Organic & Biomolecular Chemistry

www.rsc.org/obc

Volume 8 | Number 18 | 21 September 2010 | Pages 4029–4184

ISSN 1477-0520

RSC Publishing

1477-0520(2010)8:18;1-W

Picolylamine as an organocatalyst template for highly diastereo- and enantioselective aqueous aldol reactions†

Thomas C. Nugent,* M. Naveed Umar and Ahtaram Bibi

Received 27th April 2010, Accepted 10th June 2010
First published as an Advance Article on the web 12th July 2010
DOI: 10.1039/c0ob00049c

A pyridine based 1,2-diamine containing only one stereogenic center has been identified for fast aldol reactions (16–48 h). Using 2–5 mol% of (*R*)- or (*S*)-PicAm-**2**, cyclohexanone (3.3 equiv) readily undergoes aldol reactions with *o*-, *m*-, and *p*-substituted aromatic aldehyde partners (limiting reagent), including the poor electrophile 4-methylbenzaldehyde (95–99% ee). Furthermore, functionalized cyclic ketone substrates have been converted into four aldol products **9–12** using the lowest catalyst loading (5.0 mol%) to date with the highest yield and enantioselectivity.

Introduction

Perhaps the most convincing argument for organocatalyst development is the mild reaction conditions organocatalysts can perform under. The expectation is greater functional group compatibility when examining future drug like substrates while maintaining high stereoselectivity. For now organocatalysis researchers continue to define reaction types and substrate breadth, with organocatalyst design, testing, and modification central to those efforts.

Enantioselective organocatalytic aldol reactions have a distinct advantage over many of their transition metal variants—they do not require preformed silyl enol ethers. As a consequence, development of organocatalytic aldol reactions is of practical importance due to improved reaction step efficiency and the vital role (carbon–carbon bond formation) the reaction fulfils.

The resurgence of aldol organocatalysis can be directly linked to List's investigation of proline catalyzed reactions beginning in 2000.[1] Today's aldol organocatalysts[2] continue to overwhelmingly be bifunctional, and generation based refinement has allowed a handful of high value aldol organocatalysts to emerge. The top organocatalysts for *cyclic ketones*, the topic of this manuscript, fall within the following profile: low organocatalyst loading (0.5–5.0 mol%), good to high *dr* (5 : 1 to 99 : 1), high *ee* (90–99%), and ketone/aldehyde ratios (1 : 1 to 4 : 1) meeting or approaching those required of practical applications. This set of top performing catalysts, for cyclic ketones, is synthesized exclusively from three templates: proline or *trans*-4-hydroxyproline, threonine, and a 1,2-*trans*-cyclohexanediamine-BINOL derivative.[3] For example, Hayashi's *trans*-4-OTBDPS-proline,[4] Armstrong's *trans*-4-(4-*tert*-butylphenoxy)-proline/β-cyclodextrin,[5] Gruttadauria's *trans*-4-acyloxy-proline,[6] Lu's OTBS-threonine,[7] the proline-amide alcohols[8] of Gong[9] and Singh,[10] the proline thioamides of Alonso/Nájera,[11,12] and Shao's cyclohexadiamine-BINOL[13] typify the current state of the art regarding aldol organocatalyst performance with six-membered cyclic ketones.[14,15] When substrate breadth, reaction time, and catalyst synthesis are additionally considered, individual shortcomings are noted and spurred our consideration of alternatives.

The chemical design space within the above noted templates, especially regarding proline, might now be considered more restricted. Wary of this we considered the value of introducing a new bifunctional organocatalyst template: pyridine based 1,2-diamines.

