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PAPER

Chiral picolylamines for Michael and aldol reactions: probing substrate boundaries†

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Here we report on inroads concerning increased substrate breadth *via* the picolylamine organocatalyst template, a vicinal chiral diamine based on a pyridine-primary amine motif. The addition of cyclohexanone to β-nitrostyrene has many catalyst solutions, but cyclopentanone and isobutyraldehyde additions continue to be challenging. PicAm-**3** (10 mol%) readily allows the Michael addition of cyclopentanone or isobutyraldehyde (5.0 equiv.) to β-nitrostyrene derivatives. By contrast, PicAm-**1** (7.0 mol%) is optimal for catalyzing the aldol reaction of cyclohexanone or cycloheptanone (3.3 equiv.) with aromatic aldehydes. Eighteen products are reported and for each reaction type new products are reported (**4b–d**, **9c**). Very good yields and stereoselectivities are generally noted. The reactions, which require an acid additive, proceed *via* a transient chiral enamine and a mechanistic case is put forth for a bifunctional catalysis model.

Introduction

Enzymes often use multiple noncovalent interactions and transient covalent bonds in unison to control substrate conformation and activation during bond forming and breaking processes.[1,2] These enviable catalyst traits evolved hand in hand with the narrow substrate tolerances demanded by a cellular milieu, but accordingly dictate that broadening their substrate scope would require a detailed knowledge of the critical *versus* the superfluous units of an enzyme. This reality currently makes the rational modification of enzymes less accommodating and helps in part to explain the torrent of research activity recently devoted to organocatalysis research.

Regarding monocarbonyl additions to β-nitrostyrene derivatives, unmodified amino acids were found to be poor organocatalysts.[3,4] But it was also noted very early[5,6] that chiral diamine catalysts with a pyrrolidine moiety (proline derivatives) were important catalyst templates. For example Barbas showed that (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine (20 mol%, Fig. 1) allowed cyclopentanone addition to β-nitrostyrene in 78% yield with a 4 : 1 *syn*-to-*anti* ratio in 78% and 71% ee respectively.[5a,7] The result was impressive at the time, but also represented a clear target for optimization. Despite this and many reports showing progress,[8] it can be arguably stated that only the proline catalyst derivatives of Zhao, Xu, and Chandrasekhar represent clear multi-parameter reaction advancements (catalyst loading, starting material stoichiometry, product profile, *etc.*) (Fig. 1). Thus while many catalyst solutions already exist for cyclohexanone addition to β-nitrostyrene,[9] those catalyst successes have not translated into success with the cyclopentanone substrate, the noted exceptions withstanding (Fig. 1, bottom line of catalysts).

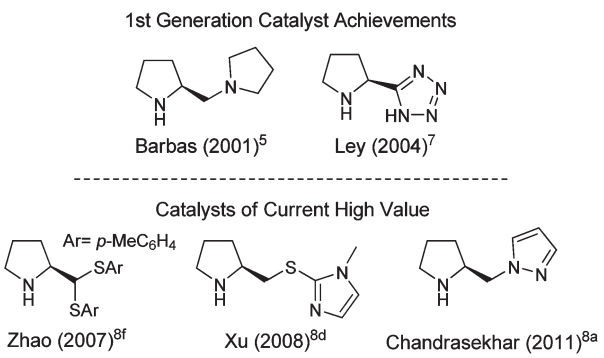

Fig. 1 Catalysts of historical and current value for cyclopentanone addition to β-nitrostyrene.

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Results and discussion

The development of primary–tertiary (*versus* secondary–tertiary) diamines for organocatalysis was less intuitive because they rely on an efficient tautomerization of the *in situ* formed imine to an unstable, but nucleophilic, enamine.[10] Despite the late successful entry of this template, primary amine based catalysts have gained increasing attention due to their alternative chiral space filling abilities which can benefit sterically encumbered donor carbonyl substrates. Examples are the α-amination of aromatic ketones[11] and Michael reactions forming quaternary carbons.[4,12] Based on these prior accomplishments, we considered 2-picolylamine to be predisposed for development as an organocatalyst template (Fig. 2).

To the best of our knowledge the primary amine template found in 2-picolylamine (1,2-diamine) has not been examined (Fig. 2), save for our initial report concerning PicAm-**1** (Fig. 3) for the aldol reaction.[13] But 1,2- and 1,3- and 1,4-pyrrolidine–pyridine combinations have been reported on for aldol[14,15] and Michael[16,17] reactions. From these studies, only Kotsuki[9h] employed protonation of the pyridine ring to give the active catalyst. Here we investigate new PicAm catalysts (Fig. 3), each containing a lone stereogenic center, and report on challenging Michael substrate additions and less examined aldol reactions, in the presence of an acid additive.

