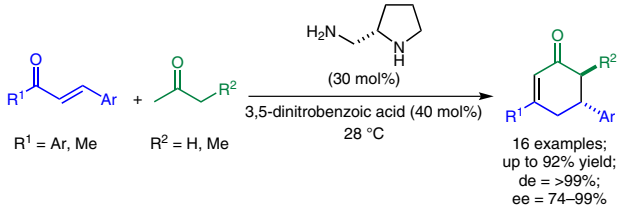
Synlett S. J. Wagh, G. R. Dhage Letter

Primary-Secondary Diamine Catalyzed Enantioselective Synthesis of Substituted Cyclohex-2-enones by Cascade Michael–Aldol–Dehydration of Ketones with Chalcones

Sandip J. Wagh *[a]
Ganesh R. Dhage[b]

[a] Bio-Organic Division, Bhabha Atomic Research Centre, Trombay, Mumbai, 400085, India
sandipwagh10@gmail.com
[b] Department of Chemistry, Ahmednagar College, Ahmednagar, Station Road, Ahmednagar, Maharashtra, 414001, India



Received: 06.02.2017
Accepted after revision: 27.02.2017
Published online: 20.03.2017
DOI: 10.1055/s-0036-1588976; Art ID: st-2017-d0088-l

Abstract A simple primary-secondary diamine organocatalyst catalyzes the cascade Michael–aldol–dehydration of chalcones and unmodified ketones to produce substituted cyclohex-2-enones under mild conditions with good yields and high enantio- and/or diastereoselectivities. The success of the catalyst system is possibly due to simultaneous activation of the electrophilic chalcone by iminium formation and the nucleophilic ketone by enamine formation with an overall intramolecular iminium–di-enamine mechanism.

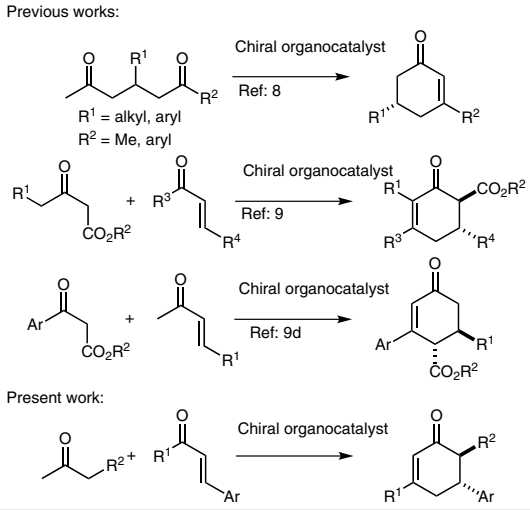
Key words cascade reaction, chalcone, chiral cyclohex-2-enone, organocatalysis

Asymmetric organocatalysis[1] has now become a complement to metal- and enzyme-catalyzed reactions, spurred by the development of a number of highly enantioselective transformations of carbonyl substrates catalyzed by chiral secondary amines involving enamine[2] or iminium intermediates.[3]

Cascade reactions,[4] in which more than one bond is formed in a multistep one-pot reaction sequence, are an attractive tool for quick assembly of complex structures without isolation and purification of the intermediates. Recently, organocatalyzed cascade reactions are gaining popularity because they can be performed in an asymmetric fashion with high levels of stereocontrol.[5]

Chiral cyclohex-2-enones are an important class of scaffolds and are important starting materials for organic synthesis.[6] Thus, considerable attention has been paid to the development of simple but efficient methods for the synthesis of chiral cyclohex-2-enones using organocatalysis.[7] Two approaches described involve either an asymmetric aldol cyclization–dehydration of prochiral 1,5-dicarbonyl compounds[8] or a Robinson annelation, comprising consecutive asymmetric Michael addition of an activated methylene/methyne substrate to an α,β-unsaturated ketone or aldehyde followed by an intramolecular aldol reaction and subsequent dehydration.[9,10]

