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N-Prolinylanthranilamide Pseudopeptides as Bifunctional Organocatalysts for Asymmetric Aldol Reactions

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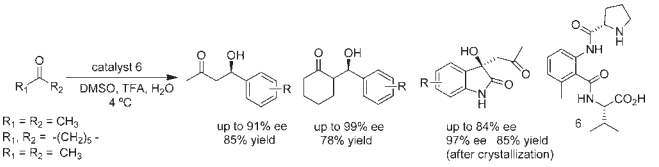
ABSTRACT



Proline anthranilamide-based pseudopeptides were shown to be effective organocatalysts for enantioselective direct aldol reactions of a selection of aldehydes with various ketones with excellent yield, enantioselectivity up to 99% and *anti* to *syn* diastereoselectivity up to 25:1.

Over the past decade or so, interest in organocatalysis has continued to grow, and much of this interest has focused on asymmetric aldol reactions,[1] the earliest reports of which used L-proline as the catalyst for intramolecular reactions,[2] later extended to intermolecular processes by List and co-workers.[3] Proline derivatives have since been popular targets as small molecule organocatalysts. We recently reported the use of *N*-prolinylanthranilic acids **1** and **2**, which are very effective for aldol reactions of cyclic ketones with aromatic aldehydes; in most cases, catalyst **2** gives >95% ee.[4] During that study, it was found that methyl substitution ortho to the carboxylic acid (as in **2**) led to superior performance (compared to **1**), but methyl substitution ortho to the anilide (not shown here) did not. However, for aldol reactions of acetone with, for example, *p*-nitrobenzaldehyde, catalyst **2** (80% ee) is only marginally better than proline itself (70−75% ee). Using the anthranilic acid unit as a convenient platform for structural variation, we are currently seeking to develop catalysts that perform well over a broader spectrum of aldol reactions. One possible structural modification is to extend the anthranilic carboxyl terminus by attaching an additional amino acid to create a pseudotripeptide. We anticipated that such a structure would show a preferred conformation that results from the intramolecular hydrogen bonding shown in Figure 1A, which has been characterized for anthranilamide oligomers.[5] Thus, one can engineer a reverse turn that might lead to a minimal binding pocket for the aldol partners, one of which is temporarily bound covalently as a prolinyl enamine (Figure 1B). While small peptides have previously been used as catalysts for aldol[6] and other[7] reactions, we are not aware of this particular structural motif being employed. A selection of catalyst structures that were chosen for evaluation is summarized in Figure 1C; in addition, we screened the methyl ester of catalyst **5** (numbered **13** in this report) to assess the role of

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the carboxylic acid group as an activator of the electrophilic aldehyde partner.

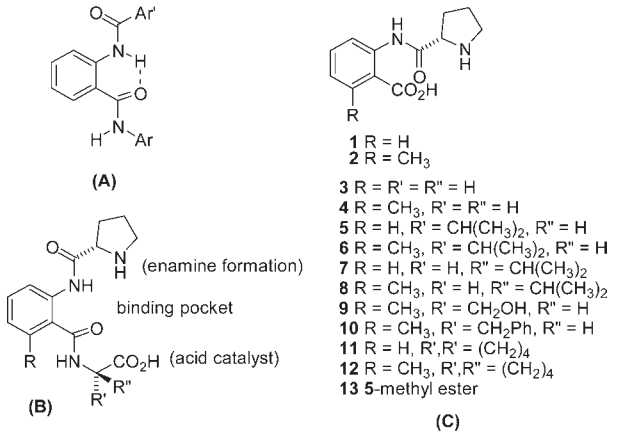

Figure 1. (A) Intramolecular hydrogen bonding for *N*-acylanthranilamides (dashed line).[5] (B) Proposed binding pocket model for anthranilic acid derived pseudotripeptides. (C) Catalyst structures investigated.

