Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 3881–3884
Tetrahedron Letters

Organocatalytic asymmetric direct Michael addition of aromatic ketones to alkylidenemalononitriles

Lei Yue [a], Wei Du [a], Yan-Kai Liu [a], Ying-Chun Chen [a,b,*]

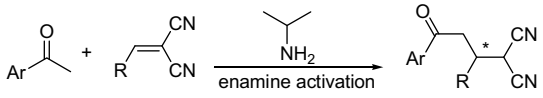
[a] *Key Laboratory of Drug-Targeting of Education Ministry and Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu 610041, China*
[b] *State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China*

Received 22 December 2007; revised 7 April 2008; accepted 11 April 2008
Available online 14 April 2008

Abstract

The asymmetric direct Michael addition of aromatic ketones to highly active alkylidenemalononitriles was investigated by employing a chiral primary amine 9-amino-9-deoxyepicinchonine. In general modest to good enantioselectivities (71–84% ee) could be obtained in acceptable isolated yields (48–85%) for an array of substrates.

The catalytic asymmetric Michael reaction is generally regarded as one of the most powerful and efficient transformations in carbon–carbon bond forming reactions, because a diversity of nucleophiles and activated olefins could be expected to give versatile arrangements.[1] In particular, the recently developed small organic molecule catalyzed asymmetric Michael additions triggered special interest.[2] Among them, a number of successful examples in the asymmetric direct Michael reactions of aldehydes and ketones through enamine activation have been reported; however, further expansion of the substrate scopes is still desirable.[3] Most studies in this area are focused on the reactions of simple aliphatic ketones and aldehydes, while much less attention has been paid on the application of aromatic ketones as enamine precursors due to their more crowded structures.[4] On the other hand, the development of asymmetric Michael addition of rarely applied olefinic electrophiles is also attractive because new chiral skeletons could be constructed. Very recently we and Melchiorre have established that primary amines derived from natural cinchona alkaloids could serve as excellent iminium catalysts for the asymmetric Michael reactions of α,β-unsaturated ketones.[5] Subsequently, we found that these primary amines also could activate aromatic ketones for the highly enantioselective direct α-amination reaction with diethyl azodicarboxylate (DEAD).[6] Encouraged by these results, here we would like to present the asymmetric direct Michael addition of aryl ketones to alkylidenemalononitriles[7] promoted by primary aminocatalysts,[8] giving a facile route to multifunctional enantiomerically enriched compounds (Eq. 1). To the best of our knowledge, this reaction has not been well explored in the literature.[9]



(1)

In the initial study, primary aminocatalysts **1a**–**c**[5] (Fig. 1) were tested for the asymmetric Michael addition of acetophenone **2a** and benzylidenemalononitrile **3a** in the

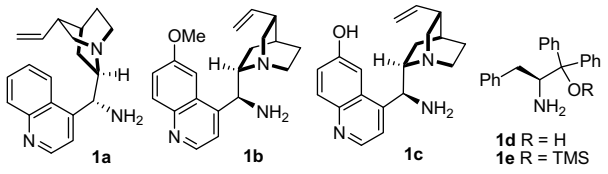


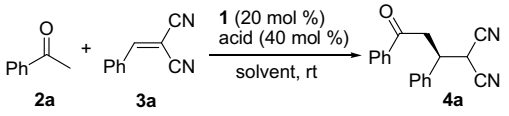
Fig. 1. Structures of primary aminocatalysts.

* Corresponding author. Tel./fax: +86 28 85502609.
E-mail address: ycchenhuaxi@yahoo.com.cn (Y.-C. Chen).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.04.069

presence of PTSA in THF. The reaction was sluggish at ambient temperature and high concentration was required to ensure better conversion. Addition product **4a** was commonly isolated in low yield after 72 h. ADC **1a** emerged as a superior catalyst in terms of both isolated yield and enantioselectivity (Table 1, entry 1). ADQ **1b** gave slightly lower ee value while the product has the opposite configuration (entry 2). Nevertheless, the ee was greatly reduced when the reaction was catalyzed by **1c**[5d] with a free OH group (entry 3). In addition, primary amines **1d** and **1e** derived from L-phenylalanine were almost inert in the tested Michael reaction (entries 4 and 5). Then other acidic additives were screened in combination with catalyst **1a**, and only sulfonic acids gave reasonable results (entries 6–10). Various solvents were also investigated, and inferior results were generally obtained (entries 11–17). Interestingly, the stereoselectivity was inversed when the reaction was conducted in DMF (entry 14). Notably the reaction could proceed smoothly in H_2O,[10] but much lower ee was obtained (entry 17). We found that the enantioselectivity was not affected with slightly higher yield at 45 °C in a diluted solution (entry 18), and good isolated yield could be attained after the time was extended to 6 d (entry 19).

