Tetrahedron Letters 53 (2012) 3865–3868

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Highly enantioselective Michael addition of cyclic ketones to chalcones catalyzed by pyrrolidine-based imides

Hong-Yu Xie, Shu-Rong Ban *, Ju-Na Liu, Qing-Shan Li *

*School of Pharmaceutical Science, Shanxi Medical University, Taiyuan 030001, People's Republic of China*

ARTICLE INFO

*Article history:*
Received 9 March 2012
Revised 4 May 2012
Accepted 11 May 2012
Available online 29 May 2012

*Keywords:*
Enantioselective
Michael addition
Cyclic ketones
Chalcones

ABSTRACT

An efficient procedure for asymmetric Michael addition reaction of cyclic ketones with low activated chalcones catalyzed by pyrrolidine-based phthalimide and 1,8-Naphthalimide catalysts was developed. The corresponding products were obtained in high yields with high diastereoselectivities (up to 99:1 dr) and high enantioselectivities (up to 96% ee) under mild conditions.



The most intriguing aspect of organic synthesis of paramount concern is that of the carbon–carbon bond formation reaction. The efficient generation of a carbon–carbon bond is the essence of synthetic organic chemistry leading to the formation of various valuable molecules. For a long time chemists have focused considerable and consistent attentions on the development of efficient and operationally simple protocols for the formation of carbon–carbon bonds.[1] Among many methods of carbon–carbon bond formation the Michael addition reaction is extremely popular and very powerful which involves two major reagents: Michael donors and Michael acceptors.[2] The importance of this methodology has stimulated significant interest in the development of catalytic, asymmetric versions of the process.[3,4] Lewis acid-based catalytic[5] and organocatalytic systems[6] have been reported. However, most of the organocatalyzed Michael addition reactions employ highly activated Michael acceptors, such as nitroalkenes.[7] We noticed that organocatalytic asymmetric Michael addition reactions of simple cyclic ketones with chalcones still remain a challenge and were rarely reported, probably due to the low reactivity and high steric hindrance of the substrates.[8] In our previous work the pyrrolidine-based phthalimides and 1,8-Naphthalimide (**I–III**) (Fig. 1) were synthesized and found to be efficient in the asymmetric Michael reaction of ketones to nitroalkenes as enamine-type organocatalysts.[9] Considering the consistency of catalytic mechanism, herein we tested these pyrrolidine-based imides (**I–III**) in the asymmetric Michael addition of cyclic ketones to lower activated Michael acceptors chalcones. The experimental results showed this catalytic system performed well over a broad scope of substrates, furnishing various 1,5-diketone compounds in high diastereoselectivity (up to 99:1) and excellent enantioselectivity (up to 96% ee) under mild conditions.

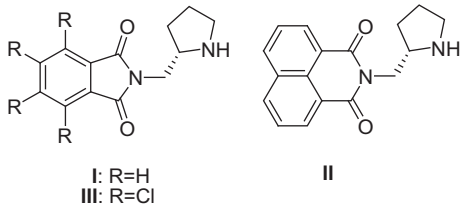


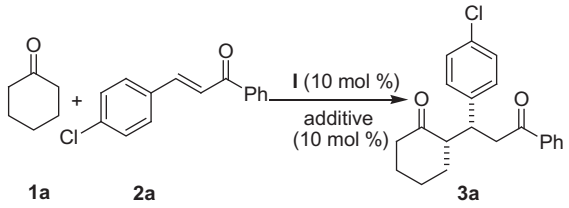

**Figure 1.** Imide catalysts (**I–III**).

Using **I** as the catalyst, a number of parameters were firstly screened in the model asymmetric Michael addition of cyclohexanone to chalcones. The results are summarized in Table 1. Initially, the conjugate addition was examined in a few solvents at room temperature with benzoic acid as additive. Among the various organic solvents tested, toluene, dichloromethane, THF, and solvent-free were better in terms of both the diastereoselectivity and enantioselectivity, with 93%, 94% ee, 95% ee, and 95% ee in enantioselectivity, respectively (Table 1, entries 1, 2, 4, and 7). When the reaction proceeded in polar solvents (DMSO, *t*-BuOH, *i*-PrOH, and THF), the yields of **3a** were very poor (Table 1, entries 3, 4, 5, and 6). Solvent-free was chosen for the following study of the influence of additive, catalyst, and temperature. The additive carboxylic acid was found to be an essential factor to this reaction.

