Asymmetric Bisprolinamide-Catalyzed Cross-Aldol Reaction of Aldehydes

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Abstract: A C_2-symmetric *para*-orientation bisprolinamide catalyst has been designed to effectively promote the enantioselective coupling reactions of aldehydes, which delivered the systematic investigation on amine–amide catalysis. Transforming the monoprolinamide **1a** into the bisprolinamide **2a** improved not only the stereoselectivities but also the reactivities. With this strategy, the functionalized β-hydroxyaldehydes could be furnished in high yields (up to 99%) with good selectivities (up to 8:92 *syn*/*anti* and 99% ee) even in the presence of 5 mol% of catalyst **2a**. Based on the preliminary experiment and the absolute configuration of cross-aldol adduct, a rational transition state **A** was proposed to explain the origin of reactivity and selectivity.

Key words: asymmetric catalysis, bisprolinamide, cross-aldol reactions, hydroxyaldehydes, nonlinear effect

Asymmetric organocatalysis has recently provided a new research approach to explore the fundamental chemical characterizations such as reactivity, selectivity, and mechanism, which has also led to the discovery of many valuable reactions and catalysts.[1] In this endeavor, the design and development of multifunctional chiral organocatalysts are of great importance: One catalyst molecule possesses two or more reaction-promoting functionalities, so that reactivity and selectivity can be tuned by a simple structural modification of the catalyst.

The cross-aldol reaction of aldehydes ranks among the most important carbon–carbon bond-forming reactions in organic synthesis and provides β-hydroxyaldehydes, which could be transferred to some biologically active compounds.[2] Several efficient asymmetric methodologies for this reaction using proline and its derivative organocatalysts have been developed, in which the secondary amine of pyrrolidine has been confirmed to efficiently provide the active enamine intermediate.[3] According to the Houk–List model,[4] hydrogen bonding undoubtedly plays the crucial role in stabilizing the transition state. In cross-aldol reaction of aldehydes, although hydrogen bond between carbonyl oxygen of aldehydes and carboxyl, protonated amine or sulfonyl amide has been introduced successfully, investigation on the amide has not yet been specialized systematically. In addition, it is apparently troublesome to control the occurrence of unexpected aldol condensation in coupling reaction of aldehydes. Herein, we report amine–amide-catalyzed cross-aldol reaction of aldehydes, with secondary amine activating the donor via enamine and hydrogen of amide activating the acceptor via hydrogen bond.

Based on the skeleton of L-proline, the monoprolinamide catalysts **1a–e** (Figure 1) were synthesized.[5] With a phenyl substituent on nitrogen atom of amide **1a**, the solvent effects were initially investigated.

Although good enantioselectivities (90% ee) could be obtained in different media such as CH_2Cl_2, $ClCH_2CH_2Cl$, DMSO and *N*-methyl-2-pyrrolidinone (NMP), the diastereoselectivities were generally better when the reaction was conducted in DMSO (75:25) or NMP (70:30). With DMSO, the unsubstituted **1b** and *t*-Bu-substituted **1c** provided inferior selectivities (Table 1, entries 2 and 3). On

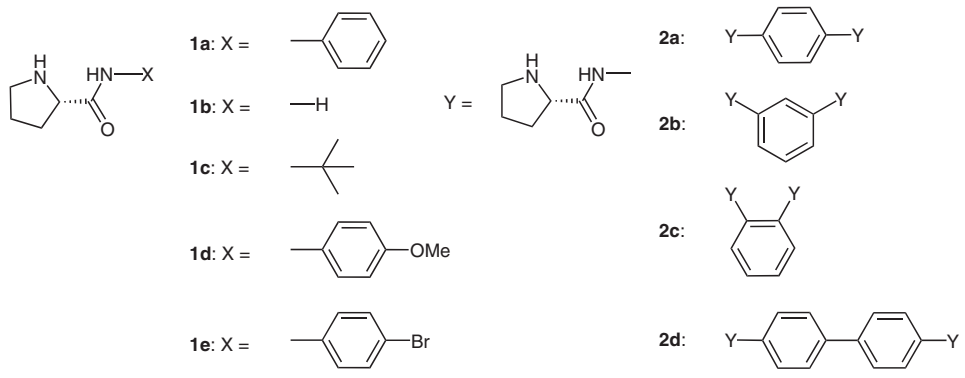

Figure 1 The studied catalysts.