Michael additions of simple ketones to chalcones have received less attention because of the lower reactivity of the later.[11] Furthermore, Michael–aldol or Michael–aldol–dehydration cascades on chalcone substrates leading to cyclohexanone or cyclohex-2-enone systems are limited to β-keto ester nucleophiles.[9] Jørgensen et al.[9a] were among the first to show an enantio- and diastereoselective Michael–aldol reaction of β-keto esters and enones that provided functionalized cyclohexanones. A separate dehydration step then provided chiral cyclohex-2-enones. Chiral phosphoric acids have been shown[9b] to catalyze the Robinson annulation reaction between β-keto esters and enones to provide substituted chiral cyclohex-2-enones with excellent enantioselectivities. Substituted chiral cyclohex-2-enones can be obtained by Michael–aldol–dehydration sequence from a β-keto ester such as benzoyl acetate and chalcones.[9d] More recent studies[9f–i] have shown that primary amine catalyzed Robinson annelation of β-keto esters with enones can provide substituted chiral cyclohex-2-enones with good diastereo- and enantioselectivities. In continuation with our previous study[12] on organocatalyzed Michael–aldol–dehydration sequence reactions for the direct synthesis of nonchiral 3,5-diaryl-cyclohexenones from acetone and chalcones, we herein disclose an organocatalyzed enantioselective cascade Michael–aldol cyclization–dehydration reaction of chalcones and ketones to give synthetically useful functionalized cyclohex-2-enones in high yields, and good to high regio- and enantioselectivities (Scheme 1).



Scheme 1 Preparation of cyclohex-2-enone systems

Secondary amines have proved to be useful for generation of activated enamines from aldehydes and ketones or iminium activation of α,β-unsaturated aldehydes.[2,3] Chiral primary amines have recently been extensively used in enamine activation of aldehyde and ketones.[13] However, α,β-unsaturated ketones do not tend to form iminium ions with secondary amines due to steric reasons but do so with primary amines derived from natural cinchona alkaloids and other molecules.[14] We proposed that, for a successful organocatalytic cascade annelation of simple ketones and chalcones, simultaneous enamine activation of the ketone and iminium activation of chalcone would probably be necessary in an intramolecular fashion to facilitate the process. Based on this hypothesis, we selected commercially available chiral primary diamines **1**,[15] **2**[16], and primary-secondary diamine **3**[17] (Figure 1).

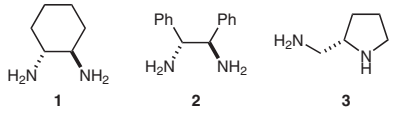
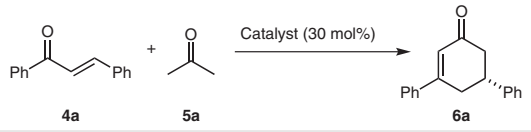


Figure 1 Structure of diamine catalysts used in this study

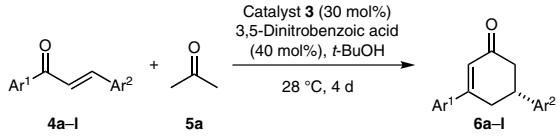
The reaction of chalcone **4a** and acetone **5a** to give 3,5-diphenylcyclohex-2-enone (**6a**) was chosen as the model reaction for the catalyst evaluation (Scheme 2). A large number of experiments was performed to optimize the process in terms of catalyst, solvent, additive, and conditions (see Supporting Information). The optimum conditions found utilized one equivalent of chalcone **4a**, 15 equivalents of acetone **5a**, 0.3 equivalents of catalyst **3**, and 0.4 equivalents of additive 3,5-dinitrobenzoic acid in *t*-BuOH (0.4 M) as solvent at 28 °C for **4**, furnishing 3,5-diphenylcyclohex-2-enone **6a** in 80% yield and with 88% ee.[18]



Scheme 2 Michael–aldol–dehydration cascade of chalcone **4a** and acetone **5a**

The generality of the catalytic system was examined under the optimized reaction conditions using chalcones **4a–l** and acetone (Table 1). The 3,5-diarylcyclohex-2-enones **6a–l** were obtained in moderate to good yields (54–92%) with good to excellent enantioselectivities (74–98% ee).

Table 1 Organocatalyzed Tandem Michael-Aldol Dehydration of Chalcones and Acetone[a]

