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Solvent-effects tuning the catalytic reactivity of prolinamides in asymmetric aldol reactions

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ABSTRACT

Novel prolinamides were prepared and applied as organocatalysts in the asymmetric aldol reaction. Stable imidazolidinones were formed between prolinamides and aromatic aldehydes in organic solvents. It was found that aqueous conditions can significantly suppress the formation of the unwanted imidazolidinone intermediate and improve the catalytic activity of the prolinamides. As a consequence, high chemical yields (up to 99%) and good diastereoselectivity (up to >20:1 dr) and enantioselectivity (up to 95% ee) were achieved in 2-Me-THF or brine. This strategy could serve as a general solution to enhance the performance of prolinamides as organocatalysts.

1. Introduction

The asymmetric aldol reaction is one of the most commonly used C—C bond-forming pathways in the synthesis of complex natural products or biologically active molecules.[1] The corresponding aldol products, β-hydroxy carbonyl compounds or α,β-unsaturated carbonyl compounds, are very important and versatile building blocks in synthetic chemistry.[2] In all of the developed asymmetric aldol methodologies, the organocatalytic asymmetric aldol reaction has received extra attention over the last decade, and has evolved to be one of the major methods to prepare enantiomerically enriched compounds, besides metal-catalysis or enzymes.[3] Additionally, from the perspective of environmental friendliness, organocatalytic asymmetric aldol reactions would be the premium choice for making enantiomerically pure organic compounds.[4]

Since the first asymmetric direct intermolecular aldol reaction, catalyzed by L-proline, was reported by List et al. in 2000,[5] numerous efforts have been made to design more effective organocatalysts based on proline to improve their performance in aldol reactions. In particular, prolinamides have attracted a great deal of research interest due to their easy preparation and modification, beneficial chemical structural features, and upgraded physical profiles over proline. In 2003, Gong et al. first applied L-proline-derived amides to catalyze direct aldol reactions of aldehydes with acetone.[6] Subsequently, a wide range of functionalized prolinamides have been successfully designed and synthesized to secure their superior performance in direct aldol reactions and many of them have shown excellent stereoselectivities toward various direct aldol reactions.[7]

Despite these achievements in the development of prolinamide organocatalysts for asymmetric aldol reactions, an intrinsic hurdle has been set up due to the structural features of the prolinamides. It has been found that prolinamides can readily react with carbonyl compounds to form imidazolidinones, especially with aldehydes. Unfortunately, this specific reactivity usually has a negative effect on the catalytic performance of prolinamides in aldol reactions. Gryco et al. observed the generation of imidazolidinones between L-prolinethioamide and both acetone and aldehydes, which was found to diminish the chemical yield and enantioselectivity in the direct aldol reaction.[8] Subsequently, Morán et al. also identified aldol imidazolidinone intermediates.[9] Similarly, the formation of an imidazolidinone was detrimental to the chemical yield and enantioselectivity. The addition of TFA slowed down the accumulation of this intermediate and improved the catalytic performance of the prolinamide to some degree (Scheme 1, Eq. a).[10] In 2011, Andreu et al. proposed an interesting solution to inhibit the formation of the unwanted imidazolidinone intermediate by employing zinc complexation with prolinamides, leading to faster reactions with higher enantioselectivity (Scheme 1, Eq. b).[11] Apparently, the unwanted imidazolidinone changed the reaction pathway and undermined the catalytic activity of the prolinamide, which would hamper the development of prolinamides as organocatalysts in aldol reactions. Undoubtedly, a deeper insight into the formation of imidazolidinones and facile pathways to inhibit their formation would be highly demanding and necessary to overcome this essential drawback for the use of prolinamides as organocatalysts.

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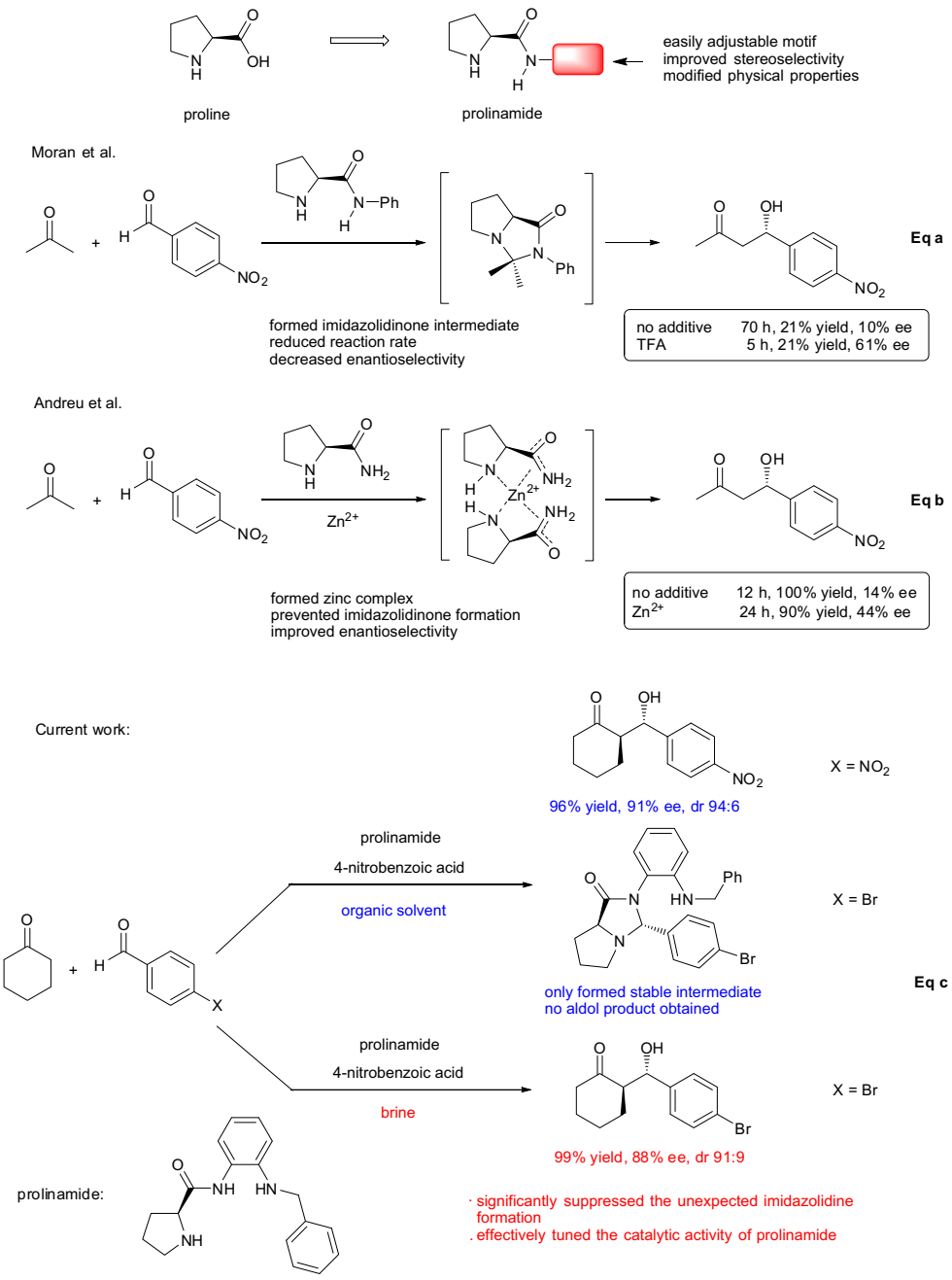
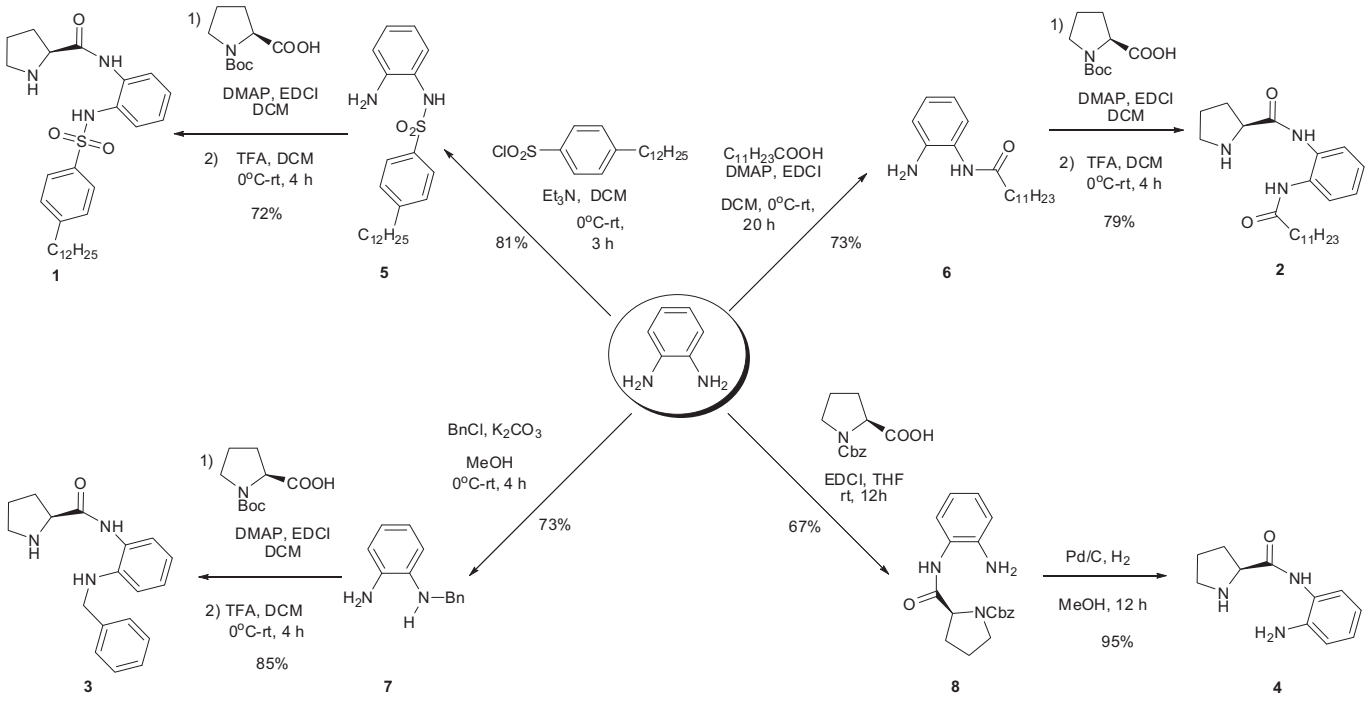


