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Highly Efficient Small Organic Molecules for Enantioselective Direct Aldol Reaction in Organic and Aqueous Media

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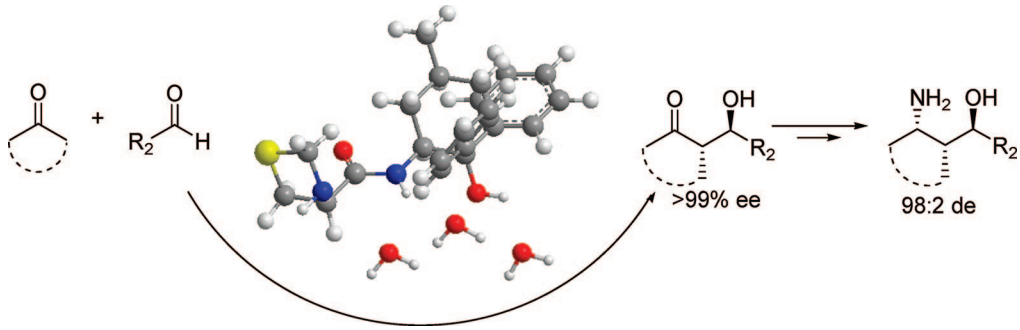

A series of highly efficient organocatalysts have been derived from naturally available amino acids for carrying out enantioselective direct aldol reaction in both organic and aqueous medium. The aldol products were obtained in high diastereoselectivities (up to 99:1) and enantioselectivities (up to >99% ee) for a broader range of substrates using 1 mol % of a catalyst. The results demonstrate that the structural features of organocatalysts play a crucial role in obtaining high optical purity of aldol adducts in an aqueous medium. Further, the role of water in increasing the rate and enantioselectivity of the reaction has been illustrated. Moreover, the aldol products have been employed in the synthesis of chiral amino alcohols which act as useful intermediates for building up complex natural products.

Introduction

Enantioselective C−C bond formation reaction catalyzed by chiral organic molecule (asymmetric organocatalysis)[1] has become an important area of research in organic synthesis. Aldol is one such reaction where a great emphasis has been given to design of new chiral organocatalysts,[2] mainly for two reasons: first, one can avoid the use of transition metals in the reaction, and second, the reaction can directly be done by taking aldol donors and acceptors.[3] The latter objective has been achieved previously with the use of heterobimetallic catalysts,[4] where preactivation of carbonyl compounds, like in the asymmetric Mukaiyama aldol reaction,[5] was not required. Proline has long been known for its use in asymmetric intramolecular aldol reaction.[6] The major breakthrough came from the findings by List,[7] Barbas,[8] and co-workers that L-proline could also act as a catalyst in the intermolecular direct aldol reaction. It functions as a "microaldolase" similar to type I aldolase enzyme.[9] Since

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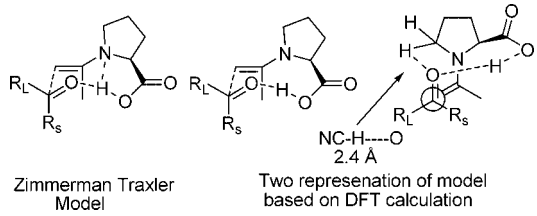

FIGURE 1. Transition-state models.

then, L-proline[10] and its derivatives[11] have been evaluated for use in enantioselective direct aldol reaction.

Organocatalyzed aldol reaction is presumed to proceed via an enamine intermediate. Initially, the enantiofacial selectivity was explained with a metal-free version of the Zimmerman−Traxler six-membered ring chairlike model[12] having a tricyclic hydrogen-bonded framework (Figure 1).[7a] Later, based on DFT calculations, the transition-state model was modified (Figure 1). This model indicates that the nitrogen of L-proline does not participate in hydrogen bonding with the carboxylic hydrogen, resulting in a nine-membered-ring-like transition state.[13] Second, enamine

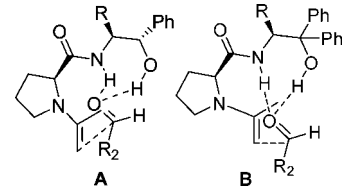

FIGURE 2. Design of new chiral organocatalysts.

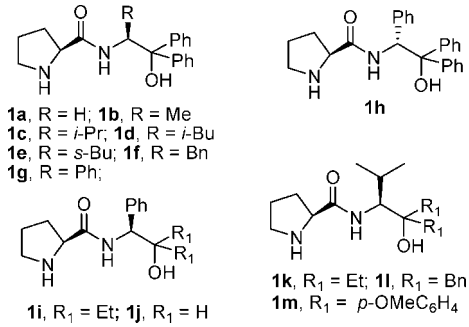

FIGURE 3. L-Proline-based organocatalysts.

formed should be *anti* to the carboxylic group, and in this *anti* arrangement, NCH--O also contributes to lowering the energy of the transition state [NCH--O (*anti*) distance = 2.44 Å vs NCH--O (*syn*) distance = 3.42 Å]. The main aspect of this model is that the transition state is stabilized through hydrogen bondings. Therefore, a small change in the pK_a value of an organic compound would affect its catalytic activity and selectivity in the aldol reaction.

It is a great challenge for organic chemists to find a suitable organic compound with an optimal pK_a so that excellent enantioselectivity can be obtained in the reaction. One such organic compound was synthesized by Gong et al. (**A**)[11a] (Figure 2). If the pK_a value of the hydroxyl group involved in the hydrogen bonding with the acceptor aldehyde is further increased, it would result in a structurally compact transition state that may ensure high enantioselectivity and reactivity. Based on the above rationale, we designed a small class of L-proline-based chiral organic molecules having a *gem*-diphenyl group which played a key role in realizing the goal (**B** as in Figure 2).[14]

In this paper, we have described full details of our work in this area. We have further synthesized a new series of small organic compounds from L-threonine, L-serine, and L-cysteine to determine the essential and beneficial criteria required in organocatalyst to obtain very high optical purity for direct aldol reaction in both organic and aqueous media. The methodology has been applied for the synthesis of chiral amino alcohol that acts as a useful intermediate for asymmetric organic synthesis and for building up complex natural products.

