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Synthesis of Chiral Organocatalysts derived from Aziridines: Application in Asymmetric Aldol Reaction

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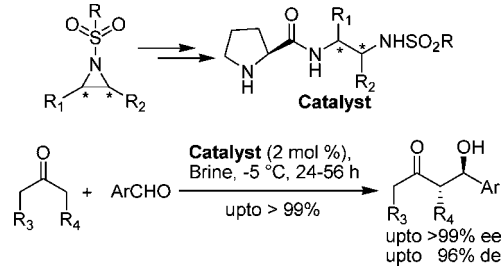

We report the synthesis of a new series of highly efficient chiral organocatalysts derived via the regio- and stereoselective ring opening of chiral aziridines with azide anions. The catalysts have proved to be very efficient for a direct asymmetric aldol reaction, both with cyclic as well as acyclic ketones in brine with 2 mol % of catalyst loading, and afforded the products in excellent yields (up to 99%) and enantioselectivities (up to >99%). The chiral aldol adduct obtained has further been converted to a chiral azetidine ring via a convenient pathway.

Introduction

Aziridines, small three-membered heterocycles, have attracted considerable attention owing to their striking chemical properties.[1] The high strain energy associated with the aziridine ring enables easy cleavage of the C−N bond. Therefore, aziridines can either undergo ring cleavage reactions with a range of nucleophiles[2,3] or cycloaddition reactions with dipolarophiles.[4] Both of these reactions have been extensively explored in organic synthesis leading to the formation of synthetically and pharmacologically useful compounds.[1,5] For the last decade, we have been actively involved in the chemistry of aziridines.[3,4a,b] Since these small molecules possess many interesting properties, in the past few years, the chemistry of chiral, nonracemic aziridines has also attracted much interest.[1b,6] The ability of these molecules to undergo regio- and stereoselective ring opening has been widely exploited for the synthesis of biologically active chiral compounds.[6a,c,7] An important transformation is the ring opening of chiral aziridines by using azides as nucleophiles that leads to the formation of products which can easily be converted to chiral functionalized amines. We have, hence, applied this chemistry for an efficient synthesis of a series of chiral compounds which have the potential to act as chiral organocatalysts in asymmetric synthesis.

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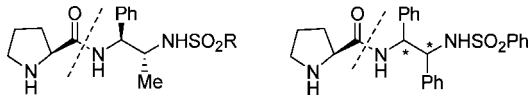
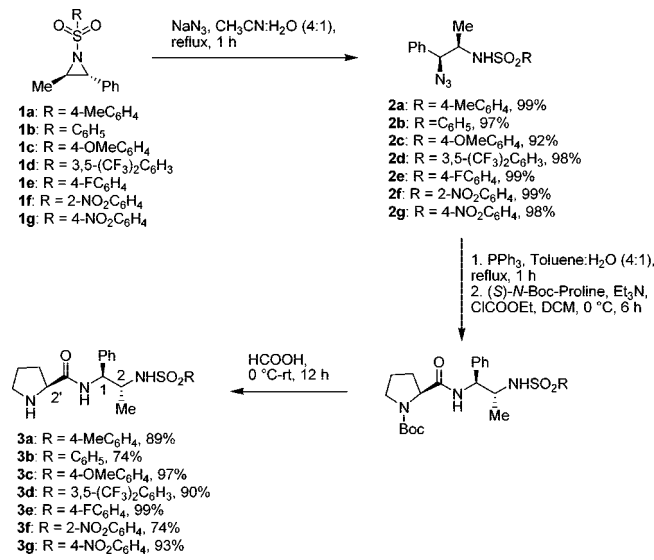


FIGURE 1. Organocatalysts derived from L-proline and β-amino sulfonamides.

Remarkable advances have been made in the field of asymmetric organocatalysis over the past few years.[8] In the realm of reactions catalyzed by organic molecules, the asymmetric aldol reaction has been an area of intense research.[9] The recent trend is toward the use of organocatalysts which can efficiently catalyze the aldol reaction in an aqueous medium since water is a safe, economical, and environmentally benign solvent.[10,11a] We have recently reported an asymmetric aldol reaction catalyzed by an organocatalyst derived from L-proline and a β-amino alcohol.[11] It will be interesting to study the change in performance of the catalyst when the β-amino alcohol in the same catalyst is replaced by a β-amino sulfonamide. Here, we disclose the synthesis of an organocatalyst derived from L-proline and a β-amino sulfonamide (Figure 1) and its application in a direct asymmetric aldol reaction. Gratifyingly, the catalyst has worked remarkably well in an aqueous medium, making it further useful from the perspective of green chemistry. We have further shown the application of aldol adduct by converting it to a chiral azetidine ring. This N-containing four-membered heterocycle is one of the important structural motifs in modern synthetic chemistry.[12] The aldol adduct obtained by the reaction between a cyclic ketone and aldehyde was converted to a bicyclic fused ring system. A cyclohexane ring fused with an azetidine ring finds applications in the synthesis of analogues of paclitaxel (Taxol) and docetaxel (Taxotere).[13]

