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Asymmetric aldol reactions between cyclic ketones and benzaldehyde catalyzed by chiral Zn^{2+} complexes of aminoacyl 1,4,7,10-tetraazacyclododecane: effects of solvent and additives on the stereoselectivities of the aldol products

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ABSTRACT

The direct aldol reaction between cyclic ketones and 4-nitrobenzaldehyde catalyzed by chiral Zn^{2+} complexes of aminoacyl 1,4,7,10-tetraazacyclododecane is reported. The *anti*-aldol products were mainly formed in cyclohexanone/*N*-methylpyrrolidone(NMP)/MeOH with good diastereo- and enantioselectivity, while *syn*-aldol adducts were obtained as major products with good enantioselectivity in cyclohexanone/H_2O and cyclohexanone/NMP/H_2O. The fact that the UV/vis spectra of 2,6-diphenyl-4-(2,4,6-triphenyl-1-pyridinio)phenolate (Reichardt's dye) were nearly identical in these solvent systems suggests that the switch in the relative configuration of the aldol products is induced by a large excess of H_2O rather than the polarity of the solvent system. Furthermore, the addition of a small amount of TFA improved the enantioselectivity of the *syn*-aldol adducts produced in cyclohexanone/H_2O with up to 92% ee (*anti*/*syn* ratio = 30:70).

1. Introduction

Optically active β-hydroxy carbonyl compounds are versatile intermediates in the synthesis of natural products, pharmaceutically active compounds, and related materials.[1] The aldol reaction is one of the most important C–C bond forming reactions for producing β-hydroxy carbonyl compounds bearing two new stereogenic centers at the α- and β-positions of the carbonyl groups.[2] To date, a number of methods for controlling the stereochemistry of the aldol products have been reported, most of which involve the use of stoichiometric amounts of chiral auxiliaries.[3–5] In addition, direct catalytic aldol reactions using metallocatalysts,[6,7] organocatalysts,[8,9] and bio-catalysts[10] have recently been reported. Asymmetric aldol reactions of cyclic ketones with aldehydes are particularly attractive and valuable strategies for the synthesis of β-hydroxy carbonyl derivatives. Although some asymmetric aldol reactions of cyclic ketones have been reported, only a few studies on direct catalytic asymmetric aldol reactions of cyclohexanone with aldehydes to afford *syn*-aldol products have been reported.[11,12] Besides, the development of methods for changing the diastereo- and enantioselectivity of the reaction products produced using the same chiral catalysts would be very useful from a practical point of view.[13,14]

In a previous study, we reported on the direct aldol reactions of acetone and benzaldehydes in aqueous solution, catalyzed by chiral Zn complexes of aminoacyl 1,4,7,10-tetraazacyclododecane ([12]aneN$_4$ or cyclen) derivatives such as **1**–**4** (L-ZnL^1–L-ZnL^4).[15] A mechanistic study suggested that the Zn^{2+}-bound OH^- of the ZnL complexes **5** (ZnL(OH^-)) acts as a base to deprotonate the α-proton of the acetone to generate the ZnL–$(enolate)^-$ complex **6** in these aldol reactions (Scheme 1).[15b] We also reported on the one-pot synthesis of optically active 1,3-diols **9a**–**c** by a combination of enantioselective aldol reactions catalyzed by ZnL complexes to give aldol adducts **8a**–**c** with the successive reduction of **8a**–**c** by the recombinant oxidoreductase system 'Chiralscreen® OH' (Scheme 1).[16]

These results prompted us to investigate the diastereo- and enantioselective aldol reaction of cyclic ketones such as cyclohexanone **10** and cyclopentanone **11** with 4-nitrobenzaldehyde **7c** in the presence of the above chiral ZnL catalysts (Scheme 2). An inversion of the stereoselectivities of the aldol products was observed by simply changing the solvent system and the additive used in the reaction. The mechanism of these phenomena is discussed based on the UV/vis spectra measurements of solvent systems using 2,6-diphenyl-4-(2,4,6-triphenyl-1-pyridinio)phenolate (Reichardt's dye), which has been reported as an indicator of solvent polarity.[17] The

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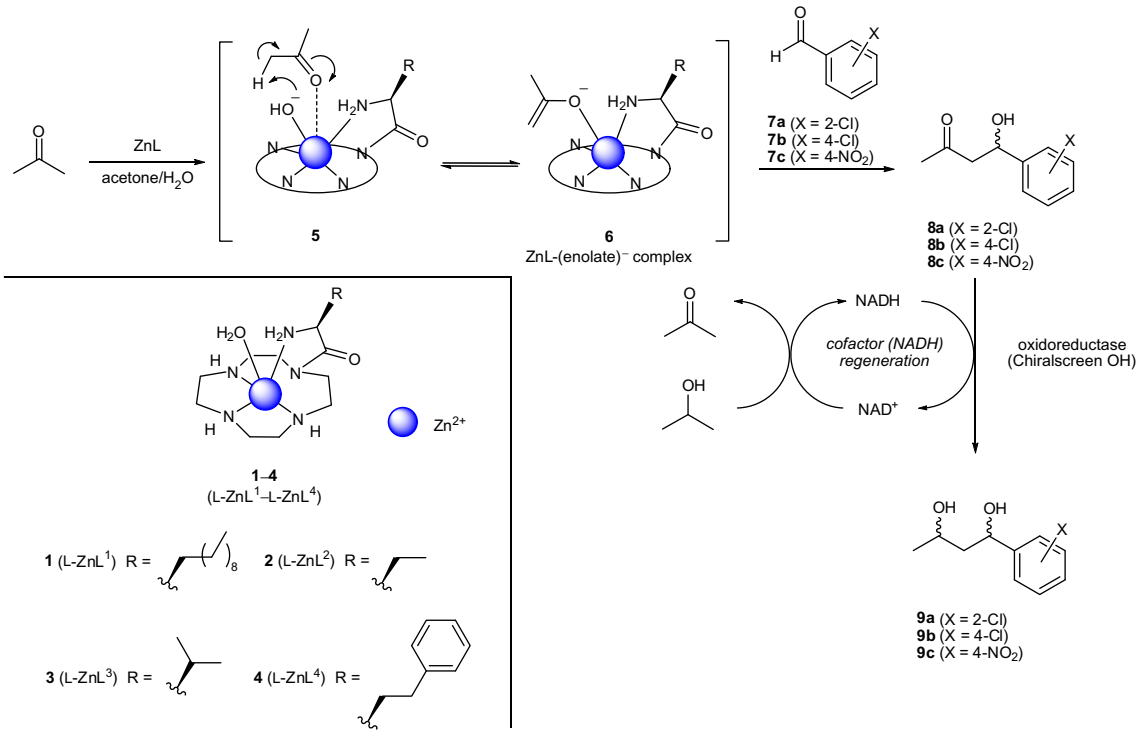
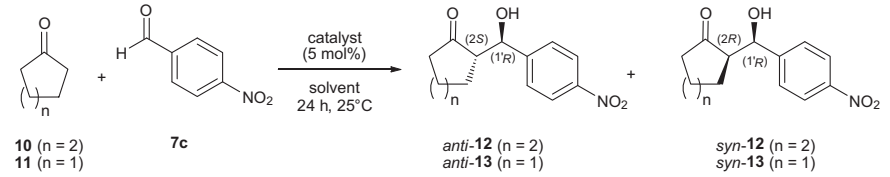