Michael reactions

Using 10 mol% of PicAm-**1** cyclohexanone, cyclopentanone, and isobutyraldehyde (5.0 equiv.) could not be induced to react with β-nitrostyrene over extended reaction times (<10% product formation). When examining PicAm-**2** (10 mol%) with cyclohexanone or cyclopentanone, the expected *syn* products formed albeit in low yield (<40%) and with poor or mediocre ee, respectively 41% and 77%. As with PicAm-**1**, PicAm-**2** also failed to provide an isobutyraldehyde donor product.

PicAm-**3** has been previously synthesized in an enantiopure form,[18,19] but has not been investigated as an organocatalyst. Examination of this catalyst (10 mol%) with cyclopentanone permitted practical to quantitative yields of the Michael product (**4a**), Table 1. Regarding protic solvent use, a dramatic yield increase was noted upon replacing MeOH with H_2O, and then finally with brine, resulting in a quantitative yield of the desired *syn*-product (**4a**) but with mediocre ee (74%) (entries 1–4). Chloroform, on the other hand, proved to be optimal from the perspective of diastereo- and enantioselectivity. It should be noted that replacement of chloroform with dichloromethane resulted in indistinguishable results (not shown in Table 1), while other organic solvents, *e.g.* CH_3CN, $PhCH_3$, and hexane, were simply inferior.

All of the experiments were performed in the presence of 2,4-dinitrobenzenesulfonic acid (2,4-DNBSA), when it was removed the rate of the reaction and diastereoselectivity decreased unacceptably (Table 1, compare entry 5 *vs.* 6). The positive influence of a sulfonic acid (Table 2), on the stereoselectivity, implied that a strong acid was required, but the structure of the conjugate anion was critical. For example the use of HCl (4.0 M in H_2O) did not allow the reaction to proceed. Further investigation of this point led us to the fact that adding a reduced mol% of 2,4-DNBSA (2.5 mol%) in the presence of a sulfonic acid salt, *i.e.* dodecylbenzenesulfonic acid sodium salt (DBSAS, 10 mol%), provided a positive stereochemical outcome (Table 2,

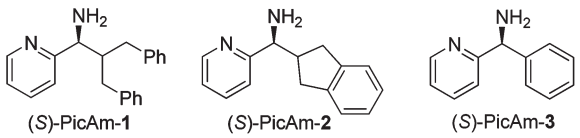
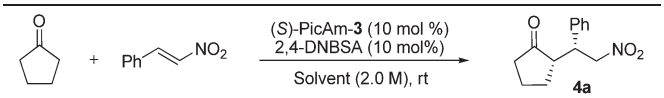


Fig. 3 Chiral picolylamine organocatalysts examined.

Table 1 Solvent screening: cyclopentanone addition to *trans*-β-nitrostyrene



Entry	Solvent	Time (h)	*syn*/*anti*[a]	ee[a] (%)	Yield[b] (%)
1	H_2O	24	60 : 40	64	65
2	MeOH	24	60 : 40	80	10
3	MeOH/H_2O[c]	14	70 : 30	67	60
4	Brine	24	77 : 23	74	100
5	$CHCl_3$	24	82 : 18	83	60
6[d]	$CHCl_3$	24	60 : 40	80	20
7	$CHCl_3$/H_2O[c]	14	70 : 30	77	70
8	THF	24	70 : 30	77	15

[a] Determined by chiral HPLC analysis. [b] Yield estimated by TLC, large error margins can be expected. HPLC analysis was not possible, β-nitrostyrene could not be quantified (overlapped with (*S*)-PicAm-**3**) from the crude reaction aliquots. [c] 1 : 1 ratio of the solvents. [d] The reaction was performed without an acid.

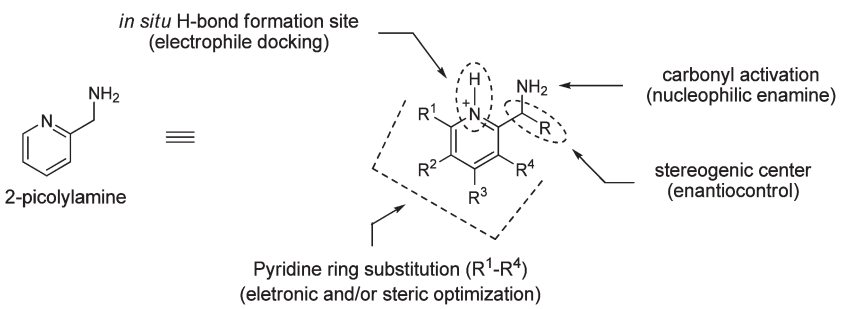
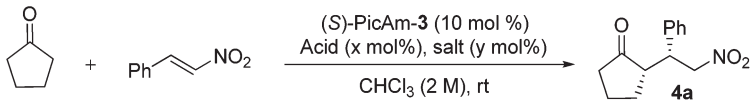


Fig. 2 An unexplored primary amine-pyridine organocatalyst template.