Results and Discussion

At the outset, the organic compounds (**1a**−**m**) were synthesized from L-proline and the corresponding β-amino alcohols (Figure 3).[14] These were evaluated as catalysts for the direct aldol reaction between benzaldehyde and acetone (Table 1). The reactions were done using 10 mol % of these compounds in an excess of acetone at different temperatures. Initially, a comparison was made among catalysts **1a**−**g** having different R

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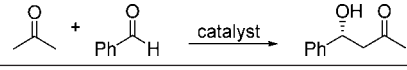
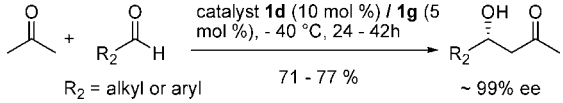
TABLE 1. Direct Aldol Reaction of Benzaldehyde with Acetone Catalyzed by Organocatalysts 1a−m[a]



entry	catalyst	*T* (°C)	time (h)	% yield	% ee[b]
1	**1a**	−40	48	64	89
2	**1b**	−40	48	52	99
3	**1c**	−40	26	62	92
4	**1d**	rt	03	68	92
5	**1d**	0	14	72	98
6	**1d**	−40	48	52	>99
7	**1e**	−40	24	55	79
8	**1f**	−40	48	53	95
9	**1g**	rt	06	71	84
10	**1g**	0	08	76	91
11	**1g**	−40	22	77	99
12	**1h**	rt	06	65	24
13	**1i**	−40	30	57	64
14	**1j**	−40	26	67	42
15	**1k**	−40	48	65	46
16	**1l**	−40	45	57	43
17	**1m**	0	06	67	59

[a] The reaction was carried out in neat acetone (1 M) using 10 mol % of the catalyst except for the catalysts **1g**, **1i**, and **1j** which were used in 5 mol %. [b] Determined by HPLC using a chiral column.

SCHEME 1. Direct Aldol Reaction of Acetone with Various Aldehydes



groups with (*S*)-configuration at the α-carbon while keeping a *gem*-diphenyl group constant at the *β*-carbon. The results showed that the chirality at α-carbon is not essential but beneficial for obtaining high enantioselectivity (entries 1 and 2, Table 1).

It is worth mentioning here that when the configuration of the phenyl substituent at the α-carbon (**1g** vs **1h**) was changed from *S* to *R*, the enantioselectivity dropped from 84 to 24% (entries 9 and 12). Further, to see the effect of the *gem*-diphenyl group (R_1) at the *β*-carbon, it was replaced by ethyl (**1i**) and H (**1j**) and then evaluated for the aldol reaction. These turned out to be poor at inducing asymmetric induction in the reaction (entries 13 and 14; 64% ee with **1i**; 42% ee with **1j**). The importance of the *gem*-diphenyl group at the *β*-carbon was further seen in compounds **1k** (R_1 = Et) and **1l** (R_1 = Bn), which gave poor asymmetric induction (entries 15 and 16; 43−46% ee) as compared to **1c** (R_1 = Ph), which gave 92% ee (entry 3) for the same reaction. When an electron-donating group was present on the *para* position of the phenyl group as in the case of **1m**, the effectiveness of the catalyst was depleted (entry 17, 59% ee). From Table 1, it became clear that the organic compounds **1d** (R = *i*-Bu) and **1g** (R = Ph) were found to be the best catalysts, providing excellent enantioselectivities of >99% at −40 °C. The advantage of catalyst **1g** is that it is effective even with low catalyst loading (5 mol %).

In order to increase the scope of the methodology, the aldol reaction of acetone was extended to several aromatic and aliphatic aldehydes using **1d** and **1g**. In all cases, excellent enantioselectivities (97−99% ee) were obtained (Scheme 1).[14] The catalyst **1d** appeared to be slightly superior to **1g** for inducing enantioselectivity in all of the substrates, especially in the case of an aliphatic aldehyde.[14]

It would be a win−win situation from a green chemistry perspective if high enantiocontrol could be achieved using small organic molecules in water.[15,16] Extensive research is going on to design small organic molecules that can carry out the asymmetric aldol reaction in water. Such organocatalysts were initially reported by Barbas,[17] Hayashi,[18] and Chimni.[19] These catalysts have the limitation of giving moderate enantioselectivity with water-miscible ketones such as acetone. The other existing organocatalysts, which work in aqueous medium, are also marked with few limitations such as the use of additives,[17,20] high loading of the catalyst,[20e,21] low substrate scope,[20b,21b,22] and requirement of ketone in excess where water acts only as an additive.[20a,d,e,23] Therefore, there is a great need for a chiral organocatalyst, which can surpass these drawbacks and which could be efficient from the viewpoint of both catalysis and reactivity.

For a catalyst to work preferentially well in an aqueous medium, it should contain sufficient hydrophobic groups. Our prolinamide catalysts (**1d** and **1g**) bearing nonpolar *gem*-diphenyl group fulfill this criteria. Therefore, these were tested for aldol reactions using water as a medium.[24] The reaction of acetone (2 mmol) with benzaldehyde (0.5 mmol) was studied by using different loadings of the catalyst **1** (10−0.5 mol %) in 0.5 mL of water/brine. It was observed that yields and ee's were

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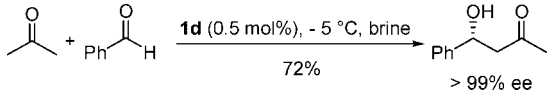
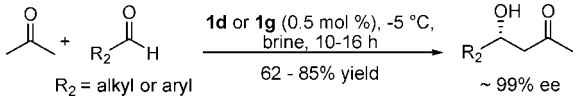
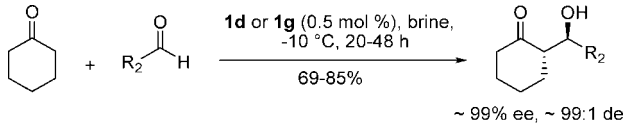
SCHEME 2. Optimized Reaction Conditions



SCHEME 3. Screening of Different Aromatic and Aliphatic Aldehydes with Acetone



SCHEME 4. Screening of Different Aromatic and Aliphatic Aldehydes with Cyclohexanone



superior in brine to those in water as the "salting out effect" increases the "hydrophobic effect".[24,25] It was found that reducing the catalyst loading to 0.5 mol % and decreasing the temperature to −5 °C resulted in increased enantioselectivity to >99% (Scheme 2). In order to show the practicality of the method, the reaction was tested on a large scale. Acetone (2.77 mL, 37.7 mmol) was allowed to react with benzaldehyde (0.955 mL, 9.4 mmol) by using the catalyst **1d** (17 mg, 0.5 mol %) in brine (9.5 mL) at −5 °C. The reaction was completed in 24 h, and the aldol product was obtained in 68% yield and 98.5% ee.

