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N-Prolinylanthranilic acid derivatives as bifunctional organocatalysts for asymmetric aldol reactions

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ABSTRACT

Several *N*-prolinylanthranilic acid derivatives were prepared and tested as bifunctional organocatalysts in the direct asymmetric aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde. It was found that methyl substitution *ortho* to the carboxylic acid improves enantioselectivity, but substitution *ortho* to the anilide group does not. The catalyst derived from 2-amino-6-methylbenzoic acid was tested over a range of direct asymmetric aldol reactions and its overall performance is equal to or better than many of the known prolinamide catalysts in terms of yield, diastereoselectivity, and enantioselectivity.

1. Introduction

Organocatalysis is currently one of the most rapidly growing areas of organic synthesis research, and one entire recent issue of Chemical Reviews was devoted to this topic.[1] The use of organocatalysts promises to allow organic reactions to proceed with high selectivity (regio and stereo) without the intervention of organometallic catalysts, some of which pose problems for use on large scale, and their eventual disposal. Moreover, recent developments in organocatalysis have shown that some can be used effectively in aqueous solution,[2] said to be a desirable environmentally benign property, although this has been the subject of some debate because the water that is used for such reactions is contaminated and cannot be discarded without scrubbing.[2d] This paper focuses on the development of some new proline-derived organocatalysts for asymmetric aldol reactions. The aldol reaction is one of the most important C–C bond-forming reactions in organic synthesis (and indeed in biosynthesis of many important classes of compounds). The earliest example of the use of L-proline to promote asymmetric aldol reactions is the intramolecular version published by Eder and co-workers in 1971, and also by Hajos and Parrish in 1974 (both groups were awarded German patents in 1971).[3] More recently, List and co-workers introduced the use of L-proline as a catalyst for asymmetric intermolecular aldol reactions.[4] The mechanism of the proline-catalyzed reaction, which proceeds via the formation of a pyrrolidine enamine of the ketone nucleophile and its subsequent reaction with the aldehyde electrophile, is well understood. The great advantage to using proline is that it is inexpensive and readily available as either enantiomer, but its solubility properties limit its compatibility with many aldol substrates. While proline does catalyze aldol reactions in water, racemic products are usually obtained.[2j] In addition, proline has a pronounced tendency to form oxazolidinones by reaction with the aldol substrates, thus potentially impairing its catalytic efficiency under certain conditions.[5] Consequently, modifications of this system have been of considerable recent interest.[6]

Many modified proline systems are amide derivatives of the proline carboxylate group that incorporate auxiliary chiral moieties, some of which are either expensive or require multistep synthesis. Simple prolinamide catalysts (as opposed to proline itself) rely on weak hydrogen bonding from the amide NH to activate the aldehyde partner in the transition state.[7] *N*-Prolinyl-2-aminophenol derivatives have been studied for enantioselective aldol reactions, utilizing the additional hydrogen bonding offered by the phenol/amide combination, but these met with modest success.[8] Improved results were obtained by modification of the pyrrolidine ring of proline, introducing a 3-alkoxy substituent.[9] Our own approach is to employ the secondary amine of L-proline as the functional catalytic unit and an anthranilic acid moiety to provide a carboxylic acid group (structures **1**–**6**). The resulting prolinamide has two important hydrogen bonding units: the NH of the amide and the OH of the carboxylic acid unit. These functionalities were anticipated to act in concert to give an ordered enamine/aldehyde reaction transition state, as a result of the structural rigidity of the aromatic template, to activate the substrates and promote high diastereoselectivity and enantioselectivity for the aldol reaction.

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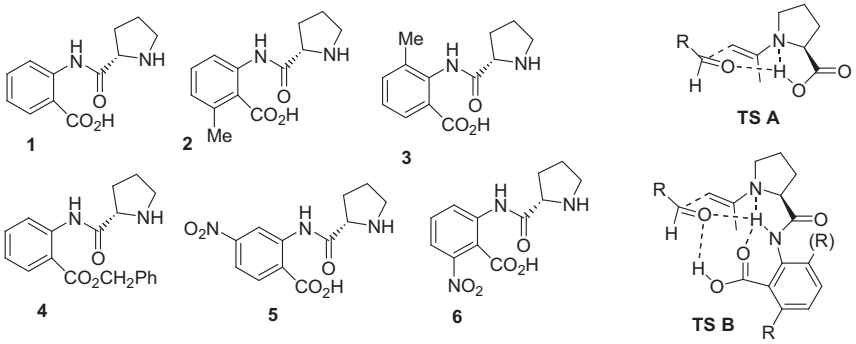
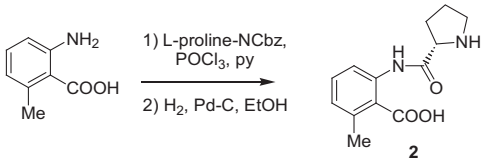
This idea is illustrated by the schematics for TS **A** and TS **B**, the former being the accepted transition state for proline-catalyzed aldol reactions, the latter being our proposed modification.



