

Design, Synthesis and Organocatalysis of 2,2'-Biphenol-Based Prolinamide Organocatalysts in the Asymmetric Direct Aldol Reaction in Water

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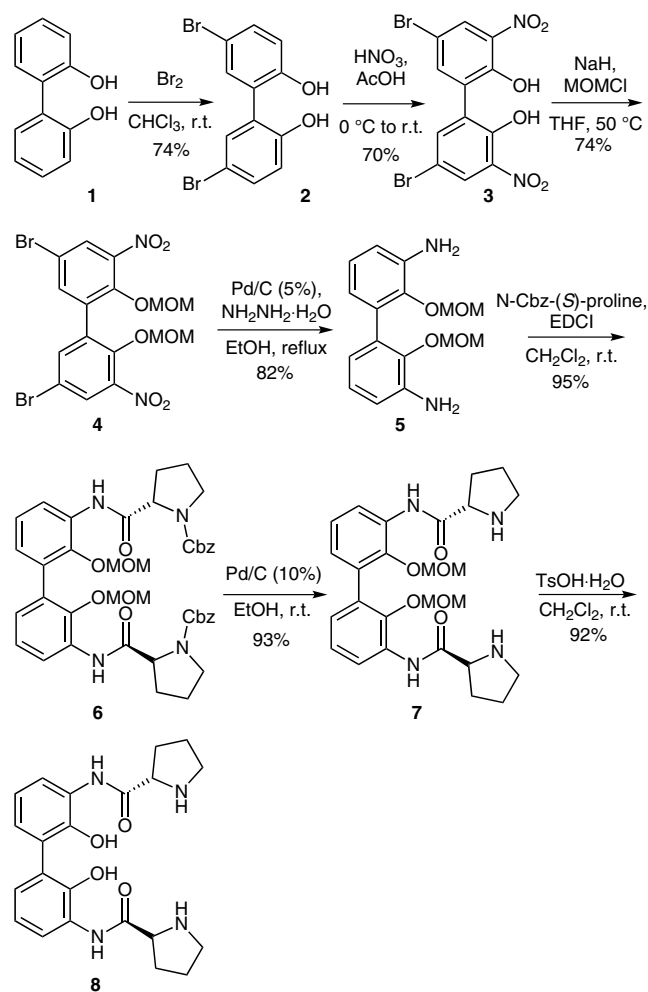
Abstract: In this work, 2,2'-biphenol-based prolinamide water-compatible C_2 - and C_1 -symmetrical organocatalysts were synthesized with the use of enantiopure *N*-Cbz-(*S*)-proline as chiral source. Under the optimal reaction conditions, the C_1 -symmetrical organocatalyst performed efficiently in the direct aldol reactions in water, thus delivering the desired aldol adducts in high yields (up to 100% yield) with excellent stereocontrol (up to 97:3 dr and 98% ee). The observed stereochemical outcome of the direct aldol reactions in water was interpreted by the proposed transition state.

Key words: axially unfixed 2,2'-biphenol, prolinamide, water-compatible organocatalyst, aldol reaction, stereoselectivity

The asymmetric organocatalytic direct aldol reaction constitutes one of the important and useful C–C bond-forming reactions,¹ and has found many successful utilities in the construction of natural products and biologically active compounds.² It is well documented that the known organocatalysts usually show the highly efficient organocatalysis in the direct aldol reactions in organic solvents under mild reaction conditions. In the past years, the use of water as the reaction medium for the direct aldol reactions has received considerable attention from organic chemists because of the low cost, safety, and environmentally friendly nature of water.³ The challenges with the development of highly efficient organocatalysts, which are useful for the direct aldol reaction in water, lie in the fact that water can interfere with organocatalysts and disrupt hydrogen bonds and other polar interactions.⁴

