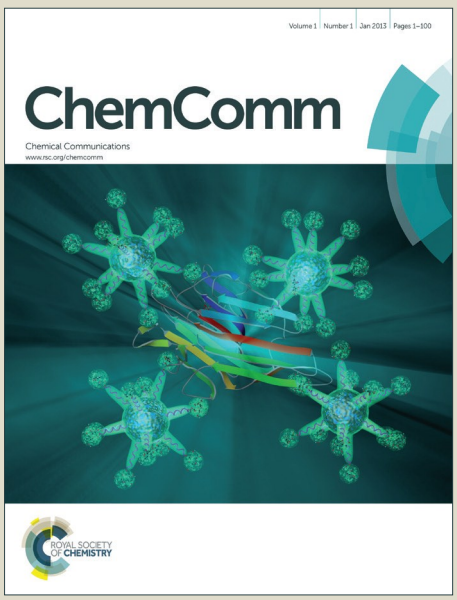
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

COMMUNICATION

Asymmetric Synthesis of 1*H*-Pyrrol-3(2*H*)-ones from 2,3-Diketoesters by Combination of AldolCondensation withBenzilicAcid Rearrangement

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

QiangSha,[a,b] HadiArman,[b] and Michael P. Doyle*[b]

An efficient two-step protocol for the asymmetric synthesis of 1*H*-pyrrol-3(2*H*)-one derivatives in 99% ee from conveniently accessed 2,3-diketoesters has been developed.

2,2-Disubstituted 1*H*-pyrrol-3(2*H*)-ones that possess a chiral center at the 2-position occur widely in naturalproducts,[1] and they are also fundamental units which have been used to build molecules with significant biological activities (Figure 1).[2] Due to their importance, a variety of methods for theirsynthesishave been developed. Cycloaddition strategies are among the most efficient ways used to access the key 1*H*-pyrrol-3(2*H*)-ones.[3] However, general highly enantioselectiveaddition methods are rare:one begins with chiral starting materials,[4]and the other employs catalytic asymmetric cycloaddition.[5] Although progress is being made in this area, the narrow substrate scope of reported methods suggests the need for more general enantioselectiveprocesses.

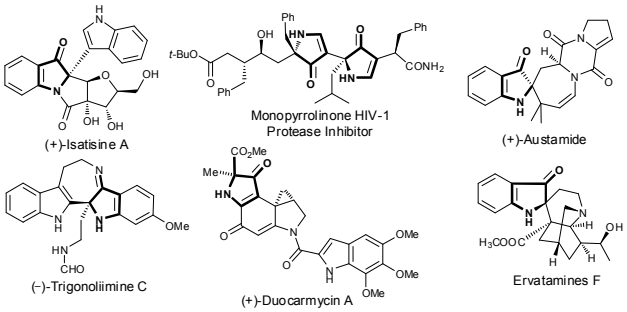
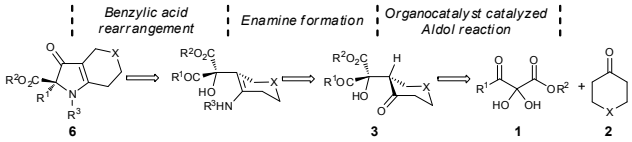


Fig1 Selected natural products containing the 1*H*-pyrrol-3(2*H*)-one unit orits analogue with atetrasubstituted carbon stereocenter.

Pioneering workby Wasserman and coworkers[6] demonstrated wideapplications of vicinal tricarbonyl compounds (VTCs)in the synthesis of natural products and synthetic intermediates. Our group has applied VTCs in the synthesis of functionalized furans[7] and pyrroles[8] and demonstrated their convenient uses as hydrates.[8b]We also reported the first diastereoselective[9] andenantioselective[10] nucleophilic addition reactions of VTC compounds. Based on our understanding of the VTC chemistry and reported benzilic acid rearrangement reactions,[11]an enantioselective strategy for the synthesis of 1*H*-pyrrol-3(2*H*)-ones starting from 2,3-diketoester hydrates was designed as shown in Scheme 1. The mixed asymmetric aldol reaction with VTCs has been unexplored. The enamine formation step is known,[12]although not in this system. To form the chiral key intermediate **3**, a chiral secondary amine-catalyzed aldol reaction was predicted to have the potential toachieve this goal.



