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Asymmetric aldol reaction organocatalyzed by bifunctional *N*-prolyl sulfinamides under solvent-free conditions†

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A class of chiral bifunctional *N*-prolyl sulfinamide and its TFA salts were prepared and proven to be effective for catalyzing the aldol reaction under solvent-free conditions. In general, the corresponding aldol adducts were obtained with high to excellent yields, and satisfactory diastereo-selectivities and enantioselectivities. A matching effect between chiral proline and sulfinamide moieties was observed in the catalysts. The enantioswitching of both enantiomers in the asymmetric aldol synthesis is found to be dominated by the prolyl moiety.

Introduction

Since the pioneering work reported by B. List and co-workers in 2000,[1] the application of organocatalyzed protocols in asymmetric reactions has been well recognized due to the practical advantages of these compared to transition-metal catalysed procedures.[2] Very recently, C. Sparr reported an organocatalytic atroposelective aldol condensation, successfully providing axially chiral biaryls by arene formation.[3] D. MacMillan described an organocatalytic photoredox-based approach to the asymmetric α-amination of aldehydes *via* the direct coupling of functionalized nitrogen and formyl precursors.[4] B. List developed a chiral disulfonimide organocatalyst in the efficient asymmetric Mannich reaction of silyl ketene acetals with amino sulfones.[5] Though great progress in the organocatalytic asymmetric synthesis has been achieved in the past few years, most of the asymmetric organocatalytic reactions are equilibrium processes, which often need a huge excess of reactant, high catalyst loading, polar solvents and long reaction times. Thus, in pursuit of a more efficient and environmentally friendly process, the application of aqueous or solvent-free reaction conditions in asymmetric organocatalyzed processes should be regarded as an improvement in the synthesis of complex molecules.[6]

The aldol reaction is one of the most powerful strategies in the stereocontrolled preparation of small optically active molecules, since it provides the formation of new C–C bonds. In past years, several solvent-free reaction conditions based on proline derivatives as organocatalysts have been developed in the direct aldol reaction, in order to overcome the drawbacks of asymmetrical organocatalysis.[7] At present, bifunctional activation of both acceptor and donor has been widely accepted as an important strategy in proline-catalyzed asymmetric aldol reaction.[8] In this bifunctional catalysis, a nucleophilic enamine as a donor is generated, while hydrogen bonding to the acceptor is regarded as one of the criteria for the desired asymmetric induction. Following these principle approaches, new and efficient bifunctional organocatalysts by using various acidic N–H bonds of amides, sulfonamide and acylsulfonamides have been developed for asymmetric reactions.[9] For example, E. Juaristi developed a dipeptide-type organocatalysts in the asymmetric aldol reaction under solvent-free conditions.[10] T. Miura reported efficient asymmetric aldol reaction catalyzed by a fluorous organocatalyst of β-aminosulfonamide.[11]

As part of our interest in developing bifunctional organocatalysts for environmentally-benign asymmetric processes, herein we report a class of easily prepared, cheap, and fine tunable chiral bifunctional organocatalysts by combining two stereogenic centers to *N*-prolyl sulfinamide. Additionally, the double chiral elements in this organocatalyst are also expected to realize the asymmetric organocatalysis. These two stereogenic centers would act favourably (matched) or unfavourably (mismatched) for stereocontrol of the desired prochiral substrates in the asymmetric aldol reaction. The matched cases would lead to dramatically higher asymmetric induction in the products. Meanwhile, an efficient enantioswitching of the synthesized enantiomers is expected to be achieved through the modification of chiral center of the organocatalyst. In this context, four bifunctional organocatalysts of neutral *N*-prolyl sulfinamides **4a**, its corresponding TFA salts **4b**, **4c**, and the

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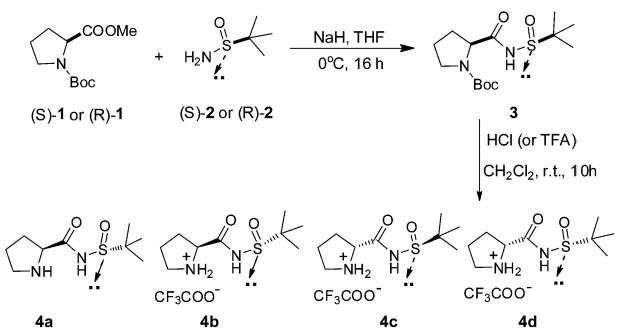
diastereoisomer **4d** were prepared. Their applications in asymmetric aldol reaction under solvent-free condition were explored. In addition, attempts to develop methods of selectively producing each one of the enantiomers with high enantiomeric excess through asymmetric aldol reactions catalyzed by enantiomeric or diastereoisomeric organocatalysts have also been performed.