Catalysts containing a pyridine moiety have been previously examined for aldol reactions, but are few in number and have meet with limited success (20–30 mol% catalyst loadings).[16,17] Many of these studies examine nornicotine (Fig. 1). More interesting to us was the only study examining a pyridine based 1,2-diamine: (±)-2-pyridyl-2′-pyrrolidine (Fig. 1). Surprisingly, under optimized conditions of pH, the authors found a depressed rate of reaction compared to nornicotine (1,3-diamine), and nornicotine itself was judged in the same study to be of no present synthetic value.[16b]

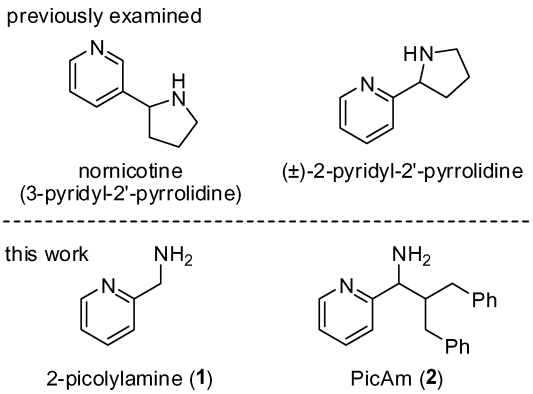


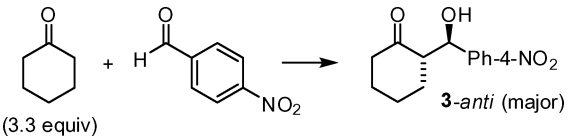
Fig. 1 Pyridine based aldol organocatalysts.

Although these combined findings were not encouraging, we felt in particular that pyridine based 1,2-diamine organocatalysts held untapped potential. Here we report on the first examination of 2-picolylamine (2-aminomethylpyridine) and a chiral version, (*R*)- and (*S*)-PicAm-**2** (Fig. 1), for aldol reactions.

Department of Chemistry, School of Engineering and Science, Jacobs University Bremen, Campus Ring 1, 28759 Bremen, Germany. E-mail: t.nugent@jacobs-university.de; Fax: +49 421 200 3229; Tel: +49 421 200 3232

† Electronic supplementary information (ESI) available: Experimental procedures, full spectroscopic data for compounds, and copies of ^{1}H NMR spectra and HPLC data. CCDC 775335. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00049c

Table 1 Aldol reaction of cyclohexanone with 4-NO_2-benzaldehyde[a]

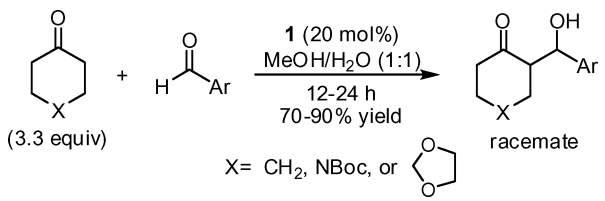


Entry	Solvent (0.5 M)	Time/h	T/°C	Yield (%)[b]	dr[c]	ee[d](*anti*)
1	Water	44	25	90	33 : 1	99
2	Water	16	45	89	17 : 1	97
3	Water	12	45	83	17 : 1	97
4[e]	Water	20	45	84	17 : 1	96
5[f]	Water	29	45	27	1 : 1	55
6	Brine	44	25	78	50 : 1	>99
7	Brine	16	45	92	22 : 1	99

[a] Reaction conditions: cyclohexanone (3.3 equiv), aldehyde (1.0 equiv, 0.5 mmol), (S)-PicAm-**2** (5.0 mol%), 2,4-DNBSA (5.0 mol%), unless otherwise stated. [b] Isolated yield after column chromatography. [c] ^{1}H NMR data of crude product after work-up, major product is *anti*. [d] HPLC data (Chiralpak AS-H or OD-H column) after silica gel chromatography. [e] 2.0 equiv of cyclohexanone were used. [f] Reaction performed without 2,4-DNBSA, HPLC yield provided.

Results and discussion

To test our concept we reacted commercially available inexpensive 2-picolylamine (20 mol%) with cyclic ketones in the presence of an array of *ortho*-, *meta*-, and *para*-substituted benzaldehydes (Scheme 1). Smooth by-product free racemic aldol formation was always observed in less than 24 h.[18] The overall findings from this study were two-fold. First, and foremost, 2-picolylamine was proven to be a viable organocatalyst template, and second a simple method for racemic aldol synthesis was identified. The latter would appear trivial, but for by-product free racemic aldol synthesis of our substrates the only other method we could confirm required anhydrous THF and $TiCl_4$.[19,20] Thus we have identified a simple non-anhydrous method that cleanly allows racemic aldol product formation (Scheme 1).