Scheme 1 A designed strategy for the asymmetric synthesis of 1*H*-pyrrol-3(2*H*)-ones.

The Hajos-Parrish-Eder-Sauer-Wiechert reaction, the first example of asymmetric enamine catalysis, was reported 50 years ago.[13] However this powerful reaction was relatively unexplored until List and coworkers[14]discovered proline-catalyzed enantioselective intermolecular aldol reaction.Explosiveprogress ensued during which various organocatalysts were developed to realize the asymmetric aldol reaction.[15]Many types of carbonyl substrates have been successfully utilized in aldol reactions, including various aromatic aldehydes, aliphatic aldehydes and activated ketonesthat include 2-ketoesters. However, 2,3-diketoesters, which are unique and highly activated ketones, have not been investigated. Herein, we present the two-step asymmetric synthesis of 1*H*-pyrrol-3(2*H*)-ones thattakes unique advantage

[a] *School of ChemicalEngineering, NanjingUniversity of Science and Technology, XiaoLingWei 200, Nanjing 210094, P. R. of China*
[b] *Department of Chemistry, The University of Texas at San Antonio,San Antonio, Texas78249, United States*
Email: michael.doyle@utsa.edu

†Electronic Supplementary Information (ESI) available: Experimental procedures, optimization of reaction conditions, HPLC and spectral data for all new compounds. See DOI:10.1039/x0xx00000x

of the 2,3-diketoester framework to couple an *L*-proline catalyzed aldol reaction with the benzilic acid rearrangement.

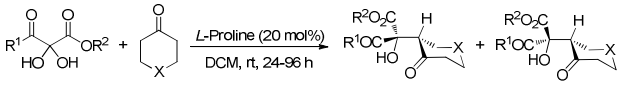
Vicinal tricarbonyl compounds easily absorb water to form theircorresponding hydrates that can be dehydrated by heating under vacuum. However, the VTC hydrates were used directly in this study due to theirconvenience in handling. Based on our initial hypothesis, benzyl 2,2-dihydroxy-3-oxobutanoate hydrate**1a** and cyclohexanone **2a** were selected for the aldol reaction. Of all the organocatalysts we examined,[16]*L*-proline was found to be optimalfor diastereoselectivity and enantiocontrol.[17]The aldol product was formed in 74:26 d.r.,and the major diasteroisomer **3a**was conveniently isolated by simple chromatography in 68% yield with 99% *ee*. All attempts to increase diastereoselectivity with alternative catalysts, lowering reaction temperatures, use of **1a** in its anhydrous form, and changing solvents were unsuccessful.[16]However, the good yield of the major diastereomer, its ease of isolation, and its excellent enantiomeric excess made this transformation very promising.

With the optimal reaction conditions in hand, we set out toexplore the substrate generality of the *L*-proline catalyzed aldol reactions.Usinghydrated2,3-diketoesters, the effect of different groups on the ester was investigated first(Table 1, entries 1-3). The size of the group did not significantly affect yield or stereoselectivity of products. The major diastereomers were isolated in moderate yields with 99% *ee*, and the minor diastereomers were also obtained with high *ee'*s. Then 2,3-diketoesters with different groups on the keto side were investigated:replacing the methyl group with ethyl or benzyl gave similar results (Table 1, entries 4-5). However, changing the methyl group bound to the keto group to aryl resulted in a significant increase in the d.r. of the aldol products (Table 1, entries 6-12) up to 89:11 (Table 1, entries 7-8). The effects of different substituents on the aromatic ring were also investigatedshowing that electron-withdrawing groups favored this process (Table 1, entry 10). An electron-donating para-substituted methoxy group, however, strongly inhibited the aldol process (Table 1, entry 9). Dihydro-2*H*-thiopyran-4(3*H*)-one (**2b**) worked well in this process as an alternative to cyclohexanonefrom which the major diasterisomer **3m** was obtained in 56% isolated yield with 99% *ee* (Table 1, entry 13).