Scheme 1. Asymmetric aldol reactions of acetone catalyzed by chiral ZnL complexes combined with the reduction of the aldol products **8a–c** by an oxidoreductase using a cofactor (NADH) regenerating system to give 1,3-diols **9a–c**.



Scheme 2. Aldol reactions between **10** and **11** with **7c** catalyzed by chiral ZnL complexes.

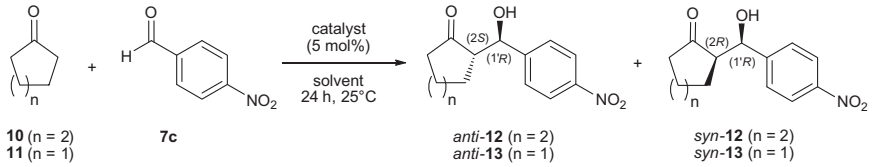
effect of additives, such as Zn^{2+} salts and trifluoroacetic acid (TFA), was also investigated.

2. Results and discussion

The aldol reaction of cyclohexanone **10** and 4-nitrobenzaldehyde **7c** was carried out using L-ZnL^1 (5 mol %, 25 mM) in different solvent systems, as listed in entries 1–12 of Table 1. Although only trace amounts of aldol product **12** were obtained under neat conditions (entry 1), the reaction was accelerated in the case of **10**/H_2O (50:50) to give **12** in 36% yield with 77% ee (2*R*, 1′*R*) (entry 2). The chemical yield and ee value of **12** were further improved upon when a 95:5 mixture of **10**/H_2O was used (79% yield and 89% ee (2*R*, 1′*R*)), while the *anti*/*syn* ratio was almost 1:1 (entry 3). Among the alcohol solvents tested (MeOH, EtOH, and *i*-PrOH), MeOH gave *anti*-**12** in 72% ee (2*S*, 1′*R*) with an *anti*/*syn* ratio of 82:18 (entries 4–6). The use of aprotic polar solvents, such as NMP (*N*-methylpyrrolidone) or DMF, gave *anti*-**12** as the major isomer (*anti*/*syn* = 90:10) with good enantioselectivity, although the chemical yields were rather low (entries 7 and 8). Mixtures of H_2O, MeOH, and NMP were also tested as co-solvents. When a **10**/NMP/H_2O mixture was used, the reaction proceeded smoothly to afford **12** in 85% yield with 83% ee (2*R*,1′*R*) with an *anti*/*syn* ratio of ca. 1:1 (entry 9). On the other hand, *anti*-**12** was obtained as the major isomer with good diastereo- and enantioselectivity [*anti*/*syn* = 88:12, 84% ee (2*R*,1′*R*)] when **10**/NMP/MeOH was used as the solvent (entry 10). The use of **10**/NMP/MeOH/H_2O and **10**/MeOH/H_2O gave *syn*-**12** with an enantioselectivity similar to that obtained for **10**/H_2O and **10**/NMP/H_2O (entries 11 and 12), thus implying that the inversion of the stereoselectivity of **12** was induced by the presence of H_2O. A similar dependency of the stereochemistry of the aldol products on the solvent system used was observed when ZnL complexes **2–4** (L-ZnL^2–L-ZnL^4) were used (entries 13–18). In entries 19–24, in which cyclopentanone **11** was used as the substrate, *syn*-**13** was obtained as the major isomer in a **11**/H_2O system in high yield and with good enantioselectivities (entries 19–21), while the yield and stereoselectivities of **13** were low in **11**/NMP/MeOH (entries 22–24). It should be noted that the reaction mixtures in **10**/H_2O and **11**/H_2O (entries 2, 3, 13–15, and 19–21) are heterogeneous and we assume that the aldol reaction in these cases proceeds mainly in the organic layer or at the interface of the organic and aqueous layers.

To the best of our knowledge, the absolute stereochemistry of the aforementioned *syn*-**12** has not been determined, while that for *anti*-**12** has been reported.[11d,12c,14h,18,19] The absolute configuration of the major enantiomer of *syn*-**12** was determined as follows. A 5:95 mixture of *anti*- and *syn*-**12** was prepared by silica gel column chromatography (Hexane/AcOEt) of the aldol products of entry 3 in Table 1 (*anti*/*syn* = 49:51), and was then reacted with 4-bromobenzoyl chloride to give *syn*-**14** as a single stereoisomer

Table 1
The results of the asymmetric aldol reactions between cyclic ketones **10** and **11** and 4-nitrobenzaldehyde **7c** catalyzed by **1**–**4** (L-ZnL[1]–L-ZnL[4])



10 (n = 2)
11 (n = 1)