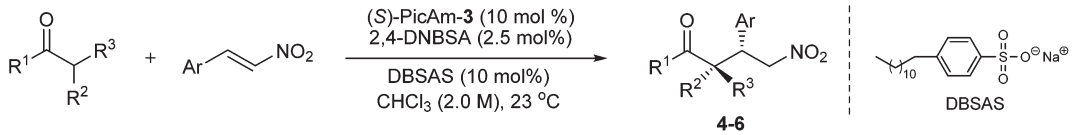
Table 2 Effect of acid and salt addition during cyclopentanone addition to *trans*-β-nitrostyrene



Entry	Acid and salt additive[a]	Time (h)	*syn*/*anti*[b]	ee[b] (%)	Yield[c] (%)
1	2,4-Dinitrobenzenesulfonic acid	14	82 : 18	84	55
2	*p*-Toluenesulfonic acid	14	75 : 25	60	60
3	*p*-Nitrobenzoic acid	14	40 : 60	65	35
4	Camphorsulfonic acid	14	75 : 25	73	35
5	Trifluoroacetic acid	24	90 : 10	80	10
6	2,4-Dinitrophenol	14	50 : 50	73	40
7	2,4-DNBSA (10 mol%) + DBSAS (10 mol%)	14	81 : 19	90	60
8	2,4-DNBSA (5.0 mol%) + DBSAS (10 mol%)	14	82 : 18	87	55
9	2,4-DNBSA (2.5 mol%) + DBSAS (10 mol%)	14	90 : 10	94	55

[a] 10 mol% acid added unless otherwise indicated. [b] Determined by chiral HPLC. [c] Yield estimated by TLC, large error margins can be expected. HPLC analysis was not possible, β-nitrostyrene could not be quantified (overlapped with (*S*)-PicAm-**3**) from the crude reaction aliquots.

Table 3 Asymmetric Michael addition of challenging carbonyl donors to nitroalkenes[a]



Entry	Product	R^1	R^2	R^3	Ar	Time (h)	Yield[b] (%)	*syn*/*anti*[c]	ee[d] (%)
1	**4a**	$-(CH_2)_3-$		H	–Ph	24	76	81/19	87
2	**4a**[e]	$-(CH_2)_3-$		H	–Ph	33	98	77/23	74
3	**4b**	$-(CH_2)_3-$		H	$-C_6H_4$-4-Me	21	92	76/24	88, >99[f]
4	**4c**	$-(CH_2)_3-$		H	$-C_6H_4$-4-OMe	24	85	88/12	77
5	**4d**	$-(CH_2)_3-$		H	-2-Furyl	30	89	57/43	81
6	**5a**	H	CH_3	CH_3	–Ph	36	58	—	78
7	**5b**	H	CH_3	CH_3	$-C_6H_4$-4-Me	40	53	—	80
8	**5c**	H	CH_3	CH_3	$-C_6H_4$-4-OMe	52	59	—	90
9	**5d**	H	CH_3	CH_3	-2-Furyl	45	70	—	90
10	**6a**	H	$-(CH_2)_5-$		–Ph	70	31	—	92
11	**6a**[e]	H	$-(CH_2)_5-$		–Ph	20	27	—	74

[a] General reaction conditions: nitroalkene (1.0 equiv.), carbonyl donor (5.0 equiv.), (*S*)-PicAm-**3** (10 mol%), DBSAS: dodecylbenzenesulfonic acid sodium salt (10 mol%), 2,4-DNBSA: 2,4-dinitrobenzenesulfonic acid (2.5 mol%), $CHCl_3$ (2.0 M), room temperature. [b] Isolated yield after column chromatography on silica gel. [c] Determined by ^{1}H NMR, crude and purified material were consistent. [d] Determined by chiral HPLC after silica gel purification. [e] Reaction conditions: *trans*-β-nitrostyrene (1.0 equiv.), carbonyl donor (5.0 equiv.), catalyst (*S*)-PicAm-**3** (4 mol%), DBSAS (4 mol%), 2,4-DNBSA (1.5 mol%), brine (0.5 M), room temperature. [f] *anti* Product ee.

compare entries 1, 7–9), whereas adding the sodium salt of 2,4-dinitrobenzenesulfonic acid in various ratios with 2,4-dinitrobenzenesulfonic acid (2.5 mol%) did not improve the reaction profile. These combined results imply a yet underappreciated role for the counter ion.[20]

