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Sterically and Electronically Tunable and Bifunctional Organocatalysts: Design and Application in Asymmetric Aldol Reaction of Cyclic Ketones with Aldehydes

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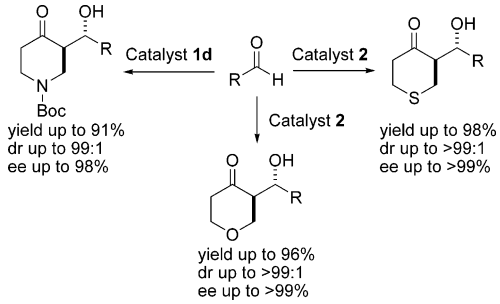

Sterically and electronically tunable and bifunctional organocatalysts have been developed and evaluated in the direct aldol reaction of heterocyclic ketones. Catalysts with different substituents showed variable catalytic efficiency for analogous substrates, indicating the importance of fine-tuning the strength of the hydrogen bonding in the two NH groups. The reactions all proceeded in good to high yield and with excellent enantioselectivities ranging from 90% to >99% ee. In most cases, high diastereoselectivities ranging from 96/4 to 99/1 were obtained for the anti aldol adduct.

Introduction

The aldol reaction is recognized as one of the most powerful methods for the construction of new carbon−carbon bonds in organic synthesis. During the carbon−carbon bond forming process, the control of both the absolute and the relative configuration of the aldol products is of paramount importance for the synthesis of natural products.[1] Since the pioneering work of Mukaiyama et al.,[2a] considerable attention has been directed toward the development of catalytic systems for asymmetric aldol reactions.[3,4] A great number of different approaches have been made in this regard, including chiral Lewis acid-catalyzed Mukaiyama reactions of silyl enol ethers,[2b] catalysis by Lewis bases,[5] and application of aldolases or antibodies.[6] While catalytic activation of aldehyde acceptors by chiral Lewis acids has achieved success for the asymmetric aldol condensation, preconversion of the donors to more reactive species such as a silyl enol ether, methyl enol ethers, or ketone silyl acetals is a necessity. Moreover, biochemical catalysis also has limitations with regard to the scope and catalyst preparation. Thus, the

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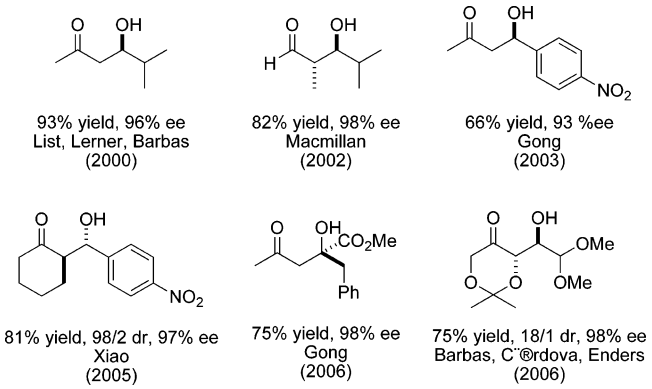
SCHEME 1. Highly Enantioselective Direct Aldol Reaction Catalyzed by L-Proline or Its Derivatives and Analogues



development of a direct catalytic asymmetric aldol reaction with aldehydes and unmodified ketones is a noteworthy endeavor.[7] A breakthrough in this strategy was realized by Shibasaki's success in developing heterobimetallic multifunctional catalyzed direct asymmetric aldol reaction, although the enantioselectivities are currently modest.[4a,8] Recently, Trost[4b,9] and Evans[10] and co-workers demonstrated the highly enantioselective direct aldol reaction catalyzed by zinc and nickel complexes. Almost three decades after the first report of the intramolecular aldol reaction catalyzed by L-proline,[11] Barbas[12a] and List[12b,c] and co-workers described the L-proline catalyzed intermolecular direct aldol reaction using unmodified ketones as donors. Since then, there has much research activity in this area, most of which has been directed toward developing novel catalysts as well as extending the substrate scope. Impressive results were obtained for various kinds of aldehydes and α-ketoesters as acceptors when L-proline[12,13] or its derivatives and analogues[14,15] were used (Scheme 1).