Results and discussion

The synthetic procedures for catalysts **4a–4d** are shown in Scheme 1. The reaction of Boc-protected proline with *R* (or *S*)-*tert*-butylsulfinamide provided **3**, which was then treated with hydrochloric acid or trifluoroacetic acid (TFA), through deprotecting the Boc-group to give neutral **4a** in moderate yields. Catalysts of TFA salts **4b**, **4c** and **4d** were also synthesized for comparison of their reactivity and efficiency. These compounds were purified by flash column chromatography and characterized by ^{1}H NMR, ^{19}F NMR, ^{13}C NMR spectra. All results were in full agreement with the proposed structures. Following the same procedure, these catalysts could be easily prepared on a gram scale.

A colorless single crystal of organocatalyst **4b** (ESI†) was obtained by diffusion of hexane into its ethyl acetate solution and the absolute stereochemistry was further confirmed by single crystal X-ray diffraction analysis in order to elucidate its molecular structure (Fig. 1). It is found that catalyst **4b** has an orthorhombic crystal lattice as shown from the XRD crystal structure. There exist a $CF_3COO\cdots H–N$ hydrogen bonds (2.774 Å) between trifluoroacetate anion and the pyrrolidine NH, and one amidic $N–H\cdots OCOCF_3$ hydrogen bond (2.725 Å) with the molecule stacked in the adjacent molecular stacking. The *tert*-butyl group was placed far from the trifluoroacetate.

Initially, the direct aldol reaction of cyclohexanone with 4-nitrobenzaldehyde catalyzed by **4b** as a model process was evaluated (Table 1). All reactions were carried out in the presence of 20 mol% of catalyst **4b** at room temperature in different solvents. Unfortunately, most reactions failed after stirring for several days even in the polar protic solvent of MeOH. To our delight, the experiment in solvent of CH_2Cl_2 and DMSO, afforded the aldol adduct $\mathbf{7a_1}$ in moderate yield with reasonable enantioselectivity (entries 4 and 5). The absolute configuration



Scheme 1 Synthesis of *N*-prolyl sulfinamide **4a**, TFA salts of **4b**, **4c** and **4d**.

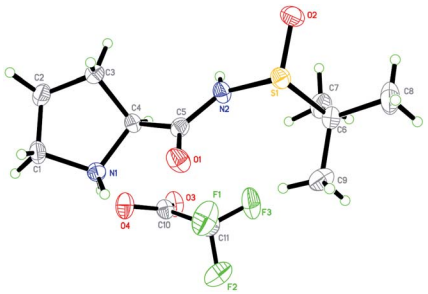


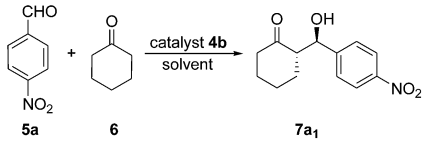
Fig. 1 ORTEP drawing of X-ray crystal structure of **4b**.

of the resulted adduct was determined by comparison of the value of the optical rotation with that of previously described and was found to (2*S*,1′*R*).[12] A slight improvement of yield, stereoselectivity was observed when a small amount of water was added in the polar aprotic solvent of DMSO (entry 6). Significantly, excellent results of yield, diastereo- and enantioselectivity were achieved when solvent-free condition was employed, in which the excess of ketone was limited to less than five equivalents (entry 7). Reducing the catalyst loading from 20 mol% to 0.5 mol% apparently affected the efficiency of the reaction, resulting in the decrease of yield, and poorer diastereo- and enantioselectivity, while maintaining the reaction temperature at 25 °C (entries 7–10). To our delight, the catalyst performance was improved when decreasing the loading of the catalyst to only 5 mol% and lowering the reaction temperature from 25 °C to 0 °C, giving the best result of the aldol product $\mathbf{7a_1}$ in 96% yield with 98 : 2 *anti*/*syn* ratio and 96% ee value (entry 11). As expected, the reaction required prolonged reaction time at 0 °C. When the reaction temperature was further lowered down to −10 °C, an increase in reaction time of six days was required without remarkable improvement of diastereo- and enantioselectivity (entry 12). It was found that the reaction became sluggish and the stereoselectivity was not improved when the reaction temperature was further lowered to −20 °C (entry 13). The yield was sacrificed remarkably and a much prolonged reaction time was required to ensure a complete conversion. Elevated reaction temperature from 0 °C to 15 °C also decreased the reaction efficiency with only 86% ee value (entry 14).

