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Importance of Chiral Phase-Transfer Catalysts with Dual Functions in Obtaining High Enantioselectivity in the Michael Reaction of Malonates and Chalcone Derivatives

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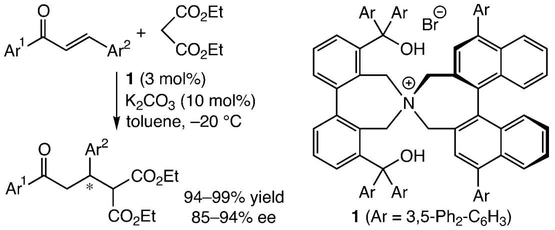
ABSTRACT



Highly enantioselective Michael addition of diethyl malonate to chalcone derivatives has been achieved under mild phase-transfer conditions by the successful utilization of *N*-spiro C_2-symmetric chiral quaternary ammonium bromide 1 as a catalyst, which possesses diarylhydroxymethyl functionalities as a recognition site for the prochiral electrophile. This simple asymmetric Michael addition process was found to be quite effective for various chalcone derivatives, including those with heteroaromatic substituents.

During the past decade, the development of asymmetric phase-transfer catalysis based on the use of structurally well-defined chiral, nonracemic catalysts has resulted in notable achievements, making it feasible to perform various bond formation reactions under mild phase-transfer-catalyzed conditions.[1] The characteristic aspect of this success is that most of the highly stereoselective transformations involve *prochiral nucleophiles* (*enolates*) pairing with chiral onium cations, as well-exemplified by the asymmetric functionalization of glycinate Schiff bases.[1d−g] This, in turn, indicates the difficulty of controlling the stereochemical outcome of the additions of nucleophiles lacking prochirality to *prochiral electrophiles*, on which new stereogenic centers are solely created. Indeed, synthetically useful reactions of this type have been relatively restricted[1a−c] and the enantioselective oxidation of α,*β*-unsaturated ketones represents such rare examples.[2−4,7] The asymmetric carbon−carbon bond formation through the Michael addition of malonates to chalcone

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[1] For recent reviews, see: (a) Shioiri, T. In *Handbook of Phase-Transfer Catalysis*; Sasson, Y., Neumann, R., Eds.; Blackie Academic & Professional: London, 1997; Chapter 14. (b) Shioiri T.; Arai, S. In *Stimulating Concepts in* Chemistry, Vogtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley−VCH: Weinheim, 2000; p 123. (c) O'Donnell, M. J. In *Catalytic Asymmetric Syntheses*, 2nd ed.; Ojima, I., Ed.; Wiley−VCH: New York, 2000; Chapter 10. (d) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3. (e) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (f) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (g) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518.

[2] Recent representative examples of phase-transfer-catalyzed asymmetric epoxidation: (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1998**, *39*, 1599. (b) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287. (c) Lygo, B.; To, D. C. M. *Tetrahedron Lett.* **2001**, *42*, 1343. (d) Adam, W.; Rao, P. B.; Degen, H.-G.; Lévai, A.; Patonay, T.; SahaMöller, C. R. *J. Org. Chem.* **2002**, *67*, 259. (e) Arai, S.; Tsuge, H.; Oku, M.; Miura, M.; Shioiri, T. *Tetrahedron* **2002**, *58*, 1623. (f) Ye, J.; Wang, Y.; Liu, R.; Zhang, G.; Zhang, Q.; Chen, J.; Liang, X. *Chem. Commun.* **2003**, 2714. (g) Allingham, M. T.; Howard-Jones, A.; Murphy, P. J.; Thomas, D. A.; Caulkett, P. W. R. *Tetrahedron Lett.* **2003**, *44*, 8677. (h) Bakó, T.; Bakó, P.; Keglevich, G.;

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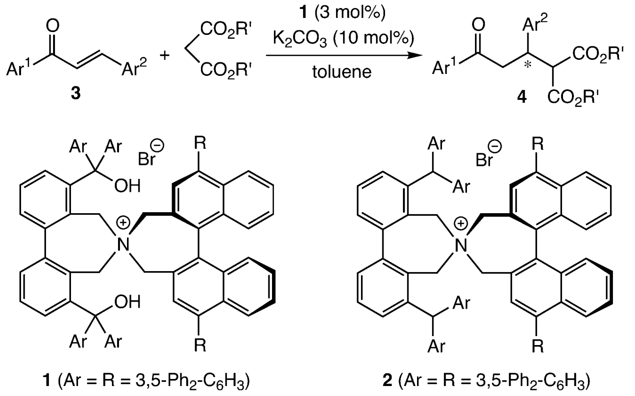
derivatives also belongs to this category, but only a few reports have appeared in the literature with limited success.[5,6] In conjunction with our recent effort toward finding a general solution to this intrinsic problem by the rational molecular design of dual-functioning chiral phase-transfer catalysts of type **1**,[7] we have been interested in evaluating the effectiveness of our approach in the Michael reaction of malonates and chalcones (Scheme 1). In this letter, we wish to describe the preliminary results of this study, demonstrating the importance of the chiral catalyst with a recognition site for the electrophile to control the absolute stereochemistry of the chiral carbon center generated on the prochiral chalcone derivatives.