Despite the substantial variety of aldol acceptors, the range of donors has remained narrow. Whereas acetone, hydroxy

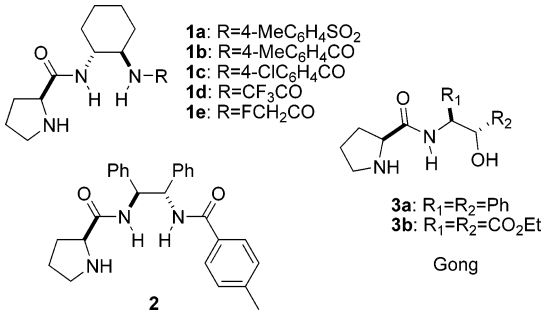


FIGURE 1. Tunable and bifunctional organocatalysts and Gong's amino alcohol catalysts.

acetone, and some enolizable aldehydes are excellent nucleophiles, a variety of other donors, e.g., acetophenone, 3-pentanone, and cyclic ketones did not yield a significant amount of the desired aldol products with satisfactory selectivity.[12a,13a] Recently, the highly diastereo- and enantioselective direct aldol reaction between heterocyclic ketones and aldehydes was reported by Pihko's group, although the process was somewhat sluggish.[16] Recent studies by the groups of Barbas,[17a] Hayashi,[17b] and Córdova[17c] revealed the enantioselective direct aldol reactions of cyclohexanone in water, which open a new way for the development of asymmetric organocatalysis in water. However, the search for an efficient organocatalyst that shows high diastereo- and enantioselectivities for a broad range of cyclic ketone donors is still a problem waiting to be solved.

In our continuing efforts to develop readily tunable organocatalysts of broad utility for chemical transformations,[15g] we combined the proline catalysis concept with hydrogen-bond activation and designed a series of tunable bifunctional organocatalysts (**1**) (Figure 1). Initial studies revealed that catalyst **1b** had the highest catalytic activity for the aldol reaction between cyclohexanone and aldehydes. More importantly, we demonstrated that an elegant alignment of the steric and

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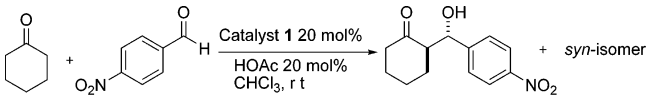
TABLE 1. Enantioselective Direct Aldol Reaction of *p*-Nitrobenzaldehyde 5a with Cyclohexanone 4 Catalyzed by Catalyst 1[a]

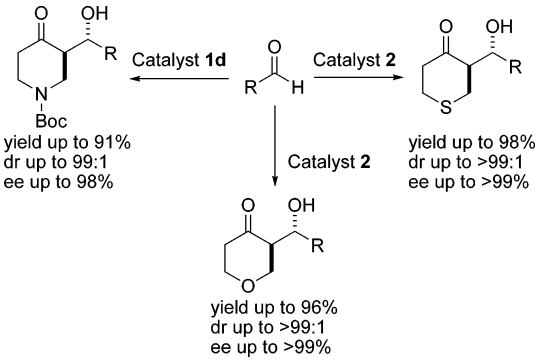


4 5a 6

entry	catalyst	yield[b] (%)	dr[c]	ee[d] (%)	entry	catalyst	yield[b] (%)	dr[c]	ee[d] (%)
1	**1a**	**73**	**84:16**	**54**	**4**	**1d**	63	77:23	73
2	**1b**	**81**	**75:25**	**86**	**5**	**1e**	79	73:27	73
3	**1c**	89	76:24	80	6[e]	**1b**	81	98:2	97

[a] The reactions were conducted with **1** (20 mol %), AcOH (20 mol %), **5a** (0.5 mmol), and **4**/$CHCl_3$ (1:1) (2 mL) for 6−24 h. [b] Isolated yields. [c] Determined by ^1H NMR spectroscopy. [d] Determined by chiral-phase HPLC analysis for the anti-product. [e] Reaction performed at −40 °C.

SCHEME 2. Highly Enantioselective Direct Aldol Reaction of Cylclic Ketones with Aldehydes



electronic properties of the catalyst is essential to maximize the reaction efficiency (Table 1).

Significantly, the absolute configuration of major aldol adduct **6** was determined to be (*2R,1′S*) by comparison of the HPLC retention time of the product with reported data.[15e,17] The improvement in enantioselectivity of catalyst **1** and the complete difference in the configuration of the anti product suggests that there is an inherent difference between L-proline and catalyst **1**. On the basis of the success of the initial study, we then examined the use of catalyst **1** for a broad range of cyclic ketones. We now present the development of the readily tunable diamide as a general catalyst for the direct asymmetric aldol reaction between cyclic ketones and aldehydes, with unprecedented high efficiency in terms of reactivity and diastereo- and enantioselectivity (Scheme 2).