Scheme 1. Formation of imidazolidinones via asymmetric aldol reactions catalyzed by prolinamides.

Driven by preparing highly effective prolinamides as organocatalysts, we designed and synthesized four prolinamides based on the *o*-phenylenediamine moiety, with the aim of providing double hydrogen-bonding formation with the corresponding substrates. It should be noted that Saha et al. employed tosyl-functionalized prolinamides to catalyze the direct aldol reaction in DMF, and obtained good enantioselectivity and diastereoselectivity.[7n] Herein, one rationale of our design was to improve the solubilities of tosyl- or acyl-functionalized prolinamides in regular organic solvents via the introduction of long lipophilic alkyl chains onto the sulphonamide or amide, in order to provide broader options for solvents. On the other hand, the *N*-(phenylmethyl)-1,2-benzenediamine motif, which could effectively provide multi-hydrogen bonding sites, was incorporated into the prolinamides to facilitate the direct aldol reaction. The catalytic activities were evaluated on the asymmetric direct aldol reactions. A stable imidazolidinone intermediate was isolated and confirmed by X-ray analysis. More importantly, it was found that the use of brine as a solvent could considerably suppress the production of this intermediate and facilitate the catalytic performance of the prolinamides, which could provide an effective solution to circumvent the problems of prolinamides in asymmetric aldol reactions (Scheme 1, Eq. c).

2. Results and discussion

Initially, four prolinamides **1**–**4** were designed and prepared in good yields, starting from the direct coupling between Cbz or Boc-protected L-proline with *o*-phenylenediamine derivatives followed by deprotection of the Cbz or Boc protecting group. The corresponding synthetic routes for **1**–**4** are presented in Scheme 2. It



Scheme 2. Synthetic routes to prolinamides **1**–**4**.

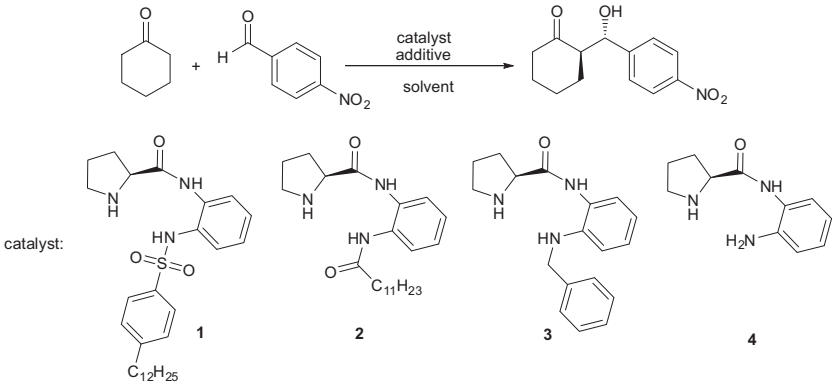
can be rationalized that acidities of the N-Hs on the benzene moiety in prolinamide **1** and **2** would be significantly increased by introducing a sulfonamide or amide. In sharp contrast, the benzyl group was combined with the *o*-phenylenediamine scaffold in prolinamide **3**. Therefore, the basicity of the corresponding N—H was increased, which could be readily protonated by an acid to enable hydrogen-bonding formation with substrates. A comparative study of **1**, **2**, and **3** with the parent compound **4** would help us to gain insight into the effect of functional groups on catalytic performance.

Subsequently, the catalytic activities were evaluated in the direct asymmetric aldol reaction between 4-nitrobenzaldehyde and cyclohexanone at room temperature (Table 1). Encouragingly, all four prolinamides smoothly catalyzed this aldol reaction to provide the corresponding product in CH_2Cl_2 (entries 1–4). The use of catalyst **3** afforded the best ee and dr, while catalyst **4** which had the least steric effects, afforded the best chemical yield. Therefore, prolinamide **3** was considered to be the superior catalyst to be used in the following tests. A series of solvents with varied polarities were screened and it was found that the more polar solvents usually gave better yields. Using 2-Me-THF as an industry-friendly and green solvent, afforded excellent yield and good enantioselectivity, albeit with a slightly decreased dr (entries 5–12). Ultimately, efforts were focused on screening additives to further improve the enantioselectivity and diastereoselectivity in 2-Me-THF. The addition of water can significantly accelerate the reaction, while lowering the ee (entry 13). Basic additives such as $NaHCO_3$, had a minor effect on the catalytic performance (entry 14). When acidic additives were employed, the diastereoselectivity was generally improved (entries 15–18). The use of 4-nitrobenzoic acid facilitated the reaction and provided excellent yield and moderate ee in a much shorter reaction time (entry 19). Finally, the reaction was carried out at 0 °C to furnish the corresponding *anti*- product in excellent yield and dr and with good ee (entry 20). Presumably, the basic nitrogen atom on the benzene ring in catalyst **3** is susceptible by an acid, which could strengthen the hydrogen-bonding between the catalyst and substrate, leading to an improved stereocontrol.

With the optimum conditions in hand, the scope of this reaction was investigated by employing a variety of benzaldehydes with different substitution patterns and various ketones (Table 2). As can be seen, when using aldehydes bearing a strong electron-withdrawing group (—NO_2) to react with cyclohexanone, no matter with the substitution pattern, excellent dr and yields as well as good ee for the corresponding *anti*-aldol product were obtained uniformly (entries 1–4). Various ketone partners were tested for this reaction with 4-nitrobenzaldehyde. As for acetone and cyclopentanone, the enantioselectivities sharply decreased. Good ee and dr were obtained for 4-methylcyclohexanone with slightly lower chemical yields (entries 5–7). When benzaldehyde or a species substituted by mild electron-withdrawing or electron-donating groups were employed in this reaction, the desired aldol product was not obtained (entries 8–12).