Table 1
Screening studies of asymmetric direct Michael addition of acetophenone **2a** to benzylidenemalononitrile **3a**[a]



2a **3a** **4a**

Entry	1	Acid	Solvent	*t* (d)	Yield[b] (%)	ee[c] (%)
1	**1a**	PTSA	THF	3	30	72
2	**1b**	PTSA	THF	3	23	−65
3	**1c**	PTSA	THF	3	43	−23
4	**1d**	PTSA	THF	3	—	—
5	**1e**	PTSA	THF	3	—	—
6	**1a**	PNBA	THF	3	14	2
7	**1a**	AcOH	THF	3	29	0
8	**1a**	TFA	THF	3	—	—
9	**1a**	$MeSO_3H$	THF	3	32	45
10	**1a**	L-CSA	THF	3	10	74
11	**1a**	PTSA	2-PrOH	2	35	14
12	**1a**	PTSA	Diox	4	38	60
13	**1a**	PTSA	DME	4	18	72
14	**1a**	PTSA	DMF	2	20	−41
15	**1a**	PTSA	Toluene	5	17	33
16	**1a**	PTSA	CH_3CN	5	10	61
17	**1a**	PTSA	H_2O	4	53	34
18[d]	**1a**	PTSA	THF	3	39	71
19[d]	**1a**	PTSA	THF	6	73	71
20[d]	**1a**	MSA	THF	3	10	43
21[e]	**1a**	PTSA	THF	6	30	70

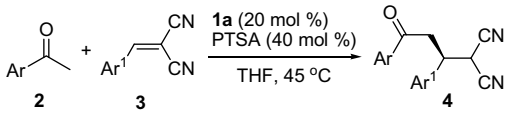
[a] Unless otherwise noted, reactions were performed with 0.2 mmol of **2a**, 0.1 mmol of **3a**, 0.02 mmol of **1** and 0.04 mmol of acid in 0.05 mL solvent at rt.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] At 45 °C in 0.3 mL of THF.
[e] At 60 °C in 0.5 mL THF.

Unfortunately, decreased ee was attained by utilizing a more bulky additive MSA (mesitylsulfonic acid, entry 20). Further increasing the temperature to 60 °C also resulted in a reduced yield due to some side reactions (entry 21).

With the optimized conditions in hand, we then examined a variety of aromatic ketones and alkylidenemalononitriles to establish the general utility of this asymmetric transformation (Table 2). The reactions were performed in THF at 45 °C in the presence of 20 mol % of **1a** and 40 mol % of TsOH for 4–6 days.[11] As outlined in Table 2, good enantioselectivities were generally obtained for a broad spectrum of acetophenones bearing electron-withdrawing or donating substitutions (entries 2–8). 2-Acetylnaphthalene exhibited relatively lower reactivity (entry 9), but heteroaryl ketones, such as 2-acetylthiophene and 3-acetylpyridine, failed to give the desired Michael adduct. On the other hand, a few substituted benzylidenemalononitriles were also tested, and higher ee values were gained for substrates with electron-withdrawing groups (entries 10–12). Most of the adducts are solid and enantiopure products could be attained after recrystallization. It should be noted that the reaction of *p*-bromoacetophenone and alkylidenemalononitriles with γ-CH was not successful, and complex mixtures were commonly observed, probably because of the side reactions resulting from the active γ-CH of alkylidenemalononitriles.[12]

Furthermore, we investigated the reaction of benzylidenemalononitrile **3a** and aryl ketones with α-substitution. Very sluggish reaction was detected when propiophenone was applied. However, cyclic 1-indanone exhibited better

Table 2
Asymmetric direct Michael addition of aromatic ketones **2** to alkylidenemalononitriles **3**[a]



2 **3** **4**

Entry	Ar	Ar^1	*t* (d)	Yield[b] (%)	ee[c] (%)
1	Ph	Ph	6	**4a**–73	71
2	4-FC_6H_4	Ph	6	**4b**–72	75
3	4-ClC_6H_4	Ph	6	**4c**–72	78
4	4-BrC_6H_4	Ph	6	**4d**–69	81[d]
5	3-BrC_6H_4	Ph	4	**4e**–79	78
6	4-MeC_6H_4	Ph	6	**4f**–77	74
7	4-$MeOC_6H_4$	Ph	4	**4g**–76	71
8	4-$NO_2C_6H_4$	Ph	6	**4h**–85	72
9	2-Np	4-$NO_2C_6H_4$	6	**4i**–48	72
10	4-BrC_6H_4	4-F C_6H_4	6	**4j**–65	80
11	4-BrC_6H_4	4-$NO_2C_6H_4$	6	**4k**–75	84
12	4-BrC_6H_4	4-$MeOC_6H_4$	6	**4l**–69	71

[a] Reactions were performed with 0.2 mmol of **2**, 0.1 mmol of **3a**, 0.02 mmol of **1a**, and 0.04 mmol of PTSA in 0.3 mL THF at 45 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] The absolute configuration of enantiopure **4d** (after recrystallization) was determined by X-ray analysis, and other products were assigned by analogy.