Moreover, application of neutral catalyst **4a** in the absence of any Brønsted acid was also investigated in this solvent-free aldol reaction. It was found that only reasonable enantioselectivity with 82% ee value was presented in this condition (Table 1, entry 15). Screening various Brønsted acids, such as HCl, HOAc, CF_3COOH, Benzoic acid, *p*-toluenesulfonic acid, as a cocatalyst with catalyst **4a** in the solvent-free aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde indicated that loading 5 mol% TFA enabled the completion of the reaction in three day with 95% yield, and 94 : 6 dr, 95% ee.

Based on all of the above results, the scope of the solvent-free aldol reaction of various aromatic benzaldehydes with cyclohexanone was examined to test the substrate generality (Table 2). All reactions were performed in solvent-free system in presence of 5 to 10 mol% of catalyst either at ambient

Table 1 Optimization of reaction conditions between cyclohexanone and *p*-nitrobenzaldehyde[a]



Entry	Solvent	Catalyst[c] (mol %)	Time (day)	Yield[d] (%)	dr[e] *anti*/*syn*	ee[f] (%)
1	Toluene	20	1	Trace	—	—
2	CH_3OH	20	1	Trace	—	—
3	THF	20	1	Trace	—	—
4	CH_2Cl_2	20	1	75	—	68
5	DMSO	20	1	70	90 : 10	75
6	DMSO/H_2O (10/1)	20	1	93	93 : 7	80
7	Neat	20	1	98	95 : 5	94
8	Neat	10	1	92	94 : 6	89
9	Neat	1	2	92	92 : 8	89
10	Neat	0.5	2	60	89 : 11	83
11	Neat[b] (0 °C)	5	3.5	97	98 : 2	96
12	Neat[b] (−10 °C)	5	6	90	98 : 2	96
13	Neat[b] (−20 °C)	5	6	40	98 : 2	96
14	Neat[b] (15 °C)	5	1	98	94 : 6	86
15	Neat[b] (0 °C)	5[g]	3	97	86 : 14	82

[a] Unless otherwise stated, reaction conditions were as follows: cyclohexanone (2.5 mmol), *p*-nitrobenzaldehyde (0.5 mmol), temperature (25 °C), and indicated solvents. [b] Reaction at indicated temperature. [c] Catalyst **4b** for indicated loading. [d] Isolated yield. [e] Determined by ^{1}H NMR of the crude product. [f] Determined by chiral-phase HPLC analysis for the *anti* isomer. [g] Reaction conducted with catalyst **4a**.

temperature or at 0 °C. The nitro, cyano, trifluoromethyl, fluoro, were chosen as electron-withdrawing groups, and the furanyl substituent as representative electron-donating group. It could be seen that a wide range of aromatic aldehydes effectively participated in the aldol reaction, and both enantiomers of aldol adducts **7a–7k** derived from their corresponding aromatic aldehydes and cyclohexanone could be accessed, when enantiomeric catalysts (*S*,*R*)-**4b** and (*R*,*S*)-**4c** were applied in this direct aldol reaction. In all cases, the *anti* aldol products were obtained as major isomers and the chemical yield, diastereo- and enantioselectivity, and the reaction rates were found to obviously depend upon the position and nature of the substituents on the aromatic moiety.

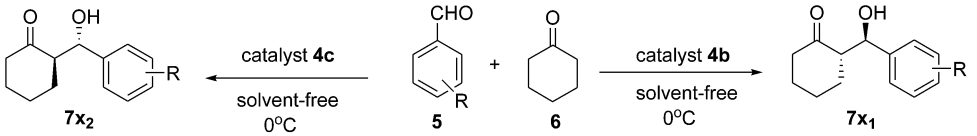
It was appreciated in Table 2 that benzaldehydes substituted by electron-withdrawing groups, such as nitro, cyano, could be converted to the corresponding *anti*-aldol products in moderate to high yields and enantioselectivities, the latter within 87–98% ee range (entries 1–9). Excellent enantioselectivity (ee 98%) and diastereoselectivity (*anti*/*syn* > 99 : 1) were observed when 3-nitrobenzaldehyde was employed as the acceptor (entry 2). The products **7d**, **7e** and **7f** (entries 4–6) bearing cyano, trifluoro or 2,4-dichloro substitution were obtained in comparable selectivity with those of aldol adducts with nitro substitution. The reaction of 4-bromo and 4-chloro benzaldehydes with cyclohexanone gave the aldol adducts **7g** and **7h** in moderate yields with good enantioselectivities (entries 7 and 8). In some cases, the 10 mol% of catalyst loading was applied in order to improve the reactivities (entries 5–8). On the other hand, use of the less reactive substrate of benzaldehyde, such as **5j**, heterocyclic 2-furaldehyde **5k**, provided moderate yield and acceptable ee value (entries 10 and 11). In general, very similar results are obtained for the enantiomeric aldol adducts, including the yields, de and ee values which are within the experimental errors, when the enantiomeric catalysts of **4b** and **4c** were applied in the reactions.

