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An enantioselective Michael addition of malonate to nitroalkenes catalyzed by low loading demethylquinine salts in water

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Abstract—An enantioselective Michael addition of malonate to nitroalkenes is efficiently catalyzed by low loading demethylquinine salts in water; the yield range from 49% to 93% and the ee up to 90%.

Michael addition reaction of various nucleophiles to highly electron deficient nitroalkenes has been proven to be a very versatile transformation. It provides a convenient access to valuable synthones and building blocks, which may lead to a variety of multifunctional compounds of synthetic interests.[1] The nitro group has been described as a 'synthetic chameleon' because it serves as a masked precursor to many useful functionalities. Notable examples[2] include Nef reaction, Meyer reaction, reduction to an amino group, and conversion into the nitrile oxide for 1,3-dipolar cycloaddition reactions. Considerable progress has been made in recent years in developing efficient asymmetric Michael addition reaction under stoichiometric[3] and catalytic conditions by using chiral metal complexes[4] and transition metal-free organocatalysts.[5] Figure 1 shows some representative chiral organocatalysts used for asymmetric Michael additions. In most cases these organocatalytic reactions are conducted in organic solvents, and the catalyst loadings are as high as 10–30 mol %.

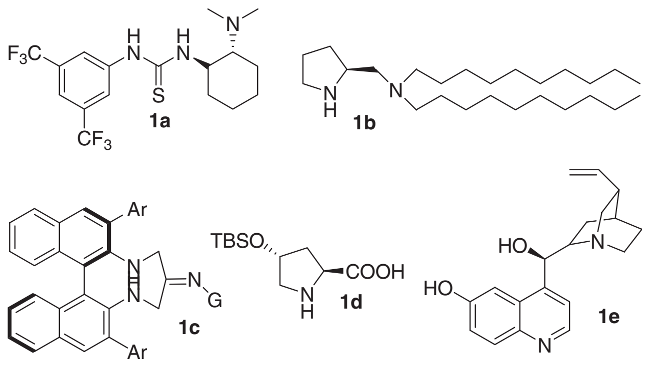

Figure 1. Representative organocatalysts used for Michael addition.

In the past few years, utilization of water as a solvent has emerged as an extensively investigated topic[6] in the area of asymmetric organic transformations for its environmental friendly character and low cost. Although water has been employed for the Michael addition reactions in recent reports,[7] however, the donor of Michael addition is limited to ketones or diketones and most catalysts are not easily obtained. We envisioned a great opportunity to develop water-soluble salts as they may lead to a new class of chiral organocatalysts with high catalytic efficiency and enantioselectivity toward organic reactions. Herein, we wish to report a novel catalyst derived from the vastly available natural product quinine, which catalyzed the Michael addition reactions of malonate to various nitroalkenes in aqueous conditions with low catalyst loading.

Keywords: Organocatalysis; Michael addition; Salt catalysis; Nitroalkenes; Water.

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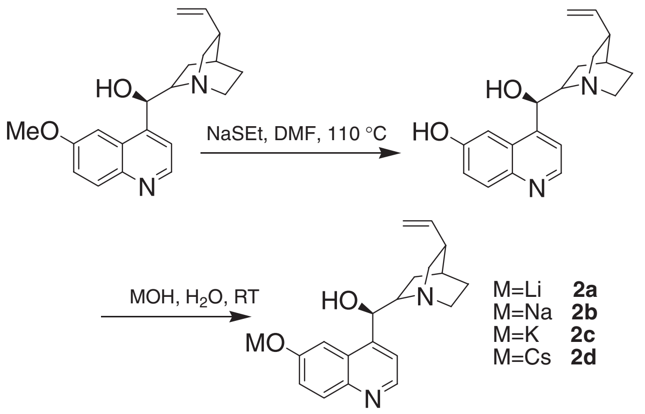
All of these demethylquinine salts **2** were easily prepared from quinine with overall yield of 78–85% (Scheme 1). To the best of our knowledge, this is the first example of salts used as a catalyst in Michael addition of malonate to nitroalkenes in water.