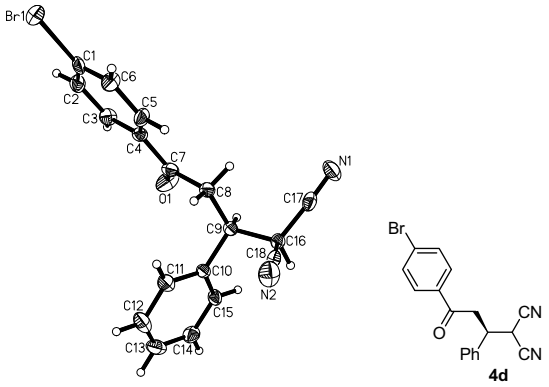
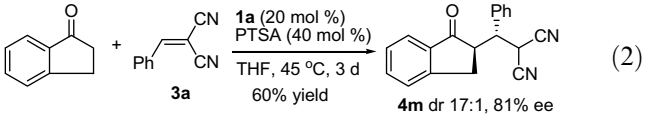


Fig. 2. X-ray structure of enantiopure **4d**.

reactivity, and moderate yield was obtained with good stereoselectivity (dr 17:1, 81% ee) under the optimal conditions after 3 d (Eq. 2). It is also found that diethyl benzylidenemalonate[13] and cinnamonitrile are almost inert in the catalytic reaction with acetophenone, indicating that the more electrophilic alkylidenemalononitriles are of the essence to the success of primary amine catalyzed direct Michael addition of aryl ketones.



(2)

In order to determine the absolute configuration of the Michael addition products, single crystals suitable for X-ray crystallographic analysis were obtained from compound **4d** bearing a bromine atom. Over 99% ee could be gained after recrystallization from **4d** (81% ee) in a mixture of ethyl acetate and hexane. The absolute configuration of **4d** was determined to be (*S*) in the benzylic carbon (Fig. 2).

In conclusion, we have developed the new asymmetric direct Michael addition of aromatic ketones to alkylidenemalononitriles catalyzed by a primary amine derived from cinchonine. The reaction proceeds well at higher temperature (45 °C), and good enantioselectivities are generally obtained (71–84% ee) for an array of substrates. Further developments of the asymmetric direct reactions of aryl ketones catalyzed by chiral primary amines are in progress in our laboratory.

Acknowledgements

We are grateful for the financial support from the National Natural Science Foundation of China (20772084), Ministry of Education (NCET-05-0781), and Sichuan Province Government (07ZQ026-027).

Supplementary data

Supplementary data (experimental procedures, characterization, and HPLC spectra of the products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.069.

References and notes

1. For reviews, see: (a) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033; (b) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171.
2. For recent reviews, see: (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701; (b) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299; For general reviews on organocatalysis, see: (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138; (d) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719; (e) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005.
3. For selected reviews on enamine catalysis, see: (a) List, B. *Acc. Chem. Res.* **2004**, *37*, 548; (b) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580; (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. For selected examples of direct Michael addition of carbonyl compounds in enamine catalysis, see: nitroolefins (d) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423; (e) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737; (f) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559; (g) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966; (h) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093; (i) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861; α,β-Unsaturated ketones (j) Chi, Y.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 4253; (k) Peelen, T. J.; Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11598; (l) Hechevarria Fonseca, M. T.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958; (m) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036; Vinyl sulfones (n) Mossé, S.; Alexakis, A. *Org. Lett.* **2005**, *7*, 4361; Vinyl phosphates (o) Sulzer-Mosse, S.; Tissot, M.; Alexakis, A. *Org. Lett.* **2007**, *9*, 3749.
4. For limited examples, see: (a) Liu, K.; Cui, H.-F.; Nie, J.; Dong, K.-Y.; Li, X.-J.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 923; (b) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. For 1,2-addition reactions of aryl ketones, see: (c) Chowdari, N. S.; Ahmad, M.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2006**, *8*, 2839; (d) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983.
5. (a) Xie, J.-W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 389; (b) Xie, J.-W.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J.-G.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 413; (c) Chen, W.; Du, W.; Yue, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2007**, *5*, 816; (d) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 7667; (e) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403; (f) Carlone, A.; Bartoli, G.; Bosco, M.; Pesciaioli, F.; Ricci, P.; Sambri, L.; Melchiorre, P. *Eur. J. Org. Chem.* **2007**, 5492.
6. Liu, T.-Y.; Cui, H.-L.; Zhang, Y.; Jiang, K.; Du, W.; He, Z.-Q.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 3671.
7. Alkylidenemalononitriles are rarely applied in the catalytic asymmetric synthesis despite their highly electrophilic features, probably because of the relatively lower affinity of manolonitrile group to Lewis acids or Brønsted acids. For limited applications in asymmetric Michael addition, see: (a) Kojima, S.; Suzuki, M.; Watanabe, A.; Ohkata, K. *Tetrahedron Lett.* **2006**, *47*, 9061; (b) Kojima, S.; Fujitomo, K.; Itoh, Y.; Hiroike, K.; Murakami, M.; Ohkata, K. *Heterocycles* **2006**, *67*, 679; (c) Fernández, I.; Araújo, C. S.; Romero, M. J.; Alcudia, F.; Khiar, N. *Tetrahedron* **2000**, *56*, 3749; (d) Marco, J. L. *J. Org. Chem.* **1997**, *62*, 6575.
8. For selected examples on enamine catalysis with primary amines, see: (a) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2007**, *129*, 288; (b) Wu, X.; Jiang, Z.; Shen, H.-M.;