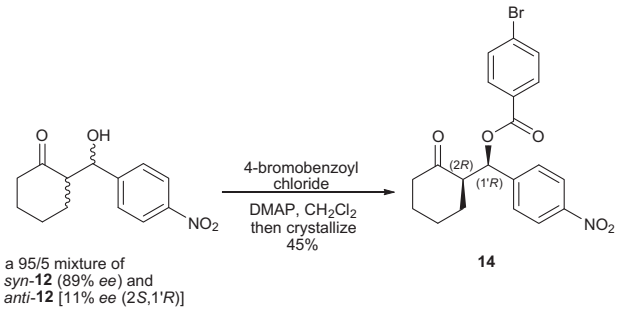
7c

anti-**12** (n = 2)
anti-**13** (n = 1)

syn-**12** (n = 2)
syn-**13** (n = 1)

Entry	Catalyst[a]	Solvent	Product	Yield[b] (%)	CTN[c]	d.r.[d] (*anti*/*syn*)	ee[e] (%) (*anti*/*syn*)
1	**1** (L-ZnL[1])	**10**[f]	**12**	4	1	99:1	28 (2*S*,1′*R*)/19 (2*R*,1′*R*)
2	**1** (L-ZnL[1])	**10**/H_2O (50:50)[g]	**12**	36	7	54:46	6 (2*R*,1′*S*)/77 (2*R*,1′*R*)
3	**1** (L-ZnL[1])	**10**/H_2O (95:5)[g]	**12**	79	16	49:51	11 (2*S*,1′*R*)/89 (2*R*,1′*R*)
4	**1** (L-ZnL[1])	**10**/MeOH (50:50)[f]	**12**	81	16	82:18	72 (2*S*,1′*R*)/61 (2*R*,1′*R*)
5	**1** (L-ZnL[1])	**10**/EtOH (50:50)[f]	**12**	61	12	67:33	68 (2*S*,1′*R*)/86 (2*R*,1′*R*)
6	**1** (L-ZnL[1])	**10**/*i*-PrOH (50:50)[f]	**12**	13	3	80:20	68 (2*S*,1′*R*)/54 (2*R*,1′*R*)
7	**1** (L-ZnL[1])	**10**/DMF (50:50)[f]	**12**	4	1	91:9	84 (2*S*,1′*R*)/52 (2*R*,1′*R*)
8	**1** (L-ZnL[1])	**10**/NMP (50:50)[f]	**12**	19	4	90:10	88 (2*S*,1′*R*)/17 (2*R*,1′*R*)
9	**1** (L-ZnL[1])	**10**/NMP/H_2O (40:50:10)[f]	**12**	85	17	49:51	7 (2*R*,1′*S*)/83 (2*R*,1′*R*)
10	**1** (L-ZnL[1])	**10**/NMP/MeOH (40:50:10)[f]	**12**	96	19	88:12	84 (2*S*,1′*R*)/46 (2*R*,1′*R*)
11	**1** (L-ZnL[1])	**10**/NMP/MeOH/H_2O (40:50:5:5)[f]	**12**	83	17	59:41	16 (2*S*,1′*R*)/80 (2*R*,1′*R*)
12	**1** (L-ZnL[1])	**10**/MeOH/H_2O (50:25:25)[f]	**12**	70	14	47:53	1 (2*R*,1′*S*)/78 (2*R*,1′*R*)
13	**2** (L-ZnL[2])	**10**/H_2O (95:5)[g]	**12**	1	—	50:50	24 (2*R*,1′*S*)/85 (2*R*,1′*R*)
14	**3** (L-ZnL[3])	**10**/H_2O (95:5)[g]	**12**	41	8	61:39	5 (2*R*,1′*S*)/76 (2*R*,1′*R*)
15	**4** (L-ZnL[4])	**10**/H_2O (95:5)[g]	**12**	62	12	51:49	6 (2*S*,1′*R*)/90 (2*R*,1′*R*)
16	**2** (L-ZnL[2])	**10**/NMP/MeOH (40:50:10)[f]	**12**	52	10	85:15	85 (2*S*,1′*R*)/64 (2*R*,1′*R*)
17	**3** (L-ZnL[3])	**10**/NMP/MeOH (40:50:10)[f]	**12**	26	5	93:7	90 (2*S*,1′*R*)/11 (2*S*,1′*S*)
18	**4** (L-ZnL[4])	**10**/NMP/MeOH (40:50:10)[f]	**12**	89	18	87:13	83 (2*S*,1′*R*)/51 (2*R*,1′*R*)
19	**1** (L-ZnL[1])	**11**/H_2O (95:5)[g]	**13**	92	18	33:67	14 (2*R*,1′*S*)/85 (2*R*,1′*R*)
20	**3** (L-ZnL[3])	**11**/H_2O (95:5)[g]	**13**	85	17	44:56	7 (2*R*,1′*S*)/81 (2*R*,1′*R*)
21	**4** (L-ZnL[4])	**11**/H_2O (95:5)[g]	**13**	90	18	31:69	23 (2*R*,1′*S*)/87 (2*R*,1′*R*)
22	**1** (L-ZnL[1])	**11**/NMP/MeOH (40:50:10)[f]	**13**	21	4	51:49	39 (2*S*,1′*R*)/3 (2*R*,1′*R*)
23	**3** (L-ZnL[3])	**11**/NMP/MeOH (40:50:10)[f]	**13**	2	—	46:54	27 (2*R*,1′*S*)/9 (2*S*,1′*S*)
24	**4** (L-ZnL[4])	**11**/NMP/MeOH (40:50:10)[f]	**13**	6	1	55:45	37 (2*R*,1′*S*)/7 (2*R*,1′*R*)

[a] Concentrations of the catalysts in the solvent were 25 mM. ZnL complexes were formed in situ. The L-forms of ZnL complexes were used in all entries.
[b] Isolated yield.
[c] Catalytic Turnover Number (= yield/equivalents of catalyst).
[d] Determined by ^1H NMR spectroscopy and HPLC analysis.
[e] Determined by HPLC analysis using a chiral column (Refs. 14h,18).
[f] Reaction solution is homogeneous.
[g] Reaction solution is heterogeneous.



a 95/5 mixture of
syn-**12** (89% *ee*) and
anti-**12** [11% *ee* (2*S*,1′*R*)]

14

Scheme 3. Synthesis and crystallization (Fig. 1) of **14** for the determination of the absolute configuration of *syn*-**12**.