We were interested in the abnormal catalytic reactivity of catalyst **3**. Accordingly, extra caution and further attempts were made to gain an insight into this unexpected situation. The reaction between 4-bromobenzaldehyde with cyclohexanone was monitored closely. It was observed that catalyst **3** was completely consumed in several hours to generate an unknown compound with less polarity. After being purified via silica gel column chromatography and characterized by analytical methods, a stable imidazolidinone was found to be formed between 4-bromobenzaldehyde and prolinamide **3** (Scheme 3). The structure of this compound was unequivocally confirmed by X-ray analysis of a single crystal (Fig. 1).[12] Morán et al. observed that the imidazolidinone intermediate was formed slowly in the reaction of acetone with 4-nitrobenzaldehyde catalyzed by a prolinamide after nine days.[10] These observed results could help us to explain the different reactivities of various benzaldehydes. Presumably, the formation of the imidazolidinone intermediate between 4-nitrobenzaldehyde and prolinamide **3** was extremely sluggish, which would have a negligible effect on the progress of the aldol reaction. As a result, the desired

Table 1
Optimization of the direct asymmetric aldol reaction of 4-nitrobenzaldehyde and cyclohexanone catalyzed by prolinamides **1**–**4**[a]



Entry	Catalyst	Solvent	*T* (°C)	Additive (0.2 equiv)	Time (h)	Yield[b] (%)	ee[c] (%, *anti*/*syn*)	dr[d] (*anti*/*syn*)
1	**1**	CH_2Cl_2	Rt	—	48	68	31/47	74/26
2	**2**	CH_2Cl_2	Rt	—	48	63	61/62	72/28
3	**3**	CH_2Cl_2	Rt	—	48	77	69/38	74/26
4	**4**	CH_2Cl_2	Rt	—	48	87	50/48	62/38
5	**3**	EtOAc	Rt	—	48	99	65/3	68/32
6	**3**	CH_3OH	Rt	—	48	95	52/31	69/31
7	**3**	DMSO	Rt	—	48	89	63/51	78/22
8	**3**	THF	Rt	—	48	95	68/32	77/23
9	**3**	Brine	Rt	—	48	98	66/16	72/28
10	**3**	TFT[e]	Rt	—	48	91	56/6	69/31
11	**3**	2-Me-THF	Rt	—	48	98	88/4	62/38
12	**3**	2-Methyl-*tert*-butanol	Rt	—	48	98	71/21	66/34
13	**3**	2-Me-THF	Rt	H_2O[f]	24	91	62/46	79/21
14	**3**	2-Me-THF	Rt	$NaHCO_3$	48	84	74/48	83/17
15	**3**	2-Me-THF	Rt	Trifluoroacetic acid	24	97	81/10	91/9
16	**3**	2-Me-THF	Rt	Acetic acid	24	94	75/51	74/26
17	**3**	2-Me-THF	Rt	Toluenesulfonic acid	48	74	88/29	95/5
18	**3**	2-Me-THF	Rt	Benzoic acid	24	90	76/40	74/26
19	**3**	2-Me-THF	Rt	4-Nitrobenzoic acid	12	99	78/45	82/18
20	**3**	**2-Me-THF**	**0**	**4-Nitrobenzoic acid**	**24**	**96**	**91/53**	**94/6**
21	**3**	2-Me-THF	0	Trifluoroacetic acid	66	76	91/22	97/3

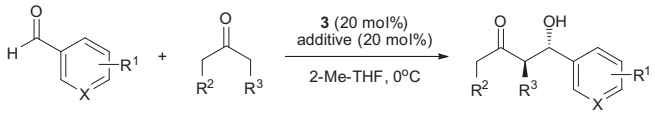
[a] Reaction conditions: 4-nitrobenzaldehyde (0.5 mmol) and cyclohexanone (5.0 mmol), catalyst **1**–**4** (0.1 mmol), solvent (0.5 mL).
[b] Isolated yield after column chromatography.
[c,d] Determined by chiral HPLC analysis.
[e] TFT = α,α,α-trifluorotoluene.
[f] One drop of H_2O was added.

aldol product was obtained in good yield and stereoselectivity. However, it would be facile for other benzaldehydes with different electronic features, such as 4-bromobenzaldehyde, to react with prolinamide **3** to completely furnish the unwanted imidazolidinone. As a result, the progress of the aldol reaction was terminated due to the loss of active catalyst and the corresponding aldol product could therefore not be obtained.

As mentioned above, we were faced with the dilemma that this developed catalytic system was unexpectedly restricted to nitro-substituted benzaldehydes. We next expected to tune the catalytic reactivity of the catalyst and broaden the tolerance of substrates. In principle, the existence of excess amounts of water in this reaction should be deleterious to the generation of the unwanted imidazolidinone, releasing the active catalyst to the catalytic cycle of the aldol reaction. Furthermore, the use of water as the solvent would cut down the consumption of organic solvents, offering an environmentally benign process for this catalytic system. Hence, the most effective and direct solution for this unexpected problem would be the use of water as the solvent. Further efforts were applied to conduct this aldol reaction under aqueous conditions. The reaction of 4-bromobenzaldehyde with cyclohexanone was chosen as the model reaction to test the feasibility of our strategy (Table 3). The corresponding aldol products were successfully obtained in good yield for catalysts **1**–**4** in water (entries 1–4). Again, catalyst **3** showed superior catalytic activity. Running this reaction in brine afforded excellent chemical yield and good ee and dr (entry 5). Acidic additives were also screened in brine. Similarly, the employment of trifluoroacetic acid provided relatively higher ee and dr with a sizeable decrease in the chemical yield (entry 7). Extremely slow reactions were observed when using toluenesulfonic acid and $NaHCO_3$ (entries 12 and 13). Among all the acidic additives studied, 4-nitrobenzoic acid was still the optimal choice for this reaction system.

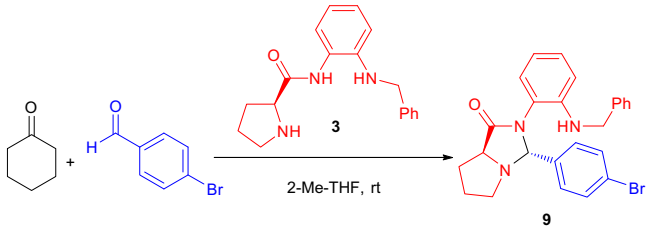
The effectiveness of this strategy using brine as the solvent was next tested on various benzaldehydes with different electronic features of the substituting groups. Benzaldehyde or benzaldehydes substituted by electron-withdrawing groups all gave good yields with slightly decreased ee and dr (Table 4, entries 1–4). In the presence of an electron-donating substituting group, the reaction rate and enantioselectivity were significantly decreased. On the contrary, the diastereoselectivity was slightly improved (entry 5). Nitro-substituted benzaldehydes were also evaluated under these conditions. Compared with the catalytic results in 2-Me-THF, excellent chemical yields were also obtained although ee and dr were all slightly decreased (entries 6–8). Only trace amounts of the desired aldol product were obtained when using acetone to

Table 2
Scope of direct asymmetric aldol reaction catalyzed by **3** in 2-Me-THF[a]



Entry	Aldehyde		Ketone (R^2, R^3)	Time (h)	Yield[b] (%)	ee[c] (%, *anti*/*syn*)	dr[d] (*anti*/*syn*)
	R^1	X					
1	2-NO_2	C	–$(CH_2)_3$–	48	88	92/55	94/6
2	3-NO_2	C	–$(CH_2)_3$–	48	90	91/26	97/3
3	2,4-NO_2	C	–$(CH_2)_3$–	36	99	92/35	93/7
4	2-NO_2-4-Br	C	–$(CH_2)_3$–	48	83	95/11	96/4
5	4-NO_2	C	H, H	48	66	59	–
6	4-NO_2	C	–$(CH_2)_2$–	48	99	34/83	68/32
7	4-NO_2	C	–$CH_2CH(CH_3)CH_2$–	48	79	91/2	91/9
8	**H**	**C**	**–$(CH_2)_3$–**	**48**	***NR***	–	–
9	**H**	**N**	**–$(CH_2)_3$–**	**48**	***NR***	–	–
10	**4-Br**	**C**	**–$(CH_2)_3$–**	**48**	***NR***	–	–
11	**4-CF_3**	**C**	**–$(CH_2)_3$–**	**48**	***NR***	–	–
12	**2-OH**	**C**	**–$(CH_2)_3$–**	**48**	***NR***	–	–

[a] Reaction conditions: substituted benzaldehyde (0.5 mmol) and ketones (5.0 mmol), catalyst (**3**, 0.1 mmol), additive (4-nitrobenzoic acid, 0.1 mmol), solvent (2-Me-THF, 0.5 mL), reaction temperature (0 °C).
[b] Isolated yield after column chromatography.
[c,d] Determined by chiral HPLC analysis.



Scheme 3. Formation of an imidazolidinone intermediate.

