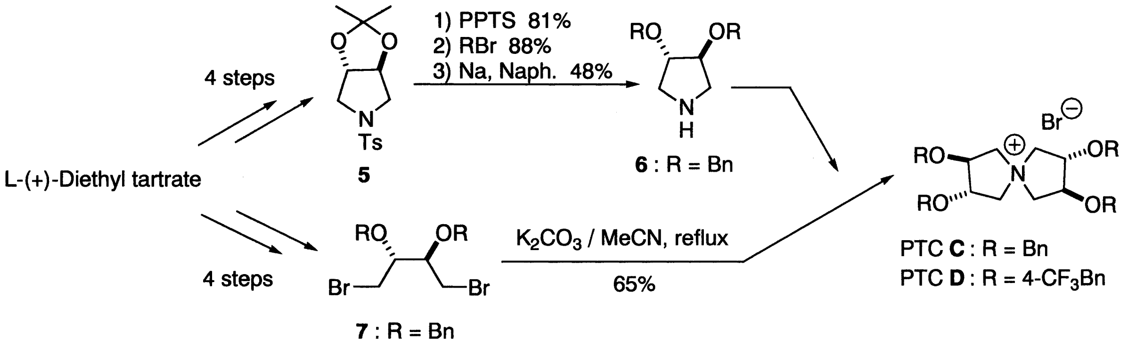


Entry	Base (equiv.)	Conditions	PTC	Yield (%)	ee (%)
1	Cs_2CO_3 (10)	0°C, 21 h	**A**	94	2
2	Cs_2CO_3 (10)	−40°C, 33 h	**B**	37	4
3	$CsOH{\cdot}H_2O$ (0.1)	−40°C, 33 h	**A**	No reaction	–
4	$CsOH{\cdot}H_2O$ (0.1)	−40°C, 33 h	**B**	57	22

hand, cesium hydroxide monohydrate acts as quite effective base even in the presence of 10 mol% and we were pleased to find that the *O*-protected salt (PTC **B**) promoted the reaction at −40°C (57% yield, 22% ee), even though the PTC **A** did not give **4** at all under similar conditons (entries 3 and 4). Encouraged by these results, a novel spiro ammonium salt, PTC **C**, which includes two tartrate moieties, was expected to efficiently construct an asymmetric environment. This compound could also be quite easily prepared from L-tartrate, as outlined in Scheme 2. Deprotection of known compound **5**[14] with PPTS gave diol in good yield and subsequent benzylation with BnBr under PTC conditions (10 mol% of tetrahexylammonium bromide, KOH, toluene, rt) and removal of the tosyl group with sodium naphthalenide gave the corresponding protected amine **6**. Quaternalization of **6** with dibromide **7**[15] in acetonitrile in the presence of K_2CO_3 gave the desired PTC **C** in 65% yield after recrystallization from ethyl acetate.

Solvent-screening in the asymmetric Michael reaction using PTC **C** (2.5 mol%) with $CsOH{\cdot}H_2O$ (10 mol%) revealed that the diethyl ether gave better results than other solvents such as toluene (37%, 46% ee) and CH_2Cl_2 (16%, 43% ee) at −40°C (Table 2, entry 1). In particular, *t*-butyl methyl ether gave the best results (59% ee). Moreover, the reaction proceeded smoothly even at −60°C to give **4** with 73% ee, although the reaction was too slow at −78°C (entries 3 and 4). On the other hand, in the case of the analogue with a 4-CF_3 benzyl group (PTC **D**), prepared by a similar method, the reaction proceeded quickly to give **4** within 26 h and its ee was slightly increased (entry 5). The absolute configuration of **4** was determined by comparison to the literature result to be *S*.[10] These results are summarized in Table 2.[16]

In conclusion, we have developed new PTCs derived from diethyl tartrate and have applied them to the catalytic asymmetric Michael reaction. PTC **C**, which



Scheme 2. Synthesis of PTCs **C** and **D**.

Table 2. Asymmetric Michael reaction of **3** to **4** using PTCs **C** and **D**

Entry	PTC (mol%)	Solvent	Time (h)	Temp. (°C)	Yield (%)	ee (%)
1	**C** (2.5)	Et_2O	58	−40	90	52
2	**C** (2.5)	*t*-BuOMe	48	−40	81	59
3	**C** (10)	*t*-BuOMe	70	−60	86	73
4	**C** (10)	*t*-BuOMe	38	−78	Trace	54
5	**D** (10)	*t*-BuOMe	26	−60	73	77

All reactions were carried out in the presence of 10 mol% of $CsOH{\cdot}H_2O$.

has a spiro ammonium cation, exhibits catalytic activity and the product was obtained with moderate to good enantioselectivity. Further studies on the application of these compounds to other asymmetric reactions and the modification of PTC based on the spiro structure are underway.

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16. *Typical experimental procedure* (Table 2, entry 3): To a test tube containing CsOH monohydrate (1.6 mg, 0.01 mmol), Schiff base **3** (29 mg, 0.1 mmol) and PTC **C** (6.0 mg, 10 mol%) at rt was added *t*-butyl methylether (0.3 mL), and the mixture was stirred for 5 min at −60°C. *t*-Butyl acrylate (73 μL, 0.5 mmol) was then added slowly at −60°C. After stirring for 70 h, the reaction was quenched with water and extracted with AcOEt (3×10 mL), and the combined organic layers were washed with water and dried over Na_2SO_4. The solvents were removed in vacuo and subsequent flash column chromatography gave the desired product **4** (35 mg, 86%, 73% ee). The enantiomeric excess was determined by HPLC [Daicel Chiralcel OD, hexane:*i*-PrOH = 97:3, flow rate: 0.5 mL/min (254 nm), retention times: 9.1 min (minor) and 11.8 min (major)]. Spectral data for PTC **C**: mp 120–120.5°C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.14 (dd, $J = 12.8, 4.4$ Hz, 4H), 4.22 (dd, $J = 12.4, 5.2$ Hz, 4H), 4.29 (br s, 4H), 4.50 (s, 8H), 7.25–7.36 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.6, 71.4, 80.4, 128.1, 128.4, 128.7, 136.3; IR (Nujol): ν 1455, 1366, 1129, 1059, 731 cm^{-1}; LRMS (FAB): m/z 550 (M^+–Br); HRMS (FAB) calcd for $C_{36}H_{40}NO_4$: 550.2957, found: 550.2957; $[\alpha]_D^{24} = +3.8$ (c 1.0, $CHCl_3$).