* Corresponding authors. Tel./fax: +86 351 4690322.
*E-mail addresses:* shurongban@163.com (S.-R. Ban), qingshanl@yahoo.com (Q.-S. Li).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.05.106

**Table 1**
Screening of reaction conditions for the conjugate addition of cyclohexanone to chalcone[a]




1a 2a 3a

| Entry | Additive | Temp (°C) | Solvent | Time (d) | Yield[b] (%) | dr | % ee [c] |
|---|---|---|---|---|---|---|---|
| 1 | Benzoic acid | 20 | Toluene | 12 | 11 | 98:2 | 93 |
| 2 | Benzoic acid | 20 | DCM | 11 | 42 | 98:2 | 94 |
| 3 | Benzoic acid | 20 | DMSO | 11 | 6 | 99:1 | 86 |
| 4 | Benzoic acid | 20 | THF | 12 | 18 | 98:2 | 95 |
| 5 | Benzoic acid | 20 | *t*-BuOH | 7 | 6 | 98:2 | 77 |
| 6 | Benzoic acid | 20 | *i*-PrOH | 8 | Trace | — | — |
| 7 | Benzoic acid | 20 | Neat | 11 | 38 | 98:2 | 95 |
| 8 | 2,4-Dichlorobenzoic acid | 20 | Neat | 7 | 20 | 98:2 | 91 |
| 9 | Trifluoroacetic acid | 20 | Neat | 7 | 0 | — | — |
| 10 | Acetic acid | 20 | Neat | 7 | 28 | 99:1 | 94 |
| 11 | Hydrochloric acid | 20 | Neat | 7 | Trace | — | — |
| 12 | No additive | 20 | Neat | 7 | 0 | — | — |
| 13 | Benzoic acid | 50 | Neat | 7 | 17 | 96:4 | 71 |
| 14 | Benzoic acid | 75 | Neat | 7 | 11 | 67:33 | 62 |

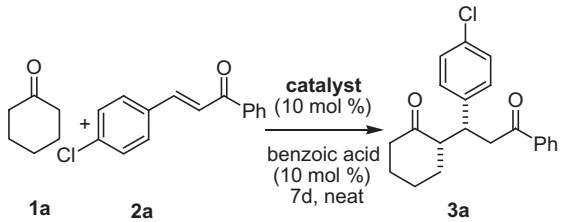
[a] All reactions were carried out with cyclohexanone (**1a**; 0.5 mL, absolutely excess) and chalcone (**2a**; 63 mg, 0.26 mmol) in the presence of catalyst **I** (10 mol %).
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determined by chiral HPLC on a Chiralpak AS-H column with *n*-hexane and 2-propanol as eluents.

In the absence of any carboxylic acid or in the presence of $CF_3COOH$ no product was obtained (Table 1, entries 9 and 12). The yield of the reaction was very low in the presence of hydrochloric acid (Table 1, entry 11). Almost the same level of diastereoselectivity was observed for substituted benzoic acid such as benzoic acid (Table 1, entry 7, 98:2 dr), and 2,4-dichlorobenzoic acid (Table 1, entry 8, 98:2 dr). Benzoic acid is the best choice because of the higher enantioselectivity and reaction rate. Increasing reaction temperature could improve the reaction rate but reduced the stereoselectivity (Table 1, entries 7, 13, and 14) obviously.

Catalysts **II** and **III** were then screened employing above optimized conditions (Table 1, entry 7), and the results are summarized in Table 2. Compounds **I** and **II** facilitated the asymmetric ichael addition of cyclohexanone to chalcone with good to excellent stereoselectivities while using **III** as catalyst gave no product. The possible reason is that catalyst **III** could not form the transition state with ketone to chalcone (Fig. 2) because of the high electron-withdrawing inductive effect. We also found that for catalyst **I** the yield was increased slightly by augmenting the catalyst loading from 0.1 equiv to 0.3 equiv (Table 2, entries 1 and 4) but still unsatisfactory (Table 2, entry 4, 45% yield). To our delight, 30% of **II** had the right properties to achieve good product formation (Table 2, entry 5) with an excellent yield in 7 d and high enantioselectivity, albeit with slightly diminished diastereoselectivity (92:8 vs 97:3 dr).