SCHEME 1



Results and Discussion

The chiral aziridines, required as precursors for the synthesis of organocatalysts, were synthesized in two steps starting from (1*S*,2*R*)-norephedrine as per the literature known procedure.[4a] Thus, a series of chiral aziridines **1a**−**g** with different *N*-sulfonyl groups was prepared. The azidolysis of activated aziridines was carried out with NaN_3. The reaction proceeded in a regio- and a stereoselective manner, leading to diastereomerically pure β-azido sulfonamides **2a**−**g**. The reduction of the azide group with triphenylphosphine led to the synthesis of β-amino sulfonamides, which were then directly coupled to (*S*)-*N*-Boc proline. The Boc protecting group was then cleaved by using formic acid leading to the synthesis of final catalysts in high yields. A series of catalysts **3a**−**g** with different sulfonamide groups was thus prepared (Scheme 1).

For catalyst **3**, the chirality of proline will dictate the stereochemistry of the product. But there are two other chiral centers C-1 and C-2 in the catalyst. To figure out the stereochemistry at C-1 and C-2 that will match/mismatch with the stereochemistry of proline to effect stereoselectivity in the reaction, catalysts **6a**−**d** were synthesized (Scheme 2). The synthesis started with the two enantiomers of 2-amino-1,2-diphenylethanol. The amino group was first sulfonylated with benzenesulfonyl chloride. The four diastereomers of β-azido sulfonamide were then prepared via two different reaction sequences. The sulfonamide protected amino alcohols were cyclized to form C-2 symmetric aziridine rings (**4a** and **4b**) which were then opened up with NaN_3 to form **5a** and **5b**, respectively. In the second pathway, the alcohols were first mesylated and then knocked off by using azide as a nucleophile forming **5c** and **5d**. Starting from the two pure enantiomers of amino alcohol, these two pathways led to the synthesis of four diastereomers of β-azido sulfonamides (**5a**−**d**). Further, following the same reaction sequence as in the synthesis of catalysts **3a**−**g**, the synthesis of four diastereomers **6a**−**d** was accomplished.

After successful completion of the synthesis of the catalysts, we decided to evaluate their role in a direct organocatalytic aldol reaction. At the outset, to optimize the reaction conditions, a series of reactions were carried out between cyclohexanone and 4-fluorobenzaldehyde as the substrates and **3a** as the catalyst.

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SCHEME 2

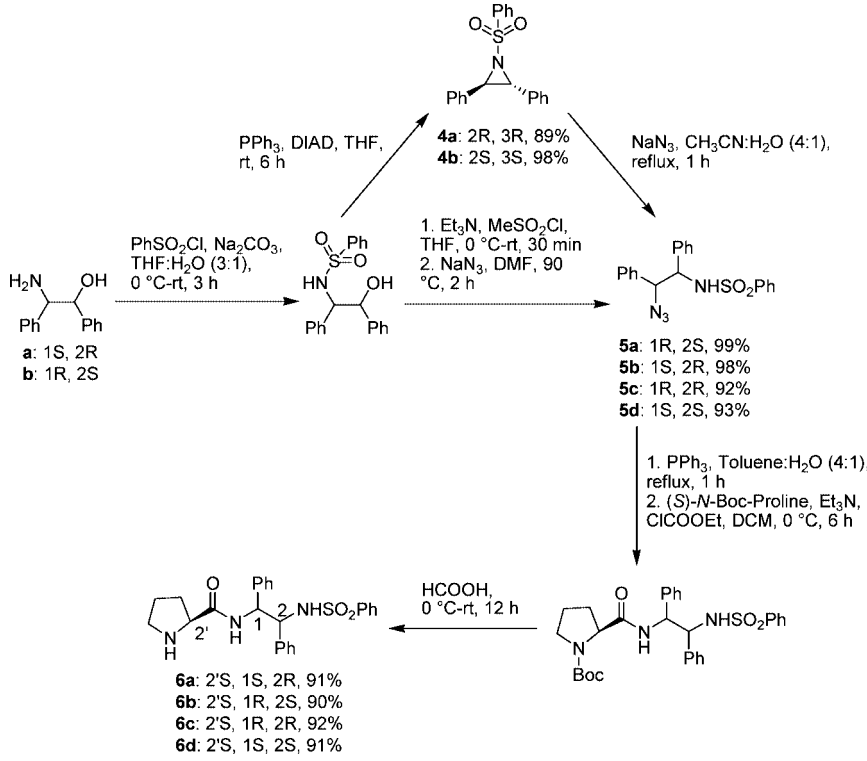
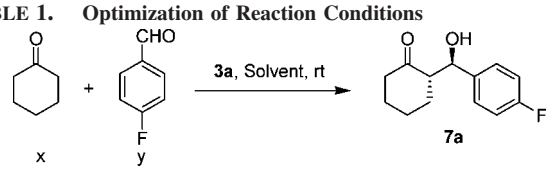