Scheme 1 2-Picolylamine (**1**) catalyzed racemic aldol product formation.

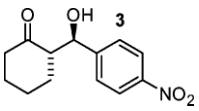
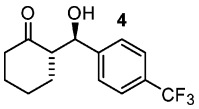
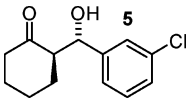
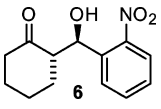
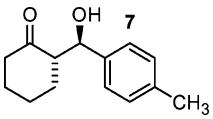
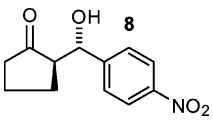
We next focused our attention on the benchmark enantioselective aldol reaction, addition of cyclohexanone to 4-nitrobenzaldehyde. Using 5 mol% of (S)-PicAm-**2** and 5 mol% of 2,4-dinitrobenzenesulfonic acid (2,4-DNBSA), various organic solvents (PhMe, CH_2Cl_2, THF, DMSO, and NMP) were screened. After 16 h at 25 °C little product formation was noted (1–11 area%, HPLC). On the other hand, water and brine proved to be excellent solvents for the reaction at room temperature (Table 1, compare entry 1 and 6), but the reaction times were long (44 h). Temperature screening showed 45 °C allowed fast reactions with only slightly compromised stereoselectivity (Table 1, compare entry 1 with 2 and 6 with 7). For example, a brine medium provided 92% yield, 22 : 1 dr, and 99% *ee* after 16 h at 45 °C (Table 1, entry 7).

When examining 2-picolylamine (**1**), 5 mol% loading in water or MeOH–H_2O (1 : 1), an acid additive was not required for racemic aldol product formation. Additionally the reaction was complete within 16 h at 25 °C. It is perhaps reasonable to assume that unhindered 2-picolylamine (**1**), compared to PicAm-**2**, is able to form higher concentrations of the required imine of cyclohexanone. If operative, intermolecular aldol reactions would occur under the acid free conditions, as opposed to acid catalyzed *intramolecular* reactions arising from starting material assembly at a two-centered bifunctional organocatalyst.[21] This is supported by the fact that (S)-PicAm-**2**, in the absence of an acid additive, provides very little product, a complete lack of diastereoselectivity, and low ee (Table 1, entry 5). The dramatically different reaction profile of (S)-PicAm-**2** in the absence of an acid strongly suggests an alternative mechanistic pathway, likely intermolecular (sterically driven), is occurring. The optimized conditions consequently use an acid additive (bifunctional organocatalysis), which can be considered as a flexible modular reaction component for substrate-catalyst optimization as demonstrated shortly.

Table 2 provides a summary for the aldol reaction of cyclohexanone and cyclopentanone with five different aromatic aldehydes. Reaction of cyclohexanone with *p*-NO_2-, *p*-CF_3-, or *o*-NO_2–PhC(O)H permitted high dr and ee (Table 2, products **3**,**4**,**6**). *m*-Cl–PhC(O)H is less frequently studied and considerably less electrophilic. Under our standard conditions (Table 2) significant quantities of the aldol elimination product were noted in addition to desired product **5** (Table 2). The elimination product was completely suppressed by replacing the 2,4-DNBSA acid additive with 5 mol% each of (S,S)-D-tartaric acid and sodium dodecylbenzenesulfonate (NaDBSA) in a brine reaction medium. An unintended consequence was very slow, but clean, product formation. By further changing the reaction medium from brine to water the reaction rate increased allowing the optimized conditions to be found (Table 2, product **5**).