Synthesis of catalysts **3**–**13** began with reaction of the selected amino benzyl ester (methyl ester for **13**) with the corresponding isatoic anhydride[8] followed by amide coupling[9] with *N*-Cbz-L-proline then global deprotection (details can be found in the Supporting Information). Each amide coupling product was shown to be optically pure by chiral HPLC analysis. Catalyst **6** was chosen for NMR studies to test for intramolecular hydrogen bonding and to secure data on conformation. The ^{1}H NMR chemical shift in $CDCl_3$ for the anilide NH was observed at δ10.73 ppm, which agrees with Hamilton's data that supports the proposed intramolecular hydrogen bonding depicted in Figure 1,[5a] (see details in Supporting Information). In contrast, the valinyl amide NH was observed at a higher field (δ6.53 in chloroform). In addition, the anilide NH showed a much lower sensitivity to solvent than the valinyl NH (in d_6-DMSO: δ10.88 [$\Delta\delta$ = 0.15] vs, 7.8 [$\Delta\delta$ = 1.3], respectively). We observed small dependence of the anilide NH chemical shift on temperature in 20% DMSO in chloroform, also consistent with this hydrogen bonding motif.[10] A linear shift to a lower field was observed as the temperature was decreased, with a temperature coefficient ($\Delta\delta/\Delta T$) of 4.6 ppb/K for the anilide NH(A) versus 10.2 ppb/K for the valinyl NH(B) (see Figure 2 for NH labeling).[5a,10] These observations support the proposed intramolecular hydrogen bonding for NH(A) but not NH(B), as depicted in Figure 1A. NOE difference experiments in $CDCl_3$ are consistent with the conformation shown in Figure 2 (full details are in the Supporting Information).

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Upon irradiation of NH(A) NOE was observed for the CH (2.6%) and one each of 2× CH_2 (1.1 and 0.8%) proline residue protons. Enhancement (0.6%) of the aromatic H ortho to the anilide NH(A) was also observed, but irradiation of the aromatic proton had no effect on NH(A), from which we conclude that the NH is not *syn* to the aromatic residue (the internuclear distance is 3.7 Å in the *anti* conformation shown). NOE (1.5%) was observed between NH(A) and NH(B), and between NH(B) and the isopropyl CH_3 as well as the aromatic CH_3, indicating the proximity of these groups.

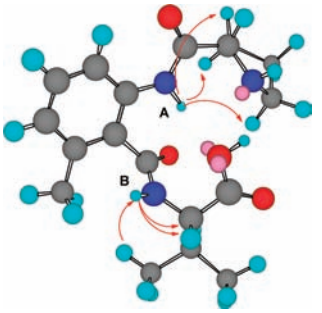
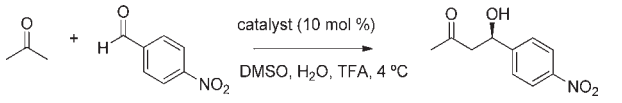


Figure 2. Selected NOE difference results for catalyst **6** in $CDCl_3$.

NOE signals were not observed between the aromatic proton *ortho* to NH(A) and any proton in the proline nucleus. Assuming this conformation persists over the entire aldol reaction profile, we expect significant connectivity between enamine, aldehyde, and carboxylic acid in the key transition state.

The aldol reaction between *p*-nitrobenzaldehyde and acetone is a commonly used benchmark to study organocatalytic aldol reactions. Optimized reaction conditions that were developed in our earlier work[4] were used for the present study, and the results are presented in Table 1. Catalyst **2** was superior to catalyst **1**, which is consistent with our earlier observation.[4] Modification of the acid side chain started with the introduction of glycine, which appears to be effective when comparing catalyst **3** vs **1**. Introducing a 6-methyl group, as in catalyst **4**, markedly improves the ee vs catalyst **3**, possibly due to conformational bias that further favors the desired trans amide structure. Modification of catalyst structure by introducing a second stereogenic center (catalysts **5** and **6**) further improved the yield and ee. However, the change compared with **3** or **4** was rather modest, so we examined D-valine as a subunit (catalysts **7** and **8**) to test for possible mismatching of chirality. A negligible change in enantioselectivity resulted from this modification (entries 5 vs 7, and 6 vs 8). Introduction of a serine unit for possible reinforced hydrogen bonding was not effective (entry 9). Also, introduction of a phenylalanine unit that might show a *pi*-stacking interaction with the aromatic aldehyde did not lead to any improvement (entry 10). The fact that both isomers of valine provide better catalysts might be due to a conformational biasing that results from alpha substitution, related

Table 1. Optimization of Organocatalytic Aldol Reaction of *p*-Nitrobenzaldehyde and Acetone



entry[a]	catalyst	yield (%)[b]	ee (%)[c]
1	**1**	50	60
2	**2**	50	80
3	**3**	55	69
4	**4**	58	81
5	**5**	55	77
6	**6**	55	87
7	**7**	60	78
8	**8**	58	85
9	**9**	45	68
10	**10**	52	70
11	**11**	55	74
12	**12**	58	83
13	**13**	28	63