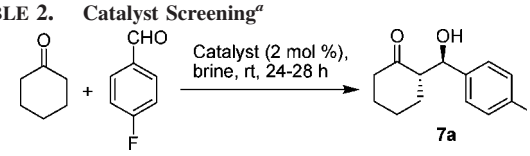
TABLE 1. Optimization of Reaction Conditions



entry	catalyst mol %	solvent	x:y	time, h	% yield	anti/syn[a]	% ee (anti)[b]
1	15	$CHCl_3$	4:1	72			
2	15	DMF	4:1	72			
3	15	H_2O	4:1	12	91	73:27	48
4	5	H_2O	4:1	16	82	87:13	75
5	2	H_2O	4:1	24	82	93:07	80
6	2	H_2O	10:1	20	85	93:07	79
7	2	H_2O	2:1	30	73	90:10	76
8	1	H_2O	4:1	30	78	92:08	84
9	5	brine	4:1	22	85	89:11	84
10	2	brine	4:1	24	87	94:06	86
11	1	brine	4:1	36	75	93:07	89

[a] Determined by ^{1}H NMR analysis. [b] Determined by HPLC with chiral column.

TABLE 2. Catalyst Screening[a]



entry	catalyst	% yield	anti/syn[b]	% ee (anti)[c]
1	**3a**	87	94:6	86
2	**3b**	82	93:7	84
3	**3c**	85	91:9	83
4	**3d**	69	91:9	86
5	**3e**	76	92:8	87
6	**3f**	71	92:8	88
7	**3g**	78	92:8	84
8	**6a**	75	91:9	89
9	**6b**	75	92:8	87
10	**6c**	78	92:8	90
11	**6d**	76	92:8	87

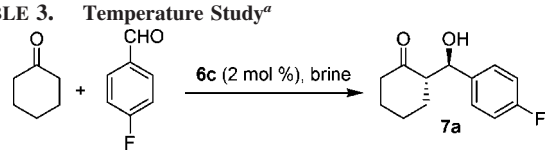
[a] Ratio of ketone:aldehyde was 4:1 in all the cases. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC with chiral column.

No product was formed when the reaction was carried out in organic solvents such as $CHCl_3$ and DMF with 15 mol % of the catalyst (Table 1, entries 1 and 2). However, on changing the reaction medium to water, the product was formed in high yield and moderate enantio- and diastereoselectivity (Table 1, entry 3). When the catalyst loading was decreased to 5 mol %, a major enhancement in ee was observed (Table 1, entry 4). There was still further enhancement in ee on decreasing the catalyst loading to 2 mol % without any loss in yield (Table 1, entry 5). No positive effect was observed on the reaction when the ratio of cyclohexanone to 4-fluorobenzaldehyde was changed from 4:1 to 10:1 (Table 1, entry 6). Decreasing the amount of cyclohexanone had a negative effect on both ee as well as yield (Table 1, entry 7). When brine was used as the solvent, there was still further enhancement in ee (Table 1, entries 9−11). Best results were obtained when 2 mol % of the catalyst was used in brine, which was thus used for further studies (Table 1, entry 10).

After optimizing the reaction conditions, the series of catalysts **3a**−**g** and **6a**−**d** were then evaluated for the reaction (Table 2). However, to our surprise, all the catalysts gave the products in high ee, yield as well as diastereoselectivity. Catalyst **6c** being slightly superior to the others was thus used for further studies (Table 2, entry 10).

To improve the enantioselectivity, we then studied the effect of temperature on the reaction (Table 3). Decreasing the temperature from rt to 0 °C−rt and then to 0 °C increased the ee as well as diastereoselectivity (Table 3, entries 1−3). Best results were obtained when the reaction was carried out at −5

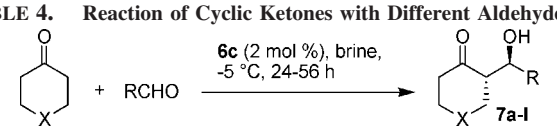
TABLE 3. Temperature Study[a]



entry	temp, °C	time, h	% yield	anti/syn[b]	% ee (anti)[c]
1	rt	24	78	92:8	90
2	0 to rt	28	73	94:6	94
3	0	30	71	96:4	95
4	−5	40	67	96:4	>99
5	−10	48	55	97:3	96

[a] Ratio of ketone:aldehyde was 4:1 in all the cases. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC with chiral column.