In addition, we designed a selection of molecules that would probe the effects of steric bias close to the functional centers of the catalyst (**2** and **3** compared with **1**), whether or not the carboxylic acid is a contributing structural component (ester **4** vs **1**), and whether catalyst activity is affected by acidity of the carboxyl group (**5** vs **1**, and **6** vs **2**). As far as we are aware, such anthranilamide derivatives have not been previously investigated as aldol catalysts, the closest reported analogs being oxazolines derived from the carboxylate group of catalyst **1**, which afforded rather modest enantioselectivities for the aldol reactions of cyclohexanone with a range of substituted benzaldehydes.[10]

2. Results and discussion

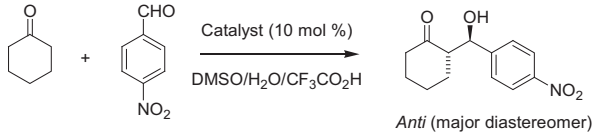
Synthesis of each catalyst requires only 2–3 steps (two steps for the best catalyst, **2**, see Eq. 1: amide coupling[11] between the anthranilic acid derivative and L-proline-*N*-Cbz using phosphorus oxychloride and pyridine at −10 °C afforded the Cbz-protected prolinylanthranilic acid derivative, which was shown to be optically pure by chiral HPLC analysis; hydrogenolytic removal of the Cbz protecting group completed the synthesis of the catalyst; others are detailed in the Experimental section).



(1)

First, the reaction conditions were screened for enantioselective aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde using DMSO as solvent (Table 1). In the presence *only* of catalyst **1**, no reaction occurred. Various additives, such as water, amines, and carboxylic acids, have previously been shown to improve the yield and ee from proline-catalyzed aldol reactions.[12] With added water, the reaction proceeded but with low conversion and poor enantioselectivity (entry 1). By using TFA as an acidic additive in the absence of water, the enantioselectivity increased somewhat but the yield was still low (entry 2). Combination of TFA and water promoted the reaction with high yield and good enantioselectivity (entry 3; TFA showed the best results compared to other acidic additives—see later). Catalyst **2** gave higher enantioselectivity compared with catalyst **1** under identical conditions, though the reaction was noticeably slower (entries 4, 5, 6 vs 1, 2, 3, respectively; reaction time for all entries was 72 h, so conversions, estimated from ^{1}H NMR of the crude product mixtures, qualitatively reflect relative rates). Lowering the temperature improved the yield and enantioselectivity (entry 7 vs 6). Varying the amount of TFA and water also affected the yield and enantioselectivity, optimum results being obtained with 12 mol % of TFA and 50 μL of water (ca. 1400 mol % relative to *p*-nitrobenzaldehyde) (entry 11). While incorporation of a methyl group *ortho* to the acid (catalyst **2**) improves the enantioselectivity, methyl substitution *ortho* to the anilide (catalyst **3**) lowers the enantioselectivity somewhat relative to the parent compound **1** (entry 13 vs 15). That the carboxylic acid indeed plays an important role in this reaction was confirmed by testing catalyst **4**, for which the reaction was very sluggish and gave poorer enantioselectivity (entry 14 vs 15). Thus, activation by hydrogen bonding expected for the amide/acid combination makes a significant contribution to both reaction rate and enantioselectivity. On the other hand, increased acidity of the pendant carboxyl group, as in catalysts **5** and **6**, does not improve the outcome, in terms of both conversion and enantioselectivity (entry 16 vs 15, and 17 vs 11); the superior performance of catalyst **6** compared with **5** again indicates the importance of substitution *ortho* to the carboxyl group, as for catalyst **2** versus **1**. Reducing the amount of catalyst gave the expected rate reduction and a small reduction in enantioselectivity (entries 18 and 19, catalyst concentration is mol % relative to *p*-nitrobenzaldehyde). Based on the results in Table 1, we chose catalyst **2** at 10 mol % loading for further study.

Table 1
Optimization of catalyst and conditions



Entry	Catalyst	TFA (mol %)	Water (μL)	Conversion (%)	ee[c] [*anti*] (%)
1[a]	**1**	0	20	20	68
2[a]	**1**	5	0	15	72
3[a]	**1**	5	20	82	75
4[a]	**2**	0	20	15	78
5[a]	**2**	5	0	10	89
6[a]	**2**	5	20	52	90
7[b]	**2**	5	20	70	92
8[b]	**2**	10	20	80	94
9[b]	**2**	12	20	85	97
10[b]	**2**	20	20	30	95
11[b]	**2**	12	50	100	98
12[b]	**2**	12	100	42	94
13[b]	**3**	12	50	75	82
14[b]	**4**	12	50	10	78
15[b]	**1**	12	50	80	85
16[b]	**5**	12	50	85	80
17[b]	**6**	12	50	90	95
18[b]	**2** (5%)	12	50	55	93
19[b]	**2** (2%)	12	50	20	95

[a] Unless specified otherwise, the concentration of aldehyde is 0.13 M, and v/v of cyclohexanone/DMSO is (1:4), the reactions were run at room temperature.

[b] Unless specified otherwise, the concentration of aldehyde is 0.40 M, and v/v of cyclohexanone/DMSO is (1:4), the reactions were run at 4 °C. Volume of DMSO=0.4 mL. Reaction time=72 h.

[c] Enantiomeric excess was determined using CHIRALPAK AD-H column; the dr varied between 5:1 (*anti*/*syn*) to 10:1 (*anti*/*syn*), determined by ^{1}H NMR.