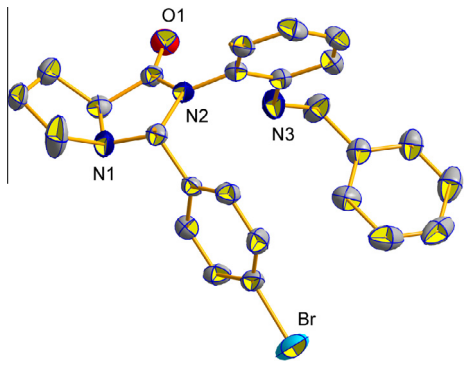


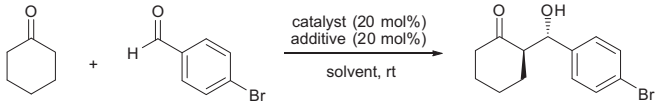
Figure 1. ORTEP diagram of imidazolidinone intermediate.

react with 4-bromobenzaldehyde, due to the ready dehydration that occurred in this reaction (entry 9). The aldol reaction of 4-bromobenzaldehyde with cyclopentanone under these conditions afforded comparatively lower stereoselectivities (entry 10).

3. Conclusion

In conclusion, three novel prolinamides have been designed and prepared to act as organocatalysts in the direct aldol reactions of cyclohexanone and benzaldehydes. It was found that the electronic features of the benzaldehydes severely affected the reaction pathway. Due to the inherent chemical features of the prolinamide, the unwanted imidazolidinone intermediate was formed and confirmed by X-ray analysis. A straightforward and concise strategy employing brine as the solvent was proven to effectively suppress the generation of the imidazolidinone. As a consequence, excellent yields as well as good ee and dr values were achieved while tolerating different functional groups. More importantly, this strategy could serve as an effective and general solution to overcome the intrinsic drawback of prolinamides and facilitate the development of prolinamides as organocatalysts.

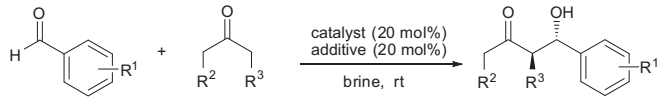
Table 3
Screening of direct asymmetric aldol reactions under aqueous conditions[a]



Entry	Catalyst	Solvent	Additive (0.2 equiv)	Yield[b] (%)	ee[c] (%, *anti*/*syn*)	dr[d] (*anti*/*syn*)
1	**1**	Water	4-Nitrobenzoic acid	80	46/7	70/30
2	**2**	Water	4-Nitrobenzoic acid	90	68/16	71/29
3	**3**	Water	4-Nitrobenzoic acid	94	79/6	84/16
4	**4**	Water	4-Nitrobenzoic acid	80	35/15	72/28
5	**3**	**Brine**	**4-Nitrobenzoic acid**	**99**	**88/13**	**91/9**
6	**3**	Brine[e]	4-Nitrobenzoic acid	96	87/19	89/11
7	**3**	Brine	Trifluoroacetic acid	63	89/47	98/2
8	**3**	Brine	Acetic acid	93	86/47	88/12
9	**3**	Brine	Benzoic acid	80	85/24	97/3
10	**3**	Brine	2-Fluorobenzoic acid	85	79/5	91/9
11	**3**	Brine	3,5-Dinitrobenzoic acid	89	85/16	86/14
12	**3**	Brine	Toluenesulfonic acid	Trace	ND	ND
13	**3**	Brine	$NaHCO_3$	Trace	ND	ND

[a] Reaction conditions: benzaldehyde (0.5 mmol) and cyclohexanone (5.0 mmol), catalyst **1**–**4** (0.1 mmol), additive (0.1 mmol), solvent (0.5 mL), reaction temperature (room temperature), and time (48 h).
[b] Isolated yield after column chromatography.
[c,d] Determined by chiral HPLC analysis.
[e] Half-saturated brine was used.

Table 4
Scope of the direct asymmetric aldol reaction in brine.[a]



Entry	Aldehyde R^1	Ketone (R^2, R^3)	Yield[b] (%)	ee[c] (%, *anti*/*syn*)	dr[d] (*anti*/*syn*)
1	H	$-(CH_2)_3-$	83	63/24	75/25
2	4-CF_3	$-(CH_2)_3-$	94	88/20	79/21
3	4-Cl	$-(CH_2)_3-$	91	71/14	75/25
4	4-F	$-(CH_2)_3-$	89	80/17	88/12
5	4-Me	$-(CH_2)_3-$	64	54/67	98/2
6	2-NO_2	$-(CH_2)_3-$	99	85/30	89/19
7	3-NO_2	$-(CH_2)_3-$	99	87/41	81/19
8	4-NO_2	$-(CH_2)_3-$	99	83/39	77/23
9	4-Br	H, H	Trace	ND	ND
10	4-Br	$-(CH_2)_2-$	97	46/64	64/36

[a] Reaction conditions: benzaldehyde (0.5 mmol), cyclohexanone (5.0 mmol), catalyst **3** (0.1 mmol), additive: 4-nitrobenzoic acid (0.1 mmol), solvent: saturated brine (0.5 mL), reaction temperature (room temperature), and reaction time (48 h).
[b] Isolated yield after silica gel column chromatography.
[c,d] Determined by chiral HPLC analysis.

4. Experimental

4.1. General

Unless noted otherwise, all the reagents were purchased from commercial suppliers and used without further purification. The reactions were monitored by TLC (thin layer chromatography). The purification of products was carried out by flash column chromatography on silica gel (200–300 mesh). Chemical yields refer to pure isolated substances. Melting points were measured on a XR-4 apparatus (thermometer uncorrected). Optical rotations were recorded with a Jasco-P-2000 digital polarimeter. Nuclear magnetic resonance (NMR) spectra were measured by Bruker Avance 400 spectrometer. ^{1}H NMR spectra were recorded at 400 MHz. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration. ^{13}C NMR data were recorded at 100 MHz with complete proton decoupling. Infrared spectra (IR) were measured by FT-IR apparatus using KBr disks in the 400–4000 cm^{-1} region. High resolution mass spectroscopy (HRMS) was recorded on TOF MS ES+ mass spectrometer. HPLC analyses were performed on Waters (2996 photodiode array detector and binary HPLC Pump). Chiralcel AD-H, AS-H, OD-H, and OJ-H columns were purchased from Daicel Chemical Industries, Ltd.

4.2. Preparation of catalysts 1–4

4.2.1. *N*-(2-Aminophenyl)-4-dodecyl-benzenesulfonamide 5

To a flask containing *o*-phenylenediamine (1.19 g, 11.0 mmol, 1.1 equiv) dissolved in CH_2Cl_2 (20 mL) was added Et_3N (1.01 g, 10.0 mmol, 1.0 equiv) at 0 °C. Next, a solution of *p*-dodecylbenzenesulfonyl chloride (3.44 g, 10.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise to it. The resulting reaction mixture was stirred at room temperature for 3 h. After quenching with water, the organic phase was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via flash column chromatography on silica gel (EtOAc:PE = 5–15%) to afford compound **5** as a yellow oil (3.37 g, yield 81%). IR (KBr) ν 3253, 2924, 1620, 1318, 1158, 746, 672 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (br s, 1H), 7.60–7.64 (m, 2H), 7.31–7.36 (m, 2H), 6.86 (t, J = 7.6 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 6.43–6.49 (m, 1H), 6.25–6.34 (m, 1H), 4.96 (br s, 2H), 2.56–2.59 (m, 1H), 1.51–1.63 (m, 4H), 0.97–1.26 (m, 14H), 0.77–0.84 (m, 5H), 0.68 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.9, 151.5, 151.2, 145.1, 137.9, 128.4, 127.6, 127.3, 121.3, 116.1, 45.5, 36.4, 36.2, 31.7, 29.7, 29.4, 29.1, 27.4, 22.5, 14.3, 12.3; HRMS (TOF-ES+) m/z: $[M+H]^+$ calcd for $C_{24}H_{37}N_2O_2S$ 417.2576, found 417.2561.

