

## Communications

### Enantioselective Michael Reaction of Fluoromalonates and Chalcones by Phase-Transfer Catalysis Using Chiral Quaternary Ammonium Salt

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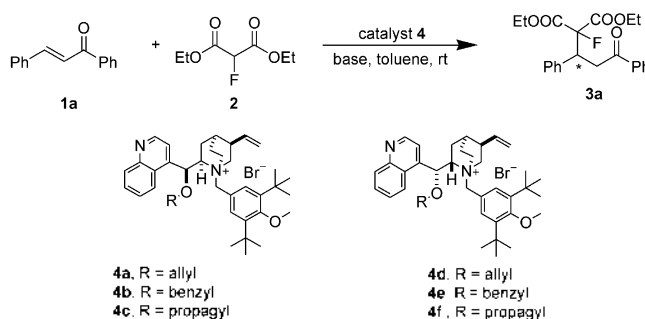
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The Michael reaction of carboanionic reagents to  $\alpha,\beta$ -unsaturated carbonyl compounds is one of the most fundamental C-C bond-forming reaction.<sup>1</sup> Catalytic asymmetric conjugate additions of malonates to enone in the presence of chiral catalysts have been studied extensively.<sup>2</sup> However, enantioselective Michael reactions of fluoro malonates to  $\alpha,\beta$ -unsaturated ketones have scarcely been studied. Phase-transfer catalysis is a clean and efficient processes involving high yields, operational simplicity, mild conditions, low cost, safety, and environmental profit.<sup>3</sup> Recently, there have been successful applications to catalytic asymmetric synthesis using cinchona alkaloid-derived quaternary ammonium salts.<sup>4</sup> As part of our research program related to the development of effective cinchona alkaloid derived phase-transfer catalysts,<sup>5,6</sup> We reported the catalytic enantioselective Michael reaction promoted by quaternary ammonium salts from cinchonidine as a phase-transfer catalyst.<sup>6</sup>

In this paper, we wish to report the catalytic enantioselective Michael reaction of diethyl fluoromalonate **2** to chalcone derivatives **1** using the cinchona alkaloid derived quaternary ammonium salts **4**. In order to determine suitable reaction conditions, we initially investigated the reaction system using 10 mol% of catalyst with diethyl fluoro malonate **2** as the Michael donor and chalcone **1a** as the Michael acceptor (Table 1).

Catalysts **4a** and **4d** having O-allyl group showed higher catalytic efficiencies than other catalysts in terms of yields

**Table 1.** Catalytic asymmetric Michael reaction of diethyl fluoromalonate **2** to chalcone **1a** with phase-transfer catalysts **4**



Entry	Catalyst	Base	Time (h)	Yield <sup>a</sup> (%)	Ee <sup>b</sup> (%)
1	<b>4a</b>	K <sub>2</sub> CO <sub>3</sub>	18	64	37
2	<b>4b</b>	K <sub>2</sub> CO <sub>3</sub>	18	38	23
3	<b>4c</b>	K <sub>2</sub> CO <sub>3</sub>	18	20	27
4	<b>4d</b>	K <sub>2</sub> CO <sub>3</sub>	15	63	39
5	<b>4d</b>	Cs <sub>2</sub> CO <sub>3</sub>	9	38	11
6	<b>4d</b>	Rb <sub>2</sub> CO <sub>3</sub>	9	63	33
7	<b>4e</b>	K <sub>2</sub> CO <sub>3</sub>	18	30	33
8	<b>4f</b>	K <sub>2</sub> CO <sub>3</sub>	18	57	31

<sup>a</sup>Isolated yields are based on chalcone. <sup>b</sup>Enantiomeric excess was determined by HPLC analysis using Chiralcel OD-H (2-propanol:hexane = 1 : 9).

and enantioselectivity (entries 1-4, and 7-8). It has been also found that K<sub>2</sub>CO<sub>3</sub> was the more effective base in this reaction than others such as Cs<sub>2</sub>CO<sub>3</sub> and Rb<sub>2</sub>CO<sub>3</sub> (entries 4-6). Compound (+)-**3a** was formed using cinchonine-derived catalysts (**4a-4c**) as the excessive enantiomer, which should

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**Table 2.** Catalytic asymmetric Michael reaction of diethyl fluoromalonate **2** to chalcones **1** with phase-transfer catalyst **4d**

Ar <sup>1</sup>	Ar <sup>2</sup>	Time (h)	Yield <sup>a</sup> (%)	EE <sup>b</sup> (%)
		15	<b>3a</b> , 63	39
		18	<b>3b</b> , 76	47
		18	<b>3c</b> , 64	37
		18	<b>3d</b> , 77	37
		18	<b>3e</b> , 60	45
		18	<b>3f</b> , 58	47

<sup>a</sup>Isolated yields are based on chalcone. <sup>b</sup>Enantiomeric excess was determined by HPLC analysis using Chiralcel OD-II (for **3a**, **3b**, **3c**, **3d**, **3e**) and Whelk-O1 (for **3f**).

be the case because all of these catalysts possess the same chirality. The cinchonidine-derived catalysts **4d-4f** leading to formation of (–)-**3a** in excess. Under the optimized reaction conditions described above (10 mol% of catalyst **4d**, K<sub>2</sub>CO<sub>3</sub>, toluene, rt), we investigated catalytic asymmetric Michael reaction of diethyl fluoromalonate to chalcone derivatives **1**.<sup>7</sup> The reaction smoothly proceeded to afford the corresponding adduct **3** with moderate enantioselectivities. Reaction of 1.0 equiv of diethyl fluoromalonate **2** with chalcone derivatives **1**, cinchonidinium salt **4d** (10 mol%), and K<sub>2</sub>CO<sub>3</sub> in toluene at room temperature with stirring for 15–18 h afforded the Michael adducts **3** in good yields with moderate enantioselectivities (35–47 %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 diethyl fluoromalonate to chalcones. We are currently involved in the further development of these catalyst systems and investigating their applicability to other asymmetric phase-transfer processes.

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- General procedure for Michael addition of fluoromalonate to chalcones:* To a suspension of diethyl fluoromalonate (**2**, 0.017 g, 0.1 mmol), K<sub>2</sub>CO<sub>3</sub> (0.069 g, 0.5 mmol) in toluene (0.5 mL) was added chiral cinchonidinium salt **4d** (6.4 mg, 0.01 mmol), chalcone **1** (0.1 mmol), and the mixture was stirred at room temperature for 15–18 h. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (220 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, concentrated, and purified by flash chromatography (silica gel, ethyl acetate : hexane = 1 : 6) to afford Michael adduct **3**.