DMSO as the solvent for these reactions has some limitations with regard to optimization of selectivity because it cannot be used (except as a co-solvent) at low temperatures, e.g., −78 °C, at which one might expect improvements in both diastereoselectivity and enantioselectivity. While DMSO and DMF are commonly used for aldol reactions catalyzed by proline and its derivatives, these solvents are generally considered to be problematic for large scale reactions because of inconvenient work-up and solvent removal/recovery, and there has been some effort to develop catalysts that can be used in THF or dichloromethane[13] (in which proline has very low solubility). Mindful of these issues, we examined the reaction of cyclohexanone with *p*-nitrobenzaldehyde, using catalyst **2** in the presence of TFA and water (per Table 1, entry 11) at 4 °C, in a selection of solvents typically used for this reaction with other catalysts. The results (Table 2) indicate that DMSO is the best solvent for this particular catalyst.

Table 2
Aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde in different solvents

Entry	Solvent[a]	Conversion[b] (%)	*anti*/*syn* ratio[b]	ee[c] [*anti*] (%)
1	DMSO	100	15:1	98
2	DMF	90	12:1	93
3	CH_2Cl_2	20	10:1	45
4	THF	80	20:1	73
5	Neat[d]	90	5:1	70
6	MeOH	30	4:1	20
7	H_2O	20	8:1	48
8	Brine	60	12:1	55
9	H_2O/ketone[e]	40	10:1	78

[a] All reactions were run under the general conditions noted for Table 1, entry 11, but replacing DMSO with the solvent noted.
[b] Conversions and diastereomeric ratios at 72 h reaction time were estimated from the ^{1}H NMR spectrum of the crude product mixture.
[c] Determined by HPLC on CHIRALPAK AD-H column.
[d] Cyclohexanone was used as the solvent.
[e] A mixture of water and cyclohexanone (1:1 v/v) was used as the solvent.

As seen from Table 2, DMF is also a reasonable solvent for this reaction (entry 2), but dichloromethane leads to slow reaction (poor conversion after 72 h) and only modest enantioselectivity, although the diastereomeric ratio is quite acceptable (entry 3). Tetrahydrofuran as solvent (entry 4) works well in terms of conversion and diastereoselectivity, but again the ee is low compared to DMSO. We were unable to improve selectivity using DCM and THF at low temperature because catalyst **2** precipitated from solution upon cooling. Omission of solvent (entry 5) allows faster conversion, but poorer diastereoselectivity and ee, while methanol as solvent is not useful (entry 6).

The results of reaction in water are actually fairly encouraging (entry 7), given the poor performance of proline itself under aqueous conditions,[2j] and suggest that future catalyst engineering might afford systems that perform well under these conditions (we independently tested L-proline under aqueous conditions identical to those used for entry 7 and observed no conversion to aldol products after several days reaction time). A significant improvement was noted when brine was used as solvent instead of water (entry 8). With high concentration of cyclohexanone in water (entry 9), reasonable conversion rate was observed and good ee and diastereoselectivity were obtained. Given the superior performance of DMSO for this reaction using catalyst **2**, we elected to use this solvent for the next set of investigations, which probed the use of acid additives other than TFA.

In order to determine whether trifluoroacetic acid is the optimum acidic additive for this reaction using catalyst **2**, we tested several alternatives that have also been shown to be effective in prolinamide-catalyzed aldol reactions[12c,14] (Table 3). The results are essentially self explanatory, confirming that TFA is much better than other carboxylic acids, there being a qualitative correlation of enantioselectivity with acidity of the carboxylic acid used. Arylsulfonic acids give poor conversion, but again show that the stronger acid gives better ee. The use of the much stronger acid HCl essentially shuts down the reaction, likely due to complete conversion of the proline residue to its ammonium salt, thereby preventing formation of the requisite enamine. We suggest that these results might reflect a pH-dependent equilibrium between various forms of the amine/acid structure that leads to an optimum concentration of the most active form of the catalyst for best yield and selectivity.

Table 3
Aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde in DMSO using various acid additives

Entry	Additive[a]	Conversion[b] (%)	*anti*/*syn* ratio[b]	ee[c] [*anti*] %
1	TFA	100	15:1	98
2	CCl_3CO_2H	80	12:1	94
3	2,4-DNB[d]	85	5:1	88
4	HCO_2H	70	8:1	80
5	$PhCO_2H$	70	8:1	78
6	CH_3CO_2H	100	10:1	82
7	Salicylic	50	8:1	58
8	2,4-DNBS[e]	10	8:1	75
9	*p*-TsOH	15	10:1	52
10	HCl	<5	nd	nd

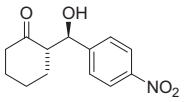
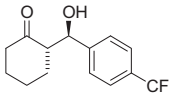
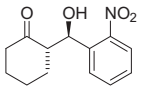
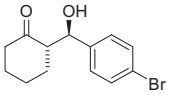
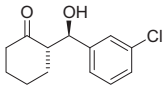
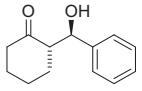
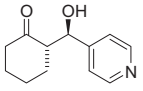
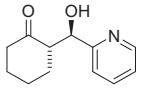
[a] All reactions were run under the general conditions noted for Table 1 entry 11, using 12 mol % of the acid additive over *p*-nitrobenzaldehyde.
[b] Conversion and diastereomeric ratios were estimated from the ^{1}H NMR spectrum of the crude product mixture.
[c] Determined by HPLC on CHIRALPAK AD-H column.
[d] 2,4-Dinitrobenzoic acid.
[e] 2,4-Dinitrobenzenesulfonic acid.