Scheme 1

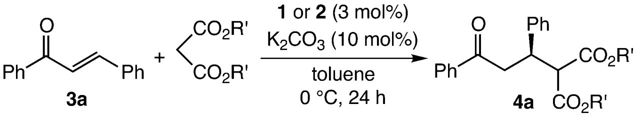


1 (Ar = R = 3,5-Ph$_2$-C$_6$H$_3$)

2 (Ar = R = 3,5-Ph$_2$-C$_6$H$_3$)

We initiated this research program by examining the applicability of chiral quaternary ammonium bromide **1**, a promising catalyst for the asymmetric epoxidation of α,*β*-unsaturated ketones,[7] to the addition of dimethyl malonate to chalcone (**3a**). Thus, a mixture of chalcone, dimethyl malonate, **1** (3 mol %), and potassium carbonate (K_2CO_3) (10 mol %) in toluene was vigorously stirred at 0 °C, and after 24 h, the desired Michael adduct **4a** ($R' = Me$) was isolated quantitatively. Fortunately, its enantiomeric excess turned out to be quite promising (84% ee) (entry 1 in Table 1).[8] This result prompted us to examine the effect of the ester substituent (R′) of malonates, which revealed that diethyl malonate appeared to be an optimal Michael donor in terms of both reactivity and selectivity (entry 2). The enantioselectivity reached 90% ee upon performing the addition at lower temperature (−20 °C) (entry 3). On the other hand, the reaction with dibenzyl malonate resulted in a substantial decrease in the stereoselectivity, in contrast to the previous report (entry 4),[5a] and no indication of the product formation was observed when di-*tert*-butyl malonate was employed (entry 6). Here, it is particularly emphasized that the control reaction with diethyl malonate by the use of catalyst **2** under otherwise identical conditions brought a significant loss of enantiomeric excess (entry 7), indicating the crucial importance of the hydroxy functionality for the adequate enantiofacial differentiation of the prochiral chalcone.

Table 1. Effect of the Ester Substituent (R′) on the Reactivity and Stereoselectivity in the Catalytic Asymmetric Michael Addition of Dialkyl Malonate to Chalcone (**3a**) under Phase-Transfer Conditions[a]



entry	catalyst	R′	% yield[b]	% ee[c] (configuration)[d]
1	**1**	Me	99	84
2	**1**	Et	99	86 (*R*)
3[e]	**1**	Et	99	90 (*R*)
4	**1**	Bn	99	61
5	**1**	*i*-Pr	99	74
6	**1**	*t*-Bu	nr[f]	
7	**2**	Et	98	15 (*R*)

[a] Unless otherwise specified, the reaction was conducted with 4 equiv of dialkyl malonate in the presence of 3 mol % of **1** or **2** and 10 mol % of K_2CO_3 in toluene at 0 °C for 24 h. [b] Isolated yield. [c] Enantiopurity of the Michael adduct **4a** was determined by HPLC analysis using a chiral column (DAICEL Chiralpak AD-H) with hexane−ethanol as a solvent. [d] Absolute configuration was determined by comparison of the optical rotation with the value previously reported.[11] [e] Performed at −20 °C. [f] No reaction.

With this information in hand, we next pursued experiments to probe the scope of the 1,4-diarylenone **3**.[9] As listed in Table 2, the present phase-transfer-catalyzed Michael addition of diethyl malonate in the presence of catalyst **1** (3 mol %) and K_2CO_3 (10 mol %) in toluene tolerated both electron-withdrawing and -donating groups on the aryl substituents, and thus the corresponding Michael adducts

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Bombicz, P.; Kubinyi, M.; Pál, K.; Bodor, S.; Makó, A.; Tõke, L. *Tetrahedron: Asymmetry* **2004**, *15*, 1589. (i) Jew, S.-s.; Lee, J.-H.; Jeong, B.-S.; Yoo, M.-S.; Kim, M.-J.; Lee, Y.-J.; Lee, J.; Choi, S.-h.; Lee, K.; Lah, M. S.; Park, H.-g. *Angew. Chem., Int. Ed.* **2005**, *44*, 1383.

(3) Asymmetric dihydroxylation: Bhunnoo, R. A.; Hu, Y.; Lainé, D. I.; Brown, R. C. D. *Angew. Chem., Int. Ed.* **2002**, *41*, 3479. See also: Brown, R. C. D.; Keily, J. F. *Angew. Chem., Int. Ed.* **2001**, *40*, 4496.

(4) For other contributions, see, for example: (a) Asymmetric Michael addition of 2-nitropropane: Bakó, P.; Czinege, E.; Bakó, T.; Czugler, M.; Tõke, L. *Tetrahedron: Asymmetry* **1999**, *10*, 4539. (b) Asymmetric cyclopropanation: Arai, S.; Nakayama, K.; Ishida, T.; Shioiri, T. *Tetrahedron Lett.* **1999**, *40*, 4215. (c) Asymmetric aldol reaction: Arai, S.; Hasegawa, K.; Nishida, A. *Tetrahedron Lett.* **2004**, *45*, 1023. See also ref 1c.