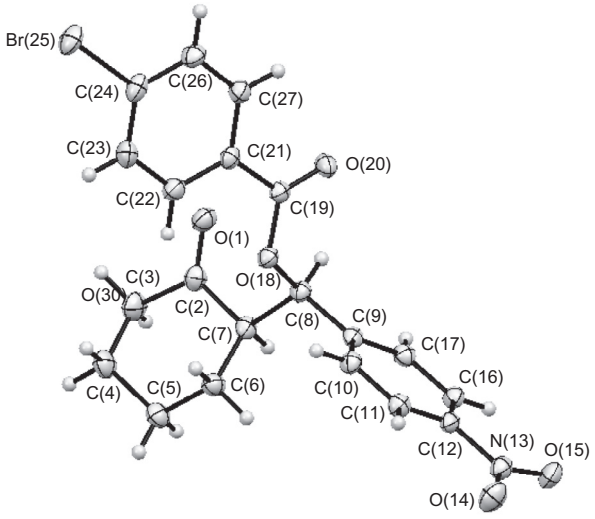


Figure 1. The ORTEP drawing (50% probability ellipsoids) of (2*R*,1′*R*)-**14**.

(Scheme 3). Recrystallization of this material from Hexanes/AcOEt gave single crystals suitable for X-ray analysis, which was found to be (2*R*, 1′*R*)-**14**, as shown in Figure 1.

As described in Table 1, *syn*-**12** was produced as the major diastereomer in **10**/NMP/H_2O (40:50:10) and *anti*-**12** was mainly obtained in **10**/NMP/MeOH (40:50:10).[20] The relationship between the solvent systems including **10**, H_2O, MeOH, and NMP with the (1′*R*/1′*S*) and (2*R*/2*S*) ratios of the aldol adduct **12** is summarized in Figure 2. The results listed in Table 1 indicate that the absolute configuration at the '1' position of *anti*- and *syn*-**12** is '1′*R*', thus implying that **7c** is attacked by the ZnL-enolate of **10** preferentially

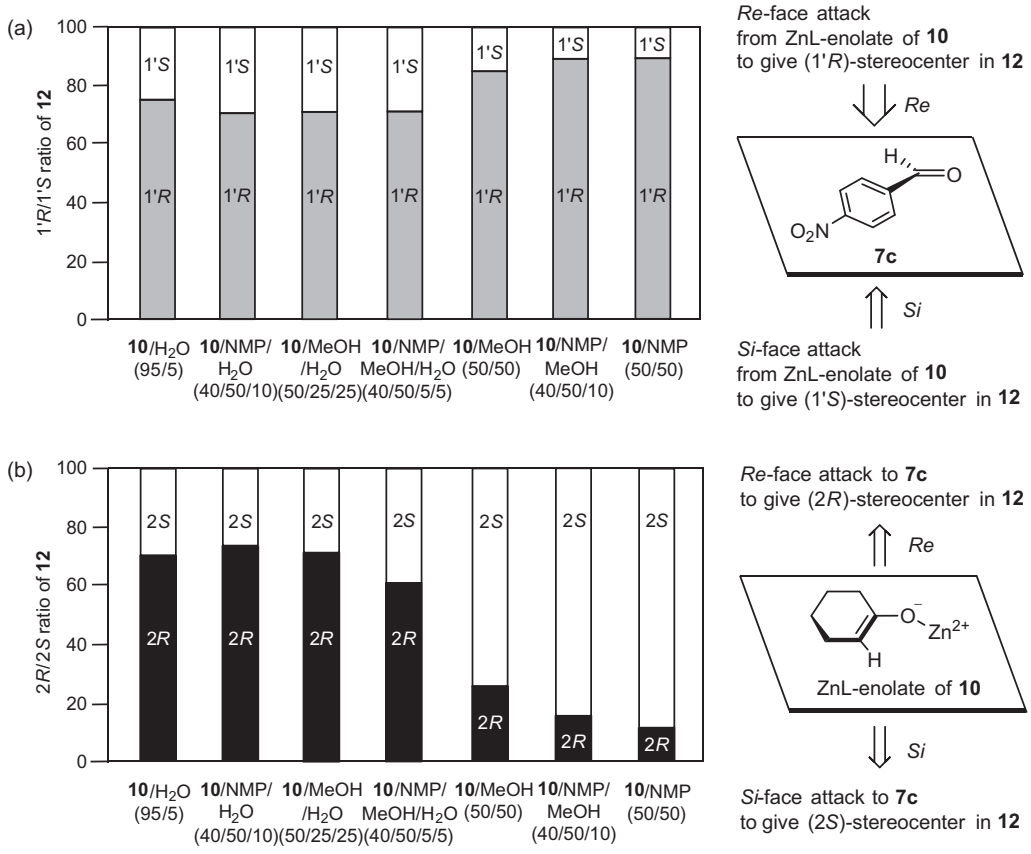
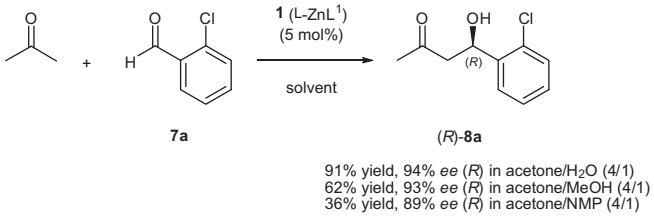


Figure 2. The relationship of solvent systems and (a) the 1′*R*/1′*S* and (b) the 2*R*/2*S* ratio of *anti*- and *syn*-**12** listed in entries 3, 4, and 8–12 in Table 1.