Using the combined reaction screening information, we performed the challenging benchmark reaction: cyclopentanone addition to β-nitrostyrene with PicAm-**3** (10 mol%). Product **4a** was formed with an 81 : 19 *syn*/*anti* ratio, the major *syn* product was observed in 87% ee, and the TLC inseparable *syn*/*anti* product was noted in 76% yield (Table 3, entry 1). Only the results of Zhao[8f] and Chandrasekhar[8a] would be considered superior when considering literature reports with a catalyst loading of <20 mol%, while also bearing in mind the starting material ratio, reaction time, and product profile.[8] Decreasing the catalyst loading from 10 to 4 mol%, and using brine instead of $CHCl_3$, enabled a significantly increased isolated yield (98%), but unfortunately with decreased diastereo- and enantioselectivity (Table 3, entry 2). These results are consistent with our screening studies (Tables 1and 2).

Encouraged by these initial yield and stereoselectivity results (Table 3, entries 1and 2), further enantioselective cyclopentanone additions with β-nitrostyrenes (*p*-Me and *p*-MeO substituted) and 2-(2-nitrovinyl)furan were performed under the optimal conditions (Table 3, entries 3–5). Products **4b** and **4c** have been previously synthesized but only in the achiral form,[21] while **4d** is reported here for the first time. That asymmetric syntheses of **4b–d** have not been previously reported justify and attest to the challenge (and perhaps the avoidance) of synthesizing cyclopentanone products in general.

α-Branched aldehyde addition to nitroalkenes provides access to contiguous quaternary–tertiary carbon centers, and like cyclopentanone additions are known to be problematic regarding stereoselectivity.[22] Isobutyraldehyde addition to the same set of nitroalkene substrates provided products **5a–d** in good ee (78–90%), albeit with a mediocre yield (53–70%) as shown in Table 3 (entries 6–9). Regarding the cyclohexanecarboxaldehyde donor substrate (entry 10), a 31% yield was observed after the reaction with β-nitrostyrene. Examination of this substrate in brine, PicAm-**3** (4 mol%), overcame the requirement for extended reaction times as observed with $CHCl_3$ (PicAm-**3**, 10 mol%), but did not increase the already low yield (Table 3, compare entries 10 and 11).

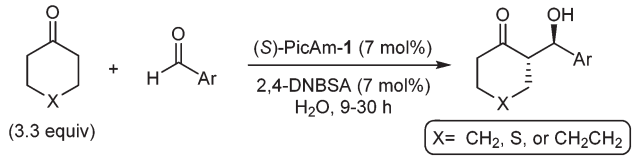
In conclusion, the results for PicAm-**3** (10 mol%) with cyclopentanone (5.0 equiv.) are noteworthy, *e.g.*, when literature catalyst loadings are not considered, only the results of Zhao, Xu, and Chandrasekhar exceed those reported here.[8a,d,f,23] Furthermore we have reported the first substituted products (**4b–d**) and these advances were achieved without a proline based catalyst.

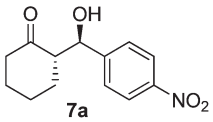
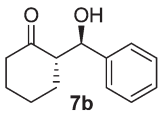
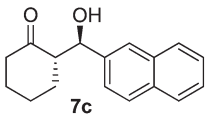
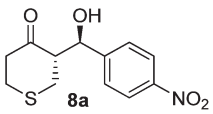
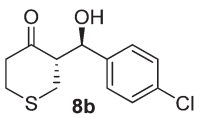
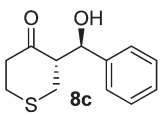
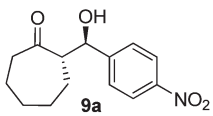
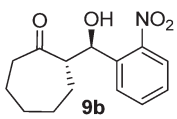
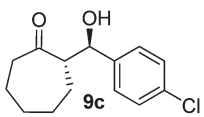
Aldol reactions

Earlier we reported on the use of PicAm-**1** (Fig. 3) for the enantioselective aldol reaction of cyclohexanone with five electronically and sterically varied aromatic aldehyde substrates,[13,24] but we noted that this catalyst excelled in particular when examining more functional group rich six-membered ring carbonyl donor substrates, *e.g. N*-Boc-piperidone and a 4-ketalcyclohexanone. Here we devote most of our attention (six compounds) to further extending the donor ketone diversity, by examining tetrahydrothiopyran-4-one and cycloheptanone additions to aromatic aldehydes. Furthermore we report, in the ESI,† on an improved resolution method for arriving at enantiopure (*R*)- or (*S*)-PicAm-**1** which is robust. Using the PicAm-**1** catalyst, obtained using our new resolution procedure (see ESI†), we recommend using 7.0 mol% of PicAm-**1** for reliably fast reactions instead of 5.0 mol% as initially reported.[13] For our new aldol results (Table 4, entries 2–9), we performed all of the reactions in water at 45 °C using 3.3 equiv. of the carbonyl donor and PicAm-**1** (7.0 mol%).