Scheme 2*L*-proline catalyzed aldol reaction of benzyl 2,2-dihydroxy-3-oxobutanoate (**1a**) with cyclohexanone (**2a**).

The high efficiency and broad generality of the aldol reaction that gave, without exception, the major diastereomerswith 99% *ee'*swas evidentthroughout investigations of substrate scope. A limitation that did appear was that ketone ring sizes other than six, especially cyclopentanone and cycloheptanone,gave intractable mixtures of products.

Table 1 Substrate scope of *L*-proline catalyzed aldol reactions of 2,3-diketoesters with cycloketones.[a]

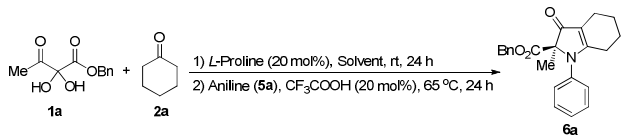


Entry	R^1	R^2	X	Time	Ratio **3**/**4**[b]	Yield[c] (ee[d]) of **3**	Yield[c] (ee[d]) of **4**
1	Me	Bn	CH_2	24 h	74/26	**3a**/68% (99%)	**4a**/24% (97%)
2	Me	Me	CH_2	32 h	79/21	**3b**/60% (99%)	**4b**/16% (97%)
3	Me	Cy	CH_2	48 h	77/23	**3c**/67% (99%)	**4c**/20% (98%)
4	Et	Me	CH_2	32 h	77/23	**3d**/65% (99%)	**4d**/19% (97%)
5	Bn	Bn	CH_2	48 h	73/27	**3e**/59% (99%)	**4e**/21% (98%)
6	C_6H_5	Et	CH_2	32 h	81/19	**3f**/51% (99%)	**4f**/12% (98%)
7	*p*-ClC_6H_4	Et	CH_2	48 h	89/11	**3g**/58% (99%)	**4g**/7% (94%)
8	*p*-BrC_6H_4	Et	CH_2	48 h	89/11	**3h**/56% (99%)	**4h**/6% (95%)
9	*p*-$OMeC_6H_4$	Et	CH_2	96 h	85/15	**3i**/25% (99%)	**4i**/4% (98%)
10	*p*-CNC_6H_4	Et	CH_2	42 h	84/16	**3j**/70% (99%)	**4j**/13% (96%)
11	2-naphthyl	Et	CH_2	54 h	79/21	**3k**/45% (99%)	**4k**/12% (97%)
12	2-thienyl	Et	CH_2	48 h	88/12	**3l**/67% (99%)	**4l**/9% (92%)
13	Me	Bn	S	48 h	76/24	**3m**/56% (99%)	**4m**/17% (89%)

[a] Reaction conditions:**1** (1.0 mmol), **2** (2.0 mmol), *L*-proline (20 mol%), DCM (5.0 mL), rt, 24-96 h. [b]Determined by^{1}H NMRspectroscopy or HPLC analysis of the reaction mixture.[c]Yield of the isolated product after column chromatography. [d]The *ee* value was determined by HPLC using a chiralstationary phase.

The high enantiocontrolin thesealdolcondensation reactions prompted us to investigate the subsequent benzilic acid rearrangement reaction. Initially, we attempted to combine the aldol reaction and the benzilic acid rearrangement reaction in one pot. As shown in Table 2, without adding any additives, **6a** was obtained in only 32% yield and 30% *ee* (Table 2, entry 1). Various additives were examined from which we discovered thatby using 20 mol% trifluoroacetic acid the yield of **6a** increased significantly. However,**6a** was always obtained in only moderate enantiomeric excess no matter what solvent was used (Table 2, entries 2-6) reflecting the uniform conversions of eachaldol product diastereomer (**3a** and **4a**) to1*H*-pyrrol-3(2*H*)-one

Table 2 Investigationof a one-pot enantioselective synthesis of 1*H*-pyrrol-3(2*H*)-onederivatives.[a]



1a 2a 6a

Entry	Additive	Solvent	Yield[b]	*Ee*[c]
1	---	MeCN	32%	30%
2	CF_3COOH	MeCN	82%	31%
3	CF_3COOH	DCM	67%	47%
4	CF_3COOH	$CHCl_3$	64%	41%
5	CF_3COOH	DCE	72%	44%
6	CF_3COOH	Toluene	55%	41%