4-Methylbenzaldehyde is considered a challenging substrate regarding yield, stereoselectivity, and reaction time. Of the thirteen previous reports we are aware of, eleven require a proline based organocatalyst.[5,6,8c,9a,10b,11,22] The remaining two organocatalysts are represented by a chiral phosphine oxide (10 mol% loading, 6.6 : 1 dr, 83% *ee*, 92% yield)[23] and a primary amine of a leucine/amide-alcohol (20 mol% loading, 10 : 1 dr, 92% *ee*, 50% yield).[24] Using

Table 2 Aldol products of cyclohexanone and cyclopentanone.[a]

Aldol product	Time	Yield (%)[b]	dr[c]	*ee*[d] (*anti*)
 **3**	16[e]	92	22 : 1	99
 **4**	22	88	12 : 1	99
 **5**	40[f]	82	5.5 : 1	95[g]
 **6**	20	84	30 : 1	98
 **7**	24[e]	55	8 : 1	96
 **8**	16[h]	81	1.2 : 1	92, 89[i]

[a] Reaction conditions: ketone (3.3 equiv), aldehyde (1.0 equiv, 0.5 mmol), (S)-PicAm-**2** (5.0 mol%), 2,4-DNBSA (5 mol%), H_2O (0.5 M), 45 °C, unless otherwise stated. [b] Isolated yield after column chromatography. [c] ^{1}H NMR data of crude product after work-up, major product is *anti*. [d] HPLC data (Chiralpak AS-H or OD-H column) after silica gel chromatography. [e] Performed in brine (0.5 M). [f] 2,4-DNBSA was replaced with 5 mol% each of: (S,S)-D-tartaric acid and NaDBSA. [g] (*R*)-PicAm-**2** (5.0 mol%) was used. [h] 2,4-DNBSA was replaced with 5 mol% of 1-NSA (1-naphthalenesulfonic acid). [i] *ee* of minor diastereostereomer.

our standard conditions we obtained a 55% isolated yield, 8 : 1 dr, and 96% ee within 24 h (Table 2, product **7**). The best performing organocatalysts are proline based, requiring 1–2 mol% loading (yield 42–75%, 88 : 12 to 99 : 1 dr, and 87–98% ee).[5,6,9a,10b]

Table 3 Aldol products of cyclohexanone: 2.0 mol% Pic-Am-**2** loading (see Table 2 for structure).[a]

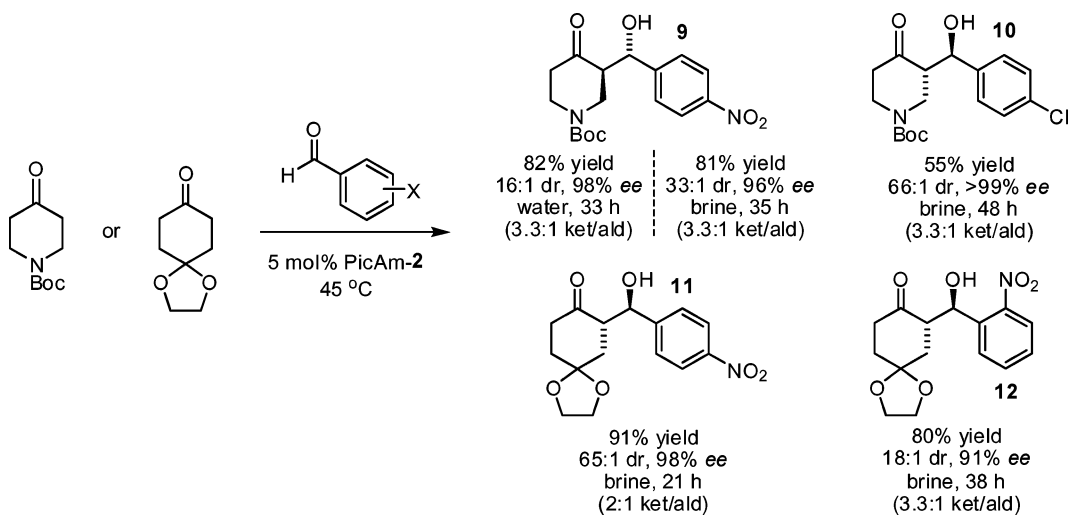
Aldol product	Time	Yield (%)[b]	dr[c]	*ee* (*anti*)[d]
3	24	89	15 : 1[e]	98
4	32	56	9 : 1	98
6	30	83	30 : 1	98