Cyclohexanone addition to benzaldehyde is difficult, and we observed the corresponding aldol product (**7b**) in 50% yield, 6 : 1 dr, and 96% ee, after 9 h. Singh and Hayashi have reported far superior results, *e.g.* using cyclohexanone (4.0 or 2.0 equiv., respectively) and different proline based catalysts (0.5 mol%[25a] or 1.0 mol%[26a,d]), **7b** was afforded with very good yield, 99 : 1 or 10 : 1 dr respectively, and 99% ee within 48 h. Our final substrate examination with cyclohexanone was with 2-naphthaldehyde, producing **7c** (Table 4, entry 3) in 85% yield, 34 : 1 dr, and 96% ee in 14 h. Aldol product **7c** has been reported on at least thirty five times and the reports by Singh, Hayashi, Gruttadauria, Fu, and Zhao/Wang are of high value.[25,26d] Of those, the lowest catalyst loading is reported by Singh at just 0.5 mol%, providing a 69–85% yield, 99 : 1 dr, and 98% ee, within 20–48 h, at −10 °C using cyclohexanone (4.0 equiv.).[25a] The next best catalyst achievement was reported by Hayashi using a 1.0 mol% catalyst loading, resulting in a 96% yield, 12 : 1 dr, and 98% ee for **7c** in 42 h using cyclohexanone (2.0 equiv.).[26d] Fu used a 5.0 mol% catalyst loading, providing a 93% yield, 93 : 7 dr, and 99% ee for **7c** in 20 h using cyclohexanone (2.0 equiv.).[25c] From these top performing organocatalysts only Fu used a non-proline based catalyst: a primary amine derivative of threonine.

Table 4 Asymmetric aldol reactions of cyclohexanone, tetrahydrothiopyran-4-one, and cycloheptanone, with various aldehydes



Entry	Product[a]	Time (h)	Yield[b]	dr[c]	ee[d]
1[e]	 **7a**	16	92	22 : 1	99
2	 **7b**	9	50	6 : 1	96
3	 **7c**	14	85	34 : 1	96
4	 **8a**	16	92	20 : 1	98
5	 **8b**	30	90	15 : 1	99
6	 **8c**	26	40	17 : 1	95
7	 **9a**	24	90	5 : 1	94
8	 **9b**	30	85	15 : 1	94
9	 **9c**	30	86	4 : 1	90

[a] Reaction conditions: ketone (3.3 equiv.), aldehyde (1.0 equiv., 0.5 mmol), (*S*)-PicAm-**1** (7.0 mol%), 2,4-DNBSA (7 mol%), H_2O (0.5 M), 45 °C. [b] Isolated yield after column chromatography. [c] ^1H NMR data of the crude product after work-up, the 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).

Concerning higher value substrate donor carbonyl additions, tetrahydrothiopyran-4-one (3.3 equiv.) adds smoothly to *p*-NO_2-PhC(O)H in the presence of PicAm-**1** (7.0 mol%), providing **8a** (Table 4, entry 4) in 92% yield, 20 : 1 dr, and 98% ee within 16 h. From no less than twenty four earlier reports, this is arguably the best currently known. For example, the independent work of Alonso, Guillena/Nájera, Pedrosa/Andŕes, Xiao, and Bolm is of high value regarding the synthesis of product **8a**.[27] The lowest documented catalyst loading to date (5.0 mol%) afforded an 82% yield, 32 : 1 dr, and 88% ee, in 40 h using tetrahydrothiopyran-4-one (2.0 equiv.).[27a] The most favorable 10 mol % result is Bolm's because he uses commercially available L-proline (10 mol%) with only 1.2 equiv. of tetrahydrothiopyran-4-one, providing a 79% yield, 24 : 1 dr, and 90% ee, within 36 h.[27e] Unlike the primary amine catalyst used here (PicAm-**1**) all of these top performing organocatalysts for accessing **8a** are proline or proline based.