Results and Discussions

Catalyst Design. According to the Houk−List model,[18] the high catalytic efficiency of proline is ascribed to the dual activation of both the electrophilic aldehyde and the nucleophilic aldol donor. This means that the carboxylic acid functionality of proline controls the approach of the electrophile to the enamine intermediate by hydrogen bonding. However, fine-tuning of the catalytic properties of proline by derivatization is difficult: the five-membered pyrrolidine ring as well as the carboxyl and the secondary amines were established to be essential for good catalytic performance.[19]

In this context, we therefore designed a series of L-proline derivatives which have two N−H groups as hydrogen bonding donors, and the strength of acidity of N−H group can readily be tuned by only changing the substitutent on the N atom (Figure 1). More importantly, compared with the synthetic route to catalyst **3**,[15c,e] all of our diamide catalysts can easily be obtained in three steps from commercially available materials in good overall yields.[15g]

Optimization of Reaction Conditions with the Use of Tunable and Bifunctional Organocatalysts 1 and 2. We previously developed highly enantioselective direct aldol reactions between cyclohexanone and aldehydes by using the bifunctional organocatalyst **1d** (Table 1). As an extension of our current strategy, we first screened the ability of this type of organocatalyst for the direct aldol reactions with heterocyclic ketones **7**−**9** and aldehyde acceptor **5a**. As summarized in Table 2, in the case of 1-Boc-4-piperidone **7**, catalyst **1c** shows the highest efficiency while catalyst **2** is the best choice for tetrahydro-4*H*-pyran-4-one **8** and tetrahydro-4*H*-thiopyran-4-one **9** (Table 2, entries 1−6). Comparing these results with previous studies revealed that **1d** had the highest activity for the aldolization of cyclohexanone. In this respect, fine-tuning the catalytic properties of organocatalyst **1** or **2** is very important to the asymmetric induction. Further reaction optimization, which included examination of solvents, temperature, and additives for the superior catalysts **1d** and **2**, revealed that as high as 99% ee and 99:1 dr can be obtained at −40 °C (Table 2, entry 13).

Catalyst Survey. A. Aldolization of Cyclic Ketone 7 with Aldehyde. After establishing the optimal reaction conditions for ketone **7**, the direct asymmetric aldol reactions of other aldehyde acceptors were carried out (Table 3). Aromatic, heteroaromatic, and aliphatic adehydes were found to be suitable substrates, with the direct aldol reactions generally giving the corresponding aldol adducts in moderate to good yields. The only exception to the generally high diastereo- and enantioselectivities was 2-thienaldehyde **5l**, although the dr was still high at 91:9 (Table 3, entry 12). Excellent diastereo- and enantioselectivities were observed in most cases (>96:4 dr; >94% ee). For instance, the reaction worked extremely well with an α-branched aliphatic aldehyde to generate nearly optically pure aldol adducts (97:3 dr; 98% ee) (Table 3, entry 13). Although the addition of a small amount of water often accelerates reactions and/or improves enantioselectivities,[14d] the positive effect of water was not observed for ketone **7** (Table 3, entries 2 versus 3).[17]

B. Aldol Reaction of Tetrahydro-4*H*-pyran-4-one 8 with Aldehydes. We then examined the ability of diamide catalyst **2** to catalyze the enantioselective direct aldol reaction of ketone **8** and various aldehydes. As illustrated in Table 4, both aromatic and heteroaromatic aldehydes react smoothly with **8** under optimal conditions to yield the aldol products in excellent selectivities (>95:5 dr, >97% ee). Both para-substituted aldehydes **5a** and **5k** proved to react with a similar level of efficiency as **5j** (Table 4, entries 1, 11, and 10), showing little dependence of the reaction on the electronic character of the aldol acceptor. Significantly, high reactivity and selectivity were also observed for heteroaromatic aldehydes **5l** and **5m** with dr and ee values of >99:1 and > 99%, respectively (Table 4, entries 12 and 13).