[a] Reaction conditions: ketone (3.3 equiv), aldehyde (1.0 equiv, 0.5 mmol), (S)- PicAm-**2** (2.0 mol%), 2,4-DNBSA (2.0 mol%), brine (0.5 M), 45 °C. [b] As in Table 2. [c] As in Table 2. [d] As in Table 2. [e] The same reaction, but in water, provided a 17 : 1 dr.

To round out our initial study, we examined cyclopentanone and noted a clear lack of diastereoselectivity (Table 2, product **8**). Be this as it may, the *ee* was good for both diastereomers (92 and 89% *ee*). For our optimization of this substrate, the acid component was again crucial, albeit not regarding the de, with 1-naphthalenesulfonic acid (1-NSA) providing by far the highest *ee*. To further test the performance of organocatalyst PicAm-**2**, we examined three substrates at the 2.0 mol% catalyst loading (Table 3).

Aldol reactions of cyclohexanone with *ortho*-, *meta*-, or *para*-substituted benzaldehydes are good for establishing the potential usefulness of a new catalyst, but the products themselves lack the functional group diversity of drug-like building blocks. Examination of functionalized ketones would begin to address this point and allowed us to realize the inherent high value of our new organocatalyst template. Notably the results outlined in Scheme 2 represent the best achieved to date at the lowest catalyst loading (5 mol%) known to date.

For example N-Boc-piperidone has been examined by at least eight research groups.[8f,11,12,15a,22a,25] Of those, the lowest catalyst loading reported to date is 5 mol%,[11,25b] resulting in product **9** (Scheme 2) with an optimal result of 56% yield, >45 : 1 *dr*, 80% *ee*, 72 h.[11] The most favorable 10 mol% result provided a 59% yield, 45 : 1 *dr*, 93% *ee*, 22 h,[22a] and the best 20 mol% result provided an 86% yield, 45 : 1 dr, and 98% *ee*. It was therefore gratifying to see



Scheme 2 Approaching drug-like highly functionalized aldol products (see the ESI† for further reaction details).

that our catalyst provided improved yield and ee at the low loading of 5 mol% (*R*)-PicAm-**2** (Scheme 2, product **9**).

A similar trend was observed for aldol products **10** and **11**. Reaction of N–Boc-piperidone with 4-Cl-benzaldehyde in the presence of 5 mol% (*S*)-PicAm-**2** provided product **10** (55% yield, 66 : 1 dr, and >99% *ee*). Two other organocatalyst reports exist for its synthesis, one uses a 10 mol% loading (40% yield, 4 : 1 dr, 74% ee),[26] while the other uses a 20 mol% loading (80% yield, 97 : 3 dr, 95% ee).[8f]

For the reaction of 4-ketalcyclohexanone with 4-nitrobenzaldehyde we examined the effect of lowering the ketone/aldehyde ratio to 2 : 1. Using 5 mol% (*S*)-PicAm-**2**, product **11** (Scheme 2) was obtained in excellent yield (91%), dr (65 : 1), and *ee* (98%). Five prior literature reports are noted for product **11**.[9a,12,22b,27] One study was clearly superior regarding catalyst loading, using 1 mol% of a *trans*-4-silylhydroxyproline/amide-alcohol (four stereogenic centers), but the yield (75%), dr (9 : 1), and *ee* (95%) are considerably lower and the reaction time significantly longer (70 h *vs.* 21 h).[9a] In another study, 5 mol% of a different *trans*-4-silylhydroxyproline/amide-alcohol resulted in a 90% yield, 45 : 1 dr, and 94% *ee*.[22b] This result was possible when using the ketone in solvent like volumes after four days of reaction. Our final aldol product (**12**) is reported here for the first time in the literature.