The scope and limitations of direct aldol reaction of cyclohexanone with various aromatic aldehydes, catalyzed by **2**, were next explored (Table 4). Benzaldehydes substituted by *p*-nitro, *p*-trifluoromethyl and *o*-nitro afforded the *anti* products with high diastereo- and enantioselectivity (entries 1–3). The aldol reaction of *o*-nitrobenzaldehyde and cyclohexanone afforded 85:1 dr, 99% ee, and excellent yield (entry 3), which illustrates the benefits of using a sterically hindered aldehyde, and compares very favorably with the best catalysts reported in the literature.[12d,15] Less reactive benzaldehydes were also studied. Using *p*-bromo- or *m*-chlorobenzaldehyde the *anti* products were obtained in modest/good yield and 95% ee (entries 4 and 5), while benzaldehyde itself reacted with good dr, good ee but modest yield (entry 6). Pyridine aldehydes (entries 7 and 8) are also good substrates[16] affording high ee's. There is a marked difference in the diastereoselectivities for 4-pyridinal versus 2-pyridinal, presumably reflecting less steric demand in the latter as a result of the missing *ortho* hydrogen compared to the 4-isomer.

We also studied the aldol reaction with various ketones using selected reactive aromatic aldehydes (Table 5). The aldol reaction between dihydro-2*H*-thiopyran-4(3*H*)-one (a valuable surrogate for 3-pentanone which, after desulfurization leads to propionyl aldol products with good selectivity[12b]) and substituted benzaldehydes gave the *anti* products with somewhat variable diastereoselectivities, but uniformally high ee's for the *anti* products. Best results were obtained using *p*-trifluoromethylbenzaldehyde, which afforded 98% ee and 30:1 dr ratio (entry 2). In the case of *o*-nitrobenzaldehyde the yield and enantiomeric excess was very good but the dr was unexpectedly modest (entry 3). At the present time this difference in behavior of cyclohexanone versus its sulfur analog is not understood.

With cyclopentanone as the aldol donor the reaction worked well with all three benzaldehydes, for example, reaction with

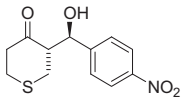
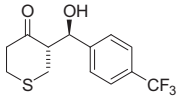
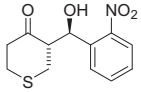
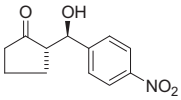
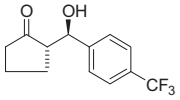
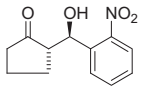
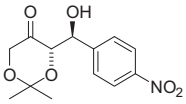
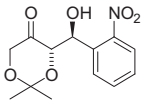
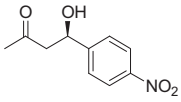
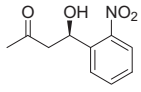
Table 4
Direct aldol reactions of cyclohexanone with various aromatic aldehydes in the presence of catalyst **2**

Entry	Product	Yield[a] (%)	*anti*/*syn* ratio[b]	ee[c] [*anti*] (%)
1		92	15:1	98
2		88	10:1	99
3		84	85:1	99
4		68	9:1	95
5[d]		58	6:1	95
6		56	13:1	92
7		96	28:1	95
8[d]		70	3:1	92

[a] Isolated yield after separation from unreacted starting materials and catalyst. All reactions were run under the general conditions noted for Table 1, entry 11.
[b] Diastereomeric ratios were estimated from the ^{1}H NMR spectrum of the *crude* product mixture.
[c] Determined by HPLC on CHIRALPAK AD-H column for isolated products after separation from unreacted starting materials and catalyst.
[d] Reaction time was 96 h.

p-nitrobenzaldehyde gave the *anti* product with 99% ee and good combined yield of the two diastereomers (Table 5, entry 4). However, we observed a decrease in diastereomeric ratio going from cyclohexanone to cyclopentanone, which is not uncommon for prolinamide catalysts.[12d,17] Interestingly, high ee's were obtained for the *syn* products from some of these reactions: entry 5 gave 95% ee, entry 6 gave 86% ee; also, entry 3 gave 94% ee. Very few publications that describe these reactions of cyclopentanone include ee's for the minor *syn* products, but our results appear to be superior to the ones that are reported.[18] With the acetonide of 1,3-dihydroxyacetone as the nucleophile, an important building block for the synthesis of carbohydrate structures,[19] the *anti* product was obtained with excellent ee and diastereoselectivity, but the reaction was slower and the yield was poorer compared with other cyclic ketones. The resulting *anti*-1,2-diol unit has a configuration complementary to the *syn*-1,2-diol that is obtained by Sharpless asymmetric dihydroxylation of α,β-unsaturated ketones.[20] When acetone was employed as the aldol donor (entries 9 and 10), the ee's were higher than the same reactions catalyzed by proline itself (which generally gives around 70–75% ee for the reaction with *p*-nitrobenzaldehyde[4]), but there is clearly still room for improvement with this particular reaction.

