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Asymmetric Michael addition of malonates to enones catalyzed by nanocrystalline MgO

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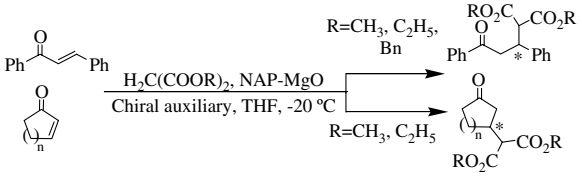
Abstract—Highly enantioselective Michael addition of malonates to cyclic and acyclic enones has been achieved by using nanocrystalline magnesium oxide at −20 °C.

Michael addition is one of the most important C–C bond-forming reactions in organic chemistry.[1] The catalytic asymmetric Michael (AM) reaction of malonates to enones, in which asymmetric induction occurs at the β-position of the enone, is an important organic transformation and the resultant compounds have been used in the synthesis of several natural products and drug molecules.[2,3] These reactions are reported in homogeneous media using in situ prepared heterobimetallic complexes,[4] ruthenium, copper, cobalt, rhodium and palladium derived catalysts[5] and phase transfer or organocatalysts[6,7] with moderate to excellent ees. Proline and its rubidium salts were successfully used in asymmetric Michael addition reactions between enones and various nucleophiles.[8] Chiral polymers were prepared and applied successfully in asymmetric Michael addition reactions.[9] Although impressive results have been achieved in many asymmetric reactions, reports on enantioselective Michael addition reactions with excellent ees have been limited mostly to cyclic substrates or the yields of the products are very low.[9a,10]

Nanocrystalline metal oxides find excellent applications as active adsorbents for gases, for the destruction of hazardous chemicals, and as catalysts for various organic transformations.[11,12] Nanomaterials with their three-dimensional structure and defined size and shape are considered to be suitable candidates for proper alignment with prochiral substrates for unidirectional introduction of reacting species to induce asymmetry. Recently, we have reported asymmetric Henry, Michael, and epoxidation reactions using heterogeneous nanocrystalline MgO.[12a,b] The asymmetric Michael addition of acyclic enones with various nitroalkanes in the presence of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane using heterogeneous nanocrystalline MgO has been carried out.[12b]

Herein, we report the AM addition of malonates to cyclic and acyclic enones to afford Michael adducts in good to excellent yields and ees using nanocrystalline MgO as catalyst in the presence of the chiral auxiliary (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethylenediamine (DPED) (Scheme 1). This method provides an easy synthetic route to optically active keto esters.

The applications of simple MgO (CM-MgO) as a basic catalyst in liquid phase reactions have been very



Scheme 1. AM addition between malonates and enones catalyzed by NAP-MgO in the presence of Chiral auxiliary.

Keywords: Asymmetric Michael; Malonates; Nanocrystalline MgO.
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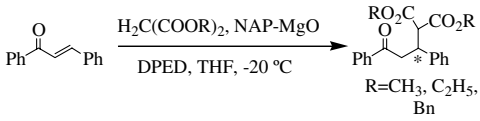
limited.[13] Various forms of MgO crystals, NAP-MgO (NanoActive Plus MgO, aerogel prepared MgO, SA: 600 m^2/g), NA-MgO (NanoActive MgO, conventionally prepared MgO, SA: 250 m^2/g), and CM-MgO (Commercial MgO, SA: 25 m^2/g), were initially evaluated for the AM reaction between chalcone and dimethyl malonate (DMM). None of these showed any activity. When we used various chiral amine ligands to induce the reaction and enantioselectivity, the Michael product was obtained in good yields and ees because of their high nucleophilicity. We also tested the reaction with (*S*)-Binol and (+)-DET ligands, and there was no reaction, but they gave the best ee in the asymmetric Henry and epoxidation reactions.[12a,b]