Although preliminary, a mechanism justifying the observed diastereo- and enantiocontrol is offered in Fig. 2. Whether these types of reactions are occuring in, on, or at the organic–water interface is still a matter of intense discussion in the literature. For now we can say that a concentrated organic phase is observed on the water during our reactions.

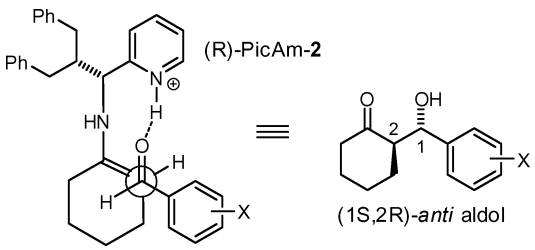


Fig. 2 Proposed transition state model.

Conclusions

In summary, the 2-picolylamine template has been established as a promising new organocatalyst. A chiral version containing a single stereogenic center, (*R*)- and (*S*)-PicAm (**2**), has been identified as allowing fast and highly stereoselective *anti*-aldol product formation at a low catalyst loading (5 mol%). Importantly, PicAm-**2** excelled when examining more functionalized ketone substrates. The new template is likely to be amenable to mechanistically related organocatalytic reactions.

Experimental

General procedure for enantioselective aldol reactions (compounds 3–12)

To distilled water or brine (1.0 mL, 0.5 M) was added: (i) the 2,4-dinitrobenzenesulfonic acid (2,4-DNBSA) salt of (*S*)-PicAm-**2** (13.8 mg, 0.025 mmol, 5.0 mol%, MW = 550.58) or (ii) the 1 : 1 salt of (S,S)-D-tartaric acid and (*R*)-PicAm-**2** (11.3 mg, 0.025 mmol, 5.0 mol%, MW = 452.50) and the sodium salt of dodecylbenzenesulfonate (NaDBSA) (8.7 mg, 0.025 mmol, 5.0 mol%, MW = 348.48), or (iii) the 1-naphthalenesulfonic acid (1-NSA) salt of (*S*)-PicAm-**2** (12.8 mg, 0.025 mmol, 5.0 mol%, MW = 510.65). To this was added the ketone (1.65 mmol, 3.3 equiv) and the aldehyde (0.5 mmol, 1.0 equiv). This mixture was stirred and heated at 45 °C for the specified time. The reaction was quenched by adding water (10 mL) and extracting with EtOAc (10 mL × 3). The combined organic extracts were dried (Na_2SO_4), evaporated (Rot Vap), and high vacuum dried. The resulting crude product was examined by ^{1}H NMR to determine the dr. The crude product was then purified by column chromatography (EtOAc/petroleum ether). The chromatography purified aldol products were then examined by HPLC to determine their *ee*. The relative and absolute configurations of products **3–11** were determined by comparison with the known ^{1}H NMR data and by direct comparison with the literature available HPLC data for aldol products **3–11**. Compound **12** is new and was identified as the *anti* product based on its ^{1}H NMR chemical shift data.

