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Enantioselective Michael reaction of malonates and chalcones by phase-transfer catalysis using chiral quaternary ammonium salt

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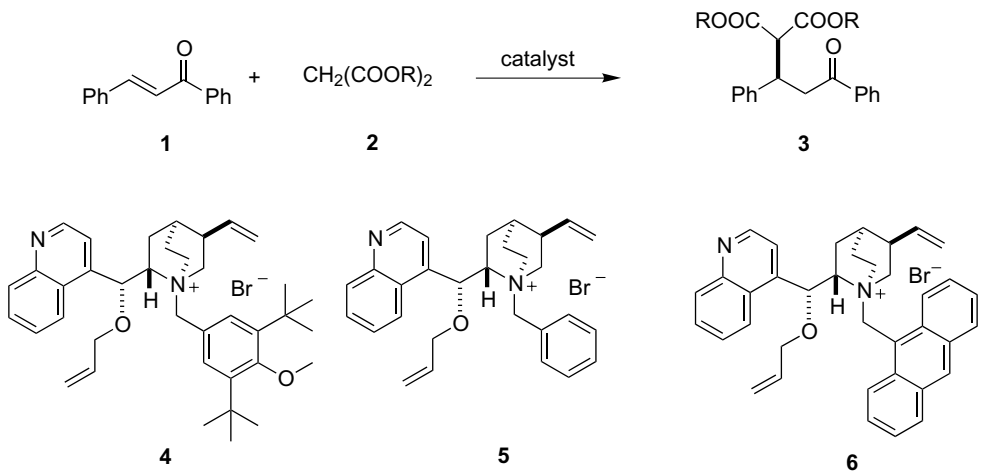
Abstract—The catalytic enantioselective Michael reaction promoted by quaternary ammonium salt from cinchonidine as a phase-transfer catalyst is described. Treatment of malonate with chalcone derivatives under mild reaction conditions afforded the corresponding Michael adducts in good yields with good to moderate enantiomeric excesses. © 2001 Elsevier Science Ltd. All rights reserved.

The formation of carbon–carbon bonds by conjugated addition of appropriate carboanionic reagents to α,β-unsaturated carbonyl compounds is one of the most useful methods of remote functionalization in organic synthesis.[1] Therefore, their catalytic asymmetric version have been studied extensively.[2] Efforts toward achieving asymmetric conjugate addition of malonates to chalcones in the presence of chiral catalysts have been the subject of several reports. For example, the reaction of malonates with chalcones catalyzed by La–BINOL complexes,[3] L-proline derivatives,[4] chiral aminoalcohol–Al complexes,[5] pyrrolidylalkyl ammonium hydroxide,[6] and chiral ammonium salts.[7]

Phase-transfer catalysis have been increasingly useful in organic synthesis.[8] Recently, there have been successful applications to catalytic asymmetric synthesis using cinchona–alkaloids-derived quaternary ammonium salts.[9] The attachment of the bulky substituents to bridgehead nitrogen leads to a quaternary ammonium structure of well-defined geometry in which tetrahedral face about ammonium nitrogen is blocked by bulky subunit. The introduction of a bulky subunit at the 1-position of cinchona alkaloids leads to enhance the stereoselectivity in catalytic phase-transfer reactions.[10] As part of our research program toward the development of a more effective cinchona–alkaloid-derived phase-transfer cata-



Scheme 1.

Keywords: phase transfer; Michael reactions; ammonium salt; asymmetric reactions.

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Table 1. Catalytic asymmetric Michael reaction of malonates to chalcone **1a** with phase-transfer catalysts

Entry	Malonate **2**, R	Catalyst	Base	Solvent	Temp. (°C)	Yield (%)	Ee[a] (%)
1	Et	**4**	*t*-BuOK	Toluene	20	**3a**, 74	35
2	Et	**4**	KOH	Toluene	20	**3a**, 74	40
3	Et	**4**	KOH	CH_2Cl_2	0	**3a**, 68	43
4	Et	**4**	K_2CO_3	Toluene	20	**3a**, 70	46
5	Et	**4**	K_2CO_3	Toluene	0	**3a**, 68	40
6	Me	**4**	K_2CO_3	Toluene	20	**3b**, 92	27
7	*i*-Pr	**4**	K_2CO_3	Toluene	20	**3c**, 77	55
8	Bn	**4**	K_2CO_3	Toluene	20	**3d**, 91	70
9	Bn	**5**	K_2CO_3	Toluene	20	**3d**, 64	6
10	Bn	**6**	K_2CO_3	Toluene	20	**3d**, 67	35