To compare the catalytic efficiency and selectivity of the two diastereomeric catalytic systems of **4b** (or **4c**) with **4d**, we further examined the asymmetric reaction of representative substrates of **5a–5f** with cyclohexanone catalyzed by **4d** in the model solvent-free aldol reaction (Table 3). Disappointingly, much poorer enantioselectivities and prolonged reaction times were presented with catalyst (*R*,*R*)-**4d**, compared with those catalyzed by its diastereoisomers (*S*,*R*)-**4b** or (*R*,*S*)-**4c**. As is shown in Table 2, the enantiomeric catalysts (*S*,*R*)-**4b** and (*R*,*S*)-**4c** afforded much higher activities and enantioselectivities under the same reaction conditions.

When studying the aldol reaction catalyzed by diastereoisomers of (*S*,*R*)-**4b** and (*R*,*R*)-**4d**, it was found that a pair of enantiomers of aldol adducts (2*S*,1′*R*) and (2*R*,1′*S*) were afforded, respectively. A reversed sense of asymmetric induction was presented, indicating that switching configuration of prolyl moiety from *S* to *R* mainly provided the stereochemical control of the reaction. These results indicated that, an efficient enantioswitching of the aldol adducts could be achieved through the modification of the prolyl structure.

Another important finding was that the same (2*R*,1′*S*)-enantiomer of the product was formed when diastereoisomeric catalyst (*R*,*S*)-**4c** or (*R*,*R*)-**4d** was applied, regardless of their overall backbone, suggesting that the chirality of prolinamide backbone overrides the other bias imposed by the sulfinyl

Table 2 Aldol reaction of cyclohexanone with substituted benzaldehydes under solvent-free conditions[a]



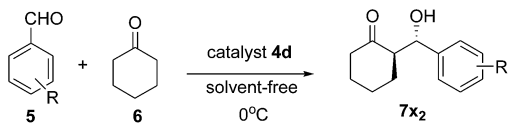
Entry	ArCHO	Product	Catalyst (mol%)	Time (day)	Yield[b] (%)	dr[c] *anti*/*syn*	ee[d] (%)
1	4-$NO_2C_6H_4$ **5a**	**7a$_1$**	5[e]	3.5	97	98 : 2	96
		7a$_2$	5[f]	3.5	95	>99 : 1	94
2	3-$NO_2C_6H_4$ **5b**	**7b$_1$**	5[e]	5	94	>99 : 1	98
		7b$_2$	5[f]	5	92	>99 : 1	94
3	2-$NO_2C_6H_4$ **5c**	**7c$_1$**	5[e]	5	95	>99 : 1	96
		7c$_2$	5[f]	5	93	95 : 5	90
4	4-CNC_6H_4 **5d**	**7d$_1$**	5[e]	5	95	96 : 4	95
		7d$_2$	5[f]	5	95	97 : 3	92
5	4-$CF_3C_6H_4$ **5e**	**7e$_1$**	10[e]	4	66	95 : 5	94
		7e$_2$	10[f]	4	71	92 : 8	94
6	2, 4-ClC_6H **5f**	**7f$_1$**	10[e]	6	66	90 : 10	93
		7f$_2$	10[f]	6	70	89 : 11	94
7	4-BrC_6H_4 **5g**	**7g$_1$**	10[e]	6	53	97 : 3	91
		7g$_2$	10[f]	6	45	96 : 4	90
8	4-ClC_6H_4 **5h**	**7h$_1$**	10[e]	6	40	96 : 4	89
		7h$_2$	10[f]	6	38	97 : 3	87
9	2-Naphthyl **5i**	**7i$_1$**	10[e]	6	45	95 : 5	93
		7i$_2$	10[f]	6	50	94 : 6	90
10[g]	4-HC_6H_4 **5j**	**7j$_1$**	10[e]	6	80	91 : 9	74
		7j$_2$	10[f]	6	83	90 : 10	69
11[g]	2-Furanyl **5k**	**7k$_1$**	10[e]	6	70	66 : 34	57
		7k$_2$	10[f]	6	62	68 : 32	54

