Novel Axially Unfixed Biaryl-Based Water-Compatible Organocatalysts: Design, Synthesis and Their Asymmetric Catalysis in Direct Aldol Reactions in Water

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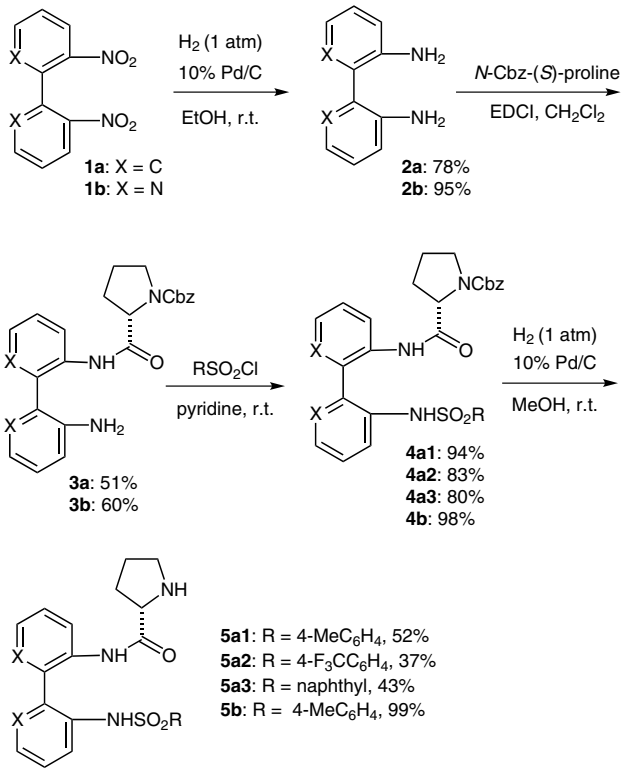
Abstract: A family of novel axially unfixed biaryl-based, water-compatible bifunctional organocatalysts were designed and synthesized for asymmetric catalytic direct aldol reactions in water. These organocatalysts are comprised of prolinamide, aromatic sulfonamide and biaryl motifs. Under the optimal reaction conditions, one organocatalyst in particular delivered excellent stereocontrol (up to 99% ee and 99:1 dr) in direct aldol reactions of cyclohexanone with a variety of aromatic aldehydes in water.

Key words: axially unfixed biaryl, water, organocatalysts, aldol reaction, stereoselectivity

The asymmetric organocatalytic aldol reaction constitutes one of the most important and powerful protocols for the formation of C–C bonds in organic chemistry[1] and has found many successful applications in the synthesis of bioactive molecules and natural products.[2] It is well documented that most asymmetric organocatalytic aldol reactions can be performed efficiently in various organic solvents under mild reaction conditions, however, the use of water as the reaction solvent in such reactions has attracted a great deal of attention from organic chemists because water is safe, cheap and environmentally benign.[3] Recently, Barbas[4] and Hayashi[5] succeeded in using proline-derived hydrophobic organocatalysts to catalyze direct organocatalytic aldol reactions in water stereoselectively. Normally, these reactions in water may suffer from low yields and stereoselectivities due to interference by water in the transition states of the reactions.[6] However, organocatalysts that are sufficiently hydrophobic in nature can sequester water from the transition states and thereby create a highly concentrated organic phase for the aldol reactions. Thus, in the presence of such hydrophobic organocatalysts, organocatalytic aldol reactions can proceed with highly efficient stereocontrol and with fast reaction rates in water.[7]

Herein, we report the design, synthesis and asymmetric catalysis of novel bifunctional organocatalysts for asymmetric direct aldol reactions in water. As shown in Scheme 1, the newly designed organocatalysts **5a1**–**a3** and **5b** mainly consist of prolinamide, aromatic sulfonamide and biaryl moieties. We reasoned that these organocatalysts, which feature both bifunctional and hydrophobic components, can activate aldol donors through the enamine mechanism and aldol acceptors through hydrogen-bonding interactions simultaneously in water. It was anticipated that the organocatalysts, which possess a hydrophobic biaryl, are able to assemble with the hydrophobic reactants more efficiently in water, and thus deliver high stereocontrol as a result of a reduced number of contacts with water in the reaction transition states. Moreover, the installation of an axially unfixed biaryl in the designed organocatalysts may afford them favorable conformational properties responsible for efficient chiral induction on the one hand; on the other hand, the same axially unfixed biaryl may also endow the organocatalysts with advantages of high modularity and versatility as well as easy synthesis without the need for resolution.[8]