Table 5
Direct aldol reactions between selected ketones and aromatic aldehydes in the presence of catalyst **2**

Entry	Product	Yield[a] (%)	*anti*/*syn* ratio[b]	ee[c] [*anti*] (%)
1		88	5:1	94
2		78	30:1	98
3		92	2:1	97
4		85	1.2:1	99
5		79	1.6:1	95
6		88	2:1	98
7[d]		65	10:1	96
8[d]		52	12:1	92
9		65	NA	80
10		52	NA	81

[a] Isolated yield after separation from unreacted starting materials and catalyst. All reactions were run under the general conditions noted for Table 1, entry 11.
[b] Diastereomeric ratios were estimated from the ^{1}H NMR spectrum of the *crude* product mixture.
[c] Determined by HPLC on CHIRALPAK AD-H column for isolated products after separation from unreacted starting materials and catalyst.
[d] Reaction time was 96 h.

3. Conclusions and outlook

In summary, we have developed a new very easily prepared prolinamide derivative that is an excellent bifunctional organocatalyst for direct asymmetric aldol reactions. High enantioselectivities were observed for the majority of aldol reactions studied, comparing very favorably with the best catalysts reported in the literature, many of which employ secondary chiral groups attached to a proline unit, such as binaphthalene moieties that are expensive or require multistep synthesis for their preparation. A catalyst with outstanding performance over *all* aldol reactions is yet to be discovered. For example, one recently reported[13] proline-sulfonamide

derivative that typifies this problem gives very impressive selectivities over a range of direct aldol reactions of cyclohexanone, but does not perform as well for several other ketone donors (catalyst **2** affords higher ee with comparable diastereoselectivity for the reactions shown in Table 5, entries 4 and 7).

The present work offers proof-of-principle and indicates that the proline/anthranilamide structural motif has significant potential. The anthranilic acid core represents a very convenient template for structural modification, with a view to further improving both the enantioselectivity and diastereoselectivity of reactions that have proved troublesome using other catalysts, such as those of cyclopentanone. The carboxyl group provides an obvious site for facile attachment of structural units that can provide alternate hydrogen bonding arrays that may or may not incorporate additional chirality. Such modifications might benefit from the known[21] intramolecular hydrogen bonding in anthranilamide derivatives, resulting in conformations that mimic a reverse turn, and might provide structurally simple but effective binding pockets suitable for aldol substrates. The beneficial effect of strategic methyl substitution (catalyst **2** vs **1** or **3**) is also interesting from the standpoint of structural modification to afford catalysts that have greater lipid solubility, as one can envision the incorporation of longer and/or branched alkyl chains that might serve to further enhance selectivity while providing catalysts that can be used in common organic solvents. These propositions will form the basis of future investigations in our laboratory, with special emphasis on ease of preparation of catalysts from readily available inexpensive starting materials.

4. Experimental section

4.1. General procedures

All reactions were performed with anhydrous solvents in oven dried and argon charged glassware unless otherwise stated. Chemicals and solvents were purchased from Aldrich and Fisher Scientific. Analytical thin layer chromatography was carried out using glass bedded Whatman silica gel 60 F_{254}; 0.25 mm thickness. Flash chromatography was carried out on silica gel 60 (200–400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 6.1C (400 MHz) or Varian INOVA (600 MHz) spectrometer and are internally referenced to residual solvent signals. High resolution mass spectra were recorded by the University of Michigan Mass spectrometry facility on a VG 70-250-S mass spectrometer manufactured by Micromass Corp. Specific rotations were measured on a Perkin Elmer polarimeter model 241. High pressure liquid chromatography (HPLC) was performed on a Beckman HPLC with 32 Karat software using Daicel Chiralpak AD-H column (4.6 mm, 25 cm) and a guard column (4 mm, 1 cm). Absolute stereochemistry of the aldol products was confirmed by direct comparison of HPLC with materials produced using L-proline as the catalyst for the same reaction.

4.2. Preparation of catalyst 1

4.2.1. (S)-Benzyl 2-(2-(benzyloxycarbonyl)phenylcarbamoyl)pyrrolidine-1-carboxylate. To a stirred solution of *N*-benzyloxycarbonyl-L-proline (548.5 mg, 2.2 mmol) and benzyl anthranilate[22] (500 mg, 2.2 mmol) in pyridine (12 mL) was added phosphorus oxychloride (0.2 mL, 2.2 mmol) dropwise maintaining the temperature at −10 °C under an argon atmosphere. The reaction mixture was stirred for 6–8 h at −10 to −5 °C. The mixture was then added to ice cooled 1 M aq HCl and extracted with ethyl acetate (3×15 mL). The combined extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate=2:1) afforded the pure compound as a pale yellow gum (790 mg, 79%). $[\alpha]_D^{25}$ −59.2 (*c* 0.13, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 8.60 and 8.52 (1H, d, *J*=8.0 Hz, rotamers), 8.05–7.93 (1H, td, *J*=8.0, 1.2 Hz), 7.52–7.43 (1H, td, *J*=8.0 Hz, 1.2 Hz), 7.43–7.00 (10H), 7.00–6.85 (1H, dd, *J*=8.0 Hz, 1.2 Hz), 5.24–4.81 (4H), 4.41–4.31 (1H), 3.77–3.44 (2H), 2.33–2.14 (1H, m), 2.02 (1H, m), 1.93–1.76 (2H); ^{13}C NMR (150 MHz, CD_3OD, rotamers) δ (ppm) 172.4, 172.1, 167.9, 167.7, 155.9, 155.1, 140.7, 140.6, 136.8, 136.4, 135.9, 134.5, 134.4, 130.9, 128.6, 128.4, 128.3, 128.1, 127.9, 127.7, 127.6, 123.2, 120.1, 115.8, 115.7, 67.3, 67.1, 66.9, 62.7, 62.4, 47.6, 47.5, 47.3, 46.9, 31.3, 30.3, 24.1, 23.5; HRMS (ESI^+) calcd for $C_{27}H_{26}N_2O_5Na$ $[M+Na]^+$ 481.1739, found 481.1730.