Notes and references

1 B. List, R. A. Lerner and C. F. Barbas III, *J. Am. Chem. Soc.*, 2000, **122**, 2395–2396.
2 (*a*) For recent reviews, see: M. Raj and V. K. Singh, *Chem. Commun.*, 2009, 6687–6703; (*b*) J. Paradowska, M. Stodulski and J. Mlynarski, *Angew. Chem., Int. Ed.*, 2009, **48**, 4288–4297; (*c*) L. M. Geary and P. G. Hultin, *Tetrahedron: Asymmetry*, 2009, **20**, 131–173; (*d*) J. Mlynarski and J. Paradowska, *Chem. Soc. Rev.*, 2008, **37**, 1502–1511; (*e*) C. Allemann, R. Gordillo, F. R. Clemente, P. H.-Y. Cheong and K. N. Houk, *Acc. Chem. Res.*, 2004, **37**, 558–569.
3 To the best of our knowledge, *Cinchona* alkaloid template examples have yet to be demonstrated with low catalyst loading, for a 10 mol% loading example see: B.-L. Zheng, Q.-Z. Liu, C.-S. Guo, X.-L. Wang and L. He, *Org. Biomol. Chem.*, 2007, **5**, 2913–2915.
4 S. Aratake, T. Itoh, T. Okano, N. Nagae, T. Sumiya, M. Shoji and Y. Hayashi, *Chem.–Eur. J.*, 2007, **13**, 10246–10256.
5 J. Huang, X. Zhang and D. W. Armstrong, *Angew. Chem., Int. Ed.*, 2007, **46**, 9073–9077.
6 F. Giacalone, M. Gruttadauria, P. L. Meo, S. Riela and R. Noto, *Adv. Synth. Catal.*, 2008, **350**, 2747–2760.
7 X. Wu, Z. Jiang, H.-M. Shen and Y. Lu, *Adv. Synth. Catal.*, 2007, **349**, 812–816.
8 Valuable proline-amide alcohols were first introduced by Gong in 2003 for acetone activation, see ref. 8*g*. By now, the development of proline-amide alcohols, proline-bisamides, and proline-amides is extensive. The following are not comprehensive but representative: (*a*) Y. Okuyama, H. Nakano, Y. Watanabe, M. Makabe, M. Takeshita, K. Uwai, C. Kabuto and E. Kwon, *Tetrahedron Lett.*, 2009, **50**, 193–197; (*b*) J. N. Moorthy and S. Saha, *Eur. J. Org. Chem.*, 2009, 739–748; (*c*) Y.-N. Jia, F.-C. Wu, X. Ma, G.-J. Zhu and C.-S. Da, *Tetrahedron Lett.*, 2009, **50**, 3059–3062; (*d*) G. Guillena, M. C. Hita, C. Nájera and D. F. Viózquez, *J. Org. Chem.*, 2008, **73**, 5933–5943; (*e*) X.-H. Chen, S.-W. Luo, Z. Tang, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang and L.-Z. Gong, *Chem.–Eur. J.*, 2007, **13**, 689–701; (*f*) J.-R. Chen, X.-Y. Li, X.-N. Xing and W.-J. Xiao, *J. Org. Chem.*, 2006, **71**, 8198–8202; (*g*) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang and Y.-D. Wu, *J. Am. Chem. Soc.*, 2003, **125**, 5262–5263.
9 (*a*) J.-F. Zhao, L. He, J. Jiang, Z. Tang, L.-F. Cun and L.-Z. Gong, *Tetrahedron Lett.*, 2008, **49**, 3372–3375; (*b*) Z. Tang, Z.-H. Yang, X.-H. Chen, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang and L.-Z. Gong, *J. Am. Chem. Soc.*, 2005, **127**, 9285–9289.
10 (*a*) M. R. Vishnumaya and V. K. Singh, *J. Org. Chem.*, 2009, **74**, 4289–4297; (*b*) S. Gandhi and V. K. Singh, *J. Org. Chem.*, 2008, **73**, 9411–9416.