Scheme 1 Synthesis of organocatalysts **5a1**–**a3** and **5b**

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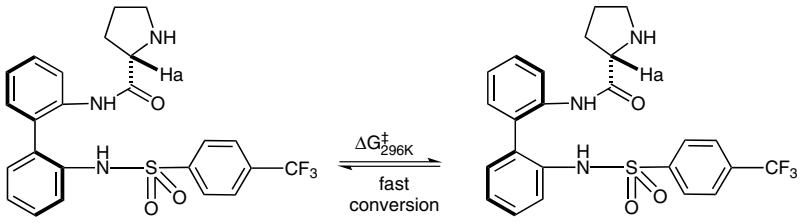


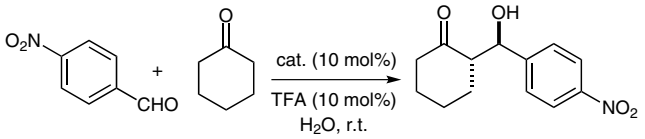
(*aR*,*S*)-**5a2** (*aS*,*S*)-**5a2**

Scheme 2 Interconversion between diastereoisomers (*aR*,*S*)-**5a2** and (*aS*,*S*)-**5a2** at room temperature

According to Scheme 1, organocatalysts **5a1**–**a3** and **5b** were prepared in 37–99% yields (see details in the Supporting Information). Based on the coalescence temperature (341 K) identified by variable-temperature ^{1}H NMR spectroscopic analysis of compound **5a2**, the rotation barrier $\Delta G^{\ddagger}_{296k}$ of the biaryl subunit of **5a2** was unambiguously calculated to be 16.6 kcal/mol by means of Erying equations.[9] Thus, it is reasonable to conclude that two diastereoisomers (*aR*,*S*)-**5a2** and (*aS*,*S*)-**5a2** can easily interconvert and, as a consequence, they are not separable from each other at room temperature, as shown in Scheme 2.[10] In addition, with an aim of simplifying the splitting patterns of the ^{1}H and ^{13}C NMR spectra of **5a1**–**a3**, their ^{1}H and ^{13}C NMR spectra were also collected at 341 K (see details in the Supporting Information).

Initially, as summarized in Table 1, with the axially unfixed organocatalysts **5a1**–**a3** and **5b** in hand, their asymmetric catalytic performance was examined in the asymmetric direct aldol reaction of cyclohexanone with *p*-nitrobenzaldehyde in water in the presence or absence of TFA as an additive. Evidently, the catalytic efficiencies of these organocatalysts were changed with the introduction of different biaryl and aromatic sulfonamide moieties.

Table 1 Screening of Biaryl Organocatalysts[a]



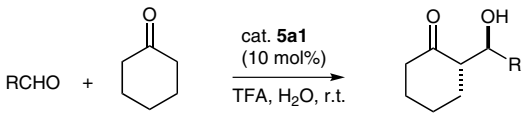
Entry	Catalyst	Time (h)	Yield (%)[b]	dr (*anti*/*syn*)[c]	ee (%) (*anti*)[c]
1	**5a1**	12	99	97:3	97
2	**5a2**	12	92	97:3	97
3	**5a3**	24	97	98:2	97
4	**5b**	24	64	83:17	27
5[d]	**5a1**	12	96	91:9	91

[a] Reaction conditions: *p*-nitrobenzaldehyde (0.1 mmol), cyclohexanone (1.0 mmol, 104.0 μL), catalyst (10 mol%), TFA (10 mol%, 0.8 μL), H_2O (0.5 mL), r.t.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] In the absence of TFA.

Generally, biphenyl organocatalysts **5a1**–**a3** exhibited higher stereocontrol than **5b** in the direct aldol reactions (Table 1, entries 1–3 vs. 4). In the case of organocatalysts **5a1**–**a3**, the aldol adducts were delivered with excellent dr and ee values. It is worth mentioning that under the catalysis of **5a3**, which bears a bulky naphthyl group, the aldol reaction proceeded slowly, furnishing the desired product in 97% yield after 24 h (Table 1, entry 3). It was also found that when the reaction was performed in the absence of TFA as an additive, organocatalysts **5a1** continued to deliver the aldol adduct in high yield, but with a slightly lower stereoselectivity (Table 1, entries 1 vs. 5). Therefore, as an acidic additive, TFA was necessary to enable the tested organocatalysts to produce high levels of asymmetric induction in the aldol reactions. Taking account of the reaction rates and stereocontrol achieved with all of the organocatalysts tested, **5a1** was identified as the most efficient organocatalyst in the aldol reaction.