TABLE 4. Reaction of Cyclic Ketones with Different Aldehydes[a]



entry	X	R	product	% yield	anti/syn[b]	% ee (anti)[c]
1	CH_2	4-F-C_6H_4	**7a**	67	96:4	>99
2	CH_2	C_6H_5	**7b**	82	98:2	96
3	CH_2	4-OMe-C_6H_4	**7c**	60	93:7	85
4	CH_2	4-CN-C_6H_4	**7d**	99	93:7	82
5	CH_2	4-Cl-C_6H_4	**7e**	92	97:3	94
6	CH_2	4-NO_2-C_6H_4	**7f**	95	90:10	81
7	CH_2	4-Me-C_6H_4	**7g**	75	97:3	95
8[d]	CH_2	4-CF_3-C_6H_4	**7h**	99	97:3	90
9	CH_2	2-naphthyl	**7i**	82	98:2	93
10	CH_2	2-furyl	**7j**	77	98:2	92
11[e]		4-NO_2-C_6H_4	**7k**	75	92:8	93
12[e]	S	C_6H_5	***7l***	83	94:6	89

[a] Ratio of ketone:aldehyde was 4:1 in all the cases. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC with chiral columns. [d] Reaction was carried out at −25 °C. [e] Ratio of ketone:aldehyde was 2:1.

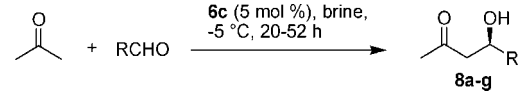
°C and the ee increased to >99% (Table 3, entry 4). Further decrease in temperature resulted a drop in both ee as well the yield of the reaction (Table 3, entry 5).

A variety of aromatic aldehydes were then tested by using cyclic ketones as donors (Table 4). High enantioselectivities were obtained in almost all the cases. Aldehydes such as naphthaldehyde and furaldehyde also formed the products in high yields and enantioselectivities (Table 4, entries 9 and 10). Apart from cyclohexanone, cyclic ketones such as cyclopentanone and tetrahydrothiopyran-4-one also afforded the aldol adducts in high enantio- and diastereoselectivities (Table 4, entries 11 and 12).

The reaction was then extended to acetone and a variety of aromatic aldehydes were explored (Table 5). Again, high enantioselectivities were obtained in almost all the cases. The aldehyde having an electron-withdrawing group gave low enantioselectivity as compared to all other aldehydes (Table 5, entry 7).

The proposed transition state model to explain the stereochemical outcome of the reaction is shown in Figure 2. The model has been explained by using benzaldehyde as the electrophile and can be generalized to all other aromatic aldehydes. The aldehyde is activated by bifurcated H-bonding with NH of amide as well as NH of sulfonamide as shown in TS1 and TS2. TS2 is unfavored because of nonbonding interactions between the aromatic ring of aldehyde and the bulky amino sulfonamide moiety. Therefore, the C−C bond formation

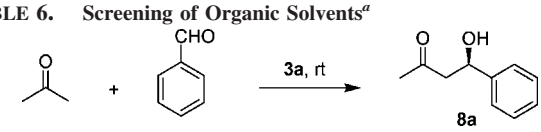
TABLE 5. Reaction of Acetone with Different Aldehydes[a]



entry	R	product	% yield	% ee[b]
1	C_6H_5	**8a**	75	89
2	4-F-C_6H_4	**8b**	80	86
3	3-OMe-C_6H_4	**8c**	72	86
4	4-Cl-C_6H_4	**8d**	78	82
5	3-Br-C_6H_4	**8e**	70	84
6	3-Me-C_6H_4	**8f**	68	88
7	4-CF_3-C_6H_4	**8g**	93	67

[a] Ratio of ketone:aldehyde was 4:1 in all the cases. [b] Determined by HPLC with chiral columns.