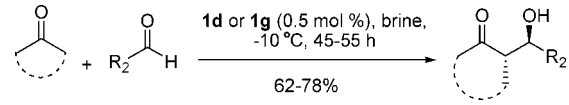
Having optimized the reaction conditions for enantioselective aldol reaction in brine, it was extended to other substrates using the catalysts **1d** and **1g**. A variety of aromatic and aliphatic aldehydes were tested for the reaction using acetone as a donor (Scheme 3). In most of the cases, excellent enantioselectivities (98−>99% ee) were obtained.

When cyclohexanone was used as a donor, high diastereoselectivities and excellent enantioselectivities (95−99% ee) were obtained with different aromatic and aliphatic aldehydes (Scheme 4). It is gratifying to see that along with aromatic aldehydes, aliphatic aldehydes such as isobutyraldehyde and cyclohexancarboxaldehyde also proved to be better acceptors.[24] Other cyclic ketones such as pyranone and thiopyranone were also found to be highly active donors resulting in products with up to >99% enantioselectivities and diastereoselectivities up to 99:1(*anti*/*syn*) (Table 2). [24]

The catalyst **1g** exhibited a better catalytic performance (99% ee) for carrying out the aldol reaction between acetone and benzaldehyde as compared to catalyst **2**[11a] (83% ee) (Figure 4). From these results we have concluded that it is not essential to have phenyl groups at the β-carbon atom with any particular stereochemistry.

In order to get more information about the catalyst, it was planned to modify the second half of the catalyst **1d** to generate a new series of organocatalysts **3a**−**d** which can be synthesized from L-proline and the corresponding γ-amino alcohols by a

TABLE 2. Screening of Other Ketones and Aldehydes



			anti/*syn*[a]		% ee[b] *anti*	
entry	ketone	R_2	**1d**	**1g**	**1d**	**1g**
1	acetone	*i*-Pr			>99	>99
2	acetone	cyclohexyl			99	>99
3	$-CH_2CH_2CH_2-$	cyclohexyl	94:6	99:1	99	99
4	$-CH_2OCH_2-$	Ph	97:3	95:5	>99	99
5	$-CH_2SCH_2-$	Ph	99:1	94:6	>99	99

[a] Determined by ^{1}H NMR analysis of the products. [b] Determined by HPLC using chiral columns.

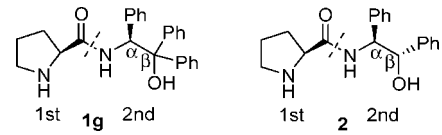
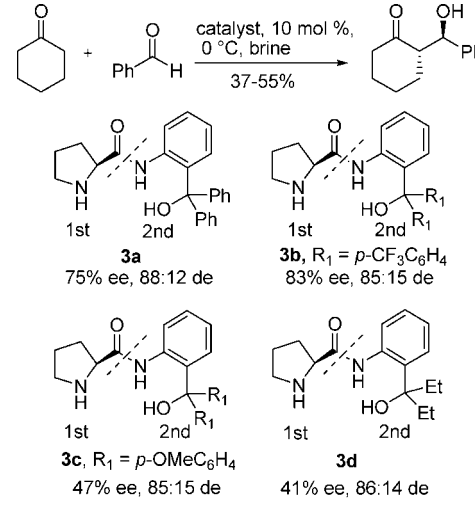


FIGURE 4. Role of stereocenter at the β-carbon atom.

SCHEME 5. Screening of New Organocatalysts



standard reaction sequence (see the Supporting Information). The idea behind synthesizing these catalysts was that the presence of a planar benzene ring would bring more rigidity in the transition state leading to high enantioselection. It was found that the reaction of cyclohexanone with benzaldehyde in the presence of 10 mol % of **3b** at 0 °C in brine gave a maximum of 83% ee (Scheme 5). The catalyst **3c** having an electron-donating group gave the product with lower enantioselectivity (47%). The importance of the *gem*-diphenyl group was further seen from poor enantioselectivity provided by a catalyst **3d** having diethyl substitution. The use of organic solvents also did not make any difference in the results. The reaction did not go with acetone as a donor. The sense of asymmetric induction with catalysts **3a**−**d** was same as that of catalysts **1a**−**m**; hence, the stereochemical outcome can be explained by similar types of transition-state models (Figure 5).

From the above results, it was found that the second half of the catalyst **1d** gave better results as compared to second half of catalysts **3a**−**d**. Furthermore, **1d**[24] having a *gem*-diphenyl group worked very well in an aqueous medium (>99% ee) in the direct aldol reaction of acetone and benzaldehyde, as compared to proline (20 mol %, 4% ee). It was argued that the

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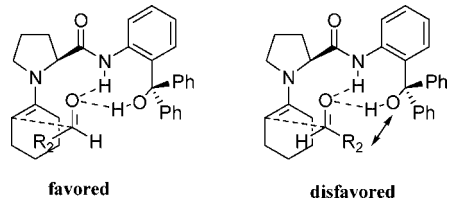


FIGURE 5. Transition-state models.

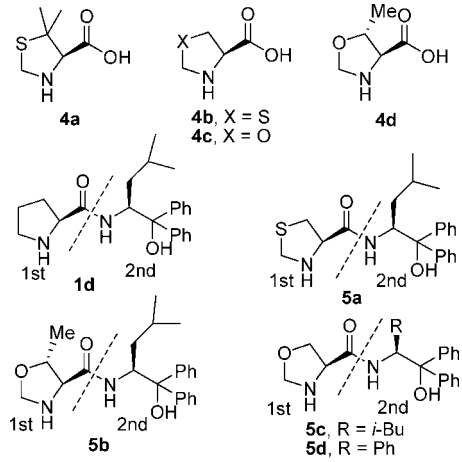


FIGURE 6. Another series of chiral organocatalysts.

second half of the catalyst **1d** acts as a hydrophobic part and forms a concentrated organic phase with hydrophobic reactants. This segregates the transition state away from the water molecules and leads to high reactivity and selectivity. In order to tune the catalyst further, it was logical to modify the first half and keep the second half same as in **1d**. This would provide insight about the role of the pyrrolidine ring.