The reaction with various primary, secondary, cyclic and acylic amines is described in Table 1. Among them (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethylenediamine (DPED) proved to be the best ligand. The AM reaction between chalcone and dimethyl malonate was studied initially. Among the MgO samples screened in the AM reaction of chalcone and dimethyl malonate using DPED as chiral auxiliary at 25 °C, NAP-MgO was found to be superior to NA-MgO and CM-MgO in terms of yields and ees. Whereas the AM reaction between chalcone and dimethyl malonate in the presence of either NAP-MgO or chiral auxiliary alone showed no catalytic activity individually (Tables 1 and 2, entry 1). In an attempt to optimize the AM reaction, the effect of temperature was studied. NAP-MgO, using DPED as chiral auxiliary in THF at −20 °C, was found to be the best system. With NAP-MgO, the rate of the reaction was faster in the presence of a chiral auxiliary. These results are in consonance with the earlier reported ligand acceleration effects which include metal-diamine accelerated Michael reactions.[14] In general, chiral bidentate systems composing of primary and secondary amines afforded better ees, while chelation with COOH or OH displayed no ees (Table 1). The nature of the ester group of the malonate affected the ee of the product. As the bulkiness of the ester group increased, the rate of reaction decreased with an increase in ee (Table 2).

Encouraged by these results, the AM reaction was also extended to various cyclic enones with different malonates. The rate of the reaction was slower with cyclic enones than with acyclic enones. As the ring size increased, the rate of reaction decreased but with an increase in ee (Table 3). The ee was found to be higher with cyclic enones than with acyclic enones. This may be due to the rigidity of the cyclic systems (Tables 2 and 3).

To understand the relationship between structure and reactivity in the AM reaction, it is important to know the structure and nature of the reactive sites of NAP-MgO. The rationale for the selection of nanocrystalline MgO is NAP-MgO has a three-dimensional polyhedral structure, which has high surface concentrations of edge/corner and various exposed crystal planes (such as 002, 001, 111), leading to inherently high surface reactivity per unit area. Thus, NAP-MgO displayed the highest activity compared to NA-MgO and CM-MgO. Besides this, NAP-MgO has a Lewis acid site, Mg^{2+}, Lewis basic sites, O^{2-} and O^{-}, lattice bound and isolated Bronsted hydroxyls, and anionic and cationic vacancies.[15] The Michael reaction is known to be driven by basic catalysts,[16] and accordingly, the surface OH and O^{2-} of these oxide crystals are expected to trigger

Table 2. AM reaction between chalcone and malonates catalyzed by NAP-MgO in the presence of the chiral auxiliary DPED at −20 °C[21]



Entry	R	Time (h)	Yield[a] (%)	ee[b] (%)
1	CH_3	12, 12[c], 12[d]	93, 90,[c] 0[d]	82, 70,[c] 0[d]
2	C_2H_5	15	95	76
3	Bn	18	92	85

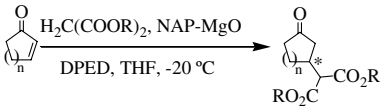
Reaction conditions: chalcone (1.0 mmol), malonate (5.0 mmol), NAP-MgO (0.125 g), dry THF (5 mL). In all cases 25 mol % of ligand was used.
[a] Isolated yields.
[b] Ee was determined by HPLC analysis using a Chiralcel AS column (2-propanol–hexane (1:9), 1.2 mL/min, $\lambda_{max} = 254$ nm for entry 1 and Chiralcel AD column for entries 2 and 3).
[c] At 0 °C.
[d] Without DPED.