With the optimized reaction conditions in hand, a variety of chalcones bearing different substituent groups were investigated, and the results are summarized in Table 3. These chalcones reacted smoothly with cyclohexanone to provide the corresponding adducts in moderate to excellent yields with excellent diastereoselectivities and enantioselectivities (Table 3, entries 1–15). Excellent diastereoselectivities (up to >99/1 dr) and enantioselectivities (81–96% ee) were observed regardless of the electronic nature of the aromatic substituent. While the nature of the substituent on the benzene ring exhibited slight influence on the reaction rate and yield: when electron-donating substituent was introduced to the benzene ring, low to moderate yields were obtained (Table 3, entries 8 and 13). Thiophenyl contained chalcone as Michael acceptor gave low yield (Table 3, entry 15). In addition, acetone-derived chalcone can also react smoothly with cyclohexanone to give the corresponding adduct with excellent enantioselectivity but slower reaction rate (Table 3 entry 16).

**Table 2**
Screening of catalysts[a]




1a 2a 3a

| Entry | Catalyst | Temp (°C) | Yield[b] (%) | dr | % ee [c] |
|---|---|---|---|---|---|
| 1 | **I** | 20 | 38 | 98:2 | 95 |
| 2 | **II** | 20 | 51 | 97:3 | 94 |
| 3 | **III** | 20 | 0 | — | — |
| 4[d] | **I** | 20 | 45 | 98:2 | 96 |
| 5[d] | **II** | 20 | 91 | 92:8 | 94 |

[a] All reactions were carried out with cyclohexanone (**1a**; 0.5 mL, absolutely excess) and chalcone (**2a**; 63 mg, 0.26 mmol) in the presence of catalysts **I–III** (10 mol %).
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determined by chiral HPLC on a Chiralpak AS-H column with *n*-hexane and 2-propanol as eluents.
[d] 30 mol % catalyst was used.

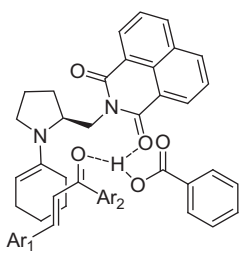
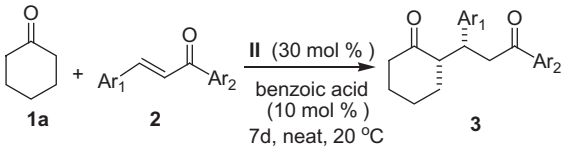