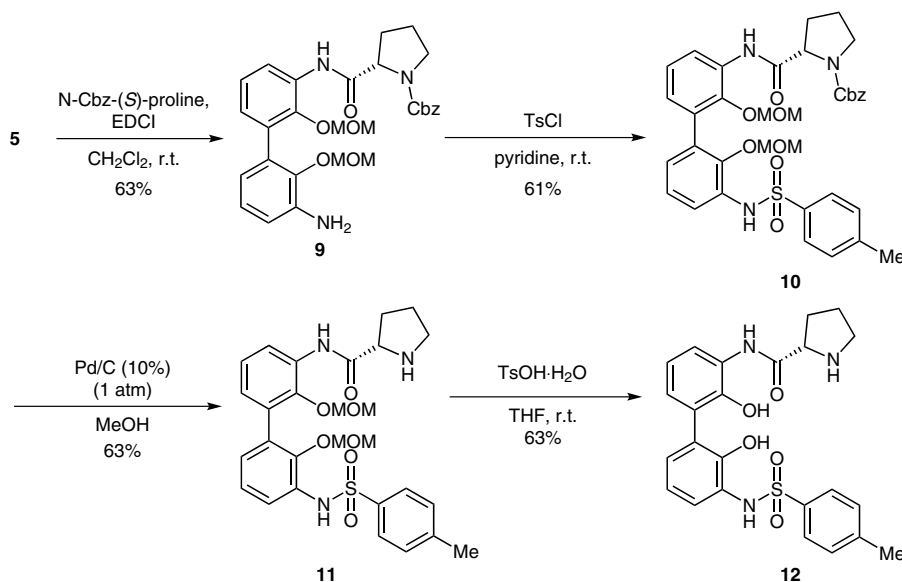
Inspired by the pioneering discoveries of Takebe,⁵ Barbas,⁶ and Hayashi⁷ et al., many highly efficient hydrophobic organocatalysts have been developed for the direct aldol reactions in water.⁸ The main rationales for the design of these organocatalysts relied on the concepts that the hydrophobic organocatalysts can assemble with the aldol partners and sequester water from the transition states efficiently via the hydrophobic interactions in the aqueous aldol reactions, and thus the direct aldol reactions in water actually proceeded in a highly concentrated organic phase. Therefore, a water-compatible organocatalyst should bear a sufficient hydrophobicity with a goal to offer a high stereocontrol in aqueous aldol reactions. Despite of a number of remarkable advances achieved in the

development of the water-compatible organocatalysts for the aldol reactions in water, there continues to be an increasing demand for searching for novel and efficient water-compatible organocatalysts.



Scheme 1 Synthesis of C_2 -symmetrical organocatalyst **8**

Herein, in continuation of our recent work,⁹ in this work we report the design, synthesis, and asymmetric catalysis of novel axially unfixed 2,2'-biphenol-based organocatalysts. The newly designed organocatalysts are constructed by the introduction of 2,2'-biphenol, prolinamide, or sulfonamide motifs. The designed organocatalysts are envisioned to activate aldol donor and acceptor in a bifunctional nature in water: the activation of the aldol do-



Scheme 2 Synthesis of C_1 -symmetrical organocatalyst **12**

nor via the enamine formation and the activation of the aldol acceptor with the hydrogen bonds. In addition, the present 2,2'-biphenol in the organocatalysts was hoped to play a dual role: on the one hand, it serves as a key skeleton to finely tune the spatial orientations of sulfonamide and prolinamide catalytic sites and provides two free hydroxyl group as H-bond donors; on the other hand, the present hydrophobic biaryl system can enable the organocatalysts to have sufficient hydrophobicities to aggregate with the hydrophobic reactants and exclude water efficiently from the transition states of the direct aldol reactions in water via the hydrophobic interactions, and thus yielding high stereocontrol in the direct aldol reactions in water.

Organocatalysts **8** and **12** were readily accessed by following the multistep reaction sequences as shown in Scheme 1 and Scheme 2, respectively. In Scheme 1, compound **3** was obtained in two steps starting from 2,2'-biphenol on the basis of literature protocols.¹⁰ The treatment of compound **3** with MOMCl and NaH, followed by $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ and 5% Pd/C gave rise to compound **5**. The condensation of compound **5** with enantiopure *N*-Cbz-(*S*)-proline afforded compound **6** in 95% yield. Finally, the successive removals of Cbz and MOM groups of compound **6** furnished the desired compound **8**. According to Scheme 2, the condensation of compound **5** with enantiopure *N*-Cbz-(*S*)-proline, followed by TsCl generated product **10**. After removal of Cbz and MOM groups of **10** successively, the final compound **12** was obtained.

Initially, with the use of organocatalysts **7**, **8**, **11**, **12**, **13**, and **14**^{9b,c} (Figure 1), we began to examine their asymmetric catalytic performances in the asymmetric direct aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde in water in the presence of TFA as an additive as summarized in Table 1. Catalyzed by C_2 -symmetrical organocatalyst **7**, the aldol reaction furnished the desired aldol adduct in 100% yield with a diastereomeric ratio of 89:11

dr (*anti/syn*) and 70% enantiomeric excess (*anti*). In comparison with **7**, organocatalyst **8** (containing free phenol groups) gave the desired product in significantly increased enantiomeric excess (Table 1, entries 1 vs. 2).