[a] Enantiopurities of **3a–d** were determined by HPLC analysis with Chiralcel AD column (for **3a** and **3c**) and Chiralcel AS column (for **3b** and **3d**), 2-propanol–hexane (1:9), 1.2 mL/min, $\lambda_{max}=254$ nm. It was established by analyses of racemic **3** that the enantiomers were fully resolved.

lyst, we introduced a bulky environment at the 1-position by (3,5-di-*tert*-butyl-4-methoxy)benzyl group. In this paper, we wish to report herein on the catalytic asymmetric conjugate addition of malonates **2** to chalcones **1** using *N*-(3,5-di-*tert*-butyl-4-methoxy)benzylcinchonidinium bromide (**4**). A new catalyst **4** is derived in two steps from cinchonidine.[11] In order to determine suitable reaction conditions for the catalytic asymmetric conjugate addition of malonates **2** to chalcones **1** (Scheme 1), we initially investigated the reaction system using 10 mol% of catalyst, with malonate as the Michael donor and chalcone **1a** as the Michael acceptor (Table 1).

Catalyzed by **4** (10 mol%), malonate reacted with chalcone in the presence of K_2CO_3, at room temperature, to afford the Michael adduct **3a** in 70% yield and 46% ee (Table 1, entry 4). In the presence of other bases such as KOH or *t*-BuOK, **3a** was obtained in good yield and low enantioselectivity (entries 1–3). Toluene as solvent was effective in this reaction. The reaction temperature is not critical in this reaction (entries 4 and 5). As increased bulkiness of malonates, the enantioselectivity was increased in this reaction (entries 6–8). Known cinchona-type phase-transfer catalysts **5** and **6**[10] were less effective than catalyst **4** in this reaction (entries 9 and 10). The stirring rate does not appear to influence the enantioselectivity of this reaction, however it does affect the rate of reaction and substantially decreased reaction time can be achieved with high stirring rate. The absolute configuration of the major enantiomer of **3b** was determined to be *R* from the optical rotation and chiral HPLC analysis.[3]

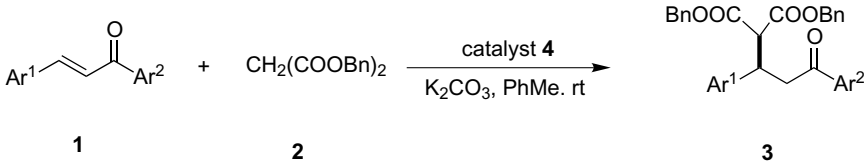
Under the optimized reaction conditions described above (10 mol% of catalyst **4**, K_2CO_3, toluene, rt), we investigated catalytic asymmetric Michael reaction of dibenzyl malonate to chalcone derivatives **1**.[12] The reaction smoothly proceeded to afford the corresponding adducts **3** with good enantioselectivities. Reaction of 1.5 equiv. of dibenzyl malonate with chalcone derivatives **1**, cinchonidinium salt **4** (10 mol%), and K_2CO_3 in toluene at room temperature with stirring for 18–24 h afforded the Michael adducts **3** (Scheme 2) in good yields with moderate enantioselectivities (45–70% ee) (Table 2). In all cases the enantiomeric excesses were determined by HPLC analysis.

In conclusion, we have developed a new class of asymmetric phase-transfer catalyst, which shows good enantioselectivity in the Michael reaction of malonates to chalcones. We are currently involved in the further development of these catalyst systems and investigating their applicability to other asymmetric phase-transfer processes.