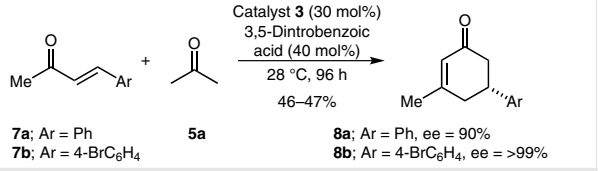


Entry	Chalcone	Ar^1	Ar^2	Product yield (%)[b]	ee (%)[c]
1	**4a**	Ph	Ph	**6a** 80	89
2	**4b**	Ph	4-ClC_6H_4	**6b** 80	89
3	**4c**	Ph	4-BrC_6H_4	**6c** 92	98
4[d]	**4d**	Ph	4-$MeOC_6H_4$	**6d** 54 [83][e]	96
5[f]	**4e**	Ph	4-$F_3CC_6H_4$	**6e** 87	94
6	**4f**	Ph	4-FC_6H_4	**6f** 75	80
7[f,g]	**4g**	Ph	4-NCC_6H_4	**6g** 80	78
8	**4h**	Ph	3-ClC_6H_4	**6h** 73	74
9[d]	**4i**	4-$MeOC_6H_4$	Ph	**6i** 60 [81][e]	82
10[f,g]	**4j**	4-$O_2NC_6H_4$	Ph	**6j** 81	88
11	**4k**	4-BrC_6H_4	Ph	**6k** 70	84
12	**4l**	4-BrC_6H_4	4-FC_6H_4	**6l** 79	80

[a] Unless otherwise specified, the reaction was carried out using optimized conditions.
[b] Yield of the isolated product after flash chromatography.
[c] Determined by HPLC on a chiral stationary phase.
[d] The reaction was performed over 6 d.
[e] Yield based on recovered starting material.
[f] The reaction was performed over 3 d.
[g] The reaction was carried out in *t*-BuOH/toluene (4:1) to maintain homogeneity.

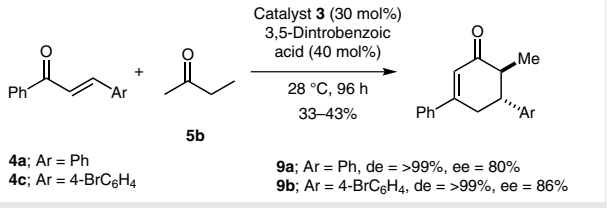
The reaction of acetone and chalcones with electron-donating substituents on aroyl or styryl components were sluggish and remained incomplete (Table 1, entries 4 and 9); whereas the reactions of acetone and chalcones substituted with electron-withdrawing groups on both the aryl rings were complete and gave very good yields of cyclohex-2-enones.

Further applications and scope of the catalytic system were examined with less reactive chalcones devoid of an aryl group adjacent to carbonyl functionality. We were pleased to see that the catalytic system worked well with chalcones **7a**,**b** and acetone to provide the desired 5-aryl-3-methylcyclohex-2-enones **8a**,**b** but with lower yield; albeit better stereoselectivity (Scheme 3).



Scheme 3 Reaction of unreactive chalcones with acetone

We also investigated butan-2-one **5b** and chalcones **4a**,**c**. Interestingly, the reaction took place with the exclusive formation of a single regio- and diastereoisomers **9a** and **9b**, respectively (Scheme 4). The yields were moderate but the enantioselectivities were uniformly high.



Scheme 4 Reaction of chalcones with 2-butanone **5b**

The absolute configuration of 5-(4-bromophenyl)-3-phenylcyclohex-2-enone (**6c**) was established by X-ray crystallography[19] and was found to be 5*R* (Figure 2).

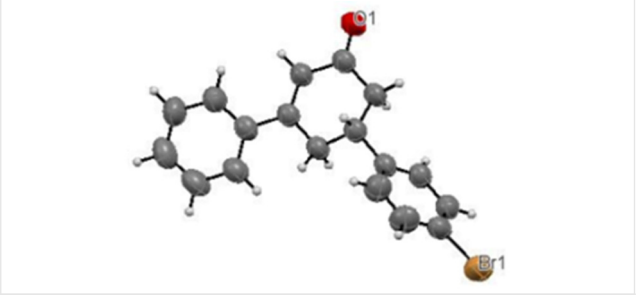


Figure 2 ORTEP diagram of **6c**

The absolute configuration of the other products **6a**,**b**,**d**–**l** and **8a**,**b** were assigned by analogy. The absolute configuration of **9b** was also established X-ray crystallography[19] and was assigned to be 5*R*,6*S* (Figure 3).

The promotion of the cascade process can be explained through simultaneous activation of the electrophilic chalcone **4a** and nucleophilic ketone by the primary-secondary diamine catalyst **3** via iminium and enamine formation,[11c] respectively (Scheme 5).