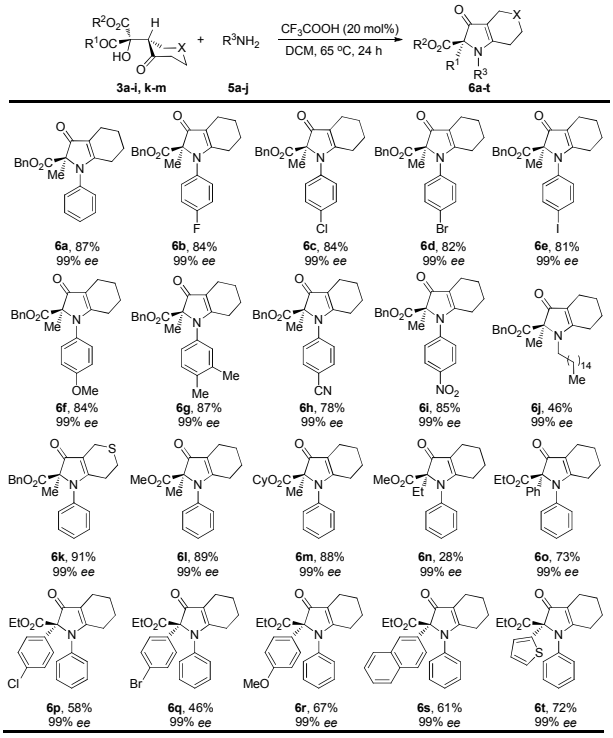
[a] Reaction conditions: 1) **1a** (0.10mmol), **2a** (0.20mmol), *L*-proline (20 mol%), solvent (0.50 mL), rt, 24 h; 2) **5a** (0.11 mmol), CF_3COOH (20 mol%), 65 °C, 24 h.[b]Yield of the isolated product after column chromatography.[c]The *ee* value was determined by HPLC using a chiral stationary phase.

6ain inverse enantiomeric excesses.This result indicated that a two-step procedure to synthesize1*H*-pyrrol-3(2*H*)-onesin which the major diastereomer from the aldol condensationis used for the benzilic acid rearrangement would be successful.

With chromatographic isolation of the major diastereomers from the asymmetric aldol reactions, weexaminedthe benzilic acid rearrangement of these compounds with aniline. By using trifluoroacetic acid as an additive and DCM as the solvent at 65 °C for 24h, the rearrangement product **6a** was isolated in 87% yield with 99% *ee* (Table 3, **6a**). Anilines with halogen atoms (F, Cl, Br, I) all gave the 1*H*-pyrrol-3(2*H*)-ones in high yield with 99% *ee* (Table 3, **6b**-**6e**). Anilines with both electron-donating groups (Me, OMe) and electron-withdrawing groups (CN, NO_2) gave the corresponding products in good yields without loss ofenantioselectivity (Table 3, **6f**-**6i**). Hexadecylamine, which was chosen as a representative aliphatic amine, gave **6j** in 46% yieldwith 99% *ee* (Table 3, **6j**). The presence of a sulfur atom on the cyclic aliphatic ring (**3m**), gave the benzilic acid rearrangementproduct **6k** in 91% yield with 99% *ee* (Table 3, **6k**). Different groups on the ester all gave the corresponding 1*H*-pyrrol-3(2*H*)-oneproducts in good yields with99%*ee* (Table 3, **6l**-**6m**). By changing the substituent from methyl to ethyl on the keto side, a significant decrease of the product yield was observed (Table 3, **6n**) and was further limited with other alkyl substituents. However, by replacing the methyl group with phenyl, **6o** was obtained in 73% yield with 99% *ee* (Table 3, **6o**). Lastly, the effects from various aryl groups were studied from which the benzylic acid rearrangement products were obtained in moderate to good yields with 99% *ee* (Table 3, **6p**-**6t**).