Table 2. Catalytic asymmetric Michael reaction of dibenzyl malonate to chalcones **1** with phase-transfer catalyst **4**

Ar^1	Ar^2	Time (h)	Yield (%)	Ee[a] (%)
Ph	Ph	18	**3d**, 91	70
Ph	*p*-OMe, Ph	18	**3e**, 91	47
Ph	2-Thienyl	18	**3f**, 94	51
p-OMe, Ph	Ph	18	**3g**, 88	45
2-Naphthyl	*m*-Br, Ph	24	**3h**, 60	67
2-Naphthyl	*p*-Br, Ph	24	**3i**, 58	59

[a] Enantiopurities of **3d–i** were determined by HPLC analysis with chiral column (Chiralcel AS for **3d–g**, OD-H for **3h** and **3i**), 2-propanol–hexane (1:9), 1.2 mL/min, $\lambda_{max}=254$ nm. In each case, it was established by analyses of racemic **3** that the enantiomers were fully resolved.



Scheme 2.

Acknowledgements

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11. To a suspension of cinchonidine (2.94 g, 10 mmol) in toluene (70 mL) was added 3,5-di-*tert*-butyl-4-methoxybenzyl bromide (4.38 g, 14 mmol), and the mixture was stirred at reflux for 4 h. The reaction mixture was cooled at room temperature, evaporated, and the residue was recrystallized from diethyl ether/CH_2Cl_2 to give the product as a dark brown solid. Purification of the residue by flash chromatography (93:7, dichloromethane:methanol) afforded the desired product *N*-(4-methoxy-3,5-di-*tert*-butylbenzyl)cinchonidinium bromide (91%, 5.57 g) as a brown solid. To a suspension of *N*-(3,5-di-*tert*-butyl-4-methoxybenzyl)cinchonidinium bromide (3.03 g, 5.0 mmol) in 40 mL of CH_2Cl_2 was added allyl bromide (0.64 mL, 7.5 mmol) and 2.8 mL of 50% of aq. KOH (25.0 mmol). The resulting mixture was stirred for 5 h. The mixture was diluted with 40 mL of water and extracted with CH_2Cl_2 (3×40 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel (93:7, dichloromethane:methanol) to give product **4** (92%, 2.98 g) as a yellow solid. $[\alpha]_D^{25}$ −142.5 (*c* 2, $CHCl_3$); mp 220–221°C; IR (film, cm^{-1}) 3407, 3000, 2949, 1704, 1625, 1596, 1567, 1510, 1502, 1491, 1470, 1454, 1400, 1350, 1210. 1115, 1070, 1010; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.47–1.50 (s, 19H), 2.09–2.17 (m, 3H), 2.63 (s, 1H), 3.34–3.47 (m, 3H), 3.75 (s, 3H), 4.01 (m, 1H), 4.28 (m, 2H), 4.64 (d, $J=11.5$ Hz, 2H), 5.01 (d, $J=8.4$ Hz, 1H), 5.05 (d, $J=10.5$ Hz, 1H), 5.32–5.43 (m, 3H), 5.77 (m, 1H), 6.18 (m, 1H), 6.23 (s, 1H), 6.31 (d, $J=11.5$ Hz, 1H), 7.70 (s, 3H), 7.80 (t, $J=7.4$ Hz, 1H), 7.93 (m, 1H), 8.14 (d, $J=8.39$ Hz, 1H), 8.71 (d, $J=8.48$ Hz, 1H), 8.97 (d, $J=4.39$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.99, 22.54, 25.28, 27.02, 31.99, 35.92, 37.77, 42.30, 51.04, 59.39, 60.31, 62.72, 64.34, 65.73, 70.30, 115.55, 118.40, 119.17, 120.04, 121.14, 124.40, 125.10, 129.10, 129.85, 130.28, 132.37, 132.47, 136.29, 139.88, 144.82, 148.40, 149.40, 161.18; MS (EI) m/z 567, 470, 394, 268, 167.
12. *General procedure for Michael addition of malonate to chalcones*: A mixture of dibenzyl malonate (0.11 mL, 0.45 mmol), K_2CO_3 (0.16 g, 2.0 mmol), chiral cinchonidinium salt **4** (18.0 mg, 0.03 mmol), and chalcone (0.3 mmol) in toluene (2 mL) was stirred at room temperature for 14–20 h. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography (silica gel, ethyl acetate:hexane = 1:5) to afford Michael adduct.