In the case of organocatalyst **11** featuring a C_1 symmetry, the aldol product was achieved in 84% yield with a diaste-

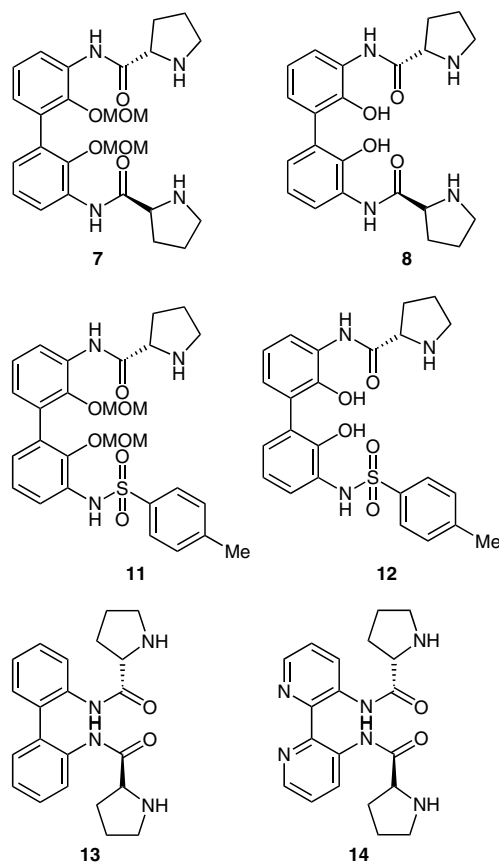
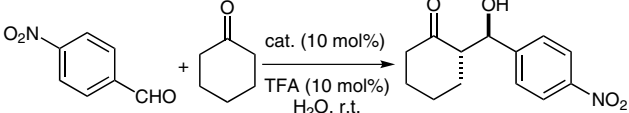


Figure 1 The examined organocatalysts in this work

Table 1 Screening of Biaryl Organocatalysts^a


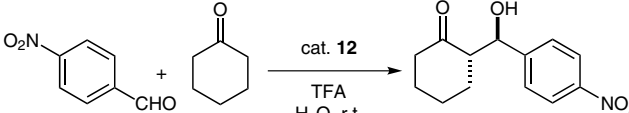
Entry	Catalyst	Time (h)	Yield (%) ^b	dr ^c (anti/syn)	ee (%) ^c (anti)
1	7	17	100	89:11	70
2	8	17	91	92:8	91
3	11	23	84	92:8	80
4	12	24	98	95:5	96
5	13	10	100	86:14	74
6	14	24	100	88:12	71

^a Reaction conditions: *p*-nitrobenzaldehyde (0.1 mmol), cyclohexanone (104.0 μ L, 1.0 mmol), catalyst (10 mol%), TFA (0.8 μ L, 10 mol%), H₂O (0.5 mL), r.t.

^b Isolated yield.

^c Determined by chiral HPLC analysis.

reomeric ratio of 92:8 (*anti/syn*) and 80% enantiomeric excess (*anti*). With the use of organocatalyst **12** containing free phenol groups, the superior stereocontrol to those of organocatalyst **11** was found in the aldol reaction, thus demonstrating that the free phenol motifs in **12** must be responsible for the stereocontrol in the aldol reaction. Moreover, the excellent organocatalytic performance of organocatalysts **8** and **12** in contrast to that of **13** and **14** also evidenced the important roles of the free phenol

Table 2 Screening of Catalytic Loading of **12** and TFA^a


Entry	Catalyst (mol%)	TFA (mol%)	Time (h)	Yield (%) ^b	dr ^c (anti/syn)	ee (%) ^c (anti)
1	10	30	66	83	90:10	92
2	10	20	62	87	91:9	93
3	20	10	17	98	95:5	95
4	15	5	17	92	94:6	95
5	20	5	17	100	92:8	93
6	20	20	17	89	94:6	95
7	5	5	82	92	95:5	96
8	2	2	94	88	95:5	96

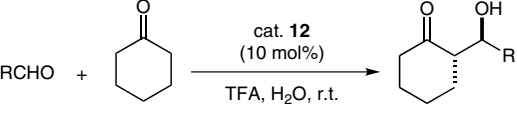
^a Reaction conditions: *p*-nitrobenzaldehyde (0.1 mmol), cyclohexanone (104.0 μ L, 1.0 mmol), in the presence of the indicated amounts of catalyst and TFA in H₂O (0.5 mL) at r.t.

^b Isolated yield.