4.2.2. (*S*)-*N*-(2-(*p*-Dodecylsulfonamido)phenyl)prolinamide 1

Sulphonamide **5** (3.37 g, 8.1 mmol) and Boc-L-proline (2.58 g, 12.0 mmol, 1.5 equiv) were dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C immediately. A solution of DMAP (0.78 g, 6.4 mmol, 0.8 equiv) and EDCI (1.84 g, 9.6 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL) was then added dropwise. The resulting reaction mixture was stirred at rt and monitored by TLC. After completion of the reaction, the mixture was partitioned between EtOAc and 1 M HCl. The organic layer was washed with half-saturated brine. The dried (Na_2SO_4) extract was concentrated in vacuo. The crude product was then dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. Trifluoroacetic acid (4.6 mL, 10.0 equiv) was added dropwise to this chilled solution and the reaction mixture was stirred at room temperature for 4 h. At the end of the reaction, the mixture was basified with NH_4OH, extracted with EtOAc, washed with brine, and dried over Na_2SO_4. The solvent was removed in vacuo, and the resulting crude product was purified via flash chromatography (MeOH:CH_2Cl_2 = 3–7%) to provide the corresponding catalyst **1** as a yellow oil (2.98 g, yield 58%). $[\alpha]_D^{25} = -18.0$ (c 0.5, $CHCl_3$); IR (KBr) ν 3241, 2926, 1663, 1596, 1524, 1454, 1161, 832, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (br s, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 1H), 7.16–7.22 (m, 3H), 7.05–7.11 (m, 2H), 3.82–3.85 (m, 1H), 3.03–3.07 (m, 1H), 2.95–2.98 (m, 1H), 2.42–2.59 (m, 1H), 2.20–2.25 (m, 1H), 1.98–2.03 (m, 1H), 1.71–1.78 (m, 2H), 1.60–1.66 (m, 2H), 1.48–1.51 (m, 2H), 1.21–1.23 (m, 9H), 1.02–1.14 (m, 4H), 0.81–0.88 (m, 6H), 0.74 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 152.1, 137.2, 133.0, 128.4, 128.1, 127.8, 127.5, 127.2, 125.8, 122.9, 60.7, 47.3, 45.9, 36.7, 31.8, 30.9, 29.6, 29.3, 27.6, 27.2, 26.3, 22.6, 20.7, 14.1, 12.1; HRMS (TOF-ES+) m/z: $[M+H]^+$ calcd for $C_{29}H_{44}N_3O_3S$ 514.3103, found 514.3096.

4.2.3. *N*-(2-Aminophenyl)-dodecanamide 6[13]

To a flask containing *o*-phenylenediamine (2.16 g, 20.0 mmol, 2.0 equiv) dissolved in CH_2Cl_2 (30 mL) cooled to 0 °C was added dropwise a solution of lauric acid (2.00 g, 10.0 mmol, 1.0 equiv), DMAP (0.98 g, 8.0 mmol, 0.8 equiv), and EDCI (2.30 g, 12.0 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL). The reaction mixture was then stirred at rt for 20 h. At the end of the reaction as judged by TLC analysis, the reaction mixture was concentrated to give the crude product, which was further purified via silica gel column chromatography (EtOAc:PE = 20–30%) to afford compound **6** as a white solid (2.12 g, yield 73%). mp: 111–113 °C; IR (KBr) ν 3264, 2920, 2849, 1643, 1534, 864, 766, 716 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (br s, 1H), 7.15 (d, J = 7.6 Hz, 1H), 6.89 (t, J = 7.6 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.54 (t, J = 7.6 Hz, 1H), 4.80 (s, 2H), 2.30 (t, J = 7.6 Hz, 2H), 1.59 (t, J = 6.4 Hz, 2H), 1.26–1.29 (m, 16H), 0.85–0.88 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.6, 142.3, 126.1, 125.7, 124.0, 116.6, 116.4, 36.2, 31.8, 29.49, 29.48, 29.4, 29.3, 29.2, 29.1, 25.8, 22.6, 14.4; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{18}H_{30}N_2ONa$ 313.2256, found 313.2252.

4.2.4. (*S*)-*N*-(2-Dodecylamidophenyl)prolinamide 2

The coupling of **6** with Boc-L-proline and the following deprotection were conducted according to the experimental procedure for **1**. The crude product was further purified through silica gel column (MeOH:CH_2Cl_2 = 1–5%) to provide compound **2** as a white solid (2.25 g, yield 58%). mp: 117–121 °C; $[\alpha]_D^{25} = -34.5$ (c 0.5, $CHCl_3$); IR (KBr) ν 3254, 2921, 2851, 1655, 1596, 1549, 879, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (br s, 1H), 8.74 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.19–7.26 (m, 2H), 7.12–7.15 (m,

1H), 3.91–3.95 (m, 1H), 3.08–3.14 (m, 1H), 2.98–3.03 (m, 1H), 2.34 (t, J = 8.0 Hz, 2H), 2.22–2.29 (m, 1H), 1.98–2.06 (m, 1H), 1.75–1.82 (m, 2H), 1.67–1.74 (m, 2H), 1.26–1.34 (m, 16H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 171.9, 131.0, 129.3, 126.4, 126.1, 125.5, 123.7, 60.7, 47.4, 37.7, 31.9, 31.2, 29.6, 29.5, 29.4, 29.3, 26.3, 25.8, 22.7, 14.1; HRMS (TOF-ES+) m/z: $[M+H]^+$ calcd for $C_{23}H_{38}N_3O_2$ 388.2964, found 388.2960.

4.2.5. N^1-(Phenylmethyl)-1,2-benzenediamine 7[14]

o-Phenylenediamine (3.24 g, 30.0 mmol, 1.5 equiv) and K_2CO_3 (4.15 g, 30.0 mmol, 1.5 equiv) were suspended in methanol (30 mL) and cooled to 0 °C. To this solution was added benzyl chloride (2.3 mL, 20.0 mmol, 1.0 equiv) very slowly. The reaction mixture was stirred at rt for 4 h. The suspension was filtered and the cake was washed twice with methanol. The filtrate was evaporated under reduced pressure. The residue was dissolved in EtOAc, washed with water and brine, and dried over anhydrous over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was further purified through silica gel column chromatography (EtOAc:PE = 5–15%) to afford compound **7** as a colorless solid (2.89 g, yield 73%). mp: 60–63 °C; IR (KBr) ν 3281, 3039, 2811, 1604, 1507, 1452, 1260, 909, 743 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39 (m, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.24 (t, J = 7.2 Hz, 1H), 6.59–6.61 (m, 1H), 6.41–6.46 (m, 2H), 6.36–6.39 (m, 1H), 5.12 (t, J = 5.6 Hz, 1H), 4.58 (s, 2H), 4.32 (d, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 140.9, 136.1, 135.7, 128.7, 127.7, 127.0, 118.0, 117.5, 114.8, 110.9, 47.5; HRMS (TOF-ES+) m/z: $[M+H]^+$ calcd for $C_{13}H_{15}N_2$ 199.1235, found 199.1234.

4.2.6. (*S*)-*N*-(2-Benylaminephenyl)prolinamide 3

The coupling of **7** with Boc-L-proline and the following deprotection were conducted according to the experimental procedure for **1**. The crude product was further purified through silica gel column chromatography (MeOH:CH_2Cl_2 = 1–5%) to provide compound **3** as a colorless solid (3.67 g, yield 62%). mp: 135–139 °C; $[\alpha]_D^{25}$ = −57.0 (c 0.5, $CHCl_3$); IR (KBr) ν 3348, 3148, 2834, 1662, 1593, 1529, 1494, 1297, 750, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (br s, 1H), 7.39–7.41 (m, 2H), 7.34 (t, J = 7.2 Hz, 2H), 7.24–7.29 (m, 2H), 7.08 (td, J = 8.0, 0.8 Hz, 1H), 6.72–6.78 (m, 2H), 4.55–4.57 (m, 1H), 4.35 (d, J = 6.0 Hz, 2H), 3.90 (q, J = 5.2 Hz, 1H), 3.04–3.10 (m, 1H), 2.94–2.99 (m, 1H), 2.16–2.24 (m, 1H), 2.00–2.10 (m, 2H), 1.71–1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 141.9, 139.4, 128.6, 127.3, 127.1, 126.9, 124.4, 124.2, 118.2, 113.3, 60.9, 48.2, 47.4, 31.1, 26.4; HRMS (TOF-ES+) m/z: $[M+H]^+$ calcd for $C_{18}H_{22}N_3O$ 296.1763, found 296.1755.