Table 1. Effect of ligand on the AM reaction between chalcone and dimethyl malonate catalyzed by NAP-MgO at 25 °C

Entry	Ligand	Time (h)	Yield[a] (%)	ee[b] (%)
1	(1*R*,2*R*)-(+)-1,2-Diphenylethylene diamine	8, 14,[c] 24,[d] 12,[e] 8,[f] 12[g]	91, 64,[c] 30,[d] 60,[e] 89,[f] 0[g]	60, 42,[c] 10,[d] 60[e], 60,[f] 0[g]
2	(1*R*,2*R*)-(−)-1,2-Diaminocyclohexane	8	95	52
3	(1*S*,2*R*)-(+)-2-Amino-1,2-diphenylethanol	12	89	50
4	(1*R*,2*S*)-(−)-*N*-Methyl ephedrine	12	88	51
5	(*S*)-(−)-1,1′-Binaphthyl-2,2′-diamine	12	90	60
6	(L)-Proline	15	No reaction	—
7	(L)-Proline methyl ester	12	30	72

Reaction conditions: chalcone (1.0 mmol), malonate (5.0 mmol), NAP-MgO (0.125 g), dry THF (5 mL). In all cases 25 mol % of ligand was used.
[a] Isolated yields.
[b] Ee was determined by HPLC analysis using a Chiralcel AS column (2-propanol–hexane (1:9), 1.2 mL/min, $\lambda_{max} = 254$ nm).
[c] With NA-MgO.
[d] With CM-MgO.
[e] With silylated NAP-MgO.
[f] Fifth cycle.
[g] Without NAP-MgO.

Table 3. AM reaction between various cyclic enones and malonates catalyzed by NAP-MgO in the presence of the chiral auxiliary DPED at −20 °C[21]



Entry	*n*	R	Time (h)	Yield[a] (%)	ee[b] (%)
1	1	Me	12	94	84
2	1	Et	12	93	86
3	2	Me	16	95	90
4	2	Et	16	90	90
5	3	Me	24	96	94
6	3	Et	24	90	96

Reaction conditions: enone (1.0 mmol), malonate (5.0 mmol), NAP-MgO (0.125 g), dry THF (5 mL). In all cases 25 mol % of ligand was used.

[a] Isolated yields.

[b] Ee was determined by HPLC analysis using a Chiralcel AS column (2-propanol–hexane (1:9), 0.5 mL/min, $\lambda_{max} = 210$ nm).

the reaction. To examine the role of OH, Sil- NAP-MgO devoid of free OH was tested in AM reactions. It was found that OH groups did not influence the enantioselectivity. However, the rate of reaction was slow, and a longer reaction time was required (Table 1, entry 1). Although both NAP-MgO and NA-MgO possess defined shapes and the same average concentrations of surface OH groups, a possible rationale for the display of a higher rate by NAP-MgO is the presence of more surface Mg^{2+}(Lewis acid) ions (20%).[17] These Mg^{2+} ions (Lewis acid) of NAP-MgO and basic chiral auxiliary have acid-base interactions and these interactions may be responsible for the induction of enantioselectivity.

Generally, the Michael addition reaction typically refers to the base- catalyzed addition of a nucleophile to an activated unsaturated carbonyl-containing compound. The choice of a base-catalyst has a tremendous effect on the reaction. The pK_a of the Michael donor is important to the choice of the base catalyst, which must have a pK_a for its conjugated acid in the same range as the Michael donor.[18] In homogeneous base catalyzed systems, the reaction rate increases with the pK_a value of the substrate and the basic strength of the catalyst. In heterogeneous catalysis, the pK_a value of the nucleophile does not affect the reaction as in homogeneous catalysis. For example, in a Michael addition reaction catalyzed by high surface area MgO, theoretically, the lower pK_a value of the donor, the easier it is to abstract a proton and therefore form a carbanion. Malononitrile (pK_a 11.1) underwent a remarkably clean and fast Michael addition to chalcone with MgO, whereas ethyl acetoacetate (pK_a 14.3) did not undergo Michael addition rapidly.[13b] In our case, to trigger the reaction and also for chiral induction, we used different chiral amines (Table 1). Heterogeneous catalysis is a surface phenomenon wherein the crystal face plays a major role. NAP-MgO has a polyhedral shape with a three-dimensional structure with reactive ions on the surface. The crystal morphology and crystal shape induce the chirality in the reaction.