The synthetic utility of the present methodologyinvolving the *L*-proline catalyzed aldol reaction was examinedon a 10 mmol scale.[16] Under the optimized reaction conditions, the aldol products were formed in 74:26 d.r. The major diasterisomer was isolated in 61% yield (1.86 g) with 99% *ee*. The minor diasterisomer was obtained in 21% yield (0.63 g) with 98% *ee*. Theseseparated aldol products were then used to perform the benzylic acid rearrangement.Products**6d** and **7d** were obtained in 82% yield (2.19 g) and 84% yield (0.77 g) respectively, both with excellent enantiomeric excess.

Table 3Benzylic acid rearrangement reactions leading to 1*H*-pyrrol-3(2*H*)-ones.[a]



[a] Reaction conditions:**3** (0.10 mmol), **5** (0.11 mmol), DCM (0.50 mL), CF_3COOH (20 mol%), 65 °C, 24 h; Yields refer to isolated yields after column chromatography; The *ee* value was determined by HPLC using a chiralstationary phase.

The relative and absolute configurationsof **3g** and **6c** were assigned (*R,S*)-**3g** and *R*-**6c** based on their single-crystal X-raydiffraction analysis (Figure 2).[18]

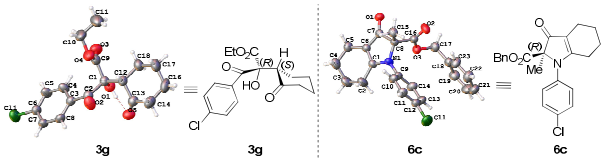
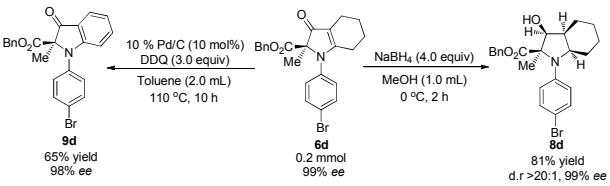


Fig 2X-ray structures of **3g** and **6c**.

Reduction of**6d** with 4.0 equiv $NaBH_4$ gave**8d**as the sole diastereomerin 81% yield with 99% *ee*. The configuration of **8d** was determined by NOESY experiments. In addition, **6d**is conveniently oxidized to **9d** in 65% yield with 98% *ee*, and thisprocess provides



Scheme 3Reduction and oxidation of 1*H*-pyrrol-3(2*H*)-one**6d**.

convenientaccess to nearly optically pure indolin-3-ones (Scheme 3).

In summary, we have developed a two-step method for the highly enantioselective synthesis of 1*H*-pyrrol-3(2*H*)-ones. 2,3-Diketoesters have beenemployedfor the first time in asymmetric aldol reactions. By combining the *L*-proline catalyzed aldol reaction withthe benzylic acid rearrangement, 1*H*-pyrrol-3(2*H*)-ones are obtained in moderate yields but with notably excellent enantiomeric excess (99% *ee* for all (*R,S*)-products). Efforts are underway to examine additional applications of 2,3-diketoesters in highly enantioselective catalytic reactions.

Qiang Sha acknowledges ChinaScholarship Council (CSC) for his financial support. We acknowledge U.S. National Science Foundation (CHE-1212446), The Welch Foundation, and the University of Texas at San Antonio for supporting this research.The HRMS used in this research was supported by a grant from the National Institutes of Health (G12MD007591).

Notes and references

1 For selected examples, see:(a) W. H. Pearson, Y. Mi, I. Y. Lee and P. Stoy, *J. Am. Chem. Soc*.,2001, **123**, 6724; (b) K. amada, T. Kurokawa, H. Tokuyama and T. Fukuyama, *J. Am. Chem. Soc*.,2003, **125**, 6630; (c) R. M. Williams, J. H. Cao, H. Tsujishima and R. J. Cox, *J. Am. Chem. Soc*.,2003, **125**, 12172; (d) A. Karadeolian and M. A. Kerr, *J. Org. Chem*.,2010, **75**, 6830; (e) D. B. Zhang, D. G. Yu, M. Sun, X. X. Zhu, X. J. Yao, S. Y. Zhou, J. J. Chen and K. Gao, *J. Nat. Prod*.,2015, **78**, 1253.