4.2.7. (2*S*)-1-Pyrrolidinecarboxylic acid-2-[[(2-aminophenyl) amino]carbonyl]-phenylmethyl ester 8[15]

To a solution of Cbz-L-proline (2.49 g, 10.0 mmol) in THF (10 mL) was added EDCI (2.00 g, 10.0 mmol). After stirring for 1 h, *o*-phenylenediamine (2.16 g, 20.0 mmol, 2.0 equiv) was then added to it. The reaction mixture was stirred overnight and the solvent was removed in vacuo. The residue was taken up in CH_2Cl_2 and washed with $NaHCO_3$, 1 M HCl, and water two times. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was further purified through silica gel column chromatography (EtOAc: PE = 20–40%) to afford compound **8** as a white solid (2.27 g, yield 67%). mp: 188–190 °C; $[\alpha]_D^{25}$ = −88.8 (c 0.5, $CHCl_3$); IR (KBr) ν 3430, 3355, 3200, 3034, 2878, 1697, 1651, 1545, 1501, 1452, 1422, 1112, 750, 700 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.33 (s, 1H), 7.29–7.40 (m, 5H), 7.07–7.09 (m, 1H), 6.91–6.92 (m, 1H), 6.74 (t, J = 6.8 Hz, 1H), 6.55 (t, J = 7.2 Hz, 1H), 5.07–5.15 (m, 2H), 4.85 (s, 1H), 4.73 (s, 1H), 4.34–4.45 (m, 1H), 3.36–3.55 (m, 2H), 2.19–2.31 (m, 1H), 1.85–2.02 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.5, 171.3, 154.8, 143.3, 137.4, 128.9, 128.3, 128.1, 127.6, 126.9, 126.6, 126.0, 123.1, 116.4, 66.4, 60.8, 47.1, 30.7, 24.6; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{19}H_{21}N_3O_3Na$ 362.1481, found 362.1468.

4.2.8. (*S*)-*N*-(2-Aminephenyl)prolinamide 4

To a solution of **8** (2.27 g, 6.7 mmol) in MeOH (50 mL) was added 10% Pd–C (0.23 g). The resulting mixture was stirred under hydrogen for 12 h before it was filtered and washed with MeOH. The filtrate was evaporated and the crude product was further purified via silica gel column chromatography (MeOH:CH_2Cl_2 = 4–8%) to give compound **4** as a white solid (1.31 g, yield 64%). mp: 118–121 °C; $[\alpha]_D^{25}$ = −55.5 (c 0.5, $CHCl_3$); IR (KBr) ν 3432, 3329, 3221, 2859, 1663, 1631, 1512, 1483, 1305, 750, 609 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (s, 1H), 7.36 (dd, J = 8.0, 1.2 Hz, 1H), 6.90 (td, J = 8.0, 1.6 Hz, 1H), 6.79 (dd, J = 8.0, 1.2 Hz, 1H), 6.60 (td, J = 8.0, 1.2 Hz, 1H), 4.73 (s, 2H), 3.72–3.74 (m, 1H), 2.91 (t, J = 6.4 Hz, 2H), 2.01–2.10 (m, 1H), 1.78–1.85 (m, 1H), 1.67–1.77 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.6, 141.5, 125.8, 124.6, 124.2, 117.4, 116.9, 61.2, 47.2, 31.0, 26.4; HRMS (TOF-ES+) m/z: $[M+H]^+$ calcd for $C_{11}H_{16}N_3O$ 206.1293, found 206.1284.

4.2.9. (3*R*,7a*S*)-Hexahydro-2-(2-benylaminophenyl)-3-(4-bromophenyl)-1*H*-Pyrrolo[1,2-*c*]imidazol-1-one 9

Colorless solid, mp: 173–175 °C; $[\alpha]_D^{25}$ = +39.5 (c 0.4, CH_2Cl_2); IR (KBr) ν 3421, 2924, 1682, 1417, 1293, 845, 747 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.25–7.28 (m, 2H), 7.17–7.21 (m, 1H), 7.13 (d, J = 7.2 Hz, 2H), 7.03 (d, J = 7.6 Hz, 1H), 6.90–6.94 (m, 1H), 6.49 (td, J = 8.2, 1.2 Hz, 1H), 6.34 (d, J = 7.6 Hz, 1H), 5.59 (s, 1H), 5.45 (t, J = 5.6 Hz, 1H), 4.22–4.33 (m, 2H), 4.16–4.19 (m, 1H), 2.98–3.12 (m, 2H), 1.97–2.14 (m, 2H), 1.66–1.92 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.4, 144.4, 140.6, 140.3, 131.4, 130.2, 128.8, 128.6, 128.2, 127.2, 126.9, 122.0, 121.9, 116.1, 112.2, 84.3, 64.9, 55.6, 46.4, 28.6, 25.1; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{25}H_{24}N_3OBrNa$ 484.1000, found 484.0989.

4.3. General procedure for the aldol reaction and characterization of the products

Method A: To a stirred solution of benzaldehyde (0.5 mmol) and ketone (5 mmol) in 2-Me-THF (0.5 mL) were added catalyst **3** (295 mg, 0.1 mmol) and 4-nitrobenzoic acid (167 mg, 0.1 mmol). The reaction was stirred at 0 °C. After the reaction was complete as monitored by TLC analysis, the mixture was purified via silica gel column chromatography to give the corresponding aldol product.

Method B: To a stirred solution of benzaldehyde (0.5 mmol) and cyclohexanone (0.52 mL, 5 mmol) were added catalyst **3** (295 mg, 0.1 mmol) and 4-nitrobenzoic acid (167 mg, 0.1 mmol), after which the aqueous solvent (0.5 mL) was added. The reaction was stirred at rt for 48 h. After the reaction was finished as monitored by TLC analysis, the mixture was purified via silica gel column chromatography to give the corresponding aldol product.

4.3.1. (2*S*,1′*R*)-2-(Hydroxy-(4-nitrophenyl)methyl)cyclohexan-1-one (Table 1)[16]

(119 mg, yield 96%); $[\alpha]_D^{25}$ = +20.4 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 4.90 (dd, J = 8.4, 2.8 Hz, 1H), 4.08 (d, J = 3.2 Hz, 1H), 2.36–2.63 (m, 3H), 1.36–2.14 (m, 6H); HPLC analysis: (Chiralpak AD-H column, hexane/2-propanol = 85:15, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 14.28 min (*syn*, minor), 16.31 min (*syn*, major), 17.75 min (*anti*, minor), 23.34 min (*anti*, major).

4.3.2. (2*S*,1′*R*)-2-(Hydroxy-(2-nitrophenyl)methyl)cyclohexan-1-one (Table 2, entry 1)[16]

(110 mg, yield 88%); $[\alpha]_D^{25}$ = +21.7 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 4.90 (d, *J* = 8.4 Hz, 1H), 4.10 (br s, 1H), 2.56–2.63 (m, 1H), 2.33–2.52 (m, 2H), 1.25–2.15 (m, 6H); HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 19.57 min (*syn*, minor), 23.39 min (*syn*, major), 25.75 min (*anti*, minor), 34.47 min (*anti*, major).

4.3.3. (2*S*,1′*R*)-2-(Hydroxy-(3-nitrophenyl)methyl)cyclohexan-1-one (Table 2, entry 2)[16]

(112 mg, yield 90%); $[\alpha]_D^{25}$ = +16.8 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 4.90 (d, *J* = 8.4 Hz, 1H), 4.14 (s, 1H), 2.59–2.66 (m, 1H), 2.38 (td, *J* = 12.8, 5.6 Hz, 1H), 2.10–2.16 (m, 1H), 1.37–1.86 (m, 6H); HPLC (Chiralpak AD-H column, hexane/2-propanol = 85:15, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 12.35 min (*syn*, minor), 12.95 min (*syn*, major), 14.35 min (*anti*, major), 17.77 min (*anti*, minor).

4.3.4. (2*S*,1′*R*)-2-(Hydroxy-(2,4-dinitrophenyl)methyl)cyclohexan-1-one (Table 2, entry 3)[16]

(145 mg, yield 99%); $[\alpha]_D^{25}$ = +16.8 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.0 Hz, 1H), 8.48 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 5.52 (d, *J* = 6.0 Hz, 1H), 4.32 (s, 1H), 2.75 (m, 1H), 2.30–2.48 (m, 2H), 1.58–2.15 (m, 6H); HPLC (Chiralpak AD-H column, hexane/2-propanol = 85:15, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 14.40 min (*syn*, major), 16.41 (*syn*, minor), 20.19 min (*anti*, minor), 22.55 min (*anti*, major).

