Asymmetric Michael Reaction Promoted by New Chiral Phase-Transfer Catalysts

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A catalytic asymmetric Michael reaction promoted by new chiral quaternary ammonium salts is described. The products are obtained with moderate ee (up to 75% ee), and the enantioselectivity is strongly dependent on both the substituents on the aromatic rings and the ammonium moiety in the catalysts.

Key word asymmetric synthesis; chiral ammonium salt; phase-transfer catalysis; Michael reaction

Phase-transfer catalysts (PTCs) offer many advantages as organic reagents for the transformation of organic molecules, including mild reaction conditions (water can be used as a solvent), simple reactions, environmental benign and low cost, and they have recently been considered to be a useful tool in the development of green chemistry. In particular, onium salts have been recognized as one of the most powerful PTCs due to their facile preparation and structural diversity, and their utility in asymmetric synthesis has been investigated. The first successful examples of asymmetric catalysis with a chiral ammonium salt as a PTC were reported independently by Dolling[2)] and O'Donnell[3)] in the mid- to late 1980's. The catalysts they have reported for use in enantioselective alkylation are both cinchona alkaloid derivatives. These two pioneering examples in asymmetric PTC chemistry have been applied to other asymmetric reactions.[4—6)] On the other hand, Maruoka and co-workers reported excellent results in the asymmetric alkylation of glycine Schiff base using designer ammonium salts.[7)] Belokon and Kagan also achieved high enantioselectivities using nickel complexes as PTCs.[8)] Nagasawa and co-workers reported chiral guanidinium salts as a new type of PTC that promoted O'Donnell's alkylation under PTC conditions.[9)] In this communication, we report the catalytic asymmetric Michael reaction of a glycine Schiff base using bis-ammonium salts as PTCs.[10—16)] Binaphthol and its derivatives are known to be a versatile starting compound for the preparation of chiral catalyst. And also the functionalization of 2, 3 and 6 positions could provide a various analogues for each asymmetric transformation. Moreover, bis-ammonium salts would be expected to accelerate the reaction due to the two reaction site and it would prevent the undesired reaction pathway which chiral PTCs do not concern. Based upon these, we started to investigate the preparation of symmetrical bis-ammonium salts and survey the asymmetric Michael reaction. First of all, we begun to prepare the 2,3-disubstituted binaphthyl and transformed to bis ammonium salt, as outlined in Chart 1. Di-MOM ether of (*S*)-BINOL **1** was formylated at the 3,3′-position and subsequent deprotection of MOM groups by treatment with acid gave **2** in 65% yield. Benzylation of the phenolic function of **2** with 4-trifluoromethylbenzyl bromide, reduction of the formyl groups and subsequent halogenation of the resulting primary diol with CBr_4–PPh_3 gave the corresponding bis(bromomethyl)binaphthyl **5** in 68% overall yield. Quaternarization of **5** with triethylamine under reflux conditions exclusively gave the bis-ammonium salt, PTC **A**, in excellent yield.[17)] This synthetic route is advantageous for introducing a variety of functional groups to the oxygen and nitrogen atoms, and is therefore a versatile strategy for preparing many types of derivatives.

Initially, the catalytic asymmetric Michael reaction of **6** with *t*-butyl acrylate **7a** as a Michael acceptor was investigated in the presence of PTC **A** with a catalytic amount of base (KOH, 0.14 eq) in toluene as a solvent. We were pleased to find that the salt **A** acts as a PTC to give the desired product **8a** with moderate enantioselectivity, although the chemical yield is unsatisfactory (entry 1). Next, we attempted solvent screening under similar conditions in the presence of a stoichiometric amount of KOH (2 eq). While the chemical yield of **8a** was increased to 49% yield, surprisingly the ee was similar even in the presence of 1 mol% of PTC **A** (entry 2). Encouraged by these results, other solvents such as diethylether and dichloromethane were investigated (entries 3, 4). The reaction proceeded quite smoothly to give the corresponding Michael adduct within 1.5 h, but the enantioselectivities were lower. On the other hand, another aromatic solvent such as benzotrifluoride gave **8a** with 52% ee. However, the chemical yield was lower, even after 2.5 h, and chlorobenzene gave the best result with 57% ee, as shown in entry 5. The absolute configuration of **8a** was determined by comparing the optical rotation to values described in the literature.[13)] The results are summarized in Table 1.