From Barbas' work, it is known that the catalyst **4a**[7a] (Figure 6) exhibited better catalytic performance (86% ee) in the aldol reaction of acetone and *p*-nitrobenzaldehyde as compared to proline[7a] (76% ee). This indicated the importance of the heteroatom and substituents in the pyrrolidine ring. Thus, we thought of combining **4b**,[7a] **4c**, and **4d** with chiral diphenyl amino alcohol so as to come up with a new series of organocatalysts **5a**−**d** (Figure 6). These cyclic amino acids **4b**, **4c**, and **4d** were synthesized from L-cysteine, L-serine, and L-threonine, respectively, and then coupled with optically active diphenyl aminoalcohol to prepare catalysts **5a**, **5b**, **5c**, and **5d** (Scheme 6). These organocatalysts were evaluated in the aldol reaction of benzaldehyde and acetone (Table 3).

In accordance with our proposition, we have found that pure amino acids and peptides having hydrophobic groups show remarkable difference in stereoselectivity for the direct aldol reaction in brine (Table 3). It is consistent that simple amino acids **4b**−**d** gave poor ee's (entries 2, 4, and 6; 17−31% ee) as compared to peptides **5a**−**d** (entries 8−12; 82−95% ee) in an aqueous medium at room temperature. This highlights the importance of hydrophobic groups for getting high enantioselectivity in an aqueous medium. Among these, **5a** and **5d** seemed to be more promising than **5b** and **5c**.

In order to optimize the conditions, the catalyst **5a** was chosen arbitrarily. It was found that reducing the catalyst loading to 1 mol %, using 4 equiv of ketone, and decreasing the temperature to 0 °C resulted in increased enantioselectivity to >99% (entry 8, Table 4). The generality of the reaction was examined in detail using catalyst **5a** for a set of different aldehydes and ketones under the optimized reaction conditions, and the results were summarized in Table 5. The reaction has broad applicability with respect to aldehydes. Importantly, aliphatic aldehyde such as isobutyraldehyde smoothly underwent reaction to give product with high enantioselectivity of >99% (entry 4, Table 5).

SCHEME 6. Synthesis of New Organocatalysts

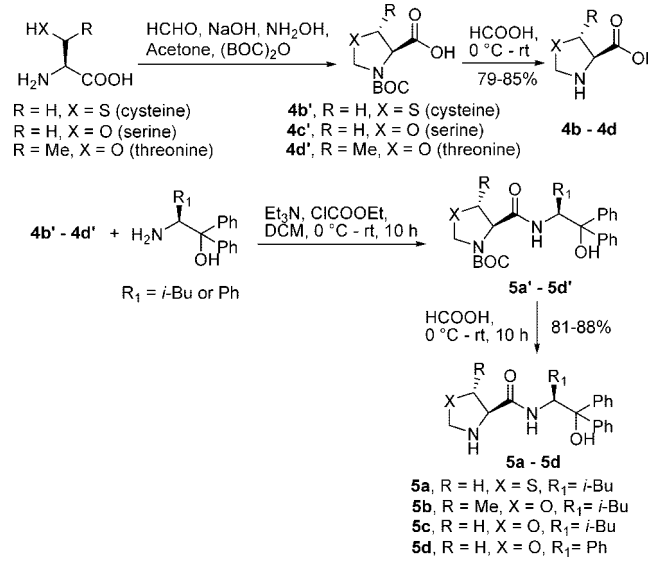
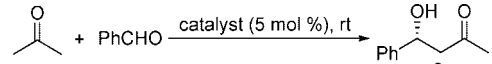


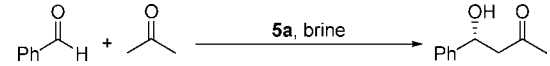
TABLE 3. Direct Aldol Reaction Catalyzed by Organocatalysts 4a−d and 5a−d



entry	catalyst	solvent	% yield[a]	% ee[b]
1	**4b**	acetone	66	73[c]
2	**4b**	brine	50	31
3	**4c**	acetone	62	61
4	**4c**	brine	48	25
5	**4d**	acetone	53	50
6	**4d**	brine	45	17
7	**5a**	acetone	71	85
8	**5a**	water	75	93
9	**5a**	brine	77	95
10	**5b**	brine	72	89
11	**5c**	brine	75	82
12	**5d**	brine	78	93

[a] Isolated yields. [b] Determined by HPLC using chiralpak AS-H column. [c] Reference 7a.

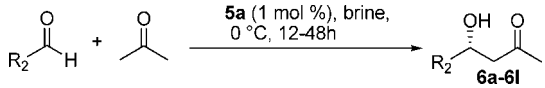
TABLE 4. Optimization of the Reaction Conditions



entry	catalyst (mol %)	ketone (equiv)	*T* (°C)	time (h)	% yield[a]	% ee[b]
1	5	4	rt	5	77	93
2	2	4	rt	7	76	96
3	1	4	rt	12	75	97
4	0.5	4	rt	24	70	97
5	1	2	rt	30	68	97
6	1	1	rt	54	60	96
7	1	4	10	20	75	98
8	1	4	0	28	74	>99

[a] Isolated yields. [b] Determined by HPLC using chiral columns.

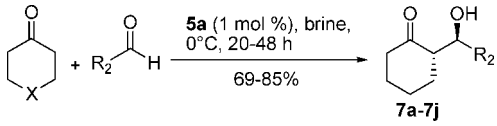
TABLE 5. Screening of Different Aldehydes with Acetone



entry	R_2	product	% yield[a]	% ee[b]
1	C_6H_5	**6a**	77	>99
2	4-FC_6H_4	**6b**	86	>99
3	3-$OMeC_6H_4$	**6c**	71	99
4	*i*-Pr	**6d**	70	>99
5	2-Cl-6−F-C_6H_3	**6e**	72	>99
6	3-ClC_6H_4	**6f**	78	96
7	3-FC_6H_4	**6g**	77	98
8	2,5-$F_2C_6H_3$	**6h**	75	98
9	2-ClC_6H_4	**6i**	73	>99
10	3-BrC_6H_4	**6j**	76	98
11	4-$CF_3C_6H_4$	**6k**	78	99
12	3-MeC_6H_4	**6l**	70	>99

[a] Isolated yields. [b] Determined by HPLC using chiral columns.