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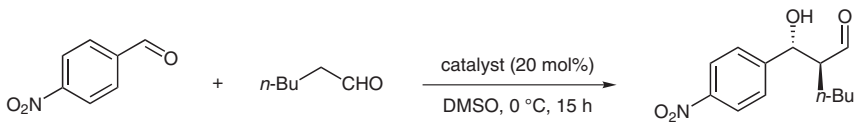
Table 1 Optimization Studies



3a

Entry	Catalyst	Yield (%)[a]	dr (*syn*/*anti*)[b]	ee (%) (*anti*)[c]
1	**1a**	56	25:75	90
2	**1b**	91	35:65	87
3	**1c**	73	46:54	65
4	**1d**	96	20:80	97
5	**1e**	99	18:82	98
6	**2a**	84	12:88	98
7	**2b**	69	35:65	53
8	**2c**	81	22:78	91
9	**2d**	99	34:66	84
10[d]	**2a**	56	13:87	98
11[d,e]	**2a**	99	8:92	99

[a] Isolated yields.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC analysis.
[d] Catalyst loading: 5 mol%.
[e] Reaction conditions: NMP as solvent, 30 h.

the other hand, *p*-methoxyphenyl (**1d**) and *p*-bromophenyl (**1e**) substituents gave better results (dr ≥ 80:20 and ee ≥ 97%), which signaled that a *para* substituent could further improve the stereoselectivities. Accordingly another catalytic active site was introduced to the *para* orientation. C_2-Symmetrical bisprolinamide **2a**[6] delivered the efficient formation of cross-aldol product in 15 hours (84% yield, 88:12 *anti*/*syn* and 98% ee) (Table 1, entry 6).

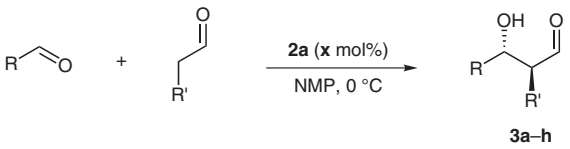
Adjusting the relative position of two prolinamide units demonstrated that the *ortho* and *meta* substituted (**2b** and **2c**) or another phenyl ring inserted (**2d**) did not give better results (Table 1, entries 7–9). In NMP, using the best catalyst **2a**, improved selectivities could be found (92:8 *anti*/*syn* and 99% ee) (Table 1, entry 11).

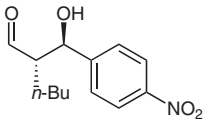
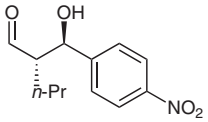
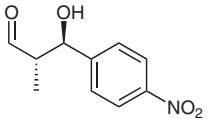
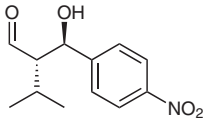
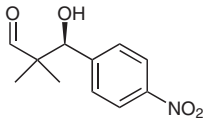
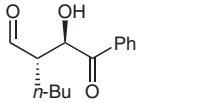
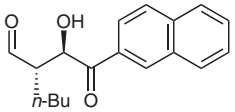
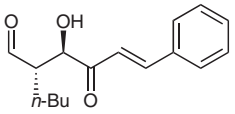
Under the optimal conditions, asymmetric inductivities of the bisprolinamide **2a** were investigated on other selected aldehydes, with the results summarized in Table 2. Good enantioselectivities were attained for linear and branched aliphatic aldehydes. The absolute configuration of the *anti*-aldol adduct **3a** was determined to be 2*S*,3*R* by comparison of the sign of the optical rotation value with that in the literature.[3m] The aldol adduct **3c** was obtained in 99% yield with 95% ee, which could be transformed into biologically active trichostatin A.[2e] Selecting hexanal as the donor, prochiral benzoyl-, naphthalene-2- and 3-carbonyl phenylacryloyl-functionalized aldehydes were all obtained in good yield and enantioselectivities.