**Figure 2.** Possible transition state.

**Table 3**
Catalytic asymmetric Michael addition of cyclohexanone to chalcones[a]



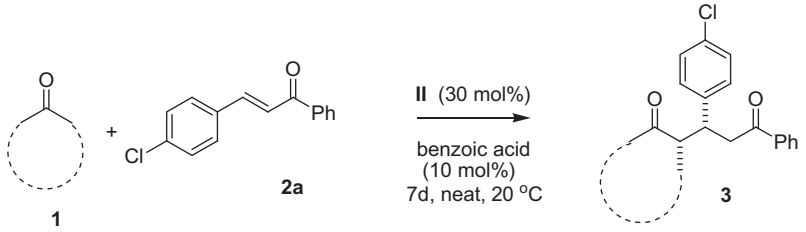

| Entry | $Ar_1$ | $Ar_2$ | Yield[b] (%) | dr | % ee [c] |
|---|---|---|---|---|---|
| 1 | 4-$ClC_6H_4$ | Ph | 91 | 92:8 | 94 |
| 2 | Ph | Ph | 98 | 96:4 | 92 |
| 3 | 2-$NO_2C_6H_4$ | Ph | 77 | 99:1 | 95 |
| 4 | 3-$NO_2C_6H_4$ | Ph | 93 | 84:16 | 94 |
| 5 | 2,4-$Cl_2C_6H_3$ | Ph | 82 | 98:2 | 96 |
| 6 | 4-$BrC_6H_4$ | Ph | 95 | 88:12 | 95 |
| 7 | 4-$FC_6H_4$ | Ph | 99 | 93:7 | 93 |
| 8 | 4-$CH_3C_6H_4$ | Ph | 78 | 96:4 | 92 |
| 9 | 4-$NO_2C_6H_4$ | Ph | 99 | 77:23 | 91 |
| 10 | Ph | 4-$BrC_6H_4$ | 99 | 90:10 | 91 |
| 11 | Ph | 4-$NO_2C_6H_4$ | 91 | 92:8 | 88 |
| 12 | Ph | 4-$FC_6H_4$ | 78 | 95:5 | 91 |
| 13 | Ph | 4-$CH_3C_6H_4$ | 66 | 99:1 | 81 |
| 14 | Ph | 4-$ClC_6H_4$ | 99 | 93:7 | 88 |
| 15 | 2-Thiophenyl | 2-Thiophenyl | 67 | 83:17 | 91 |
| 16 | 4-$ClC_6H_4$ | $CH_3$ | 43 | 81:19 | 90 |

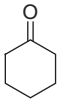
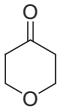
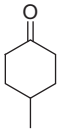
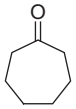
[a] All reactions were carried out with cyclohexanone (**1a**; 0.5 mL, absolutely excess) and chalcone (**2**; 0.26 mmol) in the presence of catalyst **II** (30 mol %).
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determined by chiral HPLC on a Chiralpak AS-H column with *n*-hexane and 2-propanol as eluents.

Other ketones were also found to be compatible with **1a** under the optimized conditions (Table 4). Reactions with six-membered ring ketones gave the Michael adducts with excellent enantioselectivities (92–94% ee). However, when cyclopentanone, cycloheptanone, or acetone was used as substrate, only moderate enantioselectivity was obtained. The absolute stereochemical results can be explained by the concept of an acyclic synclinal transition state, as proposed by Seebach and Golinski.[10] It is accepted that when primary or secondary chiral amines are used as organocatalysts, the reaction clearly involves an enamine pathway. As shown in Figure 2, the possible transition state was presented in which the imide carbonyl oxygen atom plays an important role in shielding the si-face of enamine double bond and activating chalcones. If the catalyst could not form a transition state, such as **III**, the catalyst would not be effective for this reaction.

In summary, we have successfully developed a procedure for catalytic asymmetric Michael addition reaction of cyclic ketones with chalcones. Moderate to excellent diastereoselectivities and enantioselectivities were obtained for the addition of ketones to a variety of chalcones under the pyrrolidine-based 1,8-Naphthalimide catalysis of **II**. The presence of a brønsted acid with proper acidity, such as benzoic acid, proved to be critical for the excellent performance of this catalyst system. The application of this new type of organocatalyst in other asymmetric reactions is under way in our laboratory.

**Table 4**
Catalytic asymmetric Michael addition reactions of cyclic ketones **1** with chalcone **2a**[a]




| Entry | Ketone **1** | Yield[b] (%) | dr | % ee [c] |
|---|---|---|---|---|
| 1 |  | 91 | 92:8 | 94 |
| 2[d] |  | 63 | 93:7 | 90 |
| 3 |  | 95 | 96:4 | 92 |
| 4 |  | 95 | 61:39 | 73 |
| 5[d] |  | 39 | 97:3 | 51 |
| 6[d] |  | 40 | — | 56 |

[a] All reactions were carried out with cyclic ketone (**1**; 0.5 mL, absolutely excess) and chalcone (**2a**; 0.26 mmol) in the presence of catalyst **II** (30 mol %).
[b] Yield of the isolated product after chromatography on silica gel.
[c] Determined by chiral HPLC on a Chiralpak AS-H column with *n*-hexane and 2-propanol as eluents.
[d] The reaction was carried out in the solvent of DCM.

