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Communications

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

Dae Young Kim,* Sung Min Kim, Kwang Oh Koh, Joo Yang Mang, and Kilsung Lee†

Department of Chemistry, Soonchunhyang University, Asan P.O. Box 97, Chungnam 336-600, Korea
†Cheil Indusries Inc., Euiwang, Kyoungki 437-010, Korea

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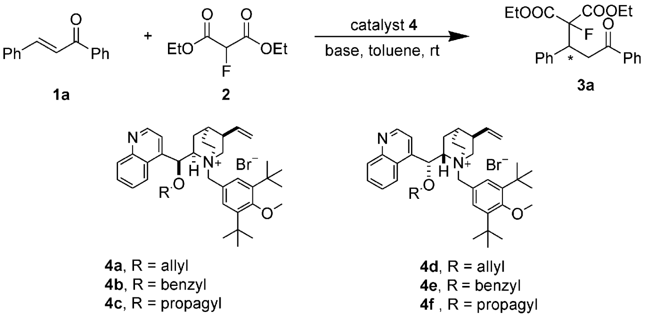
The Michael reaction of carboanionic reagents to α,β-unsaturated carbonyl compounds is one of the most fundamental C-C bond-forming reaction.[1] Catalytic asymmetric conjugate additions of malonates to enone in the presence of chiral catalysts have been studied extensively.[2] However, enantioselective Michael reactions of fluoro malonates to α,β-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.[3] Recently, there have been successful applications to catalytic asymmetric synthesis using cinchona alkaloid-derived quaternary ammonium salts.[4] As part of our research program related to the development of effective cinchona alkaloid derived phase-transfer catalysts,[5,6] We reported the catalytic enantioselective Michael reaction promoted by quaternary ammonium salts from cinchonidine as a phase-transfer catalyst.[6]

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 and enantioselectivity (entries 1-4, and 7-8). It has been also found that K_2CO_3 was the more effective base in this reaction than others such as Cs_2CO_3 and Rb_2CO_3 (entries 4-6). Compound (+)-**3a** was formed using cinchonine-derived catalysts (**4a**-**4c**) as the excessive enantiomer, which should

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



Entry	Catalyst	Base	Time (h)	Yield[a] (%)	Ee[b] (%)
1	**4a**	K_2CO_3	18	64	37
2	**4b**	K_2CO_3	18	38	23
3	**4c**	K_2CO_3	18	20	27
4	**4d**	K_2CO_3	15	63	39
5	**4d**	Cs_2CO_3	9	38	11
6	**4d**	Rb_2CO_3	9	63	33
7	**4e**	K_2CO_3	18	30	33
8	**4f**	K_2CO_3	18	57	31

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

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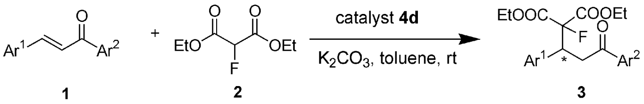
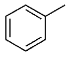
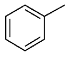
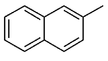
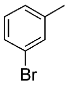
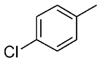
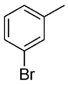
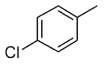
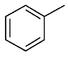
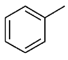
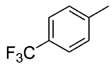
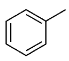
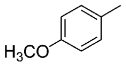
*Corresponding author. Tel: +82-41-530-1244; Fax: +82-41-530-1247; E-mail: dyoung@sch.ac.kr

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



Ar^1	Ar^2	Time (h)	Yield^a (%)	Ee^b (%)
		15	**3a**, 63	39
		18	**3b**, 76	47
		18	**3c**, 64	37
		18	**3d**, 77	37
		18	**3e**, 60	45
		18	**3f**, 58	47

^{a}Isolated yields are based on chalcone. ^{b}Enantiomeric excess was determined by HPLC analysis using Chiralcel OD-H (for **3a**, **3b**, **3c**, **3d**, **3e**) and Whelk-O1 (for **3f**).