^c Determined by chiral HPLC analysis.

groups in the stereocontrol during the aldol reaction (Table 1, entries 2 and 4 vs. 5 and 6). By comparison with the chemical yields and stereocontrol achieved with all the examined catalysts, organocatalyst **12** was disclosed as the most efficient organocatalyst in the aldol reaction.

Moreover, the optimization of the catalytic loading of **12** and TFA was conducted as shown in Table 2. Obviously, when **12**/TFA was attempted in a 1:1 ratio, the reaction rate of the aldol reaction increased with increasing the catalytic amount of **12** (Table 2, entries 6–8 and Table 1, entry 4). It should be also noted that with the use of 20 mol% of **12**, the reaction rate of the aldol reaction changed dramatically with changing the loading amount of TFA (Table 2, entries 3 and 5–6). In contrast, when 10 mol% of **12** were used, the significant change in the reaction rate of the aldol reaction was observed with changing the loading amount of TFA (Table 2, entries 1 and 2 and Table 1, entry 4). Considering the chemical yield and stereoselectivity of the aldol reaction, together with 10 mol% TFA, 10 mol% of **12** were sufficient enough to afford the desired aldol adduct in excellent chemical yield and stereoselectivity.

Table 3 Extension of the Scope of Aromatic Aldehydes^a


Entry	R	Time (h)	Yield (%) ^b	dr (%) ^c (anti/syn)	ee (%) ^c (anti)
1	4-O ₂ NC ₆ H ₄	24	100	97:3	97
2	3-O ₂ NC ₆ H ₄	24	97	97:3	98
3	2-O ₂ NC ₆ H ₄	45	90	97:3	98
4	4-MeOC ₆ H ₄	72	26	80:20	79
5	4-F ₃ CC ₆ H ₄	45	68	96:4	97
6	4-NCC ₆ H ₄	45	99	94:6	97
7	4-FC ₆ H ₄	69	77	92:8	96
8	4-ClC ₆ H ₄	69	68	96:4	97
9	4-BrC ₆ H ₄	69	83	96:4	97
10	4-MeC ₆ H ₄	69	47	88:12	92
11	Ph	69	42	91:9	93
12	4-pyridyl	4.5	100	91:9	92
13	2-furyl	69	15	76:24	89
14 ^d	2-furyl	16	50	96:4	89
15	2-thienyl	69	30	87:13	90

^a Reaction conditions: aromatic aldehydes (0.1 mmol), cyclohexanone (104.0 μ L, 1.0 mmol), catalyst **12** (10 mol%), TFA (0.8 μ L, 10 mol%), H₂O (0.5 mL) at r.t.

^b Isolated yield.

^c Determined by chiral HPLC analysis.

^d Stearic acid as additive.

Subsequently, catalyzed by organocatalyst **12**, a wide range of organic solvents and acidic additives were also screened in the aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde in water as shown in the Supporting Information. Under the optimized reaction conditions (**12**, TFA, H₂O, r.t.), the reaction scope of the aldol reaction was widely extended by reacting cyclohexanone with a wide array of aromatic aldehydes as presented in Table 3. Noticeably, in most cases, the excellent stereocontrol was achieved in up to 97:3 diastereomeric ratio (*anti/syn*) and 98% enantiomeric excess (*anti*). Moreover, the reaction rate and chemical yield of the aldol reactions were seriously influenced by the electronic nature of the R group on the benzene ring of the aromatic aldehydes. It is generally accepted that the benzaldehydes substituted with a strong electron-withdrawing group on the benzene ring tended to lead to the formation of the aldol adducts in high to excellent yields (e.g., Table 3, entries 1–3 and 6). In contrast, with the use of the benzaldehydes bearing a weak electron-withdrawing or an electron-donating group on the benzene ring as substrates, the corresponding aldol adducts were often obtained in low to moderate yields (Table 3, entries 7–10). In addition, organocatalyst **12** also showed moderate to high stereocontrol in the aldol reactions using the heteroaromatic aldehydes as aldol acceptors (Table 3, entries 12–15). Simultaneously, under the same optimal reaction conditions, the further extension of the scope of the aldol reaction was carried out by the choice of a series of ketones as aldol donors to react with *p*-nitrobenzaldehyde as shown in Table 4. In the case of acyclic aldol donors, the aldol reactions did not form the

desired aldol products at all after 72 hours (Table 4, entries 1 and 4–8). As the cyclic aldol donors are concerned, the aldol reactions produced the desired aldol adducts in 81–95 yield and 78–90% enantiomeric excess (Table 4, entries 2, 3, and 9).