Next, base screening and application to other substrates were investigated, as shown in Table 2. A stronger base such

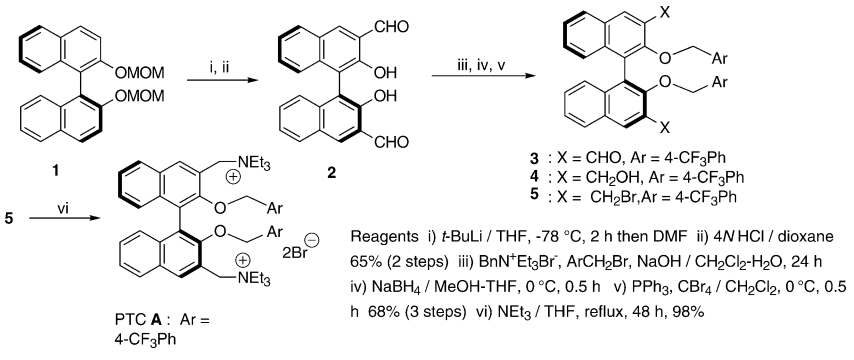

Chart 1. Synthesis of New PTC

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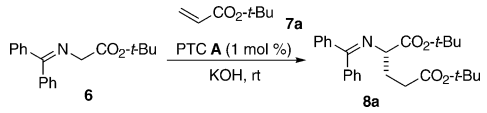
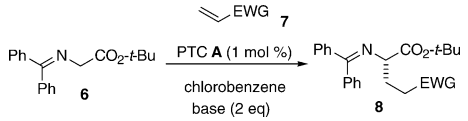
Table 1. Catalytic Asymmetric Michael Reaction of **6**



Entry	Solvent	eq of KOH	Time (h)	Yield (%)	ee (%)
1	Toluene	0.14	64	23	46
2	Toluene	2.0	8	49	42
3	Et_2O	2.0	1.5	98	9
4	CH_2Cl_2	2.0	1.5	93	30
5	$PhCF_3$	2.0	1.5	74	52
6	PhCl	2.0	2.5	55	57

Table 2. Asymmetric Michael Reaction Using Various Michael Acceptors



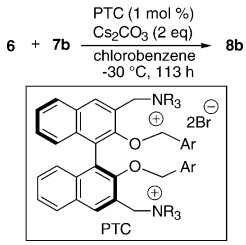
Entry	EWG	Base	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	**7a**: CO_2–*t*-Bu	$CsOH\cdot H_2O$	−10	6.5	**8a**: 86	69
2	**7b**: COMe	Cs_2CO_3	−30	114	**8b**: 100	75
3	**7c**: COEt	Cs_2CO_3	−20	18	**8c**: 83	64
4	**7d**: $CONPh_2$	Cs_2CO_3	rt	11	**8d**: 81	61
5	**7e**: CN	Cs_2CO_3	−10	20	**8e**: 49	32
6	**7f**: SO_2Ph	Cs_2CO_3	−10	113	**8f**: 60	35

as cesium hydroxide was quite effective even at −30 °C, and exclusively gave the desired product with 69% ee (entry 1). A more reactive acceptor such as α,β-unsaturated ketone also transformed to the corresponding adduct in the presence of a weaker base such as Cs_2CO_3. For example, methylvinyl ketone **7b** reacted smoothly at −30 °C to give the desired product **8b** with 75% ee in quantitative yield,[18] and **7c** also gave a similar ee (entries 2, 3). Moreover, a less reactive substrate such as amide **7d** gave moderate ee at room temperature, while the nitrile **7e** and sulfone **7f** resulted in 32 and 35% ee, respectively.