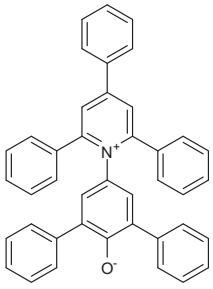
Scheme 4. Aldol reaction between acetone and 2-chlorobenzaldehyde **7a** catalyzed by **1**(L-ZnL^1)

from the *Re*-face, as indicated in Figure 2a. In the aldol reaction of acetone with 2-chlorobenzaldehyde **7a** in acetone/H_2O (4:1), acetone/MeOH (4:1), and acetone/NMP (4:1), the use of L-ZnL^1 resulted in the formation of (*R*)-**8a** in 94% ee, 93% ee, and 89% ee, respectively (Scheme 4), indicating that the enolate form of acetone attacks benzaldehyde predominantly from the same face (*Re*-face) in both cases.

As shown in Figure 2b, the attack of ZnL-enolate of **10** to **7c** occurs mainly at the *Re*-face to give the (2*R*)-stereocenter in **12** in **10**/H_2O (95:5), **10**/NMP/H_2O (40:50:10), **10**/MeOH/H_2O (50:25:25), and **10**/NMP/MeOH/H_2O (40:50:5:5) (left half of Fig. 2b). On the other hand, the *Si*-facial reaction is favorable in less polar solvent systems such as **10**/MeOH (50:50), **10**/NMP/MeOH (40:50:10), and **10**/NMP (50:50) (right half of Fig. 2b).

In order to examine the effect of the polarity of the overall solvent system on the stereochemistry of the aldol adduct **12** in each case shown in Figure 2a and b, we obtained UV/vis spectra of 2,6-diphenyl-4-(2,4,6-triphenyl-1-pyridinio)phenolate (Reichardt's dye) **15**. It is known that the absorption maximum of **15** is dependent on the polarity of the solvent: its absorption spectra exhibit a red-shift in less polar solvents.[17] Since it was observed that the absorption intensity of **15** was reduced in the presence of a large excess amount of **10**, the UV/vis spectra of **15** were measured without **10**. The absorption maximum of **15** in MeOH/H_2O (1:1) was observed at 493 nm (Fig. 3a), in which the *syn*-adduct (2*R*, 1′*R*)-**12** was predominantly obtained, while it was observed at 513 and 675 nm in MeOH and NMP, respectively (Fig. 3b and f), which gave *anti*-**12** as a major isomer. In addition, the absorption maximum of **15** was observed at the almost identical wavelength (about 590 nm) in NMP/MeOH (5:1), in NMP/MeOH/H_2O (10:1:1), and in NMP/H_2O (5:1), indicating that the polarities of these solvent mixtures are similar (Fig. 3c–e). These data indicate that the diastereoselectivity of the aldol products of **12** is affected by the presence of a large excess of H_2O rather than the polarity of the solvent used in the reaction, thus suggesting the important role of H_2O in the transition state of the aldol reactions.[21]

The effect of some additives on the aldol reaction was examined using **1** (L-ZnL^1) and **4** (L-ZnL^4) in Table 2. The addition of $Zn(NO_3)_2{\cdot}6H_2O$ and Zn-cyclen·H_2O **16** (ZnL^5) gave **12** in almost the same yield and enantioselectivity as those obtained in the absence of an additive (entry 1 vs entries 2 and 3). When 5 mol % trifluoroacetic acid (TFA) was added, the diastereo- and enantioselectivity of *syn*-**12** were improved, while 10 mol % TFA gave worse results (entry 1 vs entries 4 and 5) (it was confirmed by ^{1}H NMR that L-ZnL^1 did not decompose under these conditions). In entries 6 and 7 where **4** (L-ZnL^4) was used as a catalyst, the diastereoselectivity of *syn*-**12** was also improved upon by the addition of TFA (5 mol %). In **10**/NMP/MeOH, the addition of Zn^{2+} salt and TFA improved the diastereo- and enantioselectivity of *syn*-**12**, while the enantioselectivity of *anti*-**12** was lowered (entry 8 vs entries 9–11). It has been reported that acidic additives function as hydrogen-bonding donors in the transition states of aldol reactions catalyzed by chiral organocatalysts and switch the diastereo- or



15

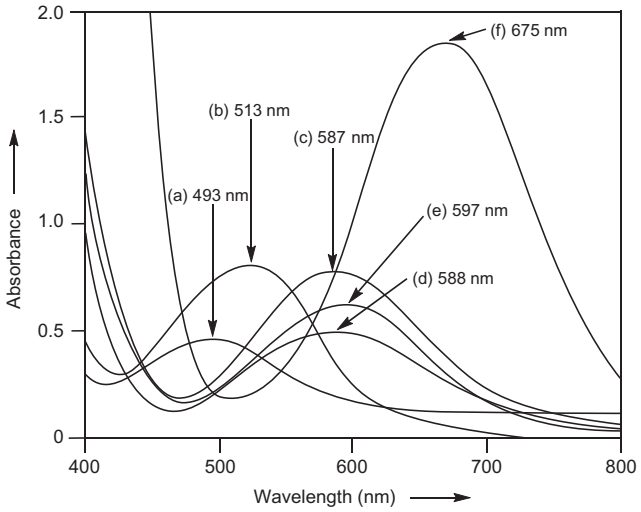
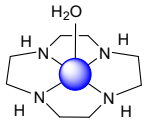


Figure 3. UV/vis spectra of **15** (0.25 mM) in (a) MeOH/H_2O (1:1), (b) MeOH, (c) NMP/MeOH (5:1), (d) NMP/MeOH/H_2O (10:1:1), (e) NMP/H_2O (5:1), and (f) NMP at 25 °C.

enantioselectivity of the aldol products.[12c,14g] In our case, TFA may exhibit a similar effect, while Zn^{2+}-bound H_2O (pK_a value is 7.8)[15a,22] of **16** has a negligible effect.