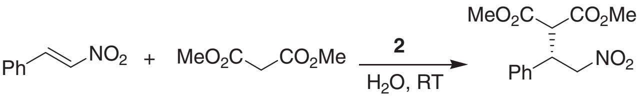
Firstly, sodium demethylquinine salt (**2b**) was used to optimize the Michael addition of malonate to nitroalkene in water and the results are summarized in Table 1. It is seen that this reaction can proceed smoothly with 10 mol % catalyst loading in either organic solvent (THF or toluene) or water (Table 1, entries 1, 2, and 6), giving high yield (~90%) of the product. However, the enantioselectivity depends significantly on the concentration of the substrates in water. Increasing the substrate concentration in water remarkably increases the enantioselectivity (Table 1, entries 3–6). In addition, decreasing the catalyst loading to 1 mol % does not appreciably influence the yield and enantioselectivity (Table 1, entries 6 and 7). The lithium, potassium, and cesium demethylquinine salts (**2a**, **2c**, and **2d**) have a similar catalytic property to the corresponding sodium salt (Table 1, entries 7–10), suggesting that the metal cation has little impact on catalytic efficiency in this asymmetric Michael addition conducted in water. Compared with unsalted catalyst **1e**, which was used by Deng in this Michael addition under 10 mol % catalyst loading in THF,[5o] catalyst **2b** has moderate to high ee value with 1 mol % loading in water.

Under the optimized reaction conditions of entry 7 (Table 1), **2b** was employed to catalyze the asymmetric Michael addition of malonate to various nitroalkenes. The results are summarized in Table 2. Moderate to good yields were obtained in each case. The yields of **5i** and **5j** with *ortho*- and *meta*-substituents (Table 2, entries 8 and 9) have a significant increase compared with *para*-substituents (Table 2, entries 2 and 3), but the enantioselectivities show a small decrease. Electron-donating groups 4-OMe and 4-OTBS on the phenyl ring were favored for higher enantioselectivity (Table 2, entries 6 and 10), while electron-withdrawing substituents were found to lower the ee's of the products



Scheme 1. Preparation of demethylquinine salts (**2a**–**2d**).

Table 1. Asymmetric Michael addition of malonate to nitroalkene under different conditions[a]



Entry	Cat loading (mol %)	Solvent[b] (M)	Reaction time (h)	Yield[c] (%)	ee[d] (%)
1	2b (10)	THF (1.0)	6	92	18
2	2b (10)	Toluene (1.0)	6	91	15
3	2b (10)	H_2O (0.1)	6	90	3
4	2b (10)	H_2O (0.25)	6	92	23
5	2b (10)	H_2O (0.5)	6	91	23
6	2b (10)	H_2O (1.0)	6	90	65
7	2b (1)	H_2O (1.0)	10	91	66
8	2a (1)	H_2O (1.0)	10	88	61
9	2c (1)	H_2O (1.0)	10	86	60
10	2d (1)	H_2O (1.0)	10	86	59

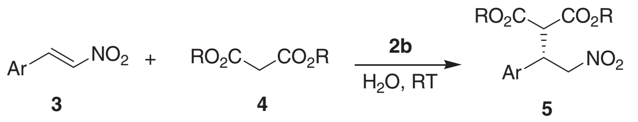
[a] The reaction was carried out with 1 equiv of nitroalkene and 1.5 equiv of malonate at room temperature on a scale of 0.4 mmol of nitroalkene.

[b] The concentration of nitroalkene.

[c] Isolated yields.

[d] Enantiomeric excess (ee) was determined by chiral HPLC analysis (Chiralcel OD-H column, and absolute configuration was determined to be *S*, see Supplementary data).

Table 2. Asymmetric Michael addition of malonate to various nitroalkenes under 1 mol % **2b**[a]



Entry	3 Ar	4 R	5	Yield[c] (%)	ee[d] (%)
1	*p*-F–C_6H_4	CH_3(4a)	5b	76	49
2	*p*-Cl–C_6H_4	CH_3(4a)	5c[e]	78	75
3	*p*-Br–C_6H_4	CH_3(4a)	5d[e]	75	84
4	*p*-CH_3–C_6H_4	CH_3(4a)	5e	74	56
5	*p*-OAc–C_6H_4	CH_3(4a)	5f	62	59
6	*p*-OMe–C_6H_4	CH_3(4a)	5g[e]	71	86
7	*m*-OMe–C_6H_4	CH_3(4a)	5h[e]	82	64
8	*o*-Cl–C_6H_4	CH_3(4a)	5i	93	70
9	*m*-Br–C_6H_4	CH_3(4a)	5j[e]	86	62
10	*p*-OTBS–C_6H_4	CH_3(4a)	5k	88	90
11	*p*-OH–C_6H_4	CH_3(4a)	5l	55	28
12	2-Furyl	CH_3(4a)	5m[e]	93	74
13	1-Naphthyl	CH_3(4a)	5n[e]	76	82
14	2-Naphthyl	CH_3(4a)	5o	78	66
15	1-Naphthyl	CH_2CH_3(4b)[b]	5p	93	85
16	2-Naphthyl	CH_2CH_3(4b)[b]	5q	90	79
17	Ph	^{i}Pr(4c)[b]	5r	49	74
18	Ph	Bn(4d)[b]	5s	85	60