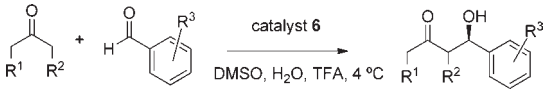
[a] Unless specified otherwise, the concentration of aldehyde is 0.13 M, and v/v of acetone/DMSO is (1/4), 10 mol % of catalyst, 5 mol % of TFA, 550 mol % of water and the reactions were run at 4 °C. [b] Isolated yield after separation from unreacted starting materials and catalyst. [c] Determined by HPLC on CHIRALPAK AD-H column for isolated products after separation from unreacted starting materials and catalyst.

to the well-known Thorpe–Ingold effect.[11] However, introduction of a cyclopentane group as a conformational lock did not give significant improvement; again, 6-methyl substitution improves the ee (catalyst **12** vs **11**). The role of the acid group was also evaluated using the methyl ester (**13**) of catalyst **5** (entry 13), which reacts slowly with reduced enantioselectivity compared with its acid counterpart **5** (entry 3).

Direct aldol reactions using various aldehydes and ketones were explored with catalyst **6** (Table 2). In most cases, the reaction afforded *anti* product with high yield and high diastereo- and enantioselectivity. The aldol reaction between *o*-nitrobenzaldehyde and acetone afforded 92% ee and good yield, an improvement over the reaction with *p*-nitrobenzaldehyde, as anticipated for a more sterically hindered aldehyde. High enantioselectivity was also observed for 2,4-dinitrobenzaldehyde with an excellent yield (entry 3). Using *p*-bromo- and 2,4-dichlorobenzaldehyde, the aldol product was obtained with comparable yield and good enantioselectivity (entries 4 and 5). The aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde afforded 99% ee with good yield and diastereoselectivity, and with *o*-nitrobenzaldehyde afforded 25:1 dr, 97% ee and good yield, the sterically hindered aldehyde giving better diastereoslectivity. Aldol reactions with cyclopentanone afforded excellent enantioselectivity but moderate diastereoselectivity, as observed for other prolinamide catalysts.[1,12]

On the other hand, the aldol reaction between *o*-nitrobenzaldehyde and cyclopentanone afforded *anti*/*syn* 5:1, 98% ee (Table 2, entry 10), which compares very favorably with

Table 2. Organocatalytic Aldol Reaction of Selected Aromatic Aldehydes and Ketones[a]



entry	R^1,R^2	R^3	yield (%)[b]	dr[c]	ee (%)[d]
1	H,H	4-NO_2	55	NA	87
2	H,H	2-NO_2	65	NA	92
3	H,H	2,4-$(NO_2)_2$	85	NA	90
4	H,H	2,4-$(Cl)_2$	50	NA	91
5	H,H	4-Br	38	NA	91
6	-$(CH_2)_3$-	4-NO_2	76	9:1	99
7	-$(CH_2)_3$-	2-NO_2	70	25:1	97
8	-$(CH_2)_3$-	4-pyridyl[e]	84	12:1	92
9	-$(CH_2)_2$-	4-NO_2	78	1.2:1	99
10	-$(CH_2)_2$-	2-NO_2	70	5:1	98
11[f]	-CH_2SCH_2-	4-NO_2	68	10:1	93
12[f]	-$OC(CH_3)_2O$-	4-NO_2	52	9:1	88

[a] All reactions were run under the general conditions noted for Table 1. [b] Isolated yield after separation from unreacted starting materials and catalyst. [c] Diastereomer ratios (anti/syn) were estimated from the ^{1}H NMR spectrum of the crude product mixture. [d] Determined by HPLC on CHIRALPAK AD-H column for isolated products after separation from unreacted starting materials and catalysts. [e] Pyridine-4-al was the aldehyde substrate. [f] Reaction time was 5 days.

other catalysts reported in the literature.[12] The aldol reaction between dihydro-2H-thiopyran-4(3H)-one (a useful surrogate for 3-pentanone) and *p*-nitrobenzaldehyde gave the *anti* product with somewhat variable diastereoselectivity but uniformly high ee for the *anti* product (entry 11). Using the acetonide of 1,3-dihydroxyacetone as the nucleophile, the *anti* product was obtained with good ee and diastereoselectivity (entry 12). Thus, with catalyst **6**, the enantioselectivity of the acetone aldol reactions were greatly improved while not compromising the aldol reactions of cyclic ketones.