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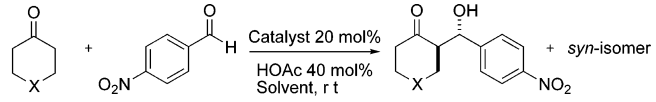
TABLE 2. Optimization of Conditions for the Direct Aldol Reactions of Heterocyclic Ketones with *p*-Nitrobenzaldehyde[a]



7 X= NBoc
8 X= O
9 X= S

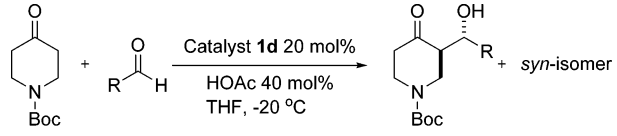
5a

10a X= NBoc
11a X= O
12a X= S

			10a			**11a**			**12a**	
entry	cat	solvent	yield[b] (%)	dr[c]	ee[b] (%)	yield[b] (%)	dr[c]	ee[b] (%)	dr[c]	ee[b] (%)
1	**1a**	$CHCl_3$	79	76:24	77	82	69:31	52	83:17	70
2	**1b**	$CHCl_3$	81	78:22	80	85	61:39	42	85:15	68
3	**1c**	$CHCl_3$	92	81:19	86	93	71:29	66	92	87:13	74
4	**1d**	$CHCl_3$	85	92:18	87	78	73:27	64	72	96:4	54
5	**1e**	$CHCl_3$	83	81:19	80	80	69:31	62	91	85:15	56
6	**2**	$CHCl_3$	94	81:19	75	82	85:15	78	83	90:10	70
7	**1d**	CH_2C_{l2}	85	79:21	82	92	83:17	71[e]	72	87:13	74[e]
8	**1d**	toluene	93	87:13	89	87	93:7	87[e]	83	93:7	88[e]
9	**1d**	CH_3CN	90	81:19	82	95	83:17	69[e]	46	93:7	82[e]
10	**1d**	DMF	98	81:19	87	93	80:20	67[e]	19	94:6	82[e]
11	**1d**	THF	89	90:10	92	92	94:6	90[e]	83	94:6	86[e]
12	**1d**	THF	89	96:4	94[f]	72	92:8	96[e,g]	88	99:1	98[e,f]
13	**2**	THF				91	99:1	99[g,h]	91	99:1	99[f,h]

[a] The reactions were conducted with catalyst (20 mol %), AcOH (40 mol %), *p*-nitrobenzaldehyde (0.5 mmol), ketone (2.5 mmol), and THF (2 mL). [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral-phase HPLC analysis for the anti-product. [e] Catalyst **2** was used. [f] Reaction performed at −20 °C. [g] Reaction performed at −40 °C. [h] 10 equiv H_2O was added.

TABLE 3. Scope of the Direct Aldol Reaction of Aldehydes 5 with Ketone 7[a]

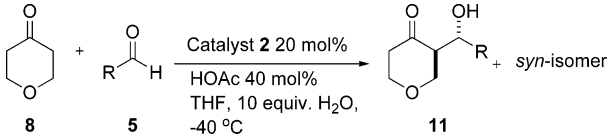


7 **5** **10**

entry	R	product	yield[b] (%)	dr[c]	ee[d] (%)
1	4-NO_2-Ph-	**10a**	89	96:4	94
2[e]	4-NO_2-Ph-	**10a**	86	98:2	98
3[f]	**4-NO_2**-Ph-	**10a**	90	96:4	96
4	**3-NO_2**-Ph-	**10b**	91	96:4	93
5	**2-NO_2**-Ph-	**10c**	80	96:4	92
6	**4-Br-Ph-**	**10d**	86	97:3	95
7	**3-Br-Ph-**	**10e**	80	99:1	96
8	**4-Cl-Ph-**	**10f**	80	97:3	95
9	**2-Cl-Ph-**	**10g**	70	97:3	94
10	**4-F-Ph**	**10h**	75	98:2	94
11	Ph-	**10i**	80	96:4	90
12[g]	**2-thienyl**	**10j**	32	91:9	86
13	i-Pr	**10k**	58	97:3	98

[a] The reactions were conducted with catalyst **1d** (20 mol %), AcOH (40 mol %), aldehyde **5** (0.5 mmol), ketone **7** (2.5 mmol), and THF (2 mL) for 41−96 h. [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral-phase HPLC analysis for the anti-product. [e] Reaction performed at −40 °C. [f] 10 equiv H_2O was added at −40 °C. [g] Reaction performed at 0 °C.