Examination of tetrahydrothiopyran-4-one addition to *p*-Cl-PhC(O)H resulted in a 90% yield, 15 : 1 dr, and 99% ee for **8b** in 30 h using our standard conditions (Table 4, entry 5). Bolm[27e] and Pihko[28a] independently reported the best prior (lowest) catalyst loading, 10 mol% L-proline, for the synthesis of **8b**; the former with the following attributes: 85% yield, 19 : 1 dr, and 85% ee, in 35 h with 1.1 equiv. of the ketone, while the latter observed a 54% yield, 20 : 1 dr, and 98% ee, in 72 h using 1.0 equiv. of the ketone. These are commendable results because of the practical ketone-to-aromatic aldehyde ratio and the commercial availability of the catalyst, *versus* our and all other reports.[28]

Indicative of how substrate dependent catalysts can be, a high value result could not be achieved when we examined tetrahydrothiopyran-4-one addition to benzaldehyde (Table 4, entry 6), in this instance several other groups reported far superior results.[25a,26a,c,29]

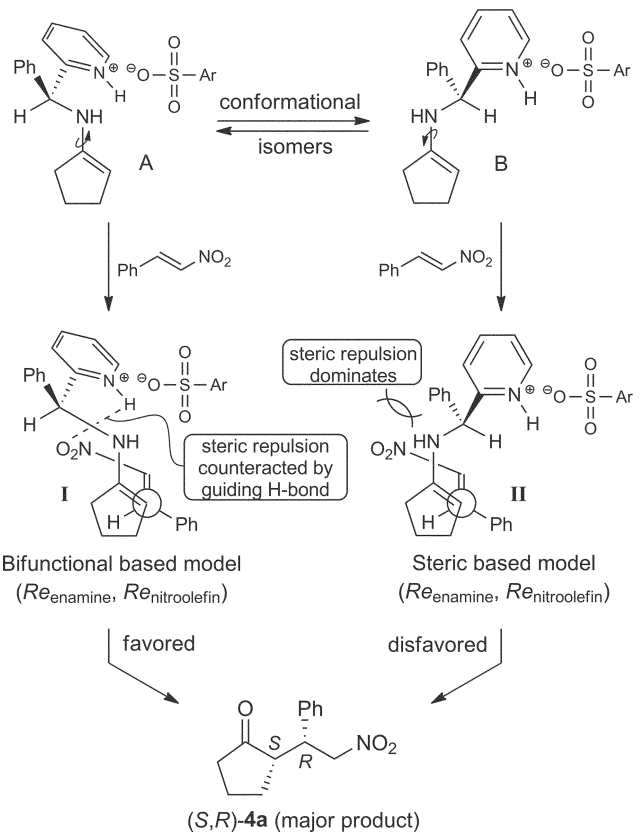
Cycloheptanone addition represents yet another diversification possibility and it smoothly added to *p*-NO_2-PhC(O)H under PicAm-**1** catalysis. Using our standard conditions, a 94% yield, 5 : 1 dr, and 96% ee were observed for **9a** (Table 4, entry 7). From the twenty three prior literature reports on product **9a**, the top organocatalysts are proline based and have been independently reported by Mase, Fu, Lombardo/Trombinia, and Zhao/Wang.[30] The lowest catalyst loading reported is 1.0 mol%, providing a 28% yield, 52 : 48 dr, and 71% ee, within 96 h, using 2.0 equiv. of cycloheptanone.[30a] The most favorable 5 mol % catalyst loading result provided a 97% yield, 3 : 1 dr, and 98% ee, after 3.5 h in the presence of 5.0 equiv. of cycloheptanone.[30c]

Surprisingly little else has been documented regarding other electrophile combinations with cycloheptanone. It consequently made sense to examine other substrates, *e.g.* its reaction with *o*-nitrobenzaldehyde resulted in **9b** (Table 4, entry 8) in 85% yield, 15 : 1 dr, and 94% ee. A lone previous report by Córdova obtained the same product in 76% yield, 10 : 1 dr, and 96% ee, using a 10 mol% catalyst loading and 10 equiv. of cycloheptanone.[31] We also examined the addition of cycloheptanone to *p*-chlorobenzaldehyde, which provided a new compound, **9c**, in 86% yield, 4 : 1 dr, and 90% ee (Table 3, entry 9).[32] These combined aldol results demonstrate the value of our new catalyst concerning the scope of this reaction.

Stereochemistry and mechanistic considerations

Using Newman projection rules in combination with concepts originating from allylic 1,2- and 1,3-strain,[33] it seems reasonable that conformational isomers **A** and **B** represent the two low energy enamine intermediates from the dehydrative combination of organocatalyst (*S*)-PicAm-**3** with cyclopentanone (Scheme 1). The reaction of enamine **A** or **B** with β-nitrostyrene can lead to the (*S*,*R*)-*syn* stereochemistry observed in the major product (**4a**). Since the relative and absolute stereochemistry are known, the possible transition states can be restricted to those represented by I and II (Scheme 1). Transition state II is less likely due to the presence of a phenyl ring blocking the *Re* face of enamine **B** (steric repulsion between the nitro group of β-nitrostyrene with the phenyl ring of the catalyst). A more plausible stereochemical explanation foresees PicAm-**3** operating as a bifunctional catalyst, transition state I, where the pyridium species acts as a hydrogen bond donor.