[a] Unless otherwise specified, the reaction was carried out with 1 equiv of **3** and 1.5 equiv of **4a** in the presence of 1 mol % **2b** on a scale of 0.4 mmol of **3**. Reaction times were run for 6–10 h (see Supplementary data).

[b] 2.5 equiv of malonates was used.

[c] Isolated yields.

[d] Enantiomeric excess (ee) was determined by chiral HPLC analysis.

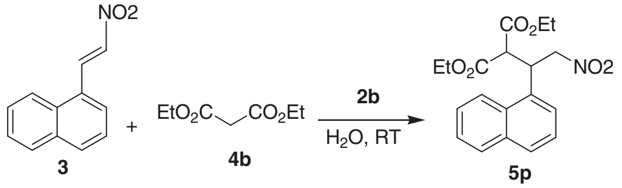
[e] Absolute configuration was determined to be *S* (see Supplementary data).

(Table 2, entry 1). It is noteworthy that both yield and enantioselectivity for compound **5l** (Table 2, entry 11) are fairly low. A possible explanation for this observation might be due to the exchange of the sodium ion between the phenolic catalyst **2b** and the unprotected *para*-hydroxy nitrostyrene. Isopropyl malonate ester also has a moderate enantioselectivty though obtained in low yield possibly due to steric hindrance (Table 2, entry 17), but the benzyl malonate ester has a good yield and moderate enantioselectivity (Table 2, entry 18). Compared with the previously reported catalytic procedures,[5] the yield and enantioselectivity are similar. However, the unique features of the current system such as transition metal-free, low catalyst loading, and the aqueous reaction media make this procedure more attractive.

Taking advantage of the big difference in solubility between sodium demethylquinine salt and the products in water, recycling of the catalyst can be easily accomplished. Thus, after the first reaction was completed as monitored by TLC, the reaction mixture was extracted by PE/Et_2O several times until the product was completely removed. Then the substrates were added to the aqueous phase containing the catalyst and stirred vigorously to conduct the reaction again. In the case of 5 mol % catalyst loading this recycling could be repeated seven times without loss in enantioselectivity, while the yield was slightly decreased (Table 3). Compared with the polymer-supported catalysts,[8] this separation process through solvent extraction is much more convenient and economical. When the tertiary amine of demethylquinine salt **2b** was alkylated with a benzyl group to form a kind of PTC catalyst,[9] the resulting quaternary ammonium salt provided poor enantioselectivity though in high yield.

In conclusion, soluble demethylquinine salt **2b** has been shown as a kind of efficient novel catalyst for asymmetric Michael addition of malonate to nitroalkenes in water. The environmental friendly solvent and simple recycling procedure make this protocol attractive. Extension of this procedure to other reactions is underway in this laboratory.

Table 3. Recycling of **2b** under 5 mol %[a]



Entry	Recycle time	Yield (%)	ee (%)
1	0	94	89
2	1	89	89
3	2	87	90
4	3	89	88
5	4	85	85
6	5	79	87
7	6	77	88
8	7	74	76

[a] The reaction was carried out with 1 equiv of **3** and 2.5 equiv of **4b** in the presence of 5 mol % of catalyst at room temperature on a scale of 0.4 mmol of **3**. All reactions were run for 10 h.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.168.