TABLE 4. Scope of the Direct Aldol Reaction of Aldehydes 5 with Ketone 8[a]



8 **5** **11**

entry	R	product	yield[b] (%)	dr[c]	ee[d] (%)
1	4-NO_2-Ph-	**11a**	91	>99:1	99
2	3-NO_2-Ph-	**11b**	96	97:3	>99
3	2-NO_2-Ph-	**11c**	94	99:1	>99
4	4-CN-Ph-	**11d**	81	97:3	99
5	4-Br-Ph-	**11e**	89	95:5	>99
6	3-Br-Ph	**11f**	81	99:1	99
7	4-Cl-Ph-	**11g**	70	>99:1	>99
8	2-Cl-Ph-	**11h**	77	>99:1	>99
9	4-F-Ph-	**11i**	85	99:1	>99
10	Ph-	**11j**	80	99:1	99
11	4-Me-Ph-	**11k**	77	>99:1	99
12	2-furyl-	**11l**	89	>99:1	>99
13	2-thienyl	**11m**	67	>99:1	>99
14	1-naphthyl	**11n**	55	>99:1	98

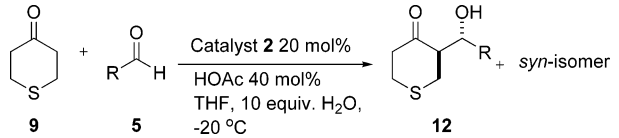
[a] Reactions were conducted with catalyst **2** (20 mol %), AcOH (40 mol %), aldehyde **5** (0.5 mmol), ketone **8** (2.5 mmol), H_2O (10 equiv based on the aldehyde), and THF (2 mL) for 18−114 h. [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral-phase HPLC analysis for the anti-product.

Note that the reactions of ketone **8** with various aldehydes were performed in the presence of 10 equiv of water. It was observed that the addition of water has a positive effect on the catalytic performance of catalyst **2** in this case (Table 2, entries 12 versus 13).

C. Aldol Reaction of Tetrahydro-4*H*-thiopyran-4-one 9 with Aldehydes. Finally, we examined the use of tetrahydro-4*H*-thiopyran-4-one **9** for the aldol-type process. Gratifying results were obtained with this ketone, which gave very high enantio- and diastereoselectivities using different kinds of aldehydes. In the reaction of **5a** with **9** (Table 5, entry 1), no dehydration products were detected by ^{1}H NMR analysis, indicating **12a** to be the sole product (99:1 dr; 99% ee). Other results are listed in Table 5. The reactions of aromatic aldehydes bearing electron-withdrawing groups with ketone **9** affords the aldol adducts **12a**−**j** in good to excellent yield, with enantioselectivities ranging from 97% to 99% ee (Table 5, entries 1−10). In general, the reactions of aromatic aldehydes with two electron-withdrawing substituents are better with ketone **9** in terms of both reactivity and selectivity (entries 7−9). By contrast, the reaction of the aliphatic aldehyde **5m** afforded somewhat lower product yield, while the dr and ee values were up to 98:2 and 99%, respectively.

A similar study was reported by Pihko's research group using L-proline as the catalyst.[16] However, our reaction times are generally shorter (24−120 h versus 72−216 h), our yields (55−98% versus 40−76%), as well as dr (91/9−99/1 versus 4/ 1−20/1) and ee values (90−99% versus 73−99%), are higher, and most importantly our catalysts have greater substrate scope.

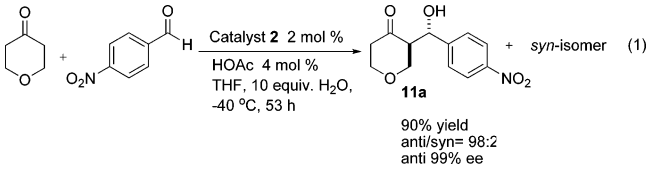
TABLE 5. Scope of the Direct Aldol Reaction of Aldehydes 5 and Ketone 9[a]



entry	R	product	yield[b] (%)	dr[c]	ee[d] (%)
1	4-NO_2-Ph-	**12a**	91	99:1	99
2	3-NO_2-Ph-	**12b**	88	92:8	98
3	2-NO_2-Ph-	**12c**	93	98:2	99
4	4-CN-Ph-	**12d**	98	98:2	99
5	4-Br-Ph-	**12e**	90	99:1	97
6	3-Br-Ph-	**12f**	78	99:1	99
7	4-Cl-Ph-	**12g**	63	99:1	99
8	2-Cl-Ph-	**12h**	91	89:11	98
9	2,4-Cl_2-Ph-	**12i**	99	97:3	99
10	4-F-Ph-	**12j**	74	99:1	97
11	Ph-	**12k**	61	97:3	90
12	1-naphthyl	**12l**	37	99:1	99
13	1-thienyl	**12m**	45	99:1	99