*4.2.2. (S)-2-(Pyrrolidine-2-carboxamido)benzoic acid (**1**).* To a solution of the above protected derivative of **1** (500 mg, 1.1 mmol) dissolved in ethanol (10 mL) was added palladium 10% on carbon wetted with 50% water (200 mg) and the mixture was stirred under hydrogen for 10 h. The reaction was monitored by TLC. The reaction mixture was filtered through Celite, washed with methanol (3×5 mL) then with methanol/water (1:1) (3×5 mL). The combined filtrate was concentrated in vacuo to afford the product (203 mg) as white powder. Yield 79% as white solid, mp 225–227 °C. $[\alpha]_D^{25}$ −93.2 (*c* 0.1, 5% TFA in CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 8.41 (1H, d, *J*=8.4 Hz), 8.04 (1H, d, *J*=7.6 Hz), 7.40 (1H, td, *J*=8.4, 2.0 Hz), 7.09 (1H, td, *J*=8.4, 1.2 Hz), 4.54 (1H, t, *J*=7.3 Hz), 3.4 (2H), 2.53 (1H, m), 2.32–1.92 (3H); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 172.9, 165.9, 139.5, 131.1, 123.0, 119.3, 61.5, 45.9, 29.3, 23.9; HRMS (ESI^+) calcd for $C_{12}H_{14}N_2O_3Na$ $[M+Na]^+$ 257.0901, found 257.0910.

4.3. Preparation of catalyst 2

4.3.1. (S)-2-(1-(Benzyloxycarbonyl)pyrrolidine-2-carboxamido)-6-methylbenzoic acid. To a stirred solution of *N*-benzyloxycarbonyl-L-proline (500 mg, 2.0 mmol) in pyridine (12 mL) was added phosphorus oxychloride (0.2 mL, 2.0 mmol) dropwise, maintaining the temperature at −10 °C under an argon atmosphere. The reaction mixture was stirred for 1 h at −10 °C, and 2-amino-6-methylbenzoic acid (302 mg, 2.0 mmol) in pyridine (2 mL) was added. The reaction mixture was stirred for 8 h at −10 °C (−5 °C), then added to ice-cooled 1 M aq HCl solution and extracted with ethyl acetate (3×15 mL). The combined extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate=1:1) afforded the pure compound as a gum (627 mg, 82%). $[\alpha]_D^{25}$ −88.1 (*c* 0.12, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 7.95, 7.78 (1H, 2 d, *J*=8.0 Hz, rotamers), 7.40–7.16 (5H), 7.12 (1H, t, *J*=8.0 Hz), 7.00 (1H, d, *J*=8.0 Hz), 5.18–4.90 (2H), 4.40–4.25 (1H, m), 3.70–3.40 (2H), 2.45 (3H, s), 2.30–1.80 (4H); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm, *N*-Cbz rotamers) 175.0, 174.0, 172.4, 172.1, 170.3, 155.9, 155.3, 138.9, 138.8, 137.1, 136.9, 136.8, 136.5, 130.9, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.66, 127.63, 127.4, 123.2, 120.1, 67.4, 67.3, 67.02, 67.0, 62.2, 61.8, 59.4, 59.0, 46.8, 46.5, 31.2, 30.7, 30.2, 29.8, 24.1, 24.0, 23.4, 23.2, 21.2, 21.1, 19.7; HRMS (ESI^+) calcd for $C_{21}H_{23}N_2O_5$ $[M+H]^+$ 383.1607, found 383.1596.

*4.3.2. (S)-2-Methyl-6-(pyrrolidine-2-carboxamido)benzoic acid (**2**).* To a solution of the above amide (450 mg, 1.17 mmol) in ethanol (8 mL) was added palladium 10% on carbon wetted with 50% water (90 mg) and the mixture was stirred under 1 atm hydrogen for 10 h. The reaction mixture was filtered through Celite, and the pad was washed with methanol (3×5 mL) then with methanol/water (1:1) (3×5 mL). The combined filtrate was evaporated to dryness in vacuo to afford the product as a white powder (224 mg, 77%), mp 195–197 °C. $[\alpha]_D^{25}$ −71.1 (*c* 0.1, 5% TFA in CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) 7.53 (1H, d, *J*=8 Hz), 7.3 (1H, t, *J*=8 Hz), 7.15 (1H, d, *J*=7.6 Hz), 4.46 (1H, dd, *J*=8.0, 7.2 Hz), 3.45–3.25 (2H), 2.50 (1H, m), 2.43 (3H, s), 2.15–2.00 (3H); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 170.5, 167.2, 137.5, 134.5, 129.9, 128.3, 122.2, 60.5,

46.2, 29.5, 23.8, 19.8; HRMS (ESI^+) calcd for $C_{13}H_{17}N_2O_3$ $[M+H]^+$ 249.1239, found 249.1238.