[a] The reaction were performed with 0.5 mmol of aldehyde, 2.5 mmol of cyclohexanone, in the presence of organocatalyst as indicated loading at temperature of 0 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude product. [d] Determined by chiral-phase HPLC analysis for the *anti* isomer. [e] The reaction was performed in the presence of catalyst **4b**. [f] The reaction was performed in the presence of catalyst **4c**. [g] The reaction were performed in the presence of organocatalyst as indicated loading at temperature of 25 °C.

skeleton chirality. The configuration of the enantiomer of the aldol adduct is predominated by prolyl moiety. This unique chiral environment with *R*-configuration of prolyl moiety and *S*-configuration of sulfinyl moiety may act as suitably matching effect, which would be attributed to the higher catalytic activities and enantio-selectivities obtained in this aldol reactions catalyzed by (*R*,*S*)-**4c**. However, *R*-configuration of prolyl moiety mismatched the *R*-configuration of sulfinyl moiety in catalyst of (*R*, *R*)-**4d**, resulting in relatively low catalytic activity and low enantioselectivity.

Compared with bifunctional organocatalyst of (*S*)-*N*-(methylsulfonyl) pyrrolidine-2-carboxamide which possesses

Table 3 Studies of aldol reaction with catalyst **4d**[a]



Entry	ArCHO	Product	Catalyst (mol%)	Time (day)	Yield[b] (%)	dr[c] *anti*/*syn*	ee[d] (%)
1	4-$NO_2C_6H_4$ **5a**	**7a$_2$**	5	5	88	90 : 10	38
2	3-$NO_2C_6H_4$ **5b**	**7b$_2$**	5	5	50	82 : 18	65
3	4-CNC_6H_4 **5d**	**7d$_2$**	5	5	32	67 : 33	33
4	4-$CF_3C_6H_4$ **5e**	**7e$_2$**	10	5	25	70 : 30	49
5	2, 4-ClC_6H_4 **5f**	**7f$_2$**	10	5	34	73 : 27	42

[a] The reaction were performed with 0.5 mmol of aldehyde, 2.5 mmol of cyclohexanone, in the presence of catalyst **4d** as indicated loading at temperature of 0 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude product. [d] Determined by chiral-phase HPLC analysis for *anti* isomer.

only one stereogenic center derived from chiral proline moiety, the (*S*, *R*)-*N*-prolyl sulfinamide **4a** or its TFA salts (*S*,*R*)-**4b** synthesized in this work provided an additional chiral center from sulfinamide moiety. In contrast to the asymmetric direct aldol reaction catalyzed by (*S*)-*N*-(methylsulfonyl) pyrrolidine-2-carboxamide, in which moderate yield and enantioselectivity were observed,[13] the aldol reaction in this work proceed well through the doubly stereocontrolled organocatalyst **4b**, affording high to excellent yield, satisfactory diastereo-selectivities and enantioselectivities. These results indicated that the introduction of the additional stereogenic center of the sulfinamide moiety (*S*) to the matched proline (*R*) would apparently improve the diastereo- and enantioselectivity in the asymmetric aldol reaction.

Finally, the feasibility of using other cyclic and acyclic ketones as aldol donors using **4b** as catalyst was investigated. As shown in Table 4, acyclic acetone **8a** provided moderate enantioselectivity and yield along with prolonged reaction time (entry 1). In case of cyclic ketone having five membered ring, cyclopentanone **8b** provided high yield with moderate diastereoselectivity and reasonable enantioselectivity under the model reaction condition (entry 2). Lowering the reaction temperature down to −20 °C gave poor yield and prolonged reaction time required, without remarkable improvement of enantioselectivity (entry 3). Cycloheptanone **8c** having seven membered ring afforded much poor reactivity, which resulted in much lower yield even at higher reaction temperature of 25 °C and with more catalyst loading. It only provided moderate diastereo- and low enantioselectivity (entry 4).