To shed light on the observed stereochemical outcome obtained with organocatalyst **12**, the transition state was presumed as illustrated in Figure 2. In the proposed model, the catalyst **12** exhibited a bifunctional organocatalytic nature. The cyclohexanone as an aldol donor was activated via the formation of enamine with the aid of acidic additive, and simultaneous activation of benzaldehyde as an aldol acceptor was realized via the multiple hydrogen-bonding interactions. Subsequent attack of the in situ formed enamine on the *Re* face of the well-oriented aromatic aldehyde resulted in the formation of the desired aldol adducts in high stereocontrol.

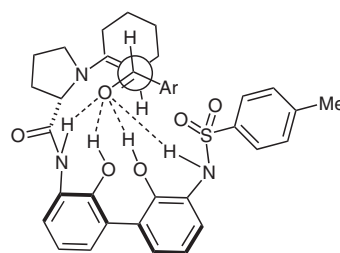


Figure 2 Proposed transition state for the aldol reactions under catalysis of **12**

In conclusion, a class of novel organocatalysts bearing an axially unfixed biaryl motif have been designed and synthesized for the asymmetric organocatalytic direct aldol reactions in water. Under optimized reaction conditions, the organocatalyst **12** performed highly efficiently and showed excellent enantioselectivities and diastereoselectivities in the aldol reactions in water. The further studies on the catalytic mechanisms and the utility of the water-compatible bifunctional organocatalyst in other asymmetric reactions in water are in progress in our laboratory and will be reported in due course.

General Procedure of the Asymmetric Aldol Reaction in Water
A mixture of catalyst **12** (4.7 mg, 0.01 mmol) and ketone (1.0 mmol) in H₂O (0.5 mL) was stirred for 30 min at r.t. The corresponding aldehyde (0.1 mmol) was added, and the mixture was stirred for 4.5–72 h. The mixture was extracted with CH₂Cl₂ (2 × 5 mL). The organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The aldol product was obtained through flash chromatography on silica gel (PE–EtOAc, 4:1). The dr and ee values were determined by chiral HPLC analysis.

(S)-2-[(R)-Hydroxy(4-nitrophenyl)methyl]cyclohexanone (Table 3, Entry 1)
Reaction time 24 h; yield 100%; dr (*anti/syn*) = 97:3, ee (*anti*) = 97%.

¹H NMR (400 MHz, CDCl₃): δ (*anti* diastereomer) = 8.21 (d, *J* = 8.4 Hz, 2 H), 7.51 (d, *J* = 8.8 Hz, 2 H), 4.90 (dd, *J* = 2.8 Hz, *J* = 8.4 Hz, 1 H), 4.07 (d, *J* = 3.2 Hz, 1 H), 2.36–2.61 (m, 3 H), 2.09–2.14 (m, 1 H), 1.36–1.85 (m, 6 H); δ (*syn* diastereomer) = 8.21 (d, *J* = 8.4 Hz,

Table 4 Extension of the Scope of Aldol Donors^a

Entry	Aldol donors	Time (h)	Yield (%) ^b	dr ^c (<i>anti/syn</i>)	ee (%) ^c (<i>anti</i>)
1	acetone	72	n.r.	–	–
2	cyclopentanone	29	95	46:54	89
3	<i>N</i> -Boc-4-piperidone	72	90	52:48	78
4	pentan-3-one	72	n.r.	–	–
5	pentan-2-one	72	n.r.	–	–
6	propionaldehyde	72	n.r.	–	–
7	isobutyraldehyde	72	n.r.	–	–
8	tetrahydropyran-4-one	72	n.r.	–	–
9	tetrahydrothiopyran-4-one	72	81	81:19	90

^a Reactions conditions (unless noted otherwise): *p*-nitrobenzaldehyde (0.1 mmol), ketone (1.0 mmol), catalyst **12** (10 mol%), TFA (10 mol%), H₂O (0.5 mL), at r.t.

^b Isolated yield; n.r. = no reaction.

^c Determined by chiral HPLC analysis.

2 H), 7.49 (d, $J = 8.8$ Hz, 2 H), 5.49 (s, 1 H), 3.17 (d, $J = 2.8$ Hz, 1 H), 2.36–2.65 (m, 3 H), 2.10–2.13 (m, 1 H), 1.51–1.88 (m, 6 H). HPLC separation conditions: Chiralcel AD, solvent: hexane-*i*-PrOH = 90:10, flow rate = 1.0 mL/min, $\lambda = 254$ nm; t_R (syn) = 13.33 min; t_R (syn) = 15.62 min; t_R (anti, minor) = 17.31 min and t_R (anti, major) = 22.91 min.

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Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

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