The reaction conditions were optimized further by screening catalyst loadings, solvents and additives (see details in the Supporting Information). Under the optimized reaction conditions (**5a1**, TFA, H_2O, r.t.), we broadened the scope of the reaction of cyclohexanone with a wide variety of aromatic aldehydes (Table 2). Notably, in most cases, the aromatic aldehydes afforded the desired aldol adducts in excellent diastereoselectivities (up to 99:1 dr, *anti*/*syn*) and enantioselectivities (up to 99% ee, *anti*) (Table 2, entries 1–3 and 5–9). Evidently, the chemical yields of the aldol reactions were closely associated with the chemical structure of the R group of the aromatic aldehydes. It was found that benzaldehydes substituted with a strong electron-withdrawing group on the benzene ring tended to form the aldol adducts in high to excellent yields (Table 2, entries 1–3 and 5–6). In contrast, starting from benzaldehydes bearing a weak electron-withdrawing or an electron-donating group on the benzene ring, the desired aldol adducts were often obtained in either trace amount or in low to moderate yields (Table 2, entries 4 and 7–10). In addition, organocatalyst **5a1** also worked reasonably well with the heteroaromatic aldehydes, and afforded the corresponding aldol adducts in high stereoselectivities (Table 2, entries 12 and 14). Moreover, it should be noted that without TFA as an additive, in the case of pyridine-4-aldehyde, the reaction rate of the aldol reaction slowed down drastically, and delivered the desired product in

Table 2 Extending of the Scope of the Reaction with Aromatic Aldehydes[a]



Entry	R	Time (h)	Yield (%)[b]	dr (%) (*anti*/*syn*)[c]	ee (%) (*anti*)[c]
1	4-$O_2NC_6H_4$	12	99	97:3	97
2	3-$O_2NC_6H_4$	14	92	97:3	99
3	2-$O_2NC_6H_4$	14	84	99:1	99
4	4-$MeOC_6H_4$	45	trace	–	–
5	4-$F_3CC_6H_4$	22	>99	96:4	97
6	4-NCC_6H_4	14	99	98:2	97
7	4-ClC_6H_4	29	60	96:4	95
8	4-BrC_6H_4	29	61	97:3	95
9	4-FC_6H_4	29	45	91:9	97
10	4-MeC_6H_4	45	26	89:11	87
11	Ph	45	20	95:5	93
12	4-pyridyl	9	>99	86:14	91
13	2-furyl	45	trace	–	–
14	2-thienyl	45	61	91:9	91
15[d]	4-pyridyl	21	75	88:12	87

[a] Reaction conditions: aromatic aldehyde (0.1 mmol) and cyclohexanone (1.0 mmol, 104.0 μL), catalyst **5a1** (10 mol%), TFA (10 mol%, 0.8 μL), H_2O (0.5 mL), r.t.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] In the absence of TFA.

75% yield after 21 h and with 88:12 dr and 87% ee (Table 2, entry 15).

Finally, under the same optimal reaction conditions described above, the scope of the aldol reaction was extended further by submitting a range of carbonyl compounds as aldol donors to the reaction with *p*-nitrobenzaldehyde (Table 3). The aldol reaction of acetone with *p*-nitrobenzaldehyde provided the aldol adduct in 29% yield with 65% ee after a reaction time of 27 h. In the case of other acyclic ketones and aldehydes, the aldol reactions did not take place even after extending the reaction time to 50 h (Table 3, entries 2–5). A series of cyclic ketones was also tested to extend the scope of the aldol reactions. The aldol reaction of cyclopentanone with *p*-nitrobenzaldehyde proceeded smoothly and afforded the aldol adduct in high yield and moderate stereoselectivity after a reaction time of 18 h (Table 3, entry 6). Under identical reaction conditions, use of *N*-Boc-4-piperidone as substrate led to the formation of the aldol adduct in 89% yield with 82:18 dr and 89% ee. To our surprise, even after a reaction time of 72 h, application of the substrate tetrahydropyran-4-one did not give the corresponding aldol product (Table 3, entry 8). The same was also observed with tetrahydropyran-4-one substrate when water was substituted by *i*-PrOH as the reaction solvent (Table 3, entry 9). With tetrahydrothiopyran-4-one, catalyzed by **5a1** together with TFA as a cocatalyst in water, the aldol reaction took place with excellent diastereoselectivity and enantioselectivity, and when water was replaced by *i*-PrOH as the reaction solvent, the aldol reaction proceeded with similar diastereoselectivity and enantioselectivity (Table 3, entries 10 vs. 11).