TABLE 6. Screening with Different Aldehydes and Ketones



entry	X	R_2	product	*anti*/*syn*[a]	% ee[b]
1	$-CH_2-$	Ph	**7a**	99:1	>99
2	$-CH_2-$	cyclohexyl	**7b**	94:6	99
3	−O−	Ph	**7c**	97:3	>99
4	−S−	Ph	**7d**	99:1	>99
5	$-CH_2-$	4-$OMeC_6H_4$	**7e**	98:2	91
6	$-CH_2-$	2-furyl	**7f**	97:3	96
7	$-CH_2-$	2-naphthyl	**7g**	99:1	96
8	$-CH_2-$	4-CNC_6H_4	**7h**	99:1	>99
9	$-CH_2-$	4-$CF_3C_6H_4$	**7i**	99:1	>99
10	$-CH_2-$	4-ClC_6H_4	**7j**	98:2	>99

[a] Determined by ^{1}H NMR analysis of the products. [b] Determined by HPLC using chiral columns.

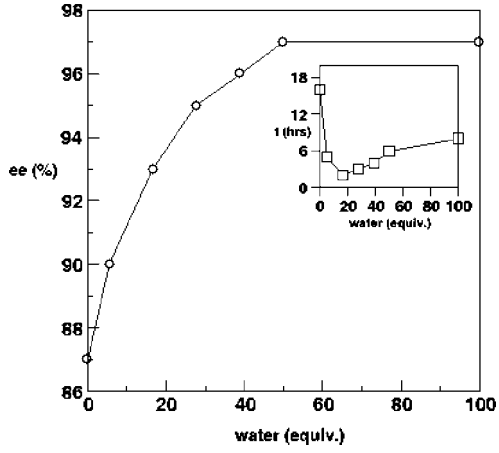


FIGURE 7. Role of water in direct aldol reaction.

The broad scope of the catalyst **5a** was further ensured by carrying out reaction with different cyclic ketones such as cyclohexanone, thiopyranone and pyranone that led to products with high enantio- and diastereoselectivities (Table 6).

As the aldol reaction occurs in water/brine, we investigated its effect on the reaction using 1 mol % of catalyst **5a**, and it is shown by graph in Figure 7. In the absence of water, the reaction took 16 h for completion at room temperature, and the product was obtained in 87% ee. As the ratio of water was gradually increased, the enantioselectivity also increased gradually and the reaction was completed in 6−8 h. It was noted that by using 50 equiv of water, the enantioselectivity reached to 97%. On increasing the amount of water to 100 mol %, there was no further improvement in ee. It is evident from Figure 7 that water not only acts as a medium but also influences the rate and enantioselectivity. Water, therefore, has a crucial role in the transition state of these reactions.

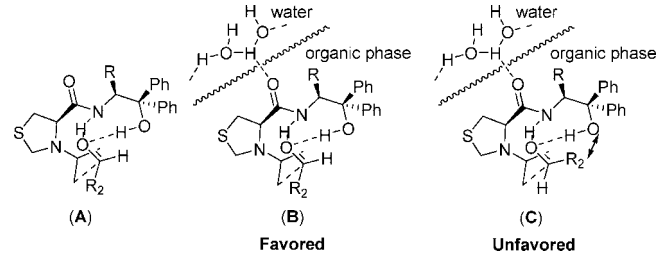


FIGURE 8. Transition-state model.

The rate enhancement in water is because of the "hydrophobic effect",[25] which is a thermodynamically favorable process due to increase in entropy. This hydrophobic effect further increases in brine due to the "salting out effect"[25] where solute molecules require more energy to enter into aqueous phase. This results in the concentrated organic phase above the aqueous phase and thus segregates the transition state away from the water molecules resulting in high reactivity.[24,25]

The stereochemical outcome in the direct aldol reaction catalyzed by **5a** can be explained by a transition state (Figure 8), which is based on the DFT calculations.[11a,14,24] The hydrogen bonding with NH and OH groups of the catalyst activate the aldehyde in such a manner that C−C bond formation takes place from its *re* face. The alternative *si* face is unfavored because of nonbonding interactions between the R_2 group and hydroxyl group. This reaction takes place in an aqueous medium, and as discussed above, hydrophobicity plays an important role in increasing the rate of the reaction. Further studies of these hydrophobic surfaces[26] showed that hydroxy groups of the surface water molecules suspended at the hydrophobic interface might form a hydrogen bond with the amide oxygen but not with NH and OH groups of the catalyst as they are surrounded by hydrophobic groups, leading to transition state **B** as shown in Figure 8. As compared to transition state **A**, the reaction via transition state **B** proceeds by forming an additional hydrogen bond, thus making amidic NH more acidic leading to compact transition state.[27] Due to this compact network, the approach of the aldehyde from *si* face (**C**) becomes more unfavorable (Figure 8). This explains the increase in enantioselectivity of the aldol products in the presence of water.

β-Hydroxy ketones, obtained from the direct aldol reaction catalyzed by **5a**, can generate a class of enantioenriched amino alcohols that are very useful in organic synthesis. The diastereoselective reductive amination of β-hydroxy ketones **6a** and **7a** was carried out with benzyl amine by using lithum aluminum hydride[28] to obtain *anti*-(1*R*,3*S*)-3-(benzylamino)-1-phenylbutan-1-ol **8a** in a diastereomeric ratio of 96:4 and *anti*-(*R*)-((1*R*,2*S*)-2-(benzylamino)cyclohexyl)phenylmethanol **9a** in a diastereomeric ratio of 98:2. The benzyl group can be further cleaved

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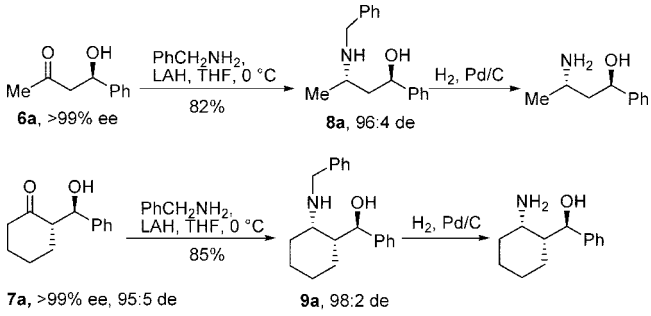
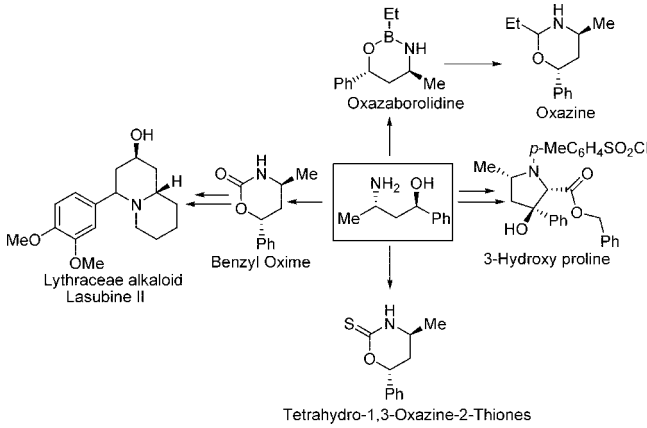
(28) Gandhi, S.; Singh, V. K. *J. Org. Chem.* **2008**, *73*, 9411.