The AM reaction proceeds via dual activation of both substrates (nucleophiles and electrophiles) by NAP-MgO. Thus, the Lewis base (O^{2-}/O^{-}) of the catalyst activates the malonates and the Lewis acid moiety (Mg^{2+}/Mg^{+}) activates the carbonyls of the enones and the chiral auxiliary. Such dual activation is essential to promote the reaction with prochiral substrates under mild conditions with complete stereoselectivity.[19] Similarly, the Lewis acid-Bronsted base dichotomy is well known in enzyme catalyzed enantioselective aldol reactions between dihydroxyacetone phosphate and various aldehydes.[20]

The NAP-MgO was reused for five cycles with consistent activity. After completion of the reaction, the recovered catalyst was washed properly and activated at 250 °C for 1 h under a nitrogen atmosphere. The crystal morphology of reused NAP-MgO was unchanged as indicated by XRD.

To conclude, highly enantioselective Michael addition of malonates to cyclic and acyclic enones has been achieved by using nanocrystalline magnesium oxide.

Acknowledgments

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References and notes

1. (a) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677–8681; (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731–1769; (c) Trost, B. M. *Science* **1991**, *254*, 1471–1477; (d) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259–281.
2. (a) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991.
3. (a) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1996; vol. 2, p 321; (b) Jha, S. C.; Joshi, N. N. *Arkivoc* **2002**, *vii*, 167–196.
4. (a) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 104–106; (b) Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *Chem. Eur. J.* **1996**, *2*, 1368–1372; (c) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506–6507; (d) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 8473–8478; (e) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420; (f) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388–7389.
5. (a) Wang, H.; Watanabe, M.; Ikariya, T. *Tetrahedron Lett.* **2005**, *46*, 963–966; (b) Guo, R.; Chen, X.; Elpelt, C.; Song, D.; Morris, R. H. *Org. Lett.* **2005**, *7*, 1757–1759; (c) Halland, N.; Velgaard, T.; Jorgensen, K. A. *J. Org. Chem.* **2003**, *68*, 5067–5074; (d) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688–1690, and references there in.
6. Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 8805–8808.