Literature support for transition state I originates from List's work with L-proline, which set the stage for the use and exploitation of bifunctional catalysts.[34] In the same manner chiral diamine catalysts, in the presence of an acid co-catalyst, have been exploited and without exception an ammonium species (protonated tertiary amine) is always shown in the transition state. It is common that these ammonium species have the defined role of a hydrogen bond donor,[35] imposing high facial selectivity *via* electrostatic guidance of the approaching electrophile. But, there are also reports in which the ammonium species is defined solely as a steric blocking unit (Fig. 4), here the



Scheme 1 Relevant Michael transition states for (*S*)-PicAm-**3**.

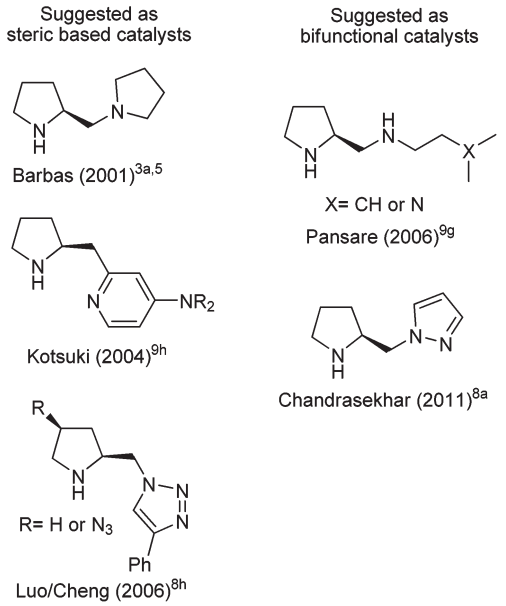


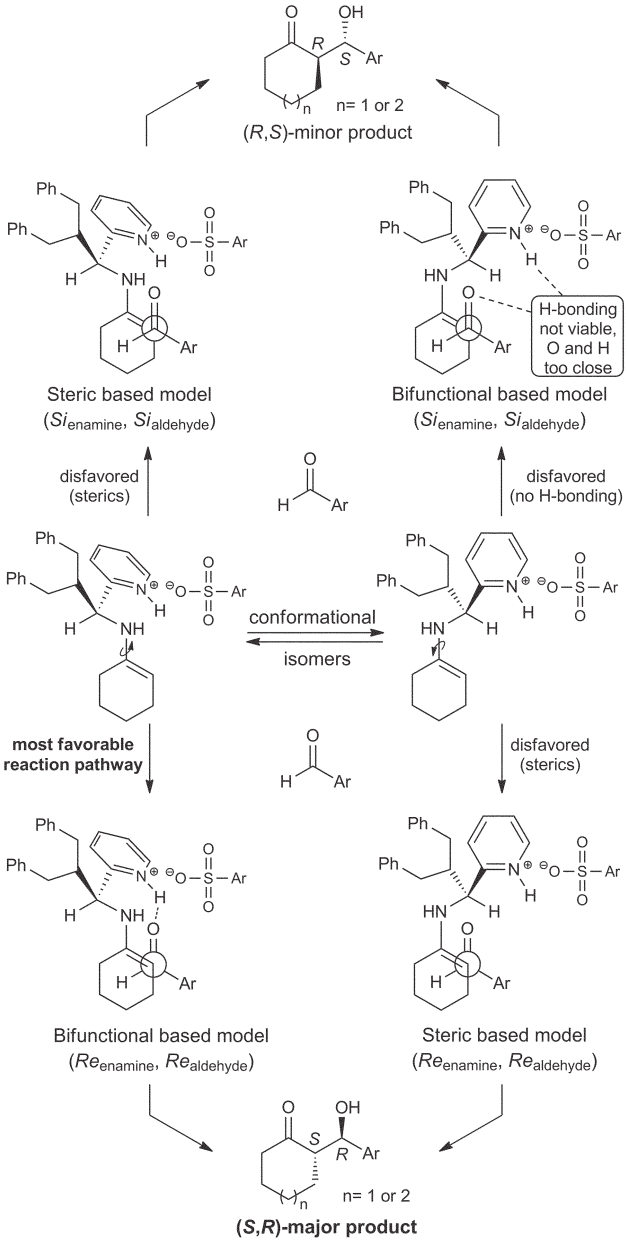
Fig. 4 Top performing catalysts that employ acid additives for carbonyl addition to β-nitrostyrenes.

