Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 837–841

Enantioselective Michael addition of malonate esters to nitroolefins organocatalyzed by diaryl-2-pyrrolidinemethanols

Alessandra Lattanzi*

Dipartimento di Chimica, Università di Salerno, Via S. Allende, 84081 Baronissi, Salerno, Italy

Received 25 January 2006; accepted 24 February 2006
Available online 23 March 2006

Abstract—Bis-(3,5-dimethylphenyl)((*S*)-pyrrolidin-2-yl)methanol, easily prepared from L-proline, was found to be an efficient bifunctional organocatalyst, amongst the different 2-pyrrolidinemethanols tested, for the enantioselective Michael addition of malonate esters to nitroolefins. The products were isolated in good to high yields and with up to 56% ee.

1. Introduction

Among the enantioselective C–C bond-forming reactions, the Michael addition of carbon nucleophiles to nitroalkenes has received great attention.[1] The highly functionalized building blocks which are obtained, can be readily transformed into a variety of important biologically active compounds and pharmaceuticals, thanks to the ease of transformation of the nitro group.[2] Several asymmetric metal-catalyzed protocols[3] have been proposed for this reaction and more recently, metal-free organocatalyzed versions have been developed, which afforded the nitro compounds in good to high enantioselectivities. Most of the methodologies have been focused on the employment of aldehydes and ketones as donors using L-proline derivatives.[4] The activation of the donors and control of asymmetric induction most likely occur through the formation of enamine intermediates.[4,5] Important results have been achieved with malonate esters and ketoesters when using enantiomerically pure bifunctional organocatalysts based on thioureas[6] and chincona derivatives.[7] This type of catalyst activates carbon nucleophiles by the basic tertiary amino group and the olefins through hydrogen bonding interaction of the nitro group with the Brønsted acid functionality of the promoter (thiourea or hydroxyl moieties). The asymmetric induction achieved is related to the spatial positions of the two functionalities, placed in an appropriate chiral molecular scaffold, which direct the approach of the nucleophile onto the nitroolefin.

We have recently reported the nucleophilic asymmetric epoxidation of α,β-unsaturated ketones using (*S*)-diaryl-2-pyrrolidinemethanols and *t*-butyl hydroperoxide as oxidant.[8] The epoxides have been isolated in high yield and enantioselectivity (up to 94% ee). We proposed that the amino alcohol played the role of a bifunctional catalyst through deprotonation of the *t*-butyl hydroperoxide by the amino group and activation of the enone via hydrogen bonding between the hydroxyl group of the promoter and the carbonyl oxygen atom. We envisaged that the double activation mechanism could be further exploited in C–C bond forming reaction such as the Michael addition of carbon nucleophiles to nitroolefins using readily available 2-pyrrolidinemethanols. The secondary amine should activate the malonate ester and the hydroxyl group the nitroolefin, through hydrogen bonding interactions orientating the reagents in close proximity (Fig. 1).

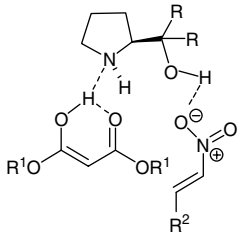


Figure 1. Proposed bifunctional mode of action of 2-pyrrolidenemethanols in Michael addition of malonates to nitroolefins.

* Tel.: +39 089 965370; fax: +39 089 965296; e-mail: lattanzi@unisa.it

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.02.024

2. Results and discussion

Commercially available α,α-diphenyl-L-prolinol **1a** was first employed in the dimethyl malonate addition to *trans*-β-nitrostyrene **3a** at room temperature (Table 1). We were pleased to observe that compound **1a** promoted the addition in different solvents.

Predictably, the enantioselectivity was markedly affected by the nature of solvent. Polar, protic or coordinating media (entries 1 and 2), which have a strong effect on hydrogen bonding interactions, can destroy the templated structure, made of catalyst, malonate and nitroolefin to afford a racemic product. In apolar solvents, the reaction showed a certain degree of enantiocontrol (entries 3–6) and in *p*-xylene the (*S*)-product was obtained in moderate 39% ee (entry 6). Under more concentrated conditions (entry 7), **4a** was recovered in better yield and slightly reduced ee.