2 For selected examples, see:(a) M. Brüggemann, A. I. McDonald, L. E. Overman, M. D. Rosen, L. Schwink and J. P. Scott, *J. Am. Chem. Soc*.,2003, **125**, 15284; (b) M. Mucedda, D. Muroni, A. Saba and C. Manassero, *Tetrahedron*,2007,**63**, 12232; (c) B. N. Reddy and C. V. Ramana, *Chem. Commun*.,2013, **49**, 9767; (d) S. Han, K. C. Morrison, P. J. Hergenrother and M. Movassaghi,*J. Org. Chem*.,2014, **79**, 473; (e) A. B.SmithIII, L. D.Cantin, A.Pasternak,L.Guise-Zawacki,W.Q.Yao, A.K.Charnley,J.Barbosa,P. A.Sprengeler, R.Hirschmann, S.Munshi, D. B.Olsen, W. A.Schleif and L. C.Kuo, *J. Med. Chem*.,2003, **46**, 1831; (f) A. B.SmithIII, A. K.Charnley and R. Hirschmann, *Acc. Chem.Res*.,2011, **44**, 180.

3 (a) M. A. Gomaa, *J. Chem. Soc., Perkin Trans. 1*.,2002, 341; (b) J. Huang, Y. J. Liang, W. Pan, Y. Yang and D. W. Dong, *Org. Lett*.,2007, **9**, 5345; (c) I. Kim and K. Kim, *Org. Lett*., 2010, **12**, 2500; (d) P. X. Zhou, Z. Z. Zhou, Z. S. Chen, Y. Y. Ye, L. B. Zhao, Y. F. Yang, X. F. Xia, J. Y. Luo and Y. M. Liang, *Chem. Commun*.,2013, **49**, 561; (e) Z. K. Wang, X. H. Bi, P. Q. Liao, X. Liu and D. W. Dong, *Chem. Commun*.,2013, **49**, 1309; (f) Z. J. Zhang, Z. H. Ren, Y. Y. Wang and Z. H. Guan, *Org. Lett*.,2013, **15**, 4822; (g) S. R. Mothe, M. L. Novianti, B. J. Ayers and P. W. H. Chan, *Org. Lett*.,2014, **16**, 4110; (h) X. Sun, P. H. Li, X. L. Zhang and L. Wang, *Org. Lett*.,2014, **16**, 2126; (k) N. Li, T. Y. Wang, L. Z. Gong and L. M. Zhang, *Chem. – Eur. J*.,2015, **21**, 3585.

4 (a) A. B.SmithIII, H. Liu, H. Okumura, D. A. Favor and R. Hirschmann, *Org. Lett.*,2000, **2**, 2041; (b) N. Gouault, M. L. Roch, C. Cornée, M. David and P. Uriac, *J. Org. Chem*.,2009, **74**, 5614; (c) R. Spina, E. Colacion, B. Gabriele, G. Salerno and J. Martinez, *J. Org. Chem*.,2013, **78**, 2698.

5 (a) J. X. Liu, Q. Q. Zhou, J. G. Deng and Y. C. Chen, *Org. Biomol. Chem*.,2013, **11**, 8175; (b) Q.Yin and S. L. You, *Chem. Sci*.,2011, **2**, 1344; (c) M. Rueping, S. Raja andA. Núñez, *Adv. Synth. Catal*.,2011, **353**, 563; (d) A. Parra, R.Alfaro, L. Marzo, A. Moreno-Carrasco, J. L. Garcia Ruano and J.Aleman, *Chem. Commun*.,2012, **48**, 9759; (e) Y.L. Zhao, Y.Wang, J. Cao, Y.M. Liang and P.F. Xu, *Org. Lett*.,2014, **16**, 2438; (f) C. Guo, M. Schedler, C. G. Daniliuc and F. Glorius, *Angew. Chem., Int. Ed*.,2014, **53**, 10232; (g) R. R. Liu, S. C. Ye, C. J. Lu, G. L. Zhuang, J. R. Gao and Y. X. Jia, *Angew. Chem., Int. Ed*.,2015, **54**, 11205.