Lu, Y., *Adv. Synth. Catal.* **2007**, *349*, 812; (c) Xu, Y.; Córdova, A. *Chem. Commun.* **2006**, 460; (d) Bassan, A.; Zou, W.; Reyes, E.; Himo, F.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7028; (e) Pizzarello, S.; Weber, A. L. *Science* **2004**, *303*, 1151; (f) Tanaka, F.; Thayumanavan, R.; Mase, N.; Barbas, C. F., III. *Tetrahedron Lett.* **2004**, *45*, 325; (g) Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451; (h) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366; (i) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599; (j) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 3074.

9. Only datum has been reported for asymmetric Michael addition of acetophenone to benzylidenemalononitrile in 10% ee, see: Yasuda, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1996**, *37*, 6343.
10. For selected examples of organocatalytic Michael addition in water, see: (a) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F., ; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966; (b) Vishnumaya, ; Singh, V. K. *Org. Lett.* **2007**, *9*, 1117; (c) Zhu, S.; Yu, S.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 545.
11. *General procedure for asymmetric Michael addition of aryl ketones to alkylidenemalononitriles*: Benzylidenemalononitrile (15.4 mg, 0.1 mmol), *p*-bromoacetophenone (40 mg, 0.2 mmol), ADC **1a** (5.9 mg, 20 mol %) and TsOH· H_2O (7.6 mg, 40 mol %) were stirred in THF (0.3 mL) at 45 °C. The reaction was monitored by TLC analysis. After 6 d, the product was purified by flash chromatography on silica gel to give product **4d**. 69% yield, white soild; $R_f = 0.1$ (petroleum ether/EtOAc = 15:1); $[\alpha]_D^{20}$ +5.6 (*c* 0.19, in EtOAc), 81% ee, determined by HPLC analysis [Daicel chiralpak AD, *n*-hexane/*i*-PrOH = 80/20, 1.0 mL/min, $\lambda = 254$ nm, *t* (minor) = 12.58 min, *t* (major) = 15.23 min]; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.83$ (d, $J = 8.6$ Hz, 2H), 7.64 (d, $J = 8.6$ Hz, 2H), 7.45–7.37 (m, 5H), 4.62 (d, $J = 5.1$ Hz, 1H), 3.98–3.92 (m, 1H), 3.72–3.58 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 195.6$, 136.3, 134.4, 132.3, 129.5, 129.4, 129.2, 127.9, 111.7, 111.6, 41.1, 40.1, 28.7 ppm; ESI-HRMS: calcd for $C_{18}H_{13}BrN_2O$+Na 375.0109; found 375.0105.
12. For direct vinylogous reactions of alkylidenemalononitriles with active γ-CH, see: (a) Xue, D.; Chen, Y.-C.; Cun, L.-F.; Wang, Q.-W.; Zhu, J.; Deng, J.-G. *Org. Lett.* **2005**, *7*, 5293; (b) Xie, J.-W.; Yue, L.; Xue, D.; Ma, X.-L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Chem. Commun.* **2006**, 1563; (c) Liu, T.-Y.; Cui, H.-L.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *J. Am. Chem. Soc.* **2007**, *129*, 1879; (d) Jiang, L.; Zheng, H.-T.; Liu, T.-Y.; Yue, L.; Chen, Y.-C. *Tetrahedron* **2007**, *63*, 5123. For independent work by Jørgensen, see: (e) Poulsen, T. B.; Alemparte, C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 11614.
13. For asymmetric Michael addition of simple ketones to alkylidenemalonates, see: (a) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 4441; (b) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Synthesis* **2004**, 1509; (c) Blarer, S. J.; Seebach, D. *Chem. Ber.* **1983**, *116*, 2250.