be the case because all of these catalysts posses 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_2CO_3, toluene, rt), we investigated catalytic asymmetric Michael reaction of diethyl fluoromalonate to chalcone derivatives **1**.[7] 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_2CO_3 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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References

1. (1) For recent reviews and monographs, see: (a) Leonard, J. *Contemp. Org. Synth.* **1994**, *1*, 387. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992. (c) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.
2. (a) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 104. (b) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506. (c) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520. (d) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975. (e) Narasimhan, S.; Balakumar, V. R.; Radhakrishnan, V. *Tetrahedron Lett.* **2001**, *42*, 719. (f) Sundarajan, G.; Prabagaran, N. *Org. Lett.* **2001**, *3*, 389. (g) Perrard, T.; Plaquevent, L.-C.; Desmurs, J.-R.; Hebrault, D. *Org. Lett.* **2000**, *2*, 2959.
3. (a) Dehmlow, E. V. and S. S. *Phase Transfer Catalysis*, 3rd Ed.; VCH: Weinheim, 1993. (b) Goldberg, Y. *Phase Transfer Catalysis: Selected Problems and Application*; Gordon & Breach Science Publ.: Reading, 1992. (c) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives*; Chapman & Hall: New York, 1994. (d) Shioiri, T. *Chiral Phase Transfer Catalysis*, Chapter 14 in Handbook of Phase Transfer Catalysis; Sasson, Y., Neumann, R., Eds.; Blackie Academic & Professional: London, 1997. (e) O'Donnell, M. J. *Asymmetric Phase Transfer Reactions*, Chapter 10 in Catalytic Asymmetric Synthesis; Ojima, I., Eds.; Wiley-VCH: 2000.
4. (a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (b) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000. (c) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347. (d) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *39*, 3843. (e) Corey, E. J.; Zhang, F.-Y. *Org. Lett* **1999**, *1*, 1287. (f) Zhang, F.-Y; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097. (g) Corey, E. J.; Zhang, F.-Y. *Angew. Chem., Intl. Ed.* **1999**, *38*, 1931. (h) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595. (i) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1998**, *39*, 1599. (j) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671. (k) Lygo, B.; Wainwright, P. G. *Tetrahedron* **1999**, *55*, 6289. (l) Oku, M.; Arai, S.; Katayama, K.; Shioiri, T. *Synlett* **2000**, 493. (m) Arai, S., Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* **1999**, *55*, 6375. (n) Arai, S.; Hamaguchi, S.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 2997. (o) Park, H.-g.; Jeong, B.-s.; Yoo, M.-s.; Lee, J.-h.; Park, B.-s.; Kim, M. G.; Jew, S.-s. *Tetrahedron Lett.* **2003**, *44*, 3497. (p) Jew, S.-s.; Yoo, M.-s.; Jeong, B.-s.; Park, I. Y.; Park, H.-g. *Org. Lett.* **2002**, *4*, 4245.
5. Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545.
6. (a) Kim, D. Y.; Huh, S. C.; Kim, S. M. *Tetrahedron Lett.* **2001**, *42*, 6299. (b) Kim, D. Y.; Huh, S. C. *Tetrahedron* **2001**, *57*, 8933. (c) Kim, D. Y.; Choi, Y. J.; Park, H. Y.; Joung, C. U.; Koh, K. O.; Mang, J. Y.; Jung, K. Y. *Synth. Commun.* **2003**, *33*, 435.
7. *General procedure for Michael addition of fluoromalonate to chalcones*: To a suspension of diethyl fluoromalonate (**2**, 0.017 g, 0.1 mmol), K_2CO_3 (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 $MgSO_4$, filtered, concentrated, and purified by flash chromatography (silica gel, ethyl acetate : hexane = 1 : 6) to afford Michael adduct **3**.