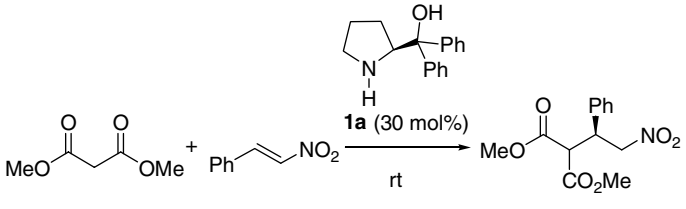
Employing these conditions (Table 1, entry 7), commercially or readily available amino alcohols from L-proline (Fig. 2) were screened in the malonate addition to **3a** (Table 2).

L-Proline was found to be a completely inactive catalyst for the addition reaction (entry 1). Simple prolinol **1c** was more active than **1a**, but **4a** was isolated in almost racemic form (entry 2). Catalyst **1d** having a tertiary amino group, was considerably less reactive and the product was obtained as the opposite enantiomer in low ee (entry 3).

Since catalyst **1a** proved to be the most efficient in terms of asymmetric induction, we then screened different aryl substituted 2-pyrrolidinemethanols.[9] Catalysts with electron-donating substituents on the phenyl ring **1e**,**f** were shown to be more active than **1a** (entries 4 and 5)[10] and the enantioselectivity was only slightly reduced. More sterically demanding **1g** afforded a comparable result with respect to **1a** (entry 6). Electron-rich and sterically hindered catalyst **1h** was found to be the most active and the enantioselectivity significantly improved (entry 7). The importance of hydrogen bond donor capability on catalyst activity was ascertained by performing the reaction using compound **1i** in which the hydroxyl group was removed (entry 8). In this case, both the activity and the enantioselectivity dropped dramatically, which supported the hypothesis of the bifunctional catalysis provided by 2-pyrrolidenemethanols. The reaction was carried out under solvent-free conditions, using an excess of dimethyl malonate, and although it proceeded faster, it furnished the product in lower ee (entry 9). When using diethyl malonate as the donor, a significant improvement in enantioselectivity was observed (entry 10). With di-*t*-butyl malonate, almost no product was recovered under the same conditions (entry 11).

To study the scope and limitations of the reaction, a variety of nitroolefins were screened using catalyst **1h** and diethyl malonate at room temperature in *p*-xylene (Table 3). When *trans*-β-nitrostyrene was reacted at lower temperature of 4 °C (entry 2), the reaction rate decreased and the asymmetric induction only improved slightly (compare with entry 1). Nitroolefins, which had electron-donating or electron-withdrawing groups on the phenyl ring (entries 3–5), were converted into the corresponding products in high yields and comparable ees. A nitroolefin bearing the 1-naphthyl group furnished the best result (entry 6). The less reactive heteroaromatic derivative furnished the product in lower ee (entry 7). The alkyl substituted nitroolefin proved to be unreactive (entry 8). Finally, when the α-methyl dimethyl malonate was reacted with **3a**, the product was obtained in moderate yield and lower ee (entry 9). Interestingly, the reaction of α-methyl ethyl acetoacetate with **3a** gave the adduct in high yield and appreciable diastereoselectivity, although in a comparable level of ee (entry 10).

Table 1. Michael addition of dimethyl malonate to **3a** using catalyst **1a** in different solvents[a]



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

Entry	Solvent	Time (h)	Yield **4a**[b] (%)	ee **4a**[c] (%)
1	THF	67	63	1
2	CH_3OH	63	66	0
3	$CHCl_3$	91	62	22
4	Hexane	97	85	22
5	Toluene	71	42	35
6	*p*-Xylene	69	50	39
7[d]	*p*-Xylene	64	62	35

[a] Conditions: 0.2 mmol **3a**, 0.06 mmol **1a**, 0.32 mmol **2a**, 340 μL solvent.
[b] Isolated products after flash chromatography.
[c] Determined by HPLC analysis using Chiralpak AD column. In all cases absolute configuration for the main enantiomer was found to be *S*.
[d] In this case 170 μL of solvent was used.