7. (a) Kim, D. Y.; Huh, S. C.; Kim, S. M. *Tetrahedron Lett.* **2001**, *42*, 6299–6301; (b) Ooi, T.; Ohara, D.; Fukumoto, K.; Muruoka, K. *Org. Lett.* **2005**, *7*, 3195–3197.
8. (a) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975–2978; (b) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1176–1178.
9. (a) Sundararajan, G.; Prabagaran, N. *Org. Lett.* **2001**, *3*, 389–392; (b) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 8473–8478; (c) Arai, T.; Sekiguti, T.; Iizuka, Y.; Takizawa, S.; Sakamoto, S.; Sasai, H. *Tetrahedron: Asymmetry* **2002**, *13*, 2083–2087.
10. (a) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520–3530; (b) Kumaraswamy, G.; Sastry, M. N. V.; Jena, N. *Tetrahedron Lett.* **2001**, *42*, 8515–8517.
11. (a) Lucas, E.; Decker, S.; Khaleel, A.; Seitz, A.; Fultz, S.; Ponce, A.; Li, W.; Carnes, C.; Klabunde, K. J. *Chem. Eur. J.* **2001**, *7*, 2505–2510; (b) Schlogl, R.; Abd Hamid, S. B. *Angew. Chem. Int. Ed.* **2004**, *43*, 1628–1637; (c) Bell, A. T. *Science.* **2003**, *299*, 1688–1691; (d) Carnes, C. L.; Klabunde, K. J. *Langmuir* **2000**, *16*, 3764–3772; (e) Sharghi, H.; Sarvari, M. H. *Synthesis* **2002**, *8*, 1057–1060; (f) Banerjee, M.; Roy, S. *Chem. Commun.* **2003**, 534–535; (g) Sarvari, M. H.; Sharghi, H. *J. Org. Chem.* **2004**, *69*, 6953–6956; (h) Kim, Y. J.; Varma, R. S. *Tetrahedron Lett.* **2004**, *45*, 7205–7208.
12. (a) Choudary, B. M.; Kantam, M. L.; Ranganath, K. V. S.; Mahendar, K.; Sreedhar, B. *J. Am. Chem. Soc.* **2004**, *126*, 3396–3397; (b) Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 13167–13171; (c) Choudary, B. M.; Ranganath, K. V. S.; Yadav, J.; Kantam, M. L. *Tetrahedron Lett.* **2005**, *46*, 1369–1371.
13. (a) Tanabe, K.; Hoelderich, W. F. *Appl. Catal., A General* **1999**, *181*, 399–434; (b) Xu, C.; Bartley, J. K.; Enache, D. I.; Knight, D. W.; Hutchings, G. J. *Synthesis* **2005**, *19*, 3468–3476.
14. (a) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059–1070; (b) Brunner, H.; Hammer, B. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 312–313; (c) Christoffers, J.; Robler, U.; Werner, T. *Eur. J. Org. Chem.* **2000**, *65*, 701–705.
15. (a) Jeevanandam, P.; Klabunde, K. J. *Langmuir* **2002**, *18*, 5309–5313; (b) Richards, R.; Li, W.; Decker, S.; Davidson, C.; Koper, O.; Zaikovski, V.; Volodin, A.; Rieker, T.; Klabunde, K. J. *J. Am. Chem. Soc.* **2000**, *122*, 4921–4925; (c) Utamapanya, S.; Klabunde, K. J.; Schlup, J. R. *Chem. Mater.* **1991**, *3*, 175–181.
16. (a) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933–972; (b) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; (c) Ma, S.; Yin, S.; Li, L.; Tao, F. *Org. Lett.* **2002**, *4*, 505–507.
17. Klabunde, K. J.; Stark, J.; Koper, O.; Mohs, C.; Park, D. G.; Decker, S.; Jiang, Y.; Lagadic, I.; Zhang, D. *J. Phys. Chem.* **1996**, *100*, 12142–12153.
18. Mather, B. D.; Viswanathan, K.; Miller, K. M.; Long, T. E. *Prog. Polym. Sci.* **2006**, *31*, 487–493.
19. Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, *10*, 1491–1508.
20. Machajewski, T. D.; Wong, C. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352–1374.
21. *General procedure for the asymmetric Michael addition between enones and malonates*: a mixture of dimethyl malonate (5.0 mmol, 660.5 mg), ligand (0.25 mmol, 53.0 mg) and NAP-MgO (0.125 g) was introduced into a 50 mL round bottomed flask containing dry THF (5.0 mL) at −20 °C and the reaction mixture was stirred for 1 h under nitrogen. To the reaction mixture, chalcone (1 mmol, 208 mg) in THF (1.0 mL) was added at the same temperature. After completion of the reaction (monitored by TLC), the reaction mixture was centrifuged to separate the catalyst and the latter was washed several times with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. After purification by flash chromatography on silica gel (100–200 mesh) using ethyl acetate in hexane (2:8), the Michael adduct was obtained as a colourless solid. ^{1}H NMR ($CDCl_3$) δ 3.51 (s, 3H), 3.52 (dd, $J = 5.3$, 7.8 Hz, 1H), 3.71 (d, $J = 5.5$ Hz, 1H), 3.73 (s, 3H), 3.86 (d, $J = 9.2$ Hz, 1H), 4.20 (dt, $J = 5.3$, 9.4 Hz, 1H), 7.17–7.56 (m, 8H), 7.88–7.91 (d, $J = 12$ Hz 2H). *m/z* (ESI-MS) 341 $(M+1)^+$ ee was measured by using HPLC analysis (DAICEL CHIRAL PAK AS column) *i*-PrOH–hexane: 1:9, t_R: 18.2 min and 26.4 min. The reusability of the catalyst was assessed as follows using the experimental conditions described above, the catalyst was washed several times with ethyl acetate and activated at 250 °C for 1 h under nitrogen. Then the catalyst was reused for five cycles with consistent activity.