## Acknowledgments

The authors would like to acknowledge financial supports from the National Natural Science Foundation of China (No. 81172938), the Shanxi Province Science Foundation for Youths of China (No. 2009021041-1) and the Main Cultivate Object of Program for the Top science and Technology Innovation Teams of Higher Learning Institutions of Shanxi.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.106.

## References and notes

1. For reviews on carbon–carbon bond formation, see: (a) Gessner, V. H.; Tannaci, J. F.; Miller, A. D.; Tilley, T. D. *Acc. Chem. Res.* **2011**, *44*, 435–446; (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527; (c) Chin, C. S.; Won, G.; Chong, D.; Kim, M.; Lee, H. *Acc. Chem. Res.* **2002**, *35*, 218–225; (d) Luh, T. Y.; Leung, M.; Wong, K. T. *Chem. Rev.* **2000**, *100*, 3187–3204; (e) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023–2035.
2. For reviews on Michael addition reaction, see (a) Hoz, S. *Acc. Chem. Res.* **1993**, *26*, 69–74; (b) Mather, B. D.; Viswanathan, K.; Miller, K. M.; Long, T. E. *Prog. Polym. Sci.* **2006**, *31*, 487–531; (c) Mukaiyama, T. *Angew. Chem., Int. Ed.* **1977**, *16*, 817–826; (d) Tokoroyama, T. *Eur. J. Org. Chem.* **2010**, 2009–2016.
3. For reviews on asymmetric Michael addition reaction, see (a) Sulzer-Mosse, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123–3135; (b) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058–11076; (c) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933–972.
4. (a) Li, X.; Li, Y. M.; Peng, F. Z.; Wu, S. T.; Li, Z. Q.; Sun, Z. W.; Zhang, H. B.; Shao, Z. H. *Org. Lett.* **2011**, *13*, 6200–6203; (b) Tian, X.; Cassani, C.; Liu, Y.; Moran, A.; Urakawa, A.; Galzerano, P.; Arceo, E.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 17934–17941; (c) Yang, H.; Wong, M. W. *J. Org. Chem.* **2011**, *76*, 7399–7405; (d) Roca-Lopez, D.; Merino, P.; Sayago, F. J.; Cativiela, C.; Herrera, R. P. *Synlett* **2011**, 249–253; (e) Freund, M. H.; Tsogoeva, S. B. *Synlett* **2011**, 503–507.
5. (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992; (b) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877–1894; (c) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171–196; (d) Sibi, M.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061.
6. Berkessel, A.; Groger, H. *Asymmetric Organocatalysis—From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005.
7. (a) Yang, W.; Du, D. M. *Adv. Synth. Catal.* **2011**, *353*, 1241–1246; (b) Lu, D. F.; Gong, Y. F.; Wang, W. Z. *Adv. Synth. Catal.* **2010**, *352*, 644–650; (c) Trost, B. M.; Hitce, J. *J. Am. Chem. Soc.* **2009**, *131*, 4572–4573; (d) Sato, A.; Yoshida, M.; Hara, S. *Chem. Commun.* **2008**, 6242–6244; (e) Ban, S. R.; Du, D. M.; Liu, H.; Yang, W. *Eur. J. Org. Chem.* **2010**, 5160–5164.
8. (a) Wang, J.; Li, H.; Zu, L. S.; Wang, W. *Adv. Synth. Catal.* **2006**, *348*, 425–428; (b) Xu, D. Z.; Shi, S.; Liu, Y. J.; Wang, Y. M. *Tetrahedron* **2009**, *65*, 9344–9349; (c) Liu, Y. F.; Wu, Y.; Lu, A. D.; Wang, Y. M.; Wu, G. P.; Zhou, Z. H.; Tang, C. C. *Tetrahedron: Asymmetry* **2011**, *22*, 476–479; (d) Qian, Y. B.; Xiao, S. Y.; Liu, L.; Wang, Y. M. *Tetrahedron: Asymmetry* **2008**, *19*, 1515–1518.
9. Ban, S. R.; Xie, H. Y.; Zhu, X. X.; Li, Q. S. *Eur. J. Org. Chem.* **2011**, 6413–6417.
10. Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413–1423.