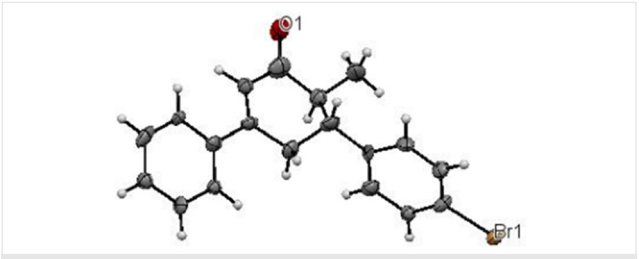
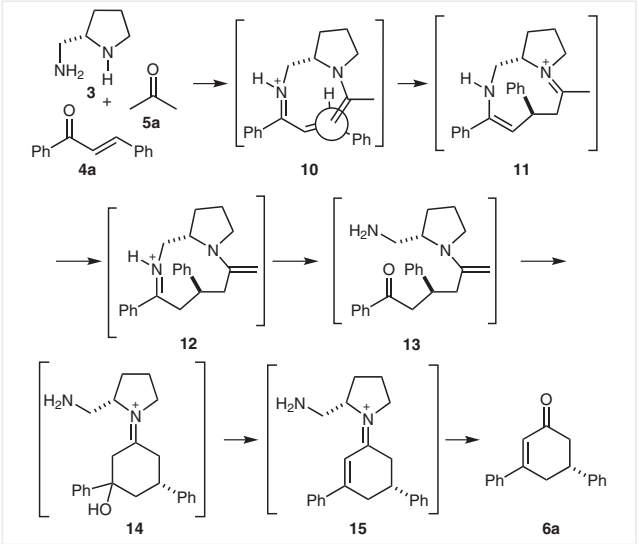


Figure 3 ORTEP diagram of **9b**



Scheme 5 Proposed mechanism of diamine-catalyzed Michael–aldol–dehydration cascade

In the doubly activated species **10**, the enamine reacts intramolecularly at the less hindered *Re*-face 4-position of the iminium of chalcone leading to intermediate **11** which reorganizes to a new iminium–enamine **12**. At this stage a probable hydrolysis of ketone iminium leads to ketone–enamine **13** which then undergoes an intramolecular aldol reaction to give the iminium intermediate **14**. Dehydration followed by iminium hydrolysis then leads to the (5*R*)-3,5-diphenylcyclohex-2-enone (**6a**).

In conclusion, we have developed a cascade Michael–aldol–dehydration of chalcones and simple ketones leading to substituted chiral cyclohex-2-enones using a readily available primary-secondary diamine derived from proline. The products were formed in good yield and with acceptable regio-, stereo-, and enantioselectivity. This provides a method for making chiral 3,5-diarylcyclohex-2-enones where both the aryl rings sourced from a chalcone substrate.

Acknowledgment

S.J.W. is grateful to the Council of Scientific and Industrial Research (CSIR), New Delhi for a Senior Research Fellowship, Professor Sunil Kumar Ghosh (BARC, Mumbai) for continuous support and guidance and Professors Mukesh Kumar (BARC, Mumbai) and S. Mobin (IIT, Indore) for providing the X-ray crystallographic data structure analyses. G.R.D. thanks CSIR, New Delhi for S.R.F.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588976.

References and Notes

(1) For selected reviews, see: (a) Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, **2007**. (b) Berkessel, A.; Grçger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, **2004**. Special issue on organocatalysis: (c) *Chem. Rev.* **2007**, *107*, 5413. Special issue on organocatalysis: (d) *Acc. Chem. Res.* **2004**, *37*, 487. (e) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138. (f) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638.

(2) Selected reviews: (a) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001. (b) Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465. (c) Bertelsen, S.; Nielsen, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 7356.

(3) Selected reviews: (a) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79. (b) Almasi, D.; Alonso, D. A.; Najera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (d) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (e) Jørgensen, K. A.; Bertelsen, S. *Chem. Soc. Rev.* **2009**, *38*, 2178. (f) Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 9748. (g) Erkkila, A.; Majander, I.; Phiko, P. M. *Chem. Rev.* **2007**, *107*, 5416.

(4) Selected reviews: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Li, G.; Wei, H.-X.; Kim, S.-H.; Carducci, M. D. *Angew. Chem. Int. Ed.* **2001**, *40*, 4277. (c) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Rabbe, G. *Nature (London, U.K.)* **2006**, *441*, 861.

(5) Selected reviews: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570. (b) Westermann, B.; Ayaz, M.; van Berkel, S. S. *Angew. Chem. Int. Ed.* **2010**, *49*, 846. (c) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (d) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (e) Vera, S.; Melchiore, P. *An. Quím.* **2010**, *106*, 277. (f) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237. (g) Marson, C. M. *Chem. Soc. Rev.* **2012**, *41*, 7712. (h) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442.