SCHEME 7. Synthesis of Chiral Amino Alcohols



SCHEME 8. Application of Chiral Amino Alcohol



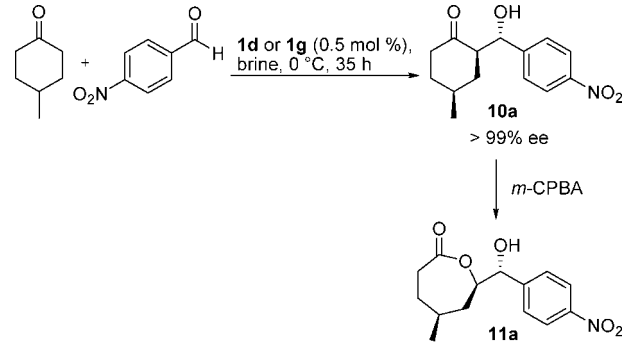
by hydrogenolysis[29] to give benzyl-deprotected chiral amino alcohols (Scheme 7). The chiral amino alcohol can be cyclized to give substituted oxazaborolidine (Scheme 8),[30] which can further be converted into oxazine[31] by reaction with aldehydes. The chiral amino alcohol can be converted into 3-hydroxyproline,[32] tetrahydro-1, 3-oxazine-2-thione,[33] and Lythraceae alkaloid lasubine II[34] via *o*-benzyloxime (Scheme 8).

Furthermore, desymmetrization of *p*-methylcyclohexanone was achieved by using catalyst **1d** and **1g** in brine at a very low catalyst loading of 0.5 mol % with high enantioselectivity of >99% (Scheme 9). Aldol adduct **10a** was further subjected to Bayer−Villager oxidation to generate lactone **11a**.[35]

Conclusion

In summary, we have developed a series of highly efficient organocatalysts for enantioselective direct aldol reaction in an aqueous medium. It has been found that the "hydrophobic effect" plays a significant role in the aldol reaction. The results demonstrate that the structural features of organocatalysts play a crucial role in obtaining high optical purity of aldol adducts in an aqueous medium. Further, the role of water in increasing the rate and enantioselectivity of the reaction has been illustrated.

SCHEME 9. Desymmetrization of *p*-Methylcyclohexanone



Moreover, diasteroselective reductive amination of β-hydroxy ketones provide an inexpensive efficient route for the synthesis of chiral amino alcohols that act as useful intermediates for asymmetric organic synthesis[30] and for building up complex natural products.[31−34]

Experimental Section

General Methods. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are expressed in ppm downfield from TMS as internal standard, and coupling constants are reported in hertz. Routine monitoring of the reaction was performed by TLC, using precoated silica gel TLC plates. The IUPAC names of ligands and aldol product were taken from Chem. ultra 9. All of the column chromatography separations were done by using silica gel (100−200 mesh). Petroleum ether used was of boiling range 60−80 °C. The organic extracts were dried over *anhydrous* sodium sulfate. Evaporation of solvent was performed at reduced pressure. Brine refers to saturated solution of NaCl in water at 25 °C. Compounds **1a**−**m** were synthesized by our procedure.[14]

General Procedure for the Synthesis of Catalysts 3a−d. Triethylamine (0.864 g, 8.54 mmol) was slowly added to a solution of Cbz proline (8.54 mmol) in DCM (40 mL) at 0 °C. Ethyl chloroformate (0.926 g, 8.54 mmol) was added dropwise, and the solution was stirred at the same temperature for 15 min. Then, optically pure amino alcohol (8.54 mmol) was added, and the resulting solution was stirred for 10 h. The whole solution was diluted with DCM. After filtration and removal of solvent under reduced pressure, the residue was purified by recrystallization with ethyl acetate. The compound obtained was then subjected to hydrogenation in the presence of Pd/C to give pure products **3a**−**d** as a white solid.

(*S*)-*N*-(2-(Hydroxydiphenylmethyl)phenyl)pyrrolidine-2-carboxamide (3a). This was prepared as per our general procedure to afford the product **3a** as a white amorphous solid: yield 86%; mp 168−172 °C; $[\alpha]^{25}_D$ −91.2 (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44−1.52 (m, 3H), 1.59 (brs, −OH), 1.93−1.95 (m, 1H), 2.58−2.62 (m, 1H), 2.78−2.84 (m, 1H), 3.46−3.50 (m, 1H), 6.57 (d, J = 7.8 Hz, 1H), 6.91−6.94 (t, J = 7.8 Hz, 1H), 7.19−7.36 (m, 11H), 8.25 (d, J = 8.32 Hz, 1H), 10.39 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.9, 30.7, 47.1, 61.2, 82.9, 123.2, 123.4, 127.7, 128.2, 128.9, 130.0, 134.9, 137.3, 145.5, 145.9, 173.8; HRMS (TOF-ES+) calcd for $C_{24}H_{24}N_2O_2$ 373.1917 [M + H]$^+$, found 373.1958.

(*S*)-*N*-(2-(Hydroxybis(4-trifluoromethyl)phenyl)methyl)phenyl)-pyrrolidine-2-carboxamide (3b). This was prepared as per our general procedure to afford the product **3b** as a white amorphous solid: yield 78%; mp 185−190 °C; $[\alpha]^{25}_D$ −111.2 (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.12−1.14 (m, 1H), 1.15−1.26 (m,2H), 1.40−1.46 (m, 1H), 1.67 (brs, −OH), 2.52−2.58 (m, 1H), 2.67−2.73 (m, 1H), 3.15−3.16 (m, 1H), 6.57−6.59 (dd, J = 1.44, 8.04 Hz, 1H), 6.96−7.0 (m, 1H), 7.34−7.44 (m, 5H), 7.56−7.58 (d, J = 8.32 Hz, 4H), 10.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz)

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δ 25.8, 30.4, 46.9, 60.9, 81.6, 122.6, 123.6, 125.1, 127.9, 129.3, 129.6, 129.9, 134.3, 136.8, 149.2, 149.3, 173.6; HRMS (TOF-ES+) calcd for $C_{26}H_{22}N_2O_2F_6$ 509.1663 $[M + H]^+$, found 509.1664.