TABLE 6. Screening of Organic Solvents[a]



entry	catalyst mol %	solvent	time, h	% yield	% ee[b]
1	15	pyridine	24	66	74
2	15	DMF	48	53	72
3	15	DMSO	48	45	70
4	15	acetonitrile	36	74	73
5	15	THF	30	78	79
6	15	dioxane	48	68	75
7	15	*c*	12	84	77
8	10	*c*	36	74	72
9	20	*c*	10	78	71
10	25	*c*	8	68	68

[a] Ratio of ketone:aldehyde was 4:1 in all the cases. [b] Determined by HPLC with chiral column. [c] Reaction was carried out in neat acetone (1 M).

takes place from the *re*-face of aldehyde as shown in TS1. When the reaction is carried out in an aqueous medium, the water molecules form H-bonding with the amide groups and the aldehyde as shown in TS3. There was no effect of stereochemistry at C-1 and C-2 on ee of the reaction when the reaction was carried out in an aqueous medium (Table 2). We anticipated that in organic solvents, since there is a direct H-bonding between the aldehyde and the N−H groups of amide and sulfonamide, there may be an observed effect of stereochemistry at C-1 and C-2 on the reaction. We studied a variety of organic solvents for the reaction between acetone and benzaldehyde to find a suitable solvent for study (Table 6). Best results were obtained in neat acetone. We then carried out the reaction with catalysts **6a**−**d**, in both acetone as well as brine, and compared the two results (Table 7). As expected, there was no effect of changing stereochemistry at C-1 and C-2 on ee of the reaction when the reaction was carried out in an aqueous medium (Table 7, condition B). Surprisingly, the change in stereochemistry at C-1 had no effect on ee of the reaction when an excess of acetone was used as the solvent (Table 7, condition A, entries 1 and 3). However, the change in stereochemistry at C-2 had a significant effect on ee of the reaction under the same conditions (Table 7, condition A, entries 2 and 4). The results can be explained by transition state models TS4 and TS5. When the stereochemistry at C-2 is inversed from R to S, there is a possibility of C−H−π interaction between the phenyl group at C-2 and hydrogen of the aromatic ring of benzaldehyde if the attack takes place from the *si*-face of aldehyde rather than the *re*-face (TS5). This interaction stabilizes TS5 to a certain extent

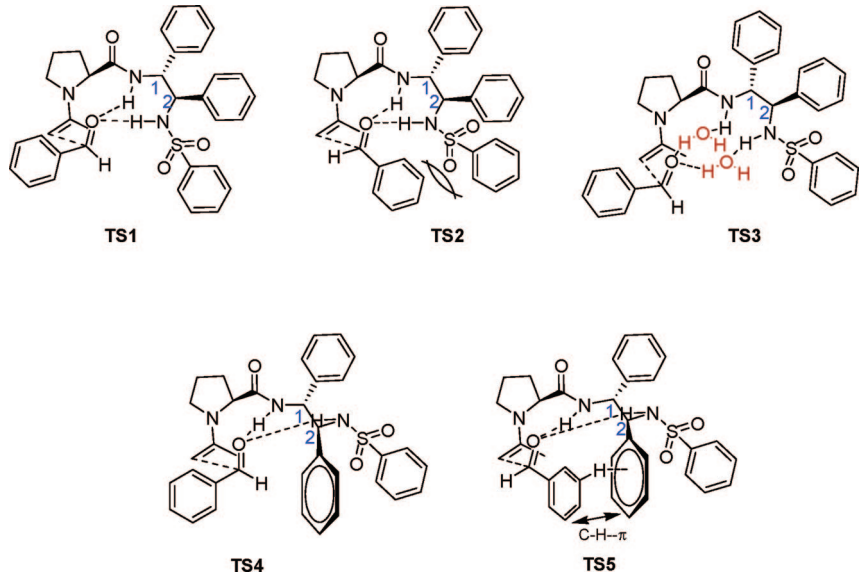
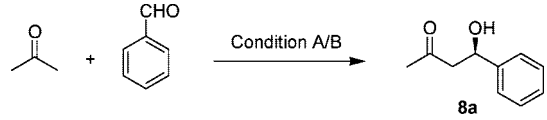


FIGURE 2. Proposed transition state model.

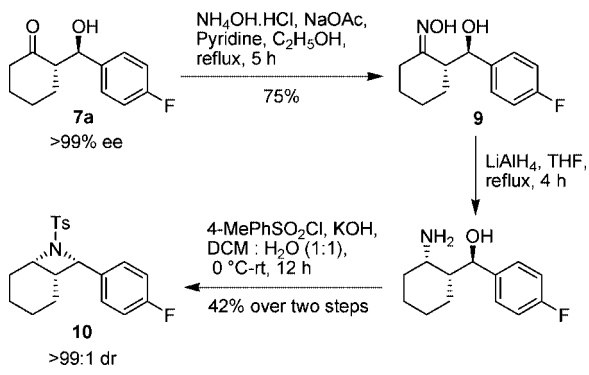
TABLE 7. Comparison of Results in Acetone and Brine



		condition A[a]			condition B[b]		
entry	catalyst	time, h	% yield	% ee	time, h	% yield	% ee
1	**6a**	24	78	82	30	70	82
2	**6b**	12	84	51	26	80	81
3	**6c**	8	93	82	24	75	89
4	**6d**	12	85	55	30	70	82

[a] Condition A: catalyst (15 mol %), acetone (1 M). [b] Condition B: catalyst (5 mol %), acetone:benzaldehyde (4:1), brine.