(6) Selected reviews: (a) Ho, T.-L. *Enantioselective Synthesis: Natural Products Synthesis from Chiral Terpenes*; Wiley: New York, **1992**. (b) Klunder, A. J. H.; Zhu, J.; Zwanenburg, B. *Chem. Rev.* **1999**, *99*, 1163. For recent selected examples, see: (c) Mohr, P. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 1712. (d) Miyashita, M.; Saino, M. *Science* **2004**, *305*, 495. (e) Baran, P. S.; Ritcher, J. M.; Lin, D. W. *Angew. Chem. Int. Ed.* **2005**, *44*, 609. (f) Goeke, A.; Mertl, D.; Brunner, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 99. (g) Lakshmi, R.; Bateman, T. D.; McIntosh, M. C. *J. Org. Chem.* **2005**, *70*, 5313.

(7) Yang, X.; Wang, J.; Li, P. *Org. Biomol. Chem.* **2014**, *12*, 2499.

(8) (a) Agami, C.; Sevestre, H. *J. Chem. Soc., Chem. Commun.* **1984**, 1385. (b) Agami, C.; Platzer, N.; Sevestre, H. *Bull. Soc. Chim. Fr.* **1987**, *2*, 358. (c) Zhong, G.; Hoffmann, T.; Lerner, R. A.; Danishefsky, S.; Barbas, C. F. III. *J. Am. Chem. Soc.* **1997**, *119*, 8131. (d) List, B.; Lerner, R. A.; Barbas, C. F. III. *Org. Lett.* **1999**, *1*, 59. (e) Zhou, J.; Wakchaure, V.; Kraft, P.; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 7656. (f) Chen, L.; Luo, S.; Li, J.; Li, X.; Cheng, J. P. *Org. Biomol. Chem.* **2010**, *8*, 2627. (g) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097.

(9) (a) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 1272. (b) Akiyama, T.; Katoh, T.; Mori, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 4226. (c) Wang, L. L.; Peng, L.; Bai, J. F.; Huang, Q. C.; Xu, X. Y.; Wang, L. X. *Chem. Commun.* **2010**, *46*, 8064. (d) Yang, Y. Q.; Chai, Z.; Wang, H. F.; Chen, X. K.; Cui, H. F.; Zheng, C. W.; Xiao, H.; Li Zhao, P. G. *Chem. Eur. J.* **2009**, *15*, 13295. (e) Cui, H. F.; Yang, Y. Q.; Chai, Z.; Li, P.; Zheng, C. W.; Zhu, S. Z.; Zhao, G. *J. Org. Chem.* **2010**, *75*, 117. (f) Li, P. F.; Wang, Y. C.; Liang, X. M.; Ye, J. X. *Chem. Commun.* **2008**, 3302. (g) Li, P. F.; Wen, S. G.; Yu, F.; Liu, Q. X.; Li, W. J.; Wang, Y. C.; Liang, X. M.; Ye, J. X. *Org. Lett.* **2009**, *11*, 753. (h) Wen, S. G.; Li, P. F.; Wu, H. B.; Yu, F.; Liang, X. M.; Ye, J. X. *Chem. Commun.* **2010**, *46*, 4806. (i) Yang, J. J.; Li, W. J.; Jin, Z. C.; Liang, X. M.; Ye, J. X. *Org. Lett.* **2010**, *12*, 5218.

(10) For selected examples, see: (a) Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jørgensen, K. A. *Chem. Commun.* **2006**, 4928. (b) Marigo, M.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475. (c) Bolze, P.; Dickmeiss, G.; Jørgensen, K. A. *Org. Lett.* **2008**, *10*, 3753. (d) Albrecht, Ł.; Richter, B.; Vila, C.; Krawczyk, H.; Jørgensen, K. A. *Chem. Eur. J.* **2009**, *15*, 3093. (e) Hayashi, Y.; Toyoshima, M.; Gotoh, H.; Ishikawa, H. *Org. Lett.* **2009**, *11*, 45.