6 H. H.Wasserman and H. Parr, *Acc. Chem. Res*.,2004, **37**, 687.

7 P.Truong,X. F. Xu and M. P. Doyle, *Tetrahedron Lett*.,2011, **52**, 2093.

8 (a) P.Truong,M. D.Mandler and M. P.Doyle, *Tetrahedron Lett*.,2015, **56**, 3042; (b) Q. Sha, H. Arman and M. P. Doyle, *Org. Lett*.,2015, **17**, 3876.

9 P.Truong, C. S.Shanahan and M. P.Doyle, *Org. Lett*.,2012, **14**, 3608.

10 P.Truong,P. Y.Zavalij andM. P.Doyle, *Angew. Chem., Int. Ed*.,2014, **53**, 6468.

11 (a) D. Askin, R. A. Reamer, T. K. Jones, R. P. Volante and I. Shinkai,*Tetrahedron Lett*.,1989, **30**, 671; (b) D. Askin, R. A. Reamer, D. Joe, R. P. Volante and I. Shinakai, *Tetrahedron Lett*.,1989, **45**, 6121; (c) M. J. Fisher, K. Chow, A. Villalobos and S. J. Danishefsky, *J. Org. Chem*.,1991, **56**, 2900; (d) H. H. Wasserman, D. S. Ennis and C. B. Vu, *Tetrahedron Lett*.,1991, **32**, 6039.

12 For selected examples, see:(a) W. Schrader, P. P. Handayani, J. Zhou and B. List, *Angew. Chem., Int. Ed*.,2009, **48**, 1463; (b) L. Ren, T. Lei and L. Z. Gong, *Chem. Commun*.,2011, **47**, 11683; (c) Y. M. Deng, L. Liu, R. G. Sarkisian, K. Wheeler, H. Wang and Z. H. Xu, *Angew. Chem., Int. Ed*.,2013, **52**, 3663; (d) Y. M. Deng, S. Kumar, K. Wheeler and H. Wang, *Chem. - Eur.J*.,2015, **21**,7874.

13 H. Pracejus,*Justus Liebigs Ann. Chem.*, 1960,**634**, 23.

14 B. List, R. A. Lerner and C. F. Barbas III, *J. Am. Chem. Soc*.,2000, **122**, 2395.

15 For selected reviews on organocatalyst catalysed aldol reactions, see:(a) M. Movassaghi and E. N. Jacobsen, *Science*, 2002, **298**,1904; (b)B. List, *Acc. Chem. Res*.,2004, **37**, 548;(c) C. Allemann, R. Gordollo, F. R. Clemente, P. H. Cheong and K. N. Houk, *Acc. Chem. Res*.,2004, **37**, 558; (d) S. Saito and H. Yamamoto, *Acc. Chem. Res*.,2004, **37**, 570; (e) M. Gruttadauria, F. Giacalone and R. Noto, *Chem. Soc. Rev*.,2008, **37**, 1666; (f) J. Seayad and B. List, *Org. Biomol. Chem*.,2005, **3**, 719; (g) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev*.,2007, **107**, 5471; (h) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem., Int. Ed*.,2008, **47**, 6138; (i) D. W. C. Macmillan, *Nature*,2008, **455**, 304; (j) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev*.,2009, **38**, 2178; (k) B. M. Trost and C. S. Brindle, *Chem. Soc. Rev*.,2010, **39**, 1600; (l) A. Moyano and R. Rios, *Chem. Rev*.,2011, **111**, 4703; (m)C. M. Marson, *Chem. Soc. Rev*.,2012, **41**, 7712.

16 See the Supporting Information for details.

17 This finding is consistent with results of Jørgensen and Maruoka for aldol reactions with 2-ketoesters (50 mol% proline with up to 99% *ee*): (a) A. Bøgevig, N. Kumaragurubaran, and K. A. Jørgensen, *Chem. Commun*.,2002, 620; (b) O. Tokuda, T. Kano, W.-G. Gao, T. Ikemoto, and K. Maruoka, *Org. Lett.* 2005, **7**, 5103.

18 The crystal data for compound **3g** and **6c** has been deposited with the Cambridge Crystallographic Data Centre (no. CCDC1417169 for **3g** and CCDC1417170for **6c**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/data_request/cif.