4.3.5. (2*S*,1′*R*)-2-(Hydroxy-(2-nitro4-bromophenyl)methyl) cyclohexan-1-one (Table 2, entry 4)

(135 mg, yield 83%); $[\alpha]_D^{25}$ = +23.4 (*c* 0.4, $CHCl_3$); IR (KBr) ν 3428, 3098, 2952, 2932, 1690, 1530, 1334, 1040, 874, 842, 799, 714, 556 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, *J* = 1.6 Hz, 1H), 7.90 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 5.69 (d, *J* = 4.4 Hz, 1H), 5.27 (dd, *J* = 7.6, 4.8 Hz, 1H) 2.77–2.83 (m, 1H), 2.22–2.46 (m, 2H), 1.24–1.91 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 210.5, 149.8, 137.6, 136.1, 132.4, 126.3, 120.6, 67.1, 57.3, 56.7, 31.1, 28.3, 24.5, 19.3; HRMS (TOF-ES+) *m*/*z*: $[M+Na]^+$ calcd for $C_{13}H_{14}NO_4BrNa$ 350.0004, found 350.0003; HPLC (Chiralpak OD-H column, hexane/2-propanol = 75:25, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 10.75 min (*syn*, major), 14.12 min (*syn*, minor), 15.20 min (*anti*, minor), 20.12 min (*anti*, major).

4.3.6. (*S*)-4-Hydroxy-4-(4-nitrophenyl)butan-2-one (Table 2, entry 5)[16]

(74.3 mg, yield 66%); $[\alpha]_D^{25}$ = +28.2 (*c* 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (m, 2H), 7.55 (m, 2H), 5.27 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.61 (s, 1H), 2.85–2.87 (m, 2H), 2.23 (s, 3H); HPLC (Chiralpak AS-H column, hexane/2-propanol = 85:15, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 27.65 min (major), 39.69 min (minor).

4.3.7. (2*S*,1′*R*)-2-(Hydroxy-(4-nitrophenyl)methyl)cyclopentan-1-one (Table 2, entry 6)[16]

(116 mg, yield 99%); $[\alpha]_D^{25}$ = +26.8 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 8.20 (m, 2H), 7.63 (m, 2H), 5.72 (d, *J* = 4.4 Hz, 1H), 5.19 (t, *J* = 3.2 Hz, 1H), 1.86–2.47 (m, 4H), 1.66–1.71 (m, 3H); HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 26.73 min (*anti*, major), 37.41 min (*anti*, minor), 48.04 min (*syn*, minor), 49.99 min (*syn*, major).

4.3.8. (2*S*,4*S*)-2-((*R*)-Hydroxy(4-nitrophenyl)methyl)-4-methylcyclohexan-1-one (Table 2, entry 7)[16]

(104 mg, yield 79%); $[\alpha]_D^{25}$ = −29.7 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 5.73 (d, *J* = 4.8 Hz, 1H), 5.19 (dd, *J* = 9.2, 4.8 Hz, 1H), 2.19–2.69 (m, 3H), 1.29–1.97 (m, 5H), 0.88 (d, *J* = 6.8 Hz, 3H); HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 16.65 min (*syn*, minor), 19.14 min (*syn*, major), 30.51 min (*anti*, major), 33.47 min (*anti*, minor).

4.3.9. (2*S*,1′*R*)-2-(Hydroxy-(4-bromophenyl)methyl)cyclohexan-1-one (Table 3)[16]

(140 mg, yield 99%); $[\alpha]_D^{25}$ = +15.3 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 5.30 (d, *J* = 4.0 Hz, 1H), 4.94 (dd, *J* = 7.6, 4.4 Hz, 1H), 2.58–2.62 (m, 1H), 2.33–2.37 (m, 2H), 1.15–1.83 (m, 6H); HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, λ = 230 nm): t_R = 9.68 min (*syn*, minor), 11.63 min (*syn*, major), 15.31 min (*anti*, minor), 18.19 min (*anti*, major).

4.3.10. (2*S*,1′*R*)-2-(Hydroxy-(phenyl)-methyl)cyclohexan-1-one (Table 4, entry 1)[16]

(84.3 mg, yield 83%); $[\alpha]_D^{25}$ = +14.1 (*c* 0.4, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 7.31–7.33 (m, 4H), 7.25 (dd, *J* = 8.4, 4.4 Hz, 1H), 5.30 (d, *J* = 4.4 Hz, 1H), 4.94 (q, *J* = 4.0 Hz, 1H), 2.57–2.62 (m, 1H), 2.38–2.44 (m, 1H), 2.29–2.36 (m, 1H), 1.13–1.81 (m, 6H); HPLC (Chiralpak OD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, λ = 220 nm): t_R = 7.23 min (*syn*, major), 8.05 min (*syn*, minor), 8.63 min (*anti*, major), 10.33 min (*anti*, minor).

4.3.11. (2*S*,1′*R*)-2-(Hydroxy-(4-(trifluoromethyl)phenyl)methyl)-cyclohexan-1-one (Table 4, entry 2)[16]

(128 mg, yield 94%); $[\alpha]_D^{25}$ = +19.1 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 7.66 (m, 4H), 5.42 (m, 1H), 5.05 (m, 1H), 2.62 (m, 1H), 2.36 (t, *J* = 6.4 Hz, 2H), 1.57–1.84 (m, 6H); HPLC (Chiralpak AD-H column, hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, λ = 220 nm): t_R = 16.48 min (*syn*, major), 21.45 min (*syn*, minor), 30.84 min (*anti*, minor), 44.25 min (*anti*, major).

4.3.12. (2*S*,1′*R*)-2-(Hydroxy-(4-chlorophenyl)methyl)cyclohexan-1-one (Table 4, entry 3)[16]

(109 mg, yield 91%); $[\alpha]_D^{25}$ = +10.9 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 7.36 (m, 4H), 5.29 (d, *J* = 4.4 Hz, 1H), 4.95 (m, 1H), 2.51–2.53 (m, 2H), 2.33–2.37 (m, 1H), 1.63–1.81 (m, 6H); HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, λ = 230 nm): t_R = 9.18 min (*syn*, major), 10.90 min (*syn*, minor), 14.22 min (*anti*, minor), 16.48 min (*anti*, major).

4.3.13. (2*S*,1′*R*)-2-(Hydroxy-(4-fluorophenyl)methyl)cyclohexan-1-one (Table 4, entry 4)[16]

(99.4 mg, yield 89%); $[\alpha]_D^{25}$ = +13.3 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 7.36 (m, 2H), 7.14 (t, *J* = 8.8 Hz, 2H), 5.23 (d, *J* = 4.0 Hz, 1H), 4.95 (m, 1H), 2.41–2.52 (m, 1H), 2.32–2.39 (m, 2H), 1.25–1.82 (m, 6H); HPLC (Chiralpak AD-H column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, λ = 210 nm): t_R = 12.86 - min (*syn*, minor), 15.64 min (*syn*, major), 21.68 min (*anti*, minor), 24.64 min (*anti*, major).

4.3.14. (2*S*,1′*R*)-2-(Hydroxy-(4-methylphenyl)methyl)cyclohexan-1-one (Table 4, entry 5)[16]

(70.1 mg, yield 64%); $[\alpha]_D^{25}$ = +52.8 (*c* 0.4, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 7.21 (m, 2H), 7.13 (m, 2H), 5.10 (d, *J* = 4.4 Hz, 1H), 4.89 (dd, *J* = 8.4, 4.4 Hz, 1H), 2.53–2.59 (m, 1H),

2.37–2.44 (m, 1H), 2.37–2.42 (m, 1H), 2.27–2.34 (m, 3H), 1.66–1.79 (m, 4H), 1.17–1.53 (m, 2H); HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, λ = 210 nm): t_R = 3.29 min (*syn*, major), 4.35 min (*syn*, minor), 6.76 min (*anti*, major), 8.39 min (*anti*, minor).

4.3.15. (2*S*,1′*R*)-2-(Hydroxy-(4-bromophenyl)methyl)cyclopentan-1-one (Table 4, entry 10)[16]

(130 mg, yield 97%); $[\alpha]_D^{25}$ = +28.8 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6) δ 7.50 (m, 2H), 7.30 (m, 2H), 5.47 (d, *J* = 3.6 Hz, 1H), 5.04 (t, *J* = 2.4 Hz, 1H), 2.03–2.51 (m, 3H), 1.55–1.93 (m, 4H); HPLC (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, λ = 220 nm): t_R = 8.73 min (*anti*, major), 10.81 min (*anti*, minor), 13.38 min (*syn*, major), 14.35 min (*syn*, minor).