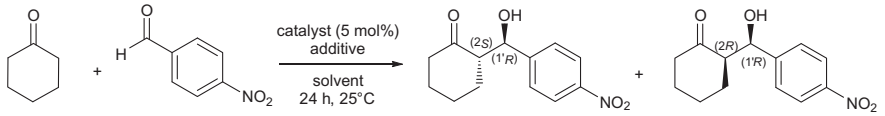
16
(ZnL^5)

Based on the information obtained herein, the transition states of the ZnL-catalyzed aldol reaction between **10** and **7c** are proposed as shown in Scheme 5. It is likely that the change in the stereoselectivity of **12** is dependent on the transition states, which may have chair- or boat-like structure, as described by Denmark et al.[23] We assumed that a chair-like transition state structure **17** was preferred in the solvent systems without H_2O, such as **10**/NMP/MeOH, and afforded *anti*-**12** as the major diastereomer. On the other hand, a boat-like transition state structure **18** is preferred in the presence of H_2O (and TFA) to give *syn*-**12** with good enantioselectivities. Our hypothesis is that H_2O and TFA may play important roles in the hydrogen-bonding network including substrates and catalysts, as reported by Yang et al.[12c] and Maruoka et al.[14g]

3. Conclusion

The findings reported herein show that the direct aldol reaction between cyclic ketones such as cyclohexanone or cyclopentanone and benzaldehyde catalyzed by ZnL complexes can result in the formation of the corresponding aldol adducts in high chemical yields and enantiomeric excess. The choice of an appropriate solvent system and additive allows the preparation of either

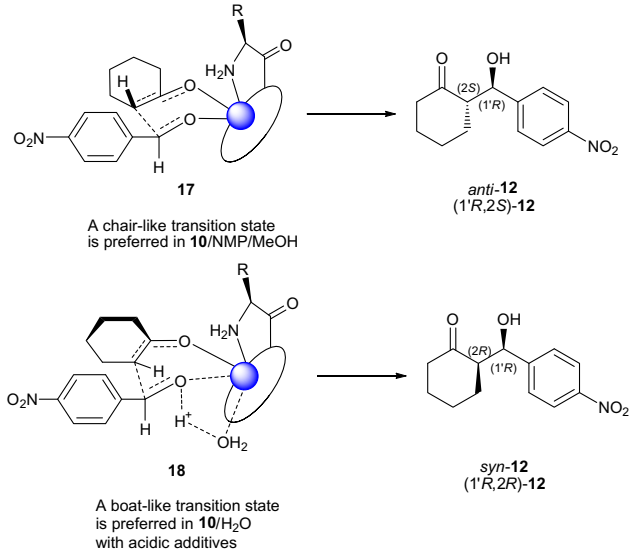
Table 2
Effect of additives on asymmetric aldol reactions between cyclohexanone **10** and 4-nitrobenzaldehyde **7c** catalyzed by **1** (L-ZnL^1) and **4** (L-ZnL^4)



10 **7c** *anti*-**12** *syn*-**12**

Entry	Catalyst[a]	Solvent	Additive	Yield[b] (%)	CTN[c]	d.r.[d] (*anti*/*syn*)	ee[e] (%) (*anti*/*syn*)
1[f]	**1** (L-ZnL^1)	**10**/H_2O (95:5)[i]	None	79	16	49:51	11 (2*S*,1′*R*)/89 (2*R*,1′*R*)
2	**1** (L-ZnL^1)	**10**/H_2O (95:5)[i]	$Zn(NO_3)_2{\cdot}6H_2O$ (5 mol %)	78	16	44:56	5 (2*S*,1′*R*)/89 (2*R*,1′*R*)
3	**1** (L-ZnL^1)	**10**/H_2O (95:5)[i]	**16** (ZnL^5) (5 mol %)	77	15	38:62	18 (2*S*,1′*R*)/89 (2*R*,1′*R*)
4	**1** (L-ZnL^1)	**10**/H_2O (95:5)[i]	TFA (5 mol %)	67	13	30:70	2 (2*R*,1′*S*)/92 (2*R*,1′*R*)
5	**1** (L-ZnL^1)	**10**/H_2O (95:5)[i]	TFA (10 mol %)	61	12	28:72	5 (2*R*,1′*S*)/86 (2*R*,1′*R*)
6[g]	**4** (L-ZnL^4)	**10**/H_2O (95:5)[i]	None	62	12	51:49	6 (2*S*,1′*R*)/90 (2*R*,1′*R*)
7	**4** (L-ZnL^4)	**10**/H_2O (95:5)[i]	TFA (5 mol %)	57	11	34:66	14 (2*R*,1′*S*)/88 (2*R*,1′*R*)
8[h]	**1** (L-ZnL^1)	**10**/NMP/MeOH (40:50:10)[j]	None	96	19	88:12	84 (2*S*,1′*R*)/46 (2*R*,1′*R*)
9	**1** (L-ZnL^1)	**10**/NMP/MeOH (40:50:10)[j]	$Zn(NO_3)_2{\cdot}6H_2O$ (5 mol %)	63	13	78:22	75 (2*S*,1′*R*)/70 (2*R*,1′*R*)
10	**1** (L-ZnL^1)	**10**/NMP/MeOH (40:50:10)[j]	**16** (ZnL^5) (5 mol %)	90	18	75:25	73 (2*S*,1′*R*)/73 (2*R*,1′*R*)
11	**1** (L-ZnL^1)	**10**/NMP/MeOH (40:50:10)[j]	TFA (5 mol %)	39	8	63:37	60 (2*S*,1′*R*)/71 (2*R*,1′*R*)

[a] Concentrations of catalysts in the solvent were 25 mM. ZnL complexes were formed in situ. The L-forms of ZnL complexes were used in all entries.
[b] Isolated yield.
[c] Catalytic Turnover Number (= yield/equivalents of catalyst).
[d] Determined by ^1H NMR spectroscopy and HPLC analysis.
[e] Determined by HPLC analysis using a chiral column.[14h,18]
[f] Taken from entry 3 in Table 1.
[g] Taken from entry 15 in Table 1.
[h] Taken from entry 10 in Table 1.
[i] Reaction solution is heterogeneous.
[j] Reaction solution is homogeneous.