(5) (a) Kim, D. Y.; Huh, S. C.; Kim, S. M. *Tetrahedron Lett.* **2001**, *42*, 6299. (b) Dere, R. T.; Pal, R. R.; Patil, P. S.; Salunkhe, M. M. *Tetrahedron Lett.* **2003**, *44*, 5351. See also: (c) Loupy, A.; Zaparucha, A. *Tetrahedron Lett.* **1993**, *34*, 473.

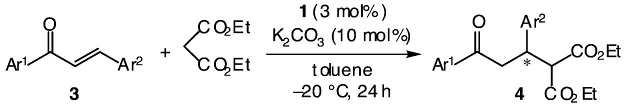
(6) For the asymmetric Michael addition of malonates to chalcone catalyzed by chiral metal complexes, see: (a) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194. (b) Kumaraswamy, G.; Sastry, M. N. V.; Jena, N. *Tetrahedron Lett.* **2001**, *42*, 8515.

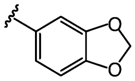
(7) Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 6844.

(8) The following results of the evaluation of the catalyst structure in the addition of dimethyl malonate to chalcone revealed the superiority of **1** (Ar = R = 3,5-Ph$_2$−C$_6$H$_3$): 56% ee (Ar = Ph, R = H); 72% ee (Ar = 4-CF$_3$−C$_6$H$_4$, R = H); 33% ee (Ar = 3,5-(CF$_3$)$_2$−C$_6$H$_3$, R = H); 50% ee (Ar = 3,5-(MeO)$_2$−C$_6$H$_3$, R = H); 76% ee (Ar = 3,5-Ph$_2$−C$_6$H$_3$, R = H).

(9) Present method could not be extended well to aliphatic enones. For example, the reaction of diethyl malonate with *trans*-4-phenyl-3-buten-2-one under the influence of **1** proceeded slowly at 0 °C to furnish the desired Michael adduct in 98% yield with 8% ee after 96 h.

Table 2. Catalytic Asymmetric Michael Addition of Diethyl Malonate to Chalcone Derivatives **3** under Phase-Transfer Conditions[a]



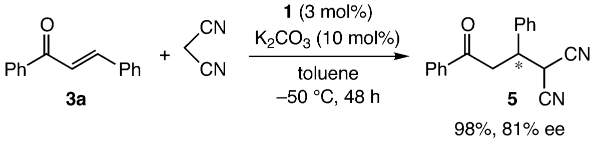
entry	enone **3**		% yield[b]	% ee[c]	prod.
	Ar^1	Ar^2			
1[d]	Ph	2-Naphthyl	94	91	**4b**
2	Ph	4-MeO-C_6H_4	99	87	**4c**
3	Ph		99	89	**4d**
4	Ph	4-Cl-C_6H_4	99	85	**4e**
5[d]	4-Cl-C_6H_4	Ph	97	86	**4f**
6[e]	Ph	2-Pyridyl	99	90	**4g**
7	Ph	2-Furyl	99	86	**4h**
8	Ph	2-Thienyl	99	94	**4i**
9	2-Thienyl	Ph	99	94	**4j**

[a] Unless otherwise noted, the reaction was carried out with 4 equiv of diethyl malonate in the presence of 3 mol % of **1** and 10 mol % of K_2CO_3 in toluene at −20 °C for 24 h. [b] Isolated yield. [c] Enantiopurity of products was determined by HPLC analysis using a chiral column with hexane−ethanol as a solvent. For detail, see Supporting Information. [d] Stirring for 48 h. [e] At −30 °C for 48 h.

were obtained in excellent chemical yields with a high level of enantiomeric excesses (entries 1−5). Notably, high enantioselectivity was also observed in the reaction with the substrates incorporating heteroaromatic substituents either on the double bond or on the carbonyl carbon, expanding the utility of this method as a practical tool for accessing a variety of useful synthetic building blocks of high optical purities (entries 6−9).

Finally, we found that dialkyl malonate was not a uniquely effective Michael donor. For instance, malononitrile underwent smooth and highly enantioselective addition to chalcone catalyzed by **1** under similar phase-transfer conditions, affording the corresponding Michael adduct **5** in 98% yield with 81% ee as shown in Scheme 2.[10]

Scheme 2



In summary, we have demonstrated that uniformly high enantioselectivity can be attained in the Michael reaction of diethyl malonate and various chalcone derivatives using a chiral phase-transfer catalyst with dual functions. This Michael addition chemistry also accommodates malononitrile as a nucleophile. The present study further underscores the effectiveness of our strategy based on the design of new chiral phase-transfer catalysts equipped with an appropriate recognition site for a requisite prochiral electrophile.

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Supporting Information Available: General experimental procedure and spectroscopic characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] For catalytic asymmetric Michael addition of malononitrile to α,β-unsaturated ketones, see: (a) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313. For related studies, see: (b) Itoh, K.; Oderaotoshi, Y.; Kanemasa, S. *Tetrahedron: Asymmetry* **2003**, *14*, 635. (c) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204.

[11] Yasuda, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1996**, *37*, 6343.