(*S*)-*N*-(2-(Hydroxybis(4-methoxyphenyl)methyl)phenyl)pyrrolidine-2-carboxamide (3c). This was prepared as per our general procedure to afford the product **3c** as a white amorphous solid: yield 72%; mp 170−173 °C; $[\alpha]^{25}_D$ −108.8 (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.24−1.28 (m, 1H), 1.31−1.38 (m,1H), 1.44−1.56 (m, 1H), 1.89−1.96 (m, 1H), 2.57 (brs, −OH), 2.65−2.69 (m, 1H), 2.82−2.87 (m, 1H), 3.55−3.57 (m, 1H), 3.78−3.80 (m, 6H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 4H), 6.89−6.93 (t, *J* = 7.5 Hz, 1H), 7.06−7.13 (m, 4H), 7.30−7.33 (t, *J* = 6.4 Hz, 1H), 8.26 (d, *J* = 6.8 Hz, 1H), 10.39 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.8, 30.6, 47.0, 55.4, 61.1, 82.5, 113.4, 123.1, 128.9, 129.9, 135.3, 137.3, 138.0, 138.3, 158.9, 173.3; HRMS (TOF-ES+) calcd for $C_{26}H_{28}N_2O_4$ 433.2128 $[M + H]^+$, found 433.2129.

(*S*)-*N*-(2-(3-Hydroxypentan-3-yl)phenyl)pyrrolidine-2-carboxamide (3d). This was prepared as per our general procedure to afford the product **3d** as a white amorphous solid: yield 77%; mp 80−83 °C; $[\alpha]^{25}_D$ −76 (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.77−0.88 (m, 6H), 1.69−1.80 (m, 2H), 1.85−2.04 (m, 5H), 2.13−2.20 (m, 1H), 2.43 (brs, OH), 2.99−3.05 (m, 2H), 3.79−3.82 (dd, *J* = 5.4, 9.04 Hz, 1H), 6.99−7.03 (m, 1H), 7.11−7.13 (dd, *J* = 1.44, 7.8 Hz, 1H), 7.22−7.26 (m, 1H), 8.40−8.42 (dd, *J* = 1.24, 6.84 Hz, 1H), 11.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.1, 26.2, 31.2, 32.2, 32.5, 47.3, 61.7, 79.5, 122.4, 122.9, 127.2, 127.6, 131.8, 137.6, 173.6; HRMS (TOF-ES+) calcd for $C_{16}H_{24}N_2O_2$ 277.1917 $[M + H]^+$, found 277.1919.

General Procedure for the Synthesis of Catalysts 4b−d[36] (Scheme 6). NaOH (2 N, 0.672 g in 8.4 mL H_2O) and formaldehyde (1.68 mL, 1.68 mmol) were added to L- serine, L-threonine, or L-cysteine (16.8 mmol) in a round-bottom flask at 0 °C, and the solution was stirred at the same temperature for 7 h. To this solution were added hydroxylamine hydrochloride (0.117 g, 1.68 mmol), acetone (9.8 mL) and NaOH solution (0.672 g, 1.68 mmol in 1.4 mL H_2O) at 0 °C, and the resulting solution was stirred for 15 min. Then, di-*tert*-butyl dicarbonate (18.15 mmol) was added at room temperature, and the solution was stirred for another 3 h. After completion, the reaction mixture was diluted with water and washed with ether. Ether extracts were discarded, and 20% citric acid was added to aqueous layer and extracted with ethyl acetate. The organic layer was dried, and the solvent was removed to obtain pure **4b′−d′** as white solid. Formic acid (60 mL) was slowly added to compound **4b′−d′** (14.3 mmol) at 0 °C, and the resulting solution was stirred for 10 h. Excess formic acid was carefully neutralized by adding solid sodium bicarbonate, and the whole mixture was extracted with ethyl acetate. The organic layer was dried, and the solvent was removed to obtain pure product as white solid.

General Procedure for the Synthesis of Catalysts 5a−d[14] (Scheme 6). Triethylamine (0.864 g, 8.54 mmol) was slowly added to a solution of compound **4b′−d′** (8.54 mmol) in DCM (40 mL) at 0 °C. Ethyl chloroformate (0.926 g, 8.54 mmol) was added dropwise, and the solution was stirred at the same temperature for 15 min. Then, optically pure amino alcohol (8.54 mmol) was added, and the resulting solution was stirred for 10 h. The whole solution was diluted with DCM. After filtration and removal of solvent under the reduced pressure, the residue was purified by recrystallization with ethyl acetate to give compounds **5a′−d′**.

Formic acid (40 mL) was slowly added to compounds **5a′−d′** (7.3 mmol) at 0 °C, and the resulting solution was stirred for 10 h. Excess formic acid was carefully neutralized by addition of solid sodium bicarbonate, and the whole mixture was extracted with ethyl acetate. The organic layer was dried, and the solvent was removed to obtain yellow solid which was further purified by recrystallization with ethyl acetate to obtain pure product **5a−d** as white solid.

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(*R*)-Thiazolidine-4-carboxylic Acid (4b) (Commercially Available). This was prepared as per our general procedure to afford the product **4b** as a white solid: yield 90%; mp 220−222 °C; IR (NaCl cell, CH_2Cl_2, cm^{-1}) 1613, 3423; ^1H NMR (D_2O, 400 MHz) δ 3.25 (m, 2H), 4.22 (m, 1H), 4.33 (m, 2H). Anal. Calcd. for $C_4H_7NO_2S$: C, 36.08; H, 5.30. Found: C, 36.09; H, 5.32.

(*S*)-Oxazolidine-4-carboxylic Acid (4c). This was prepared as per our general procedure to afford the product **4c** as a viscous liquid: yield 85%; $[\alpha]^{25}_D$ −19.0 (*c* 0.5, H_2O); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 1624, 3435; ^1H NMR (D_2O, 400 MHz) δ 2.57 (s, 2H), 3.49 (m, 1H), 3.83 (m, 2H); ^{13}C NMR (D_2O, 100 MHz) δ 33.8, 67.3, 71.5, 172.7. Anal. Calcd. for $C_4H_7NO_3$: C, 41.03; H, 6.03. Found: C, 41.04; H, 6.05.