Comparing C_2-symmetric bisprolinamide **2a** with monoprolinamide **1a** revealed that the former provided the aldol adduct with higher yield and selectivity (Table 1, entry 6 vs. 1), which indicated that the two prolinamide units might act cooperatively. The relation between the enantiomeric excess of product **3a** and the enantiopurity of catalyst **2a** was examined to be directly proportional, which indicated that asymmetric catalysis with partially resolved chiral catalysts were not amplified and depleted (Figure 2).[8] Furthermore, the catalyst loading in an investigated range of 2.5–20 mol% had no influence on the stereoselectivity.

Based on the preliminary experiment and the absolute configuration of **3a**, we proposed a transition state **A**, which also represents the lowest energy conformation (Figure 3). In transition state **A**, the *Re* face of the carbonyl of 4-nitrobenzaldehyde is much more accessible to the *Re* face of enamine to provide the product with absolute configuration of 2*S*,3*R*. The interaction of two *Si* faces will strongly increase the repulsion between phenyl subunits as seen in transition state **B**. The repulsion between pyrrolidine and the carbon chain of donor would also be unfavorable to the formation of (2*R*,3*S*)-product. *syn*-Conjugate addition would increase the repulsion either

Table 2 Investigation on Other Selected Aldehydes[7]



Products	x	Time (h)	Yield (%)[a]	dr (*syn*/*anti*)[b]	ee (%) (*anti*)[c]
 **3a**	5	30	99	8:92	99 (2*R*,3*S*)
 **3b**	10	15	99	10:90	99
 **3c**	20	30	99	25:75	95
 **3d**	20	80	87	15:85	97
 **3e**	20	80	51	–	77
 **3f**	10	20	88	15:85	99
 **3g**	10	20	93	22:78	96
 **3h**	10	20	95	19:81	92

[a] Isolated yields.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC analysis.

between phenyl subunits or between the pyrrolidine ring and the carbon chain of donor as in **C** or **D**, respectively.

In summary, enantioselective secondary amine–amide-catalyzed cross-aldol reaction of aldehydes has been developed, which could provide a practical, enantioselective organocatalytic strategy to some important carbon–carbon bond formations. The rational introduction of two catalytic active sites improves not only the stereoselectivities but also the reactivities. Further work is underway to develop, understand and apply this new method of enantioselective coupling reaction of aldehydes.

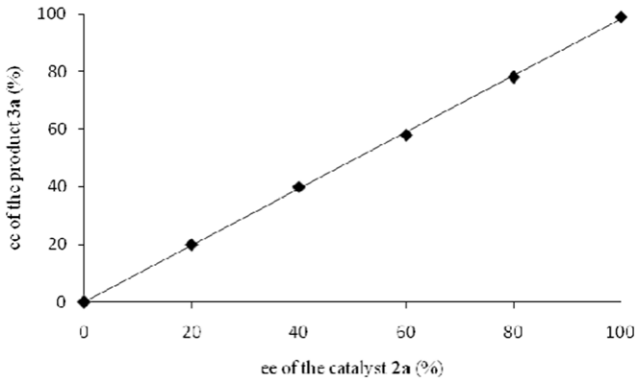


Figure 2 The relation between product **3a** and catalyst **2a** in enantioselectivity.

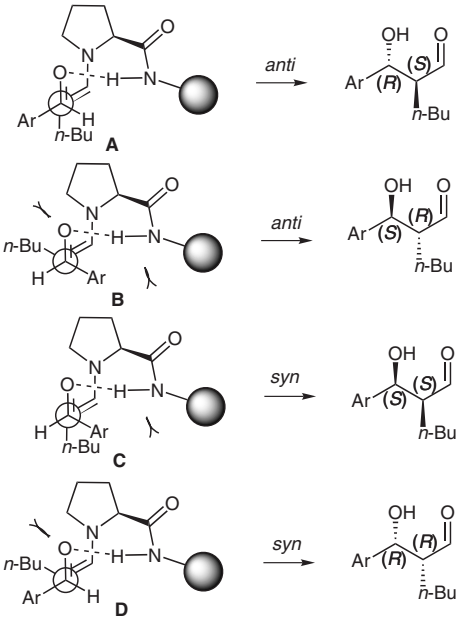


Figure 3 Proposed transition state **A** → **D** (another prolinamide unit was omitted). Ar = 4-nitrophenyl.