electrophile is redirected to the opposite face of the enamine and the ammonium species abdicates its role as a hydrogen bond donor in the transition state.[36] For example, the Barbas report[3a] of an ammonium cation (protonated tertiary amine) acting as a blocking unit is convincing,[37] while the examination of two other catalyst examples (Fig. 4, left column, lower two catalysts) showed them to hold the possibility of operating as bifunctional catalysts and simultaneously providing the correct (reported) stereochemistry.[38]

Consideration of these points and the details of our particular *primary* amine catalyst, as outlined above, increasethe likelihood that PicAm-**3** is operating as a bifunctional catalyst (Scheme 1). Furthermore, transition state I (Scheme 1) provides a definitive argument for why the α-branched aldehyde substrates are slow to reaction *versus* cyclopentanone, a strong *gauche* steric repulsion between the phenyl moiety (β-nitrostyrene) and the two methyl groups of isobutyraldehyde (not shown). This repulsion would increase considerably when considering the cyclohexanecarboxaldehyde donor (Table 3, entries 10 and 11) and directly reflects the lack of reactivity for this substrate. Regarding the aldol reactions shown here, a similar line of reasoning concludes that a bifunctional catalyst model is more likely (Scheme 2).

Conclusions

Functional group manipulations of proline, the cinchona alkaloids, and 1,2-*trans*-cyclohexadiamine have dominated the design space of amine based organocatalysts and excellent results have been noted, but their limitations are also now increasingly understood. As new emphasis is placed on more complex, drug-like, substrates, new catalysts will be required. In this context we have developed a simple (one stereogenic center) modular primary–tertiary bifunctional organocatalyst that can be sterically and electronically fine-tuned for further development.



Scheme 2 Relevant aldol transition states for (*S*)-PicAm-**1**.

In particular, here we have demonstrated that the picolylamine organocatalyst template provides good to excellent results for challenging Michael additions to β-nitrostyrenes and for broadening the ketone donor substrates for aldol reactions with aromatic aldehydes.

Experimental

General procedure for enantioselective Michael reactions

To a mixture of the nitroolefin (1.00 equiv.), (*S*)-PicAm-**3** (free amine, 10 mol% unless otherwise stated) in the presence of *p*-dodecylbenzenesulfonic acid sodium salt (10 mol%) and 2,4-dinitrobenzenesulfonic acid (2.5 mol%, sold as an undefined hydrate by Sigma-Aldrich) in chloroform (2.0 M) was added the

ketone or aldehyde (5.00 equiv.). The reactions were performed at room temperature and monitored by HPLC and/or TLC. At the indicated reaction time (see Table 3) the reaction was concentrated (low vacuum, then short exposure to high vacuum) and the resulting crude Michael product was purified by column chromatography. **4b–d** are new compounds and have been fully characterized in the ESI.†

General procedure for enantioselctive aldol reactions

The (*S*)-PicAm-**1**/2,4-dinitrobenzenesulfonic acid 1 : 1 salt (MW = 550.58, 0.035 mmol, 7.0 mol%) was added to a mixture of the aldehyde (0.5 mmol, 1.0 equiv.) and ketone (1.65 mmol, 3.3 equiv.) in distilled water (1.0 mL), the reaction mixture was stirred at 45 °C for the specified reaction time (see Table 4). Note, the aldol products, in particular, are prone to α-epimerization, do not extend the reaction times. Work-up: add EtOAc and H_2O, extract with EtOAc (15 mL × 3). The combined organic extracts were dried (Na_2SO_4), evaporated (Rot Vap), and high vacuum dried. ^{1}H NMR of the crude product allowed the dr assessment. The crude sample was then purified by chromatography (petroleum ether/EtOAc) for yield and ee assessment. **9c** is a new aldol compound and has been fully characterized in the ESI.†

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37 Our examination of hand held models confirmed either a poor or non-existent 'geometric fit' for hydrogen bond formation between the catalyst's protonated tertiary amine and the nitro group of β-nitrostyrene for the synthesis of **4a** with Barbas' catalyst (Fig. 4).

38 Our examination of hand held models of the Kotsuki and Luo/Cheng catalysts (Fig. 4) confirmed a reasonable or good 'geometric fit' for hydrogen bond formation between the catalyst's protonated tertiary amine and the nitro group of β-nitrostyrene when adding cyclohexanone to β-nitrostyrene (the reactions examined by the noted groups). It should be made clear that our current steric *vs* bifunctional model assessment has benefited from having many more literature examples to ponder and draw conclusions from than were available to Luo/Cheng (2006) or Kotsuki (2004) when they disclosed their findings. Mechanism grounded experiments would be required to better understand which catalyst model is truly operative.