Catalyst screening was also investigated using bis-ammonium salt. Both steric and electronic effects were observed in asymmetric induction, as shown in Table 3. For example, both benzyl and 4-methoxyphenethyl derivatives (PTC **B** and **C**) gave both a lower ee and chemical yields than PTC **A** in the Michael reaction between **6** and **7b**. These results indicate that the interaction between π-electrons of the aromatic rings in the catalyst and substrate is essential for achieving reasonable enatioselectivity. We found that the amine moiety also plays an important role in enantioselectivity. PTC **D** and **E**, which include a benzyl amine unit, gave 43 and 56% ee, respectively, in quite lower yield under conditions similar to those in Table 2, entry 2.

In summary, our results suggest that a novel ammonium salt, PTC **A**, derived from (*S*)-BINOL acts as an efficient promoter in the catalytic asymmetric Michael reaction using a glycine Schiff base.[19] This presents a new procedure for obtaining chiral glutamic acid derivatives. However, not all of the enantioselectivities are satisfactory, and modification

Table 3. Effect of PTC



Entry	PTC	Ar	NR_3	Yield (%)	ee (%)
1	**B**	Ph	NEt_3	66	57
2	**C**	4-MeOPh	NEt_3	trace	—
3	**D**	4-CF_3Ph	$BnNEt_2$	14	43
4	**E**	4-CF_3Ph		54	56

of PTC and its application to other asymmetric reactions are currently under investigation.

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17) Spectral data of PTC **A**: white solid; mp 173 °C (decomposed); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 1.34 (9H, t, J=6.8 Hz), 3.12 (6H, q, J=6.8 Hz), 4.27 (1H, d, J=10.8 Hz), 5.01 (1H, d, J=14.0 Hz), 5.18 (1H, d, J=14.0 Hz), 5.20 (1H, d, J=10.8 Hz), 6.70 (2H, d, J=7.8 Hz), 7.27—7.30 (3H, m), 7.54 (1H, t, J=7.6 Hz), 7.64 (1H, t, J=7.6 Hz), 8.10 (1H, d, J=7.8 Hz), 8.24 (1H, s). ^{13}C-NMR (CD_3OD, 67.0 MHz) δ: 8.7, 54.2, 77.2, 122.3, 126.4, 126.5, 127.2, 127.8, 129.6, 130.2, 130.4, 132.0, 136.0, 137.3, 141.4. IR (nujor) cm^{-1}: 2361, 1156; MS (FAB) *m*/*z*: 911, 909 (M^+−Br). FAB-MS *m*/*z*: 909.3399 (Calcd for $C_{50}H_{56}{}^{79}BrF_6N_2O_2$: 909.3429) 911.3392 (Calcd for $C_{50}H_{56}{}^{81}BrF_6N_2O_2$:

911.3421). $[\alpha]_D^{25}$ +92.5° (c=10.0, MeOH).

18) Typical experimental procedure (synthesis of **8b**); To a solution of Schiff base **6** (74 mg, 0.25 mmol) of chlorobenzene (0.83 ml) was added PTC **A** (1.2 mg, 0.00125 mmol) and cesium carbonate (82 mg, 0.25 mmol) at rt, and the mixture was cooled to −30 °C. After stirring for 5 min, methyl vinylketone **7b** was then added and stirred for 114 h. The reaction mixture was quenched with water, extracted with ethyl acetate (3 ml×3) and combined organic layers were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo* and subsequent flash column chromatography (hexane : AcOEt=5 : 1) gave the desired product **8b** (39 mg, 100%, 75% ee). The enantiomeric excess was determined by HPLC [CHIRALCEL OD, hexane : *i*-PrOH=50 : 1, flow rate: 1.0 ml/min (254 nm), retention times: 7.8 min (minor), 9.1 min (major)].

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