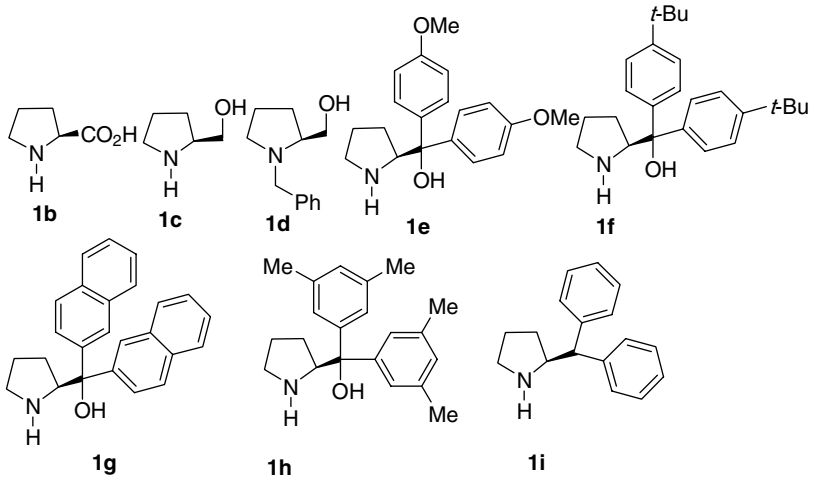
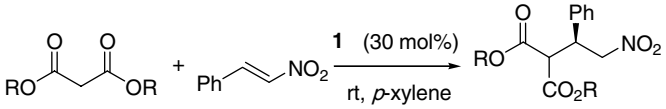


Figure 2. Structures of the catalysts used in this study.

Table 2. Michael addition of malonate esters to **3a** using different catalysts under various conditions



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

Entry	1	2	Time (h)	Yield **4**[b] (%)	ee **4**[c] (%)
1	**1b**	R = Me **2a**	78	<5	—
2	**1c**[a]	R = Me **2a**	65	62	4(*S*)
3	**1d**	R = Me **2a**	96	34	7(*R*)
4	**1e**	R = Me **2a**	71	82	31(*S*)
5	**1f**	R = Me **2a**	73	86	32(*S*)
6	**1g**	R = Me **2a**	52	65	36(*S*)
7	**1h**	R = Me **2a**	71	93	44(*S*)
8	**1i**	R = Me **2a**	90	7	4(*S*)
9[d]	**1h**	R = Me **2a**	48	97	20(*S*)
10	**1h**	R = Et **2b**	68	60	53(*S*)
11	**1h**	R = *t*-Bu **2c**	70	<5	—

[a] 20 mol % of catalyst was used.
[b] Isolated products after flash chromatography.
[c] Determined by HPLC analysis using Chiralpak AD column. The absolute configuration of the prevalent enantiomer was determined by comparison of the HPLC retention times with those reported in the literature.[3,4]
[d] The reaction was carried out in the absence of a solvent using 10 equiv of **2a** with respect to **3a**.

It is worth noting that the level of asymmetric induction observed in Table 3, although moderate, is encouraging taking into account that it is achieved by using a structurally simple chiral catalyst and most of all noncovalent bonds are involved in the activation of the reagents by the promoter.

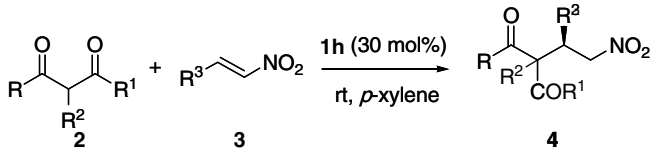
3. Conclusion

In conclusion, we have reported a user-friendly organocatalytic methodology for the Michael addition of malonate esters to β-aryl nitroolefins, which furnished the products in good yield and moderate enantioselectivity. To the best of our knowledge, the transformation is the first example of enantioselective bifunctional catalysis mediated by L-proline derivatives for C–C bond forming reactions.[11] Hence, this additional mode of activation can be employed in asymmetric organocatalysis, apart from the well-known strategies based on the formation of enamine or iminium intermediates.[12] We are currently investigating potentially more efficient L-proline derived bifunctional organocatalysts and expanding their utility in other asymmetric transformations.