An unexpected reversal of the diastereoselectivity was observed in the case of cyclopentanone (Table 4, entry 2), in which the *syn* product was found to be the predominant diastereomer, In all cases, the reactions in this work provided reasonable to high *anti* stereoselectivity except cyclopentanone applied in this aldol reactions.[14]

The possible mechanism in the aldol reaction catalyzed by proline and its derivatives has been extensively discussed, with the enamine formation being assumed.[15] To account for the stereochemical outcome of our study catalyzed by *N*-prolyl sulfinamide **4a–4d** in this work, we propose that the *N*-prolyl sulfinamide catalyst could catalyze the direct aldol reaction *via* the plausible transition state shown in Fig. 2.

The pyrrolidine moiety in bifunctional organocatalyst **4b** reacts with cyclohexanone to form nucleophilic enamine. The carbonyl group of the aldehyde could be greatly activated by hydrogen bonding with amide proton of the prolinamide unit of the catalyst **4b**, because of the inductive electron-withdrawing effect of the sulfinyl group, which can remarkably acidify the N–H bond. The *tert*-butyl group is located far from the reaction center, due to its strong steric hindrance. Thus, the favoured transition-state, **TS1** is predicted in Fig. 2. On the other hand, the phenyl group of benzaldehyde has a severe steric interaction with *tert*-butyl group, presenting the unfavoured transition-state **TS2** (Fig. 2). The approach of the aldehyde in the favourable **TS1** is facile and the enantioselective C–C bond formation takes places on the *re*-face of the aldehyde, leading to (2*S*,1′*R*)-isomer.

Meanwhile, the attractive interaction between the electron pair from chiral sulfinyl group and the electron-deficient aromatic ring, which contains strong electron-withdrawing substituents, such as NO_2-, 2,4-dichloro-, can also stabilize the favoured transition state of **TS1**. As a result, much higher ee values were obtained in this work when benzaldehydes substituted by strong electron-withdrawing groups were applied. However, benzaldehydes with electron-donating

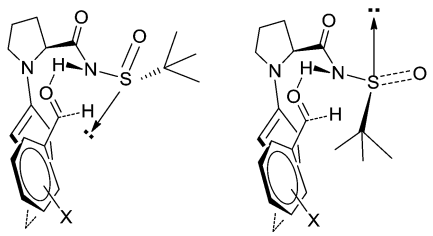
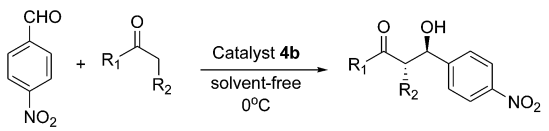


Fig. 2 Proposed transition state for the aldol reaction of cyclo-hexanone catalyzed by (*S*,*R*)-**4b**.

Table 4 Aldol reaction of acyclic or cyclic ketones with 4-nitrobenzaldehyde under solvent-free conditions[a]



Entry	R_1	R_2	Product	Catalyst (mol%)	Time (day)	Yield[b] (%)	dr[c] *anti*/*syn*	ee[d] (%)
1	CH_3–**8a**	H	**7l$_1$**	5	6	40	86 : 14	50
2	–$(CH_2)_3$–**8b**		**7m$_1$**	5	2.5	95	36 : 64	74
3	–$(CH_2)_3$–**8b**		**7m$_1$**	5[e]	6	43	35 : 65	81
4	–$(CH_2)_5$–**8c**		**7n$_1$**	10[f]	6	45	70 : 30	36

[a] The reaction were performed with 0.5 mmol of aldehyde, 2.5 mmol of cyclohexanone, in the presence of catalyst **4b** as indicated loading at temperature of 0 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude product. [d] Determined by chiral-phase HPLC analysis for the major isomer. [e] At temperature of −20 °C. [f] At temperature of 25 °C.

groups only afforded lower enantioselectivities in this aldol reaction, due to the repulsive interaction in **TS1** between the electron-rich aromatic ring and the electron pair from chiral sulfinyl group.

Conclusions

In summary, bifunctional *N*-prolyl sulfinamide and TFA as co-catalyst were applied in catalytic reaction under solvent-free conditions. The aldol products were obtained with high to excellent yield, diastereo- and enantioselectivities. The selectivity data revealed that the matched system in catalysts (*S*,*R*)-**4b** or (*R*,*S*)-**4c** afforded much higher yield and enantioselectivity, in contrast to their diastereoisomer of (*R*,*R*)-**4d**. The presence of the chiral prolyl scaffold within the backbone of the catalysts predominates the configuration of the aldol adducts. An efficient chirality switching in the asymmetric aldol addition was presented through the modification of the configuration of the prolyl moiety.

Acknowledgements

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