11 (*a*) D. Almaşi, D. A. Alonso, A.-N. Balaguer and C. Nájera, *Adv. Synth. Catal.*, 2009, **351**, 1123–1131; (*b*) D. Almaşi, D. A. Alonso and C. Nájera, *Adv. Synth. Catal.*, 2008, **350**, 2467–2472.
12 For earlier encouraging results using thioamides see: D. Gryko and W. J. Saletra, *Org. Biomol. Chem.*, 2007, **5**, 2148–2153.
13 F.-Z. Peng, Z.-H. Shao, X.-W. Pu and H.-B. Zhang, *Adv. Synth. Catal.*, 2008, **350**, 2199–2204.
14 Metal-organocatalyst hybrids with very low loading have been reported on, see: J. Li, S. Hu, S. Luo and J.-P. Cheng, *Eur. J. Org. Chem.*, 2009, 132–140.
15 Loadings of 20 or 30 mol% of commercially available proline have been used for cyclic ketones, respectively see: (*a*) B. Rodríguez, A. Bruckmann and C. Bolm, *Chem.–Eur. J.*, 2007, **13**, 4710–4722; (*b*) Y. Hayashi, S. Aratake, T. Itoh, T. Okano, T. Sumiya and M. Shoji, *Chem. Commun.*, 2007, 957–959.
16 For lead examples, see: (*a*) A. Córdova, W. Notz and C. F. Barbas III, *Chem. Commun.*, 2002, 3024–3025; (*b*) T. J. Dickerson and K. D. Janda, *J. Am. Chem. Soc.*, 2002, **124**, 3220–3221.
17 The 2-aminopyridine template (1,1-diamine) has proven to be valuable for the organocatalytic reaction of ketones with aryl and alkyl α-keto acids, see: Z. Tang, L.-F. Cun, X. Cui, A.-Q. Mi, Y.-Z. Jiang and L.-Z. Gong, *Org. Lett.*, 2006, **8**, 1263–1266.
18 Further details can be found in the ESI† of this manuscript.
19 T. Mukaiyama, K. Banno and K. Narasaka, *J. Am. Chem. Soc.*, 1974, **96**, 7503–7509.
20 We also examined a simple procedure describing aldol product formation: cyclohexanone (10 equiv) and benzaldehyde (1 equiv) in NaOH (0.2 M) at 25 °C. In our hands an intractable mixture of compounds was obtained in which the aldol elimination (condensation) product dominated, see: M. Kitamura, K. Nakano, T. Miki., M. Okada and R. Noyori, *J. Am. Chem. Soc.*, 2001, **123**, 8939–8950.
21 (*a*) For early examples of two-centered, bifunctional, diamine-based aldol organocatalysis, see: M. Nakadai, S. Saito and H. Yamamoto, *Tetrahedron*, 2002, **58**, 8167–8177; (*b*) K. Sakthivel, W. Notz, T. Bui and C. F. Barbas III, *J. Am. Chem. Soc.*, 2001, **123**, 5260–5267.
22 (*a*) M. Gruttadauria, F. Giacalone, A. M. Marculescu and R. Noto, *Adv. Synth. Catal.*, 2008, **350**, 1397–1405; (*b*) L. He, J. Jiang, Z. Tang, X. Cui, A.-O. Mi, Y.-Z. Jiang and L.-Z. Gong, *Tetrahedron: Asymmetry*, 2007, **18**, 265–270; (*c*) K. Liu, D. Häussinger and W.-D. Woggon, *Syn. Lett.*, 2007, **14**, 2298–2300; (*d*) Y. Wu, Y. Zhang, M. Yu, G. Zhao and S. Wang, *Org. Lett.*, 2006, **8**, 4417–4420.
23 S. Kotani, S. Hashimoto and M. Nakajima, *Syn. Lett.*, 2006, **7**, 1116–1118.
24 X. Ma, C.-S. Da, L. Yi, Y.-N. Jia, Q.-P. Guo, L.-P. Che, F.-C. Wu, J.-R. Wang and W.-P. Li, *Tetrahedron: Asymmetry*, 2009, **20**, 1419–1424.
25 (*a*) X.-W. Liu, T. N. Le, Y. Lu, Y. Xiao, J. Ma and X. Li, *Org. Biomol. Chem.*, 2008, **6**, 3997–4003; (*b*) G. Guillena, M. C. Hita, C. Nájera and S. F. Viózquez, *J. Org. Chem.*, 2008, **73**, 5933–5943.
26 P. M. Pihko, K. M. Laurikainen, A. Usano, A. I. Nyberg, J. A. Kaavi and J. A., *Tetrahedron*, 2006, **62**, 317–328.
27 (*a*) S. S. Chimni, S. Singh and D. Mahajan, *Tetrahedron: Asymmetry*, 2008, **19**, 2276–2284; (*b*) A. Córdova, W. Zou, I. Ibrahem, E. Reyes, M. Engqvist and W.-W. Liao, *Chem. Commun.*, 2005, 3586–3588.