Scheme 5. Proposed transition states of the ZnL-catalyzed aldol reaction between **10** and **7c**.

anti- or *syn*-aldol adducts with good diastereo- and enantioselectivity. We assume that the development of methods for controlling the diastereo- and enantioselectivity of the aldol products using the same chiral catalysts, and in different solvent systems, would be very useful from a practical point of view. These results should afford useful information for controlling the stereoselectivity of the products in aldol reactions of cyclic ketones and related substrates. Attempts at improving the aldol reactions of other substrates such as 2,2-dimethyl-1,3-dioxan-5-one (protected dihydroxyacetone) with benzaldehydes and glyceraldehyde derivatives and more detailed mechanistic studies are currently underway.

4. Experimental

4.1. General

All reagents and solvents were of the highest commercial quality and used without further purification. $Zn(NO_3)_2{\cdot}6H_2O$ was purchased from Wako Chemical Co. All aqueous solutions were prepared using deionized and distilled water. HPLC was carried out using a HITACHI AS-2000 Autosampler, an L-4000 UV Detector, an L-5025 Column oven, and an L-6200 Intelligent pump. Optical rotations were determined using a JASCO P-1030 digital polarimeter in 50-mm cells using the D line of sodium (589 nm). UV spectra were recorded on a HITACHI U-3310 UV/vis spectrophotometer at 25 ± 0.1 °C. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a JNM-A500 spectrometer, respectively. The chemical shifts (δ) in $CDCl_3$ were determined relative to an internal reference of tetramethylsilane (TMS) (for ^{1}H NMR) and $CDCl_3$ (for ^{13}C NMR). IR spectra were recorded on a Perkin–Elmer Frontier FT-IR/FIR spectrometer at room temperature. MS measurements were performed on a JEOL JMS-SX102A and a Varian 910-MS. Elemental analyses were performed on a Perkin–Elmer CHN 2400 series II CHNS/O analyzer at the Research Institute for Science and Technology, Tokyo University of Science. Melting points were measured on an ASONE ATM-02 apparatus and are uncorrected. Thin-layer (TLC) and silica gel column chromatographies were performed using a Merck silica gel 60 F_{254} plate and Kanto Chemical Co. Inc. silica gel 60N (spherical, neutral, 40–100 μm), respectively.

4.2. Representative procedure for the catalytic aldol reactions

Chiral ligands (L-L^1–L-L^4) (0.0125 mmol) were extracted from a 0.2 M NaOH aqueous solution (0.5 mL) with $CHCl_3$. After drying the combined organic layers over anhydrous Na_2SO_4, the solution was filtered and concentrated under reduced pressure. The resulting residue was added to a solution of a mixture of $Zn(NO_3)_2{\cdot}6H_2O$ (0.0188 mmol) in a solvent (0.25 mL), and the mixture was stirred for 10 min. The substrate aldehyde (0.25 mmol) was then added and the resulting reaction mixture was stirred for 24 h at 25 °C. The reaction mixture was purified by silica gel column chromatography (Hexanes/AcOEt) to provide the pure aldol product. The enantiomeric purities of the aldol products were determined by HPLC using a chiral HPLC column, as described below.[14d,18]

4.2.1. 2-(Hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one 12

^{1}H NMR (500 MHz, $CDCl_3$/TMS) *anti* isomer: δ = 1.37–2.61 (m, 9H), 4.07 (d, J = 3.0 Hz, 1H), 4.90 (d, J = 8.5 Hz, 1H), 7.51 (d, J = 8.5 Hz, 2H; ArH), 8.21 ppm (d, J = 8.5 Hz, 2H; ArH); *syn* isomer: δ = 1.37–2.61 (m, 9H), 3.17 (d, J = 3.0 Hz, 1H), 5.49 (s, 1H), 7.51 (d, J = 8.5 Hz, 2H; ArH), 8.21 ppm (d, J = 8.5 Hz, 2H; ArH); HPLC (Daicel Chiralpak AD-H column (0.46φ × 25 cm), Hexanes/*i*-PrOH = 93:7, flow rate: 0.8 mL/min, λ = 254 nm, 25 °C): t_R(*syn*) (2*R*,1′*R*) = 30.2 min, t_R(*syn*) (2*S*,1′*S*) = 40.2 min, t_R(*anti*) (2*R*,1′*S*) = 43.1 min, t_R(*anti*) (2*S*,1′*R*) = 57.6 min.

4.2.2. 2-(Hydroxy(4-nitrophenyl)methyl)cyclopentan-1-one 13

^{1}H NMR (500 MHz, $CDCl_3$/TMS) *anti* isomer: δ = 1.59–2.57 (m, 7H), 4.76 (s, 1H), 4.85 (d, J = 9.5 Hz, 1H), 7.54 (d, J = 9.0 Hz, 2H; ArH), 8.22 ppm (d, J = 9.0 Hz, 2H; ArH); *syn* isomer: δ = 1.59–2.57 (m, 7H), 5.43 (s, 1H), 7.52 (d, J = 8.5 Hz, 2H; ArH), 8.22 ppm (d, J = 8.5 Hz, 2H; ArH); HPLC (Daicel Chiralpak AD-H column (0.46φ × 25 cm), Hexanes/*i*-PrOH = 95:5, flow rate: 1.0 mL/min, λ = 254 nm, 25 °C): t_R(*syn*) (2*R*,1′*R*) = 24.5 min, t_R(*syn*) (2*S*,1′*S*) = 34.6 min, t_R(*anti*) (2*R*,1′*S*) = 42.6 min, t_R(*anti*) (2*S*,1′*R*) = 45.8 min.