(4*S*,5*R*)-5-Methyloxazolidine-4-carboxylic Acid (4d). This was prepared as per our general procedure to afford the product **4d** as a white solid: yield 83%; mp 227−230 °C; $[\alpha]^{25}_D$ −28.0 (*c* 0.5, H_2O); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 1643, 3375; ^1H NMR (D_2O, 400 MHz) δ 1.13 (d, *J* = 6.6 Hz, 3H), 2.54 (s, 2H), 3.2 (d, *J* = 7.6 Hz, 1H), 3.84 (m, 1H); ^{13}C NMR (D_2O, 100 MHz) δ 20.7, 33.6, 67.4, 71.4, 172.7. Anal. Calcd for $C_5H_9NO_3$: C, 45.80; H, 6.92. Found: C, 45.81; H, 6.93.

(4*R*)-*N*-((*S*)-1-Hydroxy-4-methyl-1,1-diphenylpentan-2-yl)thiazolidine-4-carboxamide (5a). This was prepared as per our general procedure to afford the product **5a** as a white amorphous solid: yield 86%; mp 152−154 °C; $[\alpha]^{25}_D$ −59.9 (*c* 1.0, DMSO); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 1651, 3323, 3419; ^1H NMR (DMSO, 400 MHz) δ 0.75 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H), 0.96 (m, 1H), 1.47 (m, 2H), 3.37 (m, 3H), 3.91 (m, 1H), 4.0 (m, 1H), 4.98 (t, *J* = 9.8 Hz, 1H), 5.90 (bs, 1H), 7.07−7.30 (m, 6H), 7.48 (m, 4H), 7.72 (d, *J* = 9.7 Hz, 1H); ^{13}C NMR (DMSO, 100 MHz) δ 21.6, 24.0, 24.2, 35.1, 38.6, 52.8, 53.6, 65.7, 80.0, 125.3, 125.5, 126.0, 126.2, 127.5, 128.0, 146.0, 146.7, 169.8; HRMS (TOF-ES-) calcd for $C_{22}H_{28}N_2O_2S$ $[M - H]^+$ 383.1793, found 383.1793.

(4*S*,5*R*)-*N*-((*S*)-1-Hydroxy-4-methyl-1,1-diphenylpentan-2-yl)-5-methyloxazolidine-4-carboxamide (5b). This was prepared as per our general procedure to afford the product **5b** as a white amorphous solid: yield 80%; mp 124−127 °C; $[\alpha]^{25}_D$ −64.0 (*c* 1.0, DMSO); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 1679, 3363, 3459; ^1H NMR (DMSO, 400 MHz) δ 0.66 (d, *J* = 6.1 Hz, 3H), 0.73 (d, *J* = 7.6 Hz, 3H), 0.83 (m, 2H), 1.2 (d, *J* = 7.1 Hz, 3H), 1.55 (m, 1H), 2.90 (m, 1H), 3.16 (m, 1H), 4.5 (m, 1H), 4.94 (m, 1H), 5.04 (t, *J* = 9.8 Hz, 1H), 5.67 (bs, 1H), 7.07−7.42 (m, 6H), 7.51 (m, 4H), 7.79 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR (DMSO, 100 MHz) δ 21.4, 23.8, 24.1, 27.8, 38.5, 52.9, 63.9, 78.6, 79.6, 80.2, 125.1, 125.2, 126.1, 126.2, 127.6, 128.1, 145.9, 146.9, 172.5; HRMS (TOF-ES-) calcd for $C_{23}H_{30}N_2O_3$ $[M - H]^+$ 381.2178, found 381.2173.

(4*S*)-*N*-((*S*)-1-Hydroxy-4-methyl-1,1-diphenylpentan-2-yl)oxazolidine-4-carboxamide (5c). This was prepared as per our general procedure to afford the product **5c** as a white amorphous solid: yield 81%; mp 189−192 °C; $[\alpha]^{25}_D$ −60.9 (*c* 1.0, DMSO); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 1644, 3355, 3438; ^1H NMR (DMSO, 400 MHz) δ 0.74 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H), 0.92 (m, 1H), 1.45 (m, 2H), 2.91 (m, 1H), 3.02 (m, 1H), 3.16 (m, 1H), 4.58 (m, 1H), 4.91 (m, 2H), 5.95 (bs, 1H), 7.06−7.29 (m, 6H), 7.47 (m, 4H), 7.75 (d, *J* = 10 Hz, 1H); ^{13}C NMR (DMSO, 100 MHz) δ 21.6, 23.9, 24.2, 27.8, 38.6, 53.1, 57.2, 64.1, 80.1, 125.3, 125.7, 126.3, 126.5, 127.4, 127.9, 146.3, 146.7, 172.5; HRMS (TOF-ES-) calcd for $C_{22}H_{28}N_2O_3$ $[M - H]^+$ 367.2022, found 367.2021.

(4*S*)-*N*-((*S*)-2-Hydroxy-1,2,2-triphenylethyl)oxazolidine-4-carboxamide (5d). This was prepared as per our general procedure to afford the product **5d** as a white amorphous solid: yield 76%; mp 218−221 °C; $[\alpha]^{25}_D$ −142.7 (*c* 1.0, DMSO); IR (NaCl cell, CH_2Cl_2, cm^{-1}) 1640, 3389, 3468; ^1H NMR (DMSO, 400 MHz) δ 3.07 (m, 2H), 3.21 (m, 1H), 4.60 (m, 1H), 4.81 (m, 1H), 5.78 (d, *J* = 8.5 Hz, 1H), 6.18 (bs, 1H), 6.99−7.21 (m, 11H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 2H), 8.59 (d, *J* = 9.8 Hz, 1H); ^{13}C NMR (DMSO, 100 MHz) δ 56.8, 58.5, 64.0, 79.9, 111.4, 126.0, 126.2,

126.3, 126.5, 126.7, 127.2, 127.7, 129.1, 139.6, 145.2, 146.3, 171.9; HRMS (TOF-ES-) calcd for $C_{24}H_{24}N_2O_3$ $[M - H]^+$ 387.1709, found 387.1706.

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Supporting Information Available: General experimental procedures, characterization data including ^{1}H NMR spectra, ^{13}C NMR spectra for all compounds, and HPLC chromatograms for compounds **6a**−**l**, **7a**−**j**, **12a**, and **13a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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