Acknowledgment

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(6) **Typical Procedure for the Preparation of Bisprolinamides 2a–d**:
(i) To a solution of (*S*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid (678.0 mg, 3.15 mmol) in CH_2Cl_2, dicyclohexylcarbodiimide (DCC; 649.9 mg, 3.15 mmol) and benzotriazol-1-ol (HOBt; 425.6 mg, 3.15 mmol) were added at r.t. under stirring. After 10 min, benzene-1,4-diamine (162.2 mg, 1.5 mmol) was added. The mixture was allowed to be stirred for 10 h and filtered. The filtrate was washed with 1 M $KHSO_4$, sat. $NaHCO_3$ and brine and was then dried over anhyd Na_2SO_4 and concentrated.
(ii) To the residue in CH_2Cl_2, TFA (3.15 mL) was added and stirring was continued for an hour. Then the solution was concentrated in vacuo to a glutinous phase and H_2O (4 mL) was added. The pH of the mixture was brought into the range of 8–10 by the addition of 2 M NaOH. The aqueous phase was extracted with EtOAc. The EtOAc extracts were pooled, washed with brine, dried over anhyd Na_2SO_4 and evaporated in vacuo. The residue was purified by flash column chromatography using MeOH–EtOAc (1:2) as eluent to afford the bisprolinamide **2a** as a white solid (390.1 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.71 (s, 2 H), 7.56 (s, 4 H), 3.86 (dd, J_1 = 9.2 Hz, J_2 = 5.2 Hz, 2 H), 3.06–3.12 (m, 2 H), 2.96–3.02 (m, 2 H), 2.38 (s, 2 H), 2.17–2.26 (m, 2 H), 2.00–2.08 (m, 2 H), 1.80–1.82 (m, 4 H).

(7) **Typical Procedure for the Catalytic Asymmetric Cross-Aldol Reaction of Aldehydes**:
To the mixture of bisprolinamide **2a** (1.5 mg, 0.005 mmol) and 4-nitrobenzaldehyde (15.1 mg, 0.1 mmol) in NMP (0.2 mL) was added hexanal (24.5 μL, 0.2 mmol) at 0 °C. The mixture was stirred for 30 h and purified by flash column chromatography using EtOAc–PE (1:2) as eluent to afford (2*S*)-2-[(1*R*)-hydroxy(4-nitrophenyl)methyl]hexanal (**3a**; 24.8 mg, 99% yield, 8:92 *syn*/*anti*, 99% ee).
Typical Procedure for Determining the Enantiomeric Excess of 3a–e (Table 2):
To a solution of (2*S*)-2-[(1*R*)-hydroxy(4-nitrophenyl)methyl]hexanal (**3a**; 24.8 mg) in CH_2Cl_2 (1 mL) were added 2,2-dimethyl-1,3-propanediol (10.4 mg, 0.10 mmol), triethyl orthoformate (13.3 μL, 0.08 mmol) and *p*-toluenesulfonic acid (catalytic amount) in this sequence at r.t. After 2 h of stirring, the reaction was quenched with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (PE–EtOAc, 15:1) to afford (1*R*,2*S*)-2-(5,5-dimethyl-1,3-dioxan-2-yl)-1-(4-nitrophenyl)hexan-1-ol quantitatively as a colorless oil; $[\alpha]_D^{25}$ +9.5 (*c* = 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.8 Hz, 2 H), 7.54 (d, *J* = 8.8 Hz, 2 H), 5.00 (dd, J_1 = 6.0 Hz, J_2 = 4.8 Hz, 1 H), 4.47–4.48 (m, 2 H), 3.64–3.71 (m, 2 H), 3.37–3.41 (m, 2 H), 1.97–1.99 (m, 1 H), 1.23–1.26 (m, 9 H), 0.84–0.86 (m, 3 H), 0.75 (m, 3 H). HPLC (Chiralcel OJ-H, hexane–*i*-PrOH, 96:4; flow rate: 0.5 mL/min, 23 °C, UV: λ = 215 nm): t_R(minor) = 20.665 min, t_R(major) = 22.750 min.

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