Aldol reactions between acetone and substituted isatin derivatives were next explored (Table 3). The resulting 3-substituted-3-hydroxyindolin-2-ones are desirable targets due to related structural features found in natural products and drug candidates.[13] Although this reaction has been reported in the literature,[14] only in very few cases were high ee's obtained.[15] The aldol reaction of isatin and

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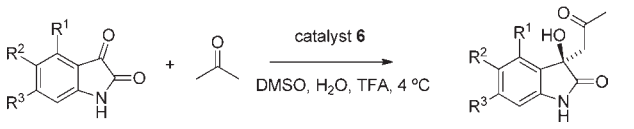
acetone catalyzed by L-proline has been reported to favor the (*S*) enantiomer,[16] whereas prolinamides generally afford the (*R*) enantiomer as the major product.[14a,15a,15c] With catalyst **6**, up to 84% ee of the (*R*) enantiomer and 100% conversion were obtained. This result was improved to 97% ee after a single recrystallization. Interestingly, while catalyst **2** works well for the aldol reaction between acetone and *p*-nitrobenzaldehyde, it gives very poor enantioselectivity for the reaction between 5-bromoisatin and acetone (Table 3, entry 2). The considerable improvement using catalyst **6**, while not compromising other aldol reactions, provides a compelling reason for investigating structural variations based on the anthranilamide scaffold. Catalysts substituted with a 6-methyl group again afforded higher enantioselectivity than the unsubstituted analogues (entries 1, 3, 5 vs 2, 4, 6), the effect being even greater than in the earlier aldol reactions. Catalyst **6** was chosen for further optimization. Lowering the catalyst loading to 5 mol % improved the enantiomeric excess without compromising the yield of the product (entry 7), while the ee was further improved by reducing the amount of acetone used in the reaction (entry 8).These optimized conditions were used to explore the reactions between acetone and other substituted isatin derivatives. Good enantioselectivity was obtained using isatin itself as an aldol acceptor (entry 12). 5-Substituted isatin derivatives reacted with somewhat better enantioselectivity than 4- and 6-substituted derivatives (entries 8–11 vs 13 and 14). Reaction of 4,6-dibromoisatin with acetone yielded (S)-convolutamydine A in quantitative yield and reasonable enantiomeric excess, which was considerably improved by crystallization (entry 15). This compound exhibits potent inhibitory activity toward the differentiation of HL-60 leukemia cells.[17]

In conclusion, a series of *N*-prolinylanthranilamide pseudopeptides were designed as catalysts for enantioselective aldol reactions. The anthranilic acid core represents a very convenient template for structural engineering, in the present case modification of the carboxylic acid by incorporation of an amino acid residue, which was found to be beneficial for a number of important aldol reactions. Future studies will focus on addressing other structural modifications that might also lead to enhanced selectivity, such as variation of the substituent at C-6 of the anthranilic acid moiety.

Table 3. Organocatalytic Aldol Reactions of Acetone and Isatin Derivatives[a]



entry	catalyst	R^1,R^2,R^3	conversion (%)[b]	ee (%)[c]
1	**1**	H,Br,H	85	5
2	**2**	H,Br,H	100	18
3	**5**	H,Br,H	100	32
4	**6**	H,Br,H	100	77
5	**11**	H,Br,H	100	35
6	**12**	H,Br,H	100	76
7[d]	**6**	H,Br,H	100	82
8[e]	**6**	H,Br,H	100 (62)[f]	84 (97)[g]
9[e]	**6**	H,F,H	100 (50)[f]	80 (92)[g]
10[e]	**6**	H,Cl,H	100 (58)[f]	82 (95)[g]
11[e]	**6**	H,CH_3,H	100 (50)[f]	81 (95)[g]
12[e]	**6**	H,H,H	90 (48)[f]	70 (89)[g]
13[e]	**6**	H,H,Br	100 (60)[f]	74 (90)[g]
14[e]	**6**	Br,H,H	90 (52)[f]	69 (85)[g]
15[e]	**6**	Br,H,Br	100 (65)[f]	76 (91)[g]

[a] Unless specified otherwise, the concentration of the isatin is 0.16 M, and v/v of acetone/DMSO is (1/5), 10 mol % of catalyst, 5 mol % of TFA, 550 mol % of water and the reactions were run at 4 °C. [b] % Conversion was determined from the crude ^{1}H NMR spectrum. [c] Determined by HPLC on CHIRALPAK AD-H column for isolated products after separation from unreacted starting materials and catalyst. [d] 5 mol % of catalyst was used. [e] 5 mol % of catalyst was used, concentration of the isatin was 0.18 M, and v/v of acetone/DMSO is (1/10), 5 mol % of TFA, 550 mol % of water and the reactions were run at 4 °C. [f] Isolated yield after recrystallization. [g] Enantiomeric excess determined after recrystallization.

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Supporting Information Available. Spectroscopic data, experimental details for the preparation of catalysts, NOE data and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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