References and notes

1. (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877; (b) Ono, N. *Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001; (c) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672; (d) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.
2. The function group transferred from Nitro group, see (a) Pinnick, H. W. *Org. React.* **1990**, *38*, 655; (b) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423; (c) Poupart, M. A.; Fazal, G.; Goulet, S.; Mar, L. T. *J. Org. Chem.* **1999**, *64*, 1356; (d) Kamlet, M. J.; Kaplan, L. A.; Dacons, J. C. *J. Org. Chem.* **1961**, *26*, 4371; (e); (e) Mukayama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.
3. (a) Johnson, T. A.; Jang, D. O.; Slafer, B. W.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2002**, *124*, 11689; (b) Schäfer, H.; Seebach, D. *Tetrahedron* **1995**, *51*, 2305.
4. (a) Kobayashi, N.; Iwai, K. *J. Org. Chem.* **1981**, *46*, 1823; (b) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192; (c) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262; (d) Ji, J.; Barnes, D. M.; Zhang, J. S.; King, A.; Wittemberg, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215; (e) Rimkus, A.; Sewald, N. *Org. Lett.* **2003**, *5*, 79; (f) Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2004**, *126*, 11148; (g) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958; (h) Lu, S.-F.; Du, D.-M.; Xu, J.; Zhang, Sh.-W. *J. Am. Chem. Soc.* **2006**, *128*, 7418.
5. Michael addition catalyzed by organocatalyst, see (a) Albrecht, B.; Harald, G. *Asymmetric Organocatalysis—From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: New York, 2005; (b) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423; (c) Hayashi, Y.; Gotoh, T.; Hayasji, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212; (d) Ender, D.; Seki, A. *Synlett* **2002**, 26; (e) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F.; III. *Org. Lett.* **2004**, *6*, 2527; (f) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *43*, 1369; (g) Kotrusz, P.; Toma, S.; Schmalz, H. S.; Adler, A. *Eur. J. Org. Chem.* **2005**, 1577; (h) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289; (i) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901; (j) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 807; (k) Huang, H. B.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170; (l) Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624; (m) Andrey, O.; Alexakis, A.; Bernardinelli, G. R. *Org. Lett.* **2003**, *5*, 2559;

(n) Terada, M.; Yaguchi, Y.. *J. Am. Chem. Soc.* **2006**, *128*, 1454; (o) Li, H.-M.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906; (p) Li, H.-M.; Wang, Y.; Tang, L.; Wu, F.-H.; Liu, X.-F.; Guo, C.-Y.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105; (q) Wang, J.; Li, H.; Duan, W.-H.; Zu, L.-S.; Wang, W. *Org. Lett.* **2005**, *7*, 4713.

6. Organic reactions in water, see (a) Li, C.-J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997; (b) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741; (c) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023; (d) Yalkowsky, S. H. *Solubility and Solubilization in Aqueous Media*; Oxford University Press: New York, 1999; (e) Gajewski, J. J. Organic Synthesis. In *Water*; Grieco, P. A., Ed.; Blackie A&P: London, 1998; (f) Mu, R.-Z.; Liu, Z.-Q.; Yang, Z.-J.; Liu, Z.-G.; Wu, L.-M.; Liu, Z.-L. *Adv. Synth. Catal.* **2005**, *347*, 1333.
7. For Michael addition of ketones to nitroolefins in aqueous media, see (a) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966; (b) Yan, Z.-Y.; Niu, Y.-N.; Wei, H.-L.; Wu, L.-Y.; Zhao, Y.-B.; Liang, Y.-M. *Tetrahedron: Asymmetry* **2006**, *17*, 3288; (c) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808; (d) Ishii, T.; Fiujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558; (e) Xu, Y.; Zou, W.; Sunden, H.; Ibrahem, I.; Cordova, A. *Adv. Synth. Catal.* **2006**, *348*, 418; (f) Luo, S.-Z.; Mi, X.-L.; Liu, S.; Xu, H.; Cheng, J.-P. *Chem. Commun.* **2006**, 3687.
8. (a) Yang, X.-W.; Sheng, J.-H.; Da, C.-S.; Wang, H.-S.; Su, W.; Wang, R.; Chan, A. S. C. *J. Org. Chem.* **2000**, *65*, 295; (b) Benaglia, M.; Puglisi, A.; Cozzi, F. *Chem. Rev.* **2003**, *103*, 3401; (c) Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217.
9. (a) Halpern, M. E. *Phase-Transfer Catalysis. Mechanism and Synthesis*; ACS: Washington, DC, 1997; (b) Sasson, Y.; Neumann, R. *Handbook of Phase-Transfer Catalysis*; Blackie A&M: London, 1997; (c) Lygo, B. *Phase-Transfer Reactions. Rodd's Chemistry of Carbon Compounds*; Elsevier Science Ltd: Oxford, U.K., 2001.