4.3. Determination of the absolute configuration of the *syn*-aldol products 12

4.3.1. Preparation of (−)-(2*R*,1′*R*)-2-((bromobenzoyl)oxy-(4-nitrophenyl)methyl)cyclohexan-1-one 14

At first, DMAP (39 mg, 0.32 mmol) was added to a solution of *syn*-**12** [*anti*/*syn* = 5:95, 89% ee (*syn*-form), 50 mg, 0.20 mmol] [the major enantiomer was determined to be (2*R*,1′*R*)-form based on the X-ray crystal structure analysis of **14**], and 4-bromobenzoyl chloride (66 mg, 0.30 mmol) in CH_2Cl_2 (8.0 mL). The mixture was then stirred at room temperature for 31 h, and the solvent was removed by concentration under reduced pressure. The resulting residue was purified by silica gel column chromatography (Hexanes/AcOEt = 4:1) to provide **14** as a colorless solid, which was crystallized from Hexanes/AcOEt (20:1) (10.5 mL) to give **14** as a colorless crystal (39 mg, 45% yield): mp = 124–126 °C; $[\alpha]_D^{25} = -75.6$ (c 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$/TMS): δ = 1.65–1.85 (m, 3H), 1.99–2.47 (m, 5H), 2.90 (ddd, J = 12.0, 9.0, 6.0 Hz, 1H), 6.52 (d, J = 6.0 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H; ArH), 7.61 (d, J = 9.0 Hz, 1H; ArH), 7.89 (d, J = 8.5 Hz, 1H; ArH), 8.20 ppm (d, J = 9.0 Hz, 1H; ArH); ^{13}C NMR (125 MHz, $CDCl_3$/TMS): δ = 24.8, 27.5, 28.6, 42.3, 55.7, 73.1, 123.4, 124.0, 127.3, 127.8, 128.5, 128.6, 130.8, 130.9, 131.4, 131.7, 132.2, 146.9, 164.5, 208.4 ppm; IR (ATR): ν = 2940, 2876, 1706, 1591, 1514, 1351, 1267, 1175, 1123, 1110, 1098, 1081, 1071, 1011, 844, 752, 700 cm^{-1}; HRMS (FAB+): calcd for [M+H]$^+$, 432.0447; found, 432.0443; elemental analysis calcd (%) for $C_{20}H_{18}BrNO_5$ (432.27): C, 55.57; H, 4.20; N, 3.24; found: C, 55.17; H, 3.81; N, 3.13.

4.3.2. Crystallographic study of 14

All measurements were made on a Bruker APEX CCD area detector using Mo-Kα radiation at 103 K. The structure was solved by direct methods.[24] All calculations were performed using the CrystalStructure crystallographic software package except for refinements, which were performed using SHELXL-97. $C_{20}H_{18}Br_1N_1O_5$, $M_r = 432.26$, a colorless prism, crystal size 0.50 × 0.11 × 0.10 mm, monoclinic, space group $P2(1)$, $a = 8.1256(8)$ Å, $b = 5.5047(5)$ Å, $c = 20.910(2)$ Å, $\beta = 90.6570(10)°$, $V = 935.23(15)$ Å^3, $Z = 2$, $D_{calc} = 1.535$ g cm^{-3}, 5216 measured reflections, 3078 unique reflections ($R_{int} = 0.0176$), $2\theta_{max} = 52.8$, $R1$ ($wR2$) = 0.0240 (0.0588), GOF = 1.148. CCDC 955434 contains the supplementary crystallographic data for this paper. These data are available free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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References

1. For some selected recent examples: (a) Kleemann, A.; Engels, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Syntheses, Patents, Applications*, 4th ed.; Thieme: Stuttgart, 2001; (b) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506–7525; (c) Matsui, R.; Seto, K.; Sato, Y.; Suzuki, T.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 680–683; (d) Coulthard, G.; Erb, W.; Aggarwal, V. K. *Nature* **2012**, *489*, 278–281; (e) Kawato, Y.; Chaudhary, S.; Kumagai, N.; Shibasaki, M. *Chem. Eur. J.* **2013**, *19*, 3802–3806.
2. Mahrwald, R. *Modern Aldol Reactions*; Wiley-VCH: Weinheim, 2004.
3. (a) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923; (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877; (c) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120–6123; (d) Xie, L.; Vanlandeghem, K.; Isenberger, K. M.; Bernier, C. *J. Org. Chem.* **2003**, *68*, 641–643; (e) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324–2336; (f) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913–3918; (g) Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett.* **1999**, *40*, 1509–1512.
4. (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129; (b) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279–8281; (c) Reetz, M. T.; Kunisch, F.; Heitmann, P. *Tetrahedron Lett.* **1986**, *27*, 4721–4724; (d) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747–5750; (e) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767–2772; (f) Nishimura, K.; Tsubouchi, H.; Ono, M.; Hayama, T.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett.* **2003**, *44*, 2323–2326.
5. (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011–1014; (b) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761–1772; (c) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041–1042; (d) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907–6910; (e) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814–5815; (f) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, *118*, 7404–7405; (g) Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 11531–11532; (h) Shirokawa, S.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604–13605.
6. For selected examples of metal catalysts: (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1871–1873; (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168–4178; (c) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466–2467; (d) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187–2209; (e) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269–279; (f) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406; (g) Hayashi, T.; Uozumi, Y.; Yamazaki, A.; Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron Lett.* **1991**, *32*, 2799–2802; (h) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 10984–10985; (i) Ohta, H.; Uozumi, Y.; Yamada, Y. M. A. *Chem. Asian J.* **2011**, *6*, 2545–2549; (j) Lalic, G.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2003**, *125*, 2852–2853; (k) Lu, Z.; Mei, H.; Han, J.; Pan, Y. *Chem. Biol. Drug Des.* **2010**, *76*, 181–186; (l) Kobayashi, S.; Kokubo, M.; Kawasumi, K.; Nagano, T. *Chem. Asian J.* **2010**, *5*, 490–492; (m) Karmakar, A.; Maji, T.; Wittmann, S.; Reiser, O. *Chem. Eur. J.* **2011**, *17*, 11024–11029; (n) Lin, L.; Yamamoto, K.; Matsunaga, S.; Kanai, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 10275–10279.
7. For selected examples of Zn^{2+} catalysts: (a) Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 1539–1542; (b) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169–2178; (c) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003–12004; (d) Trost, B. M.; Shin, S.; Sclafani, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8602–8603; (e) Nakagawa, M.; Nakao, H.; Watanabe, K.-I. *Chem. Lett.* **1985**, 391–394; (f) Calter, M. A.; Orr, R. K. *Tetrahedron