SCHEME 3



and hence leads to a drop in ee of the product. This C−H−π interaction is disturbed when the reaction is carried out in an aqueous medium because water molecules enter into the spaces between the catalyst and participate in H-bonding with the substrates and the catalyst. Hence, there is no observed effect of changing stereochemistry at C-1 and C-2 on the reaction in brine.

β-Hydroxy ketones, obtained as the products of the direct aldol reaction, contain two modifiable functional groups, which makes them highly valuable in organic synthesis. To show their applicability, the aldol adduct was converted to a chiral azetidine ring. The aldol adduct obtained by the reaction between cyclohexanone and 4-fluorobenzaldehyde was converted to a six- and a four-membered fused ring system.

The keto group was first converted to an oxime to form compound **9**, which was then reduced to form an amino alcohol (Scheme 3). Initial attempts to cyclize the amino alcohol to the azetidine ring failed. Even the use of benzoyl or benzyl as protecting groups for amine was not successful since the protected amine could not be cyclized. Finally, the amino alcohol was tosylated and cyclized in situ with KOH. The stereochemistry at the new chiral center was then assigned by NOE experiments (Figure 3). On irradiation of H_1, there was an enhancement in the peak intensity of H_2 and vice versa. This confirmed the stereochemistry at the new chiral center.

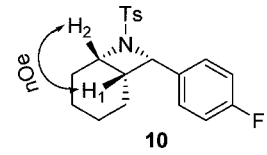


FIGURE 3. NOE studies for compound **10**.

Conclusion

In conclusion, we have synthesized a new series of highly efficient organocatalysts by regio- and stereoselective ring opening of aziridines with azide anions. The synthesis has been accomplished by coupling L-proline with a chiral β-amino sulfonamide. The catalysts have been evaluated for a direct asymmetric aldol reaction. The catalysts work efficiently in an aqueous medium and offer high yield and diastereo- and enantioselectivities. The results obtained have been rationalized on the basis of a proposed transition state model. Furthermore, the chiral aldol adduct has been derivatized to a chiral azetidine ring that finds a variety of applications in asymmetric organic synthesis.

Experimental Section

General Procedure for the Synthesis of Catalysts 3a−g. Formic acid (4.0 mL) was slowly added to *N*-Boc protected catalyst (1.0 mmol) at 0 °C and the mixture was subsequently stirred at rt for 12 h. Formic acid was then evaporated and reaction mixture

was neutralized with aqueous ammonia at 0 °C. The product was extracted with dichloromethane and the organic layer was washed with water and brine and dried over *anhydrous* Na_2SO_4. The organic layer was then concentrated and purified by column chromatography (10% MeOH−DCM) to give the pure catalyst.

(*S*)-*N*-((1*S*,2*R*)-2-(4-Methylphenylsulfonamido)-1-phenylpropyl)pyrrolidine-2-carboxamide (3a). Yield 89%; mp 160−162 °C; $[\alpha]^{25}_D$ −5.4 (*c* 1.0, $CHCl_3$); FT IR (KBr) 3357, 3326, 3212, 1658, 1511, 1332, 1152 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.65 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.31 (m, 5H), 7.18 (m, 2H), 4.84 (dd, J = 8.8, 2.9 Hz, 1H), 4.70 (m, 1H), 3.81 (dd, J = 9.0, 5.6 Hz, 1H), 3.70 (m, 1H), 3.04 (m, 1H), 2.96 (m, 1H), 2.43 (s, 3H), 2.17−2.01 (m, 2H), 1.84 (m, 1H), 1.69 (m, 2H), 0.80 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.1, 143.5, 137.6, 137.1, 129.7, 128.6, 127.9, 127.4, 127.1, 60.6, 56.4, 53.2, 47.1, 30.4, 26.0, 21.5, 17.8; HRMS (ESI) exact mass calcd for $C_{21}H_{27}N_3O_3S$ $[M + H]^+$ 402.1852, found 402.1852.