4. Typical experimental procedure

To a solution of nitroolefin (0.2 mmol) and catalyst **1h** (0.06 mmol, 18.4 mg) in *p*-xylene (220 μL) at rt was added **2b** (0.4 mmol, 60 μL). After completion of the reaction, monitored by TLC, the crude reaction mixture was directly

Table 3. Scope of the Michael addition of **2** to **3** using catalyst **1h**[a]



2 **3** **4**

Entry	3	2	Time (h)	4	Yield 4%[b]	ee 4%[c]
1	Ph	**2b**	114	**b**	88	52(*S*)
2[d]	Ph	**2b**	144	**b**	60	56(*S*)
3	*p*-CH_3–C_6H_4	**2b**	125	**c**	75	45(*S*)
4	*p*-F–C_6H_4	**2b**	88	**d**	96	52(*S*)
5	*p*-Br–C_6H_4	**2b**	92	**e**	95	50(*S*)
6	1-Naphthyl	**2b**	90	**f**	97	54(nd)[e]
7	2-Furyl	**2b**	119	**g**	77	23(*S*)
8	*n*-Pentyl	**2b**	190	**h**	<5	—
9	Ph	$R = R^1 = OMe$, $R^2 = Me$	167	**i**	52	21(*S*)
10	Ph	$R = Me$, $R^1 = OEt$, $R^2 = Me$	93	**j**	81	26(*S*,*S*)[f,g]

[a] Conditions: 0.2 mmol **3**, 0.06 mmol **1h**, 0.4 mmol **2**, 220 μL solvent.
[b] Isolated products after flash chromatography.
[c] Determined by HPLC analysis using chiral columns. The absolute configuration of the prevalent enantiomer was determined by comparison of the HPLC retention times or specific rotations with those reported in the literature.[3,4]
[d] The reaction was carried out at 4 °C.
[e] Not determined.
[f] The diastereoisomeric ratio of 70/30 for **4j** was determined by ^1H NMR analysis (400 MHz) of the crude reaction mixture.[6b]
[g] ee and absolute configuration for the prevalent enantiomer of the major diastereoisomer.

purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate mixtures (98/2–90/10) to give the final product **4**. Spectroscopic and analytical data of compounds **4** matched those reported in the literature.[3,4,6b]

Acknowledgements

We acknowledge financial support from Ministero dell'Istruzione, Università e Ricerca Scientifica (MIUR). We thank the referees for useful suggestions, which helped to improve the manuscript.

References

1. For a recent review, see: Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877.
2. Ono, N. In *The Nitro Group in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2001.
3. (a) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215; (b) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagan, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097; (c) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262; (d) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192; (e) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700; (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.
4. (a) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423; (b) Bentacort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737; (c) Enders, D.; Seki, A. *Synlett* **2002**, 26; (d) Andrey, O.; Alexakis, A.; Belardinelli, G. *Org. Lett.* **2003**, *5*, 2559; (e) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2527; (f) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558; (g) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808; (h) Bentacort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Synthesis* **2004**, 1509; (i) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369; (j) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212; (k) Mitchell, C. E. T.; Cobb, A. J. A.; Ley, S. V. *Synlett* **2005**, 611; (l) Knudsen, K. R.; Mitchell, C. E. T.; Ley, S. V. *Chem. Commun.* **2006**, 66.
5. Blarer, S. J.; Seebach, D. *Chem. Ber.* **1983**, *116*, 2250.
6. (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672; (b) Okino, T.; Hoashi, Y.; Fururkawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119; (c) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713.
7. (a) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906; (b) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105; (c) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481; (d) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367.
8. (a) Lattanzi, A. *Org. Lett.* **2005**, *7*, 2579; (b) Lattanzi, A. *Adv. Synth. Catal.* **2006**, *348*, 339.
9. Catalysts **1d–h** have been reported previously and were synthesized according to the following literature procedures: (a) Mature, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Turner Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751; (b) Bailey, D.; O'Hagan, D.; Tavash, M. *Tetrahedron: Asymmetry* **1997**, *8*, 149.
10. Electron-donating groups on the benzene ring of the catalysts increase amine basicity by means of inductive or electronic effects.

11. These results point out that the double activation does not exclusively pertain to enantiomerically pure thioureas and chincona derivatives. For examples on bifunctional catalysis in Michael addition mediated by tertiary amines derived from cinchona derivatives, see: (a) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238; (b) Latvala, A.; Stanchev, S.; Linden, A.; Hesse, M. *Tetrahedron: Asymmetry* **1993**, *4*, 173.
12. For recent reviews on organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5183; (b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719.