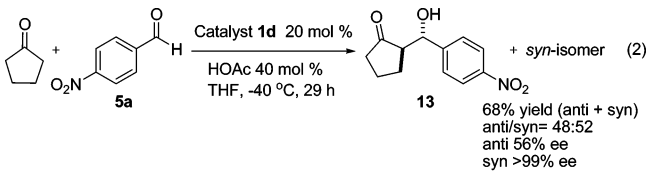
[a] Reactions were conducted with catalyst **2** (20 mol %), AcOH (40 mol %), aldehyde **5** (0.5 mmol), ketone **8** (2.5 mmol), H_2O (10 equiv based on the aldehyde), and THF (2 mL) for 24−120 h. [b] Isolated yields. [c] Determined by ^1H NMR spectroscopy. [d] Determined by chiral-phase HPLC analysis for the anti-product.

Moreover, a preliminary study showed that the catalyst loading could be reduced to as low as 2 mol % for ketone **8**, and the results were comparable with that using 20 mol % catalyst, though slightly longer reaction time was needed (eq 1).[20]

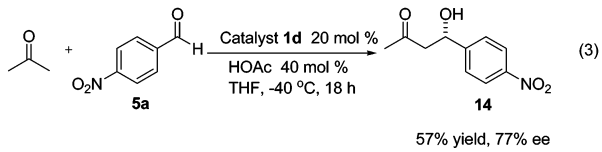


(1)

In addition, we have examined the feasibility of using other cyclic and acyclic ketones as aldol donors. In the case of cyclopentanone, excellent ee (>99%) for syn-isomer was obtained; however, the diastereomeric ratio of anti/syn was almost 1/1 (eq 2). The reaction of acetone with *para*-nitrobenzaldehyde (**5a**) went smoothly to give **14** in 57% isolated yield with 77% ee (eq 3).[15g]



(2)



(3)

Conclusion

In summary, we have demonstrated that the readily tunable and bifunctional diamide catalysts **1d** and **2** can catalyze the direct aldol reactions of heterocyclic ketones with various aldehydes, affording more than 30 different compounds in 94−99% ee. We found that different catalyst analogues showed variable catalytic activities for different aldol donors. Appropriate catalysts can easily be obtained just by changing the substitutents on the NH groups. In this regard, the design and use of **1** and **2** raise the possibility of developing sterically and electronically flexible novel catalysts that have high reactivities for asymmetric organocatalysis. Significantly, our strategy allows the use of 4-thianone, a surrogate for unreactive 3-pentanone, for the aldol reaction affording excellent diastereo- and enantioselectivies. The latter has potential for the construction of polypropionate building blocks after removal of the sulfur bridge.[21] The amount of catalyst can be reduced to 2 mol % without the loss of catalytic efficiency. Further studies about the detailed role of the two NH groups in our catalysts, and investigations of the capacity of these catalysts toward new reactions, are currently underway in our laboratory.

Experimental Section

General procedure for the Aldol Reaction of Cycloketone with Aldehyde. The organocatalyst, l-prolinamide derivatives[22] (0.1 mmol), ketone (2.5 mmol), and AcOH (0.2 mmol) were stirred in 2 mL THF for 10 min at −20 °C. The corresponding aldehyde **5** (0.5 mmol) was added, and the mixture was stirred for 41−96 h. The mixture was treated with 10 mL saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give pure aldol adduct through flash column chromatography on silica gel (hexane/ethyl acetate (3:1)).

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Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0615089

(20) equiv ketone was used.

(21) Nishide, K.; Shigeta, Y.; Obata, K.; Aksela, R. *Tetrahedron* **1996**, *37*, 2271.

(22) For the preparation of catalysts **1a**−**e** and **2**, please see: Li, X.-Y.; Chen, J.-R.; Meng, X.; Xiao, W.-J. *Acta Crystallogr*. **2005**, *E61*, o2730 and ref 15g.