(*S*)-*N*-((1*S*,2*R*)-1-Phenyl-2-(phenylsulfonamido)propyl)pyrrolidine-2-carboxamide (3b). Yield 74%; mp 85−87 °C; $[\alpha]^{25}_D$ −11.2 (*c* 1.0, $CHCl_3$); FT IR (KBr) 3284, 3063, 1656, 1517, 1324, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.64 (d, J = 7.6 Hz, 1H), 7.88 (m, 2H), 7.55 (m, 3H), 7.31 (m, 3H), 7.16 (m, 2H), 4.83 (dd, J = 8.5, 2.9 Hz, 1H), 4.74 (d, J = 9.5 Hz, 1H), 3.80 (dd, J = 9.1, 5.6 Hz, 1H), 3.72 (m, 1H), 3.03 (m, 1H), 2.94 (m, 1H), 2.08 (m, 2H), 1.83 (m, 1H), 1.69 (m, 2H), 0.82 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.2, 140.5, 136.9, 132.7, 129.2, 128.7, 127.9, 127.4, 127.1, 60.5, 56.4, 53.3, 47.1, 30.4, 26.1, 17.9; HRMS (ESI) exact mass calcd for $C_{20}H_{25}N_3O_3S$ $[M + H]^+$ 388.1696, found 388.1691.

(*S*)-*N*-((1*S*,2*R*)-2-(2-Nitrophenylsulfonamido)-1-phenylpropyl)-pyrrolidine-2-carboxamide (3f). Yield 74%; mp 85−87 °C; $[\alpha]^{25}_D$ −86.0 (*c* 1.0, $CHCl_3$); FT IR (KBr) 3356, 1661, 1540, 1452, 1345, 1167 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.62 (m, 1H), 8.16 (m, 1H), 7.86 (m, 1H), 7.75 (m, 2H), 7.31 (m, 5H), 4.89 (dd, J = 8.2, 3.2 Hz, 1H), 3.95 (m, 1H), 3.78 (dd, J = 9.2, 5.6 Hz, 1H), 3.00 (m, 1H), 2.94 (m, 1H), 2.12 (m, 2H), 1.81 (m, 1H), 1.68 (m, 2H), 0.92 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.0, 147.8, 136.6, 134.4, 133.6, 133.0, 130.8, 128.8, 128.1, 127.4, 125.5, 60.5, 56.1, 53.6, 47.2, 30.4, 26.1, 18.1; HRMS (ESI) exact mass calcd for $C_{20}H_{24}N_4O_5S$ $[M + H]^+$ 433.1546, found 433.1548.

General Procedure for the Synthesis of Catalysts 6a−d. The same procedure was followed as in the case of synthesis of catalysts **3a−g**.

(*S*)-*N*-((1*S*,2*R*)-1,2-Diphenyl-2-(phenylsulfonamido)ethyl)pyrrolidine-2-carboxamide (6a). Yield 91%; mp 180−182 °C; $[\alpha]^{25}_D$ −22.4 (*c* 0.3, THF); FT IR (KBr) 3197, 1656, 1549, 1324, 1156 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.53 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 7.3 Hz, 2H), 7.39 (m, 1H), 7.26 (m, 5H), 7.07 (m, 3H), 6.79 (d, J = 6.7 Hz, 2H), 6.68 (d, J = 7.1 Hz, 2H), 5.20 (dd, J = 8.6, 3.4 Hz, 1H), 4.79 (m, 1H), 3.81 (dd, J = 9.3, 5.4 Hz, 1H), 2.99 (m, 1H), 2.85 (m, 1H), 2.08 (m, 1H), 1.83 (m, 1H), 1.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.7, 140.3, 136.5, 136.1, 132.4, 128.8, 128.5, 128.1, 128.0, 127.7, 127.4, 127.1, 125.6, 62.2, 60.5, 57.7, 47.2, 30.4, 26.2; HRMS (ESI) exact mass calcd for $C_{25}H_{27}N_3O_3S$ $[M + H]^+$ 450.1852, found 450.1850.

(*S*)-*N*-((1*R*,2*R*)-1,2-Diphenyl-2-(phenylsulfonamido)ethyl)pyrrolidine-2-carboxamide (6c). Yield 92%; mp 135−137 °C; $[\alpha]^{25}_D$ −6.3 (*c* 1.0, $CHCl_3$); FT IR (KBr) 3197, 1656, 1549, 1324, 1156 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.48 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 7.8 Hz, 2H), 7.39 (m, 1H), 7.24 (m, 5H), 7.07 (m, 3H), 6.79 (d, J = 7.2 Hz, 2H), 6.67 (d, J = 7.5 Hz, 2H), 5.82 (m, 1H), 5.18 (dd, J = 8.5, 3.2 Hz, 1H), 4.78 (m, 1H), 3.82 (dd, J = 9.1, 5.5 Hz, 1H), 2.99 (m, 1H), 2.85 (m, 1H), 2.10 (m, 1H), 1.80 (m, 2H), 1.69−1.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.4, 140.2, 136.3, 136.0, 132.3, 128.7, 128.5, 128.0, 127.8, 127.6, 127.3, 127.0, 62.1, 60.3, 57.7, 47.1, 30.4, 26.6; HRMS (ESI) exact mass calcd for $C_{25}H_{27}N_3O_3S$ $[M + H]^+$ 450.1852, found 450.1851.