With the aim of shedding some light on the observed stereochemical outcome obtained with organocatalyst **5a1**, we speculated that the transition state illustrated in Figure 1 may be relevant. In the proposed model, catalyst **5a1** exhibits a bifunctional organocatalytic nature. Cyclohexanone, as an aldol donor, was activated through the formation of enamine with the aid of the acidic additive, and simultaneous activation of the aromatic aldehyde as an aldol acceptor was realized through the two hydrogen-bond interactions. Subsequent attack on the *Re* face of the well-oriented aromatic aldehyde of the enamine formed in situ resulted in the formation of the desired aldol adduct with high stereocontrol.

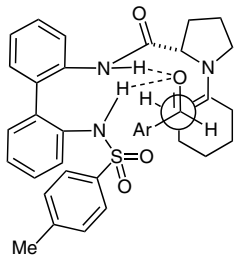


Figure 1 Proposed transition states for the aldol reaction under catalysis of **5a1**

In conclusion, a class of novel organocatalysts bearing an axially unfixed biaryl motif have been designed and synthesized for asymmetric organocatalytic direct aldol reactions in water.[11] Under the optimized reaction conditions, organocatalyst **5a1** performed with high efficiency, and showed excellent enantio- and diastereoselectivities in the aldol reactions in water. Further studies on the organocatalytic mechanism 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.

Acknowledgment

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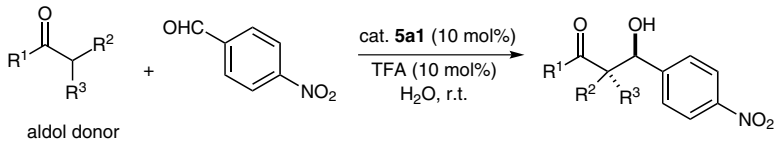
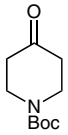
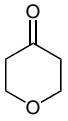
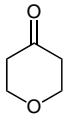
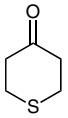
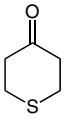
Table 3 Extending of the Scope of the Reaction with the Aldol Donor[a]



Entry	Aldol donor	Time (h)	Yield (%)[b]	dr (*anti*/*syn*)[c]	ee (%) (*anti*)[c]
1	acetone	27	29	–	65
2	pentan-3-one	50	nr	–	–
3	pentan-2-one	50	nr	–	–
4	propionaldehyde	50	nr	–	–
5	isobutyraldehyde	50	nr	–	–
6		18	98	34:66	69
7		27	89	82:18	89
8		72	nr	–	–
9[e]		48	nr	–	–
10		72	41	95:5	96
11[d]		48	50	97:3	95

[a] Reaction conditions (unless noted otherwise): *p*-nitrobenzaldehyde (0.1 mmol), acyclic aldol donor (1.0 mmol), **5a1** (10 mol%), TFA (10 mol%), in H_2O (0.5 mL), r.t.
[b] Isolated yield (nr: no reaction).
[c] Determined by chiral HPLC analysis.
[d] *i*-PrOH as solvent.

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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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(11) **Asymmetric Aldol Reaction in Water; General Procedure:** A mixture of catalyst **5a1** (4.3 mg, 0.01 mmol) and ketone (0.1 mmol) in H_2O (0.5 mL) was stirred at r.t. for 30 min. The corresponding aldehyde (0.1 mmol) was added and the mixture was stirred for 12–54 h. The mixture was extracted with CH_2Cl_2 (2 × 5 mL) and the organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The aldol product was obtained through flash chromatography on silica gel (petroleum ether–EtOAc, 4:1). The dr and ee values were determined by chiral HPLC analysis.
(*S*)-2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone (Table 2, entry 1): Reaction time: 12 h. Yield: 99%; dr = 97:3 (*anti*/*syn*); ee = 97% (*anti*). ^{1}H NMR (400 MHz, $CDCl_3$): δ (*anti*) = 8.21 (d, *J* = 8.4 Hz, 2 H), 7.51 (d, *J* = 8.8 Hz, 2 H), 4.90 (dd, *J* = 2.8, 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). ^{1}H NMR (400 MHz, $CDCl_3$): δ (*syn*) = 8.21 (d, *J* = 8.4 Hz, 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 (Chiralcel AD; hexane–*i*-PrOH, 90:10; 1.0 mL/min; λ = 254 nm): t_R = 16.68 (*syn*), 20.79 (*syn*), 23.11 (*anti*, minor), 30.89 (*anti*, major) min.