4.4. Preparation of catalyst 3

This compound was prepared by the two-step procedure described for the preparation of catalyst **2**, but using 2-amino-3-methylbenzoic acid as the starting material:

4.4.1. (S)-2-(1-((Benzyloxy)carbonyl)pyrrolidine-2-carboxamido)-3-methylbenzoic acid. Yield 82%. $[\alpha]_D^{25}$ −70.6 (*c* 0.13, CH_2Cl_2); ^1H NMR (400 MHz, CD_3OD) δ (ppm) 7.75 (1H, dd, *J*=7.6, 1.2 Hz), 7.40–7.10 (7H), 5.25 (2H), 4.46 (1H, dd, *J*=7.2, 5.6 Hz), 3.69–3.61 (1H, m), 3.55–3.40 (1H, m), 2.22 (3H, m), 2.10 (3H, s), 1.85 (1H, m); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 173.2, 169.7, 169.6, 156.8, 156.5, 137.8, 137.7, 137.6, 137.3, 136.4, 135.6, 129.5, 129.4, 129.34, 129.30, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 128.2, 127.9, 127.2, 68.3, 68.2, 68.0, 67.9, 62.4, 62.0, 47.9, 47.5, 31.9, 31.7, 30.8, 25.2, 25.0, 24.3, 24.2, 18.8, 18.7; HRMS (ESI^+) calcd for $C_{21}H_{23}N_2O_5$ $[M+H]^+$ 383.1607, found 383.1599.

*4.4.2. (S)-3-Methyl-2-(pyrrolidine-2-carboxamido) benzoic acid (**3**).* Yield 80%; mp 182–185 °C. $[\alpha]_D^{25}$ −62.6 (*c* 0.12, 5% TFA in CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ (ppm) 7.81 (1H, dd, *J*=8.0, 1.6 Hz), 7.48 (1H, dd, *J*=8.0, 1.6 Hz), 7.30 (1H, t, *J*=8.0 Hz), 4.51 (1H, dd, *J*=6.8, 1.6 Hz), 3.46–3.31 (2H), 2.55 (1H, m), 2.38 (1H, m), 2.28 (3H, s), 2.08 (2H); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 169.1, 168.3, 137.6, 135.5, 135.3, 129.7, 129.1, 128.0, 61.3, 47.1, 30.3, 24.7, 18.0; HRMS (ESI^+) calcd for $C_{13}H_{17}N_2O_3$ $[M+H]^+$ 249.1239, found 249.1235.

4.5. Preparation of catalyst 4

4.5.1. (S)-tert-Butyl 2-((2-((benzyloxy)carbonyl)phenyl)carbamoyl) pyrrolidine-1-carboxylate. (*S*)-*tert*-Butyl 2-((2-((benzyloxy)carbonyl)-phenyl)carbamoyl)pyrrolidine-1-carboxylate was prepared as described above for (*S*)-benzyl 2-(2-(benzyloxycarbonyl)phenylcarbamoyl)pyrrolidine-1-carboxylate, but using L-proline-Boc instead of L-proline-Cbz. Yield 76%. $[\alpha]_D^{25}$ −65.5 (*c* 0.11, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.61, 11.55 (1H, s, rotamers), 8.78 (1H, t, *J*=9.2 Hz), 8.08 (1H, t, *J*=9.2 Hz), 7.45–7.33 (5H), 5.35 (2H, s), 4.45, 4.30 (1H, dd, *J*=8.0, 3.6 Hz), 3.80–3.40 (2H), 2.35–1.85 (4H), 1.50, 1.30 (9H, 2 s, amide rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.6, 172.1, 167.8, 155.2, 154.3, 144.4, 141.4, 135.7, 134.9, 131.2, 130.9, 128.8, 128.6, 128.5, 128.4, 122.9, 122.7, 120.2, 115.4, 80.3, 77.9, 77.5, 77.2, 67.2, 66.9, 62.9, 62.3, 47.3, 46.9, 31.7, 30.7, 28.7, 28.4, 24.5, 23.9; HRMS (ESI^+) calcd for $C_{24}H_{29}N_2O_5$ $[M+H]^+$ 425.2076, found 425.2074.

*4.5.2. (S)-Benzyl 2-(pyrrolidine-2-carboxamido)benzoate (**4**).* To a stirred solution of the above *N*-Boc derivative (250 mg, 0.59 mmol) in 2 mL dichloromethane at room temperature was added 0.14 mL trifluoroacetic acid (1.8 mmol). The resulting mixture was stirred at room temperature for 18 h. The excess solvent was rotary evaporated and the residue was added to aq sodium bicarbonate solution, extracted with dichloromethane, and the combined extract was dried over sodium sulfate and evaporated to give compound **4** (152 mg, 79%). $[\alpha]_D^{25}$ −48.9 (*c* 0.12, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 12.19 (1H, s), 8.78 (1H, dd, *J*=8.0, 1.2 Hz), 8.07 (1H, dd, *J*=8.0, 1.6 Hz), 7.53 (1H, td, *J*=8.0, 1.6 Hz), 7.47–7.32 (5H), 7.07 (1H, td, *J*=8.0, 1.2 Hz), 5.38 (2H, ABq, J_{AB}=12.4 Hz, $\Delta\nu$=13.6 Hz), 3.90 (1H, dd, *J*=9.2, 4.8 Hz), 3.25 (2H, m), 2.20 (1H, m), 2.05 (1H, m), 1.75 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.7, 167.5, 141.0, 135.8, 134.7, 131.3, 128.9, 128.6, 128.4, 122.9, 120.8, 116.2, 67.1, 62.0, 47.5, 31.4, 26.3; HRMS (ESI^+) calcd for $C_{19}H_{21}N_2O_3$ $[M+H]^+$ 325.1552, found 325.1554.