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References

1. For recent reviews, see: (a) Sukumaran, J.; Hanefeld, U. *Chem. Soc. Rev.* **2005**, *34*, 530–542; (b) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313–354; (c) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561–3651; (d) Mlynarski, J.; Paradowska, J. *Chem. Soc. Rev.* **2008**, *37*, 1502–1511; (e) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132–3148; (f) Bartók, M. *Chem. Rev.* **2010**, *110*, 1663–1705; (g) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600–1632; (h) Selander, N. J.; Szabó, K. *Chem. Rev.* **2011**, *111*, 2048–2076; (i) Brovetto, M.; Gamenara, D.; Saenz, M. P.; Seoane, G. A. *Chem. Rev.* **2011**, *111*, 4346–4403; (j) Mlynarski, J.; Baś, S. *Chem. Soc. Rev.* **2014**, *43*, 577–587.
2. (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713–5743; (b) Carreira, E. M.; Fettes, A.; Marti, C. *Org. React.* **2006**, *67*, 1–216; (c) Hosokawa, S. *Stereoselective Synthesis of Drugs and Natural Products*; John Wiley & Sons: New York, 2013; pp 215–247; (d) Reddy, L. V. R.; Kumar, V.; Sagar, R.; Shaw, A. K. *Chem. Rev.* **2013**, *113*, 3605–3631; (e) Kalesse, M.; Cordes, M.; Symkenberg, G.; Lu, H. *Nat. Prod. Rep.* **2014**, *31*, 563–594; (f) Roiban, G.; Ilie, A.; Reetz, M. T. *Chem. Lett.* **2014**, *43*, 2–10; (g) Miura, T.; Nakamuro, T.; Hiraga, K.; Murakami, M. *Chem. Commun.* **2014**, 10474–10477.
3. (a) Barrulas, P.; Benaglia, M.; Burke, A. J. *Tetrahedron: Asymmetry* **2014**, *25*, 923–935; (b) Pearson, A. J.; Panda, S.; Bunge, S. D. *J. Org. Chem.* **2013**, *78*, 9921–9928; (c) Marjanovic, J.; Divjakovic, V.; Matovic, R.; Ferjancic, Z.; Saicic, R. N. *Eur. J. Org. Chem.* **2013**, *2013*, 5555–5560; (d) Guillena, G. *Modern Methods in Stereoselective Aldol Reactions*; Wiley-VCH: Weinheim, 2013; pp 155–268; (e) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis*; VCH: Weinheim, 2005; (f) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570–579.
4. (a) Shen, C.; Shen, F.; Xia, H.; Zhang, P.; Chen, X. *Tetrahedron: Asymmetry* **2011**, *22*, 708–712; (b) Raj, M.; Veerasamy, N.; Singh, V. K. *Tetrahedron Lett.* **2010**, *51*, 2157–2159; (c) Guo, Q.; Zhao, J. C. *Tetrahedron Lett.* **2012**, *53*, 1768–1771; (d) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 55–569; (e) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569; (f) Pousse, G.; Cavelier, F. L.; Humphreys, L.; Rouden, J.; Blanchet, J. *Org. Lett.* **2010**, *12*, 3582–3585; (g) Scheffler, U.; Mahrwald, R. *Chem. Eur. J.* **2013**, *19*, 14346–14396; (h) Chen, X.; Yu, J.; Gong, L. *Chem. Commun.* **2010**, 6437–6448; (i) Guillena, G.; Nájera, C.; Ramón, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249–2293.
5. (a) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; (b) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703–4832.
6. Tang, Z.; Jiang, F.; Yu, L.; Cui, X.; Gong, L.; Mi, A.; Jiang, Y.; Wu, Y. *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263.
7. For selected examples of prolinamides as organocatalysts, see: (a) Tanimori, S.; Naka, T.; Kirihata, M. *Synth. Commun.* **2004**, *34*, 4043–4048; (b) Gryko, D.; Kowalczyk, B.; Zawadzki, Ł. *Synlett* **2006**, 1059–1062; (c) Xiong, Y.; Wang, F.; Dong, S.; Liu, X.; Feng, X. *Synlett* **2008**, 73–76; (d) Tzeng, Z.; Chen, H.; Huang, C.; Chen, K. *Tetrahedron Lett.* **2008**, *49*, 4134–4137; (e) Sato, K.; Kuriyama, M.; Shimazawa, R.; Morimoto, T.; Kakiuchi, K.; Shirai, R. *Tetrahedron Lett.* **2008**, *49*, 2402–2406; (f) Singh Chimni, S.; Singh, S.; Mahajan, D. *Tetrahedron: Asymmetry* **2008**, *19*, 2276–2284; (g) Mitsui, K.; Parquette, J. R. *Isr. J. Chem.* **2009**, *49*, 119–127; (h) Mitsui, K.; Hyatt, S. A.; Turner, D. A.; Hadad, C. M.; Parquette, J. R. *Chem. Commun.* **2009**, 3261–3263; (i) Tzeng, Z.; Chen, H.; Reddy, R. J.; Huang, C.; Chen, K. *Tetrahedron* **2009**, *65*, 2879–2888; (j) Lu, Z.; Mei, H.; Han, J.; Pan, Y. *Chem. Biol. Drug Des.* **2010**, *76*, 181–186; (k) Kinsella, M.; Duggan, P. G.; Lennon, C. M. *Tetrahedron: Asymmetry* **2011**, *22*, 1423–1433; (l) Zhang, F.; Li, C.; Qi, C. *Tetrahedron: Asymmetry* **2013**, *24*, 380–388; (m) Moorthy, J. N.; Saha, S. *Eur. J. Org.* **2009**, 739–748; (n) Saha, S.; Moorthy, J. N. *Tetrahedron Lett.* **2010**, *51*, 912–916.
8. (a) Gryko, D.; Lipinski, R. *Eur. J. Org. Chem.* **2006**, *37*, 3864–3876; (b) Gryko, D.; Zimnicka, M.; Lipiński, R. *J. Org. Chem.* **2007**, *72*, 964–970.
9. Fuentes, Á. L.; Simón, L.; Raposo, C.; Alcázar, V.; Morán, J. R. *Tetrahedron* **2009**, *65*, 4841–4845.
10. Fuentes, Á. L.; Simón, L.; Raposo, C.; Alcázar, V.; Sanz, F.; Muñiz, F. M.; Morán, J. R. *Org. Biomol. Chem.* **2010**, *8*, 2979–2985.
11. Andreu, C.; Varea, T.; Asensio, G. *Tetrahedron* **2011**, *67*, 8705–8709.
12. CCDC 1022539 (imidazolidinone **9**) contains the supplementary crystallographic data. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
13. (a) Wang, L.; Li, C.; Wang, N.; Li, K.; Chen, X.; Yu, X. *J. Mol. Catal. B: Enzym.* **2010**, *67*, 16–20; (b) Boldyrev, I. A.; Molotkovskii, I. *Russ. J. Bioorg. Chem.* **2004**, *30*, 586–591.
14. (a) Rai, R.; Pandey, P. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2923–2925; (b) Xue, D.; Long, Y. *J. Org. Chem.* **2014**, *79*, 4727–4734; (c) Chattopadhyay, P.; Rai, R.; Pandey, P. S. *Synth. Commun.* **2006**, *36*, 1857–1861.
15. (a) Kubota, T.; Sawada, N.; Zhou, L.; Welch, C. J. *Chirality* **2010**, *22*, 382–388; (b) Vishwanatha, T. M.; Narendra, N.; Chattopadhyay, B.; Mukherjee, M.; Sureshbabu, V. V. *J. Org. Chem.* **2012**, *77*, 2689–2702.
16. (a) Wang, C.; Jiang, Y.; Zhang, X.; Huang, Y.; Li, B.; Zhang, G. *Tetrahedron Lett.* **2007**, *48*, 4281–4285; (b) Yang, H.; Mahapatra, S.; Cheong, P. H.; Carter, R. G. *J. Org. Chem.* **2010**, *75*, 7279–7290; (c) Wu, C.; Fu, X.; Li, S. *Tetrahedron* **2011**, *67*, 4283–4290; (d) Huang, J.; Chen, G.; Fu, X.; Li, C.; Wu, C.; Miao, Q. *Catal. Sci. Technol.* **2012**, *2*, 547–553; (e) Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Lo Meo, P.; Noto, R. *Eur. J. Org. Chem* **2010**, *2010*, 5696–5704; (f) Tian, H.; Gao, J.; Xu, H.; Zheng, L.; Huang, W.; Liu, Q.; Zhang, S. *Tetrahedron: Asymmetry* **2011**, *22*, 1074–1080; (g) Delaney, J. P.; Henderson, L. C. *Adv. Synth. Catal.* **2012**, *354*, 197–204.