A Representative Procedure for the Direct Aldol Reaction in Brine. An aldehyde (1.0 mmol) was added to a mixture of ketone (4 mmol) and the catalyst (0.02 mmol) in brine (1.0 mL) at the required temperature. The reaction mixture was stirred and the progress of the reaction monitored by TLC. After the completion of the reaction, the reaction mixture was diluted with EtOAc. The organic layer was separated, dried over *anhydrous* Na_2SO_4, and concentrated to give the crude product that was purified over silica gel by column chromatography. The enantiomeric excess (ee) of the aldol product was determined by chiral HPLC analysis.

Procedure for the Synthesis of Oxime 9. Hydroxylamine hydrochloride (1.5 mmol) was added to a solution of aldol adduct **7a** (1.0 mmol) in ethanol (4 mL). Sodium acetate (4.0 mmol) and pyridine (0.1 mmol) were then added and the solution was refluxed for 3 h. After the completion of the reaction, ethanol was evaporated under reduced pressure. The residue was diluted with water and extracted three times with DCM. The organic layer was washed with brine, dried over *anhydrous* Na_2SO_4, and concentrated to give the crude product. Column chromatography over silica gel (20% EtOAc/Hexane) gave the pure product.

(*R*)-2-((*R*)-(4-Fluorophenyl)(hydroxy)methyl)cyclohexanone oxime (9). Yield 75%; mp 124−125 °C; $[\alpha]^{25}_D$ +107.4 (*c* 0.85, $CHCl_3$); FT IR (KBr) 3268, 1604, 1512, 1432, 1223 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.31 (m, 2H), 7.03 (m, 2H), 4.76 (d, J = 9.0 Hz, 1H), 3.30 (m, 1H), 2.41 (m, 1H), 1.84−1.68 (m, 3H), 1.45−1.12 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.0, 137.2, 128.8, 128.7, 115.2, 115.0, 74.9, 49.9, 30.0, 25.6, 24.7, 24.3. Anal. Calcd for $C_{13}H_{16}FNO_2$: C, 65.81; H, 6.80; N, 5.90. Found: C, 65.93; H, 6.83; N, 5.92.

Procedure for the Synthesis of Product 10. $LiAlH_4$ (3.0 mmol) was added to THF (3.0 mL) at 0 °C. Oxime **9** (1.0 mmol) dissolved in THF (3.0 mL) was then added dropwise at the same temperature. The reaction mixture was allowed to warm to room temperature and then refluxed for 4 h. After the completion of reaction, the reaction mixture was cooled and quenched with ethyl acetate, 10% NaOH, and water. The solution was stirred for 30 min and filtered over celite. The residue was washed with ethyl acetate. *Anhydrous* Na_2SO_4 was added to the filterate, which was subsequently concentrated in vacuo to give the crude amino alcohol.

The crude amino alcohol was dissolved in DCM:water (1:1) (5 mL) and the solution was cooled to 0 °C. Potassium hydroxide (2.0 g) and *p*-toluenesulfonyl chloride (2.5 mmol) were then added and the solution was stirred at room temperature for 12 h. After the completion of reaction, the solution was diluted with DCM. The organic layer was extracted and washed with brine, dried over *anhydrous* Na_2SO_4, and concentrated to give the crude product, which on purification over silica gel (10% EtOAc/hexane) gave the pure compound **10**.

(1*R*,8*S*)-8-(4-Fluorophenyl)-7-tosyl-7-azabicyclo[4.2.0]octane (10). Yield 42%; dr >99:1; mp 90−92 °C; $[\alpha]^{25}_D$ +37.7 (*c* 0.3, $CHCl_3$); FT IR (KBr) 2925, 1337, 1154 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.30 (m, 2H), 7.08 (m, 4H), 6.80 (m, 2H), 4.91 (d, J = 7.5 Hz, 1H), 4.38 (m, 1H), 2.51 (m, 1H), 2.33 (s, 3H), 2.18 (m, 1H), 2.10 (m, 1H), 1.62 (m, 3H), 1.20 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.5, 161.6, 143.0, 137.5, 134.3, 129.2, 129.1, 127.4, 115.2, 115.0, 69.2, 61.9, 38.5, 26.9, 23.7, 21.5, 20.9, 20.1; HRMS (ESI) exact mass calcd for $C_{20}H_{22}FNO_2S$ $[M + H]^+$ 360.1435, found 360.1434.

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Supporting Information Available: General experimental procedures, characterization data including ^1H NMR spectra, ^{13}C NMR spectra for all compounds, and HPLC chromatograms for compounds **7a−*l*** and **8a−g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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