(11) For selected examples, see: (a) Chen, Y. C. *Synlett* **2008**, 1919. (b) Wang, J.; Li, H.; Zu, L. S.; Wang, W. *Adv. Synth. Catal.* **2006**, *348*, 425. (c) Wang, J.; Wang, X.; Ge, Z.; Cheng, T.; Li, R. *Chem. Commun.* **2010**, *46*, 1751. (d) Qian, Y.; Xiao, S.; Liu, L.; Wang, Y. *Tetrahedron: Asymmetry* **2008**, *19*, 1515. (e) Xu, D. Z.; Shi, S.; Liu, Y. J.; Wang, Y. M. *Tetrahedron* **2009**, *65*, 9344. (f) 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. (g) Ma, S.; Wu, L.; Liu, M.; Wang, Y. *Org. Biomol. Chem.* **2012**, *10*, 3721. (h) Xie, H. Y.; Ban, S. R.; Liu, J. N.; Li, Q. S. *Tetrahedron Lett.* **2012**, *53*, 3865. (i) Liu, L.; Zhu, Y.; Huang, K.; Chang, W.; Li, J. *Eur. J. Org. Chem.* **2013**, 2634. (j) Kumar, T. P.; Sattar, M. A.; Sarma, V. U. M. *Tetrahedron: Asymmetry* **2013**, *24*, 1615.

(12) Wagh, S. J.; Chowdhury, R.; Ghosh, S. K. *Curr. Organocatal.* **2014**, *1*, 71.

(13) For selected reviews on primary amine catalysis, see: (a) Peng, F.; Shao, Z. *J. Mol. Catal. A: Chem.* **2008**, *285*, 1. (b) Wu, L.-W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047. (c) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807. For a review on asymmetric primary amine catalysts based on Cinchona alkaloids, see: (d) Chen, Y.-C. *Synlett* **2008**, 1919.

(14) Bartoli, G.; Melchiorre, P. *Synlett* **2008**, 1759.

(15) For selected examples, see: (a) Inokoishi, Y.; Sasakura, N.; Nakano, K.; Ichikawa, Y.; Kotsuki, H. *Org. Lett.* **2010**, *12*, 1616. (b) Ge, Z.; Cheng, T.; Li, R. *Chem. Commun.* **2010**, 2124. (c) Liu, Y.; Wang, J.; Sun, Q.; Li, R. *Tetrahedron Lett.* **2011**, *52*, 3584. (d) Liu, Y.; Gao, P.; Wang, J.; Sun, Q.; Ge, Z.; Li, R. *Synlett* **2012**, *23*, 1031.

(16) (a) Wang, W.; Wang, J.; Zhou, S.; Sun, Q.; Ge, Z.; Wang, X.; Li, R. *Chem. Commun.* **2013**, 1333. (b) Liu, Y.; Liu, X.; Wang, M.; He, P.; Lin, L.; Feng, X. *J. Org. Chem.* **2012**, *77*, 4136.

(17) (a) Diakos, C.-I.; Zhang, M.; Beale, P.-J.; Fenton, R.-R.; Hambley, T.-W. *Eur. J. Med. Chem.* **2009**, *44*, 2807. (b) Shen, H.-M.; Ji, H.-B. *Tetrahedron Lett.* **2012**, *53*, 3541.

(18) A mixture of chalcone **4a** (0.2 mmol), acetone (3 mmol), organocatalyst **3** (0.06 mmol), 3,5-dinitrobenzoic acid (0.08 mmol) in *t*-BuOH (500 µL) was stirred at r.t. for 96 h. After column chromatography (eluent: 95:5, hexane–EtOAc) a white solid was obtained (40 mg, 80%). The enantiomeric excess (ee) was determined by HPLC using a Chiralcel OJ-H column (hexane–*i*-PrOH = 90:10); flow rate 1.0 mL/min; t_R (major) = 18.3 min, t_R (minor) = 21.3 min (ee 89%); $[\alpha]_D^{26}$ +34.8 (*c* 0.5, CH_2Cl_2); mp 92–93 °C. IR (KBr): 1663 (CO), 1605, 1497, 1444, 1372, 1265, 761 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.69–2.82 (m, 2 H, CH_2), 2.95 (ddd, = 2.4, 11.2, 17.8 Hz, 1 H, CH_AH_BCO), 3.07 (dd, *J* = 4.4, 17.8 Hz, CH_AH_BCO, 1 H), 3.43–3.51 (m, 1 H, PhCH), 6.52 (d, *J* = 1.8 Hz, 1 H, C=CH), 7.29–7.46 (m, 8 H, Ar), 7.53–7.58 (m, 2 H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 36.2, 40.9, 43.9, 125.0, 126.1 (2 C), 126.7 (2 C), 127.0, 128.8 (3 C), 130.1, 138.3, 143.1, 158.7 (2 C), 199.2 (CO).

(19) The structures of **6c** (CCDC 1041621) and **9b** (CCDC 1041622) were confirmed by single-crystal X-ray data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.