4.6. Preparation of catalyst 5

4.6.1. 2-(1-(tert-Butoxycarbonyl)pyrrolidine-2-carboxamido)-4-nitrobenzoic acid. Prepared as described above for the precursor to catalyst **2**, coupling L-proline-Boc (instead of the Cbz derivative) with 4-nitroanthranilic acid. Yield 78%. $[\alpha]_D^{25}$ −65 (*c* 0.13, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.38–8.12 (3H), 4.65 (1H, m), 3.72–3.42 (2H), 2.35 (1H, m), 2.22–1.82 (3H), 1.55, 1.18 (9H, 2s, amide rotamers); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm, rotamers) 165.5, 165.0, 158.6, 158.4, 154.7, 153.7, 153.6, 152.7, 147.8, 147.6, 130.7, 130.4, 122.6, 122.5, 122.3, 122.2, 121.7, 80.6, 80.5, 59.8, 59.7, 47.1, 46.8, 32.0, 31.1, 28.6, 28.5, 24.5, 23.8; HRMS (ESI^+) calcd for $C_{17}H_{21}N_3O_7$ $[M+H]^+$ 380.1452, found 380.1448.

*4.6.2. 4-Nitro-2-(pyrrolidine-2-carboxamido)benzoic acid (**5**).* Removal of the Boc protecting group was accomplished as described for catalyst **4**. Yield 62%. $[\alpha]_D^{25}$ −79 (*c* 0.1, 5% TFA in CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ (ppm) 9.33 (1H, d, *J*=2.0 Hz), 8.30 (1H, d, *J*=8.8 Hz), 8.03–8.00 (1H, dd, *J*=8.8, 2.0 Hz), 4.63 (1H, m), 3.58–3.39 (2H), 2.58 (1H, m), 2.35–2.02 (2H); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 169.5, 168.3, 160.0, 159.7, 159.4, 151.9, 141.7, 133.7, 123.1, 118.8, 117.3, 116.4, 115.4, 62.3, 47.1, 30.1, 24.8; HRMS (ESI^+) calcd for $C_{12}H_{13}N_3O_5$ $[M+H]^+$ 280.0928, found 280.0927.

4.7. Preparation of catalyst 6

4.7.1. 2-(1-(tert-Butoxycarbonyl)pyrrolidine-2-carboxamido)-6-nitrobenzoic acid. 2-(1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carboxamido)-6-nitrobenzoic acid was prepared as described above for the precursor to catalyst **2**, coupling L-proline-Boc with 2-amino-6-nitrobenzoic acid.[23] Yield 72%. $[\alpha]_D^{25}$ −72 (*c* 0.15, CH_2Cl_2); ^1H NMR (400 MHz, CD_3OD) δ (ppm) 8.48, 8.42 (1H, d, *J*=5.2 Hz), 7.69–7.55 (2H), 4.41–4.21 (1H, m), 3.63–3.48 (2H), 2.42–1.81 (4H), 1.58, 1.12 (9H, 2s, amide rotamers); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 174.1, 167.3, 155.7, 151.2, 138.8, 132.9, 127.1, 120.3, 120.2, 118.7, 81.8, 63.1, 62.7, 47.7, 32.1, 31.1, 28.5, 25.2, 24.5. The product was used in the next step without further characterization.

*4.7.2. 2-Nitro-6-(pyrrolidine-2-carboxamido)benzoic acid (**6**).* Removal of the Boc protecting group was accomplished as described for catalyst **4**. Yield 66%. $[\alpha]_D^{25}$ −95 (*c* 0.1, 5% TFA in CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ (ppm) 7.75–7.72 (1H), 7.64–7.60 (1H), 7.44–7.39 (1H), 4.23 (1H), 3.24–3.02 (2H, m), 2.38–1.78 (4H, m); ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 168.9, 166.9, 149.7, 136.6, 132.0, 131.5, 124.6, 122.4, 61.4, 47.2, 30.5, 24.7; HRMS (ESI^+) calcd for $C_{12}H_{13}N_3O_5$ $[M+H]^+$ 280.0928, found 280.0925.

4.8. General optimized procedure for the aldol reaction

To anhydrous DMSO (0.2 mL; anhydrous solvent was used to ensure reproducible water content throughout) was added the corresponding catalyst (0.02 mmol), trifluoroacetic acid (0.024 mmol), and water (50 μL, 14 equiv relative to the aldehyde). The reaction mixture was stirred for 5 min followed by addition of the corresponding ketone (1 mmol). The reaction mixture was stirred for 10 min at 4 °C followed by addition of a solution of the requisite aldehyde (0.2 mmol) in 0.2 mL DMSO. The resulting mixture was stirred at 4 °C for 72 h then treated with saturated ammonium chloride solution, and the mixture was extracted with ethyl acetate (3×2 mL). The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. After NMR analysis to determine conversion and diastereomeric ratio where needed, the residue was purified by flash column chromatography with hexanes/ethyl acetate (3:1) to afford the aldol products that were subjected to chiral HPLC analysis to determine enantiomeric excesses, details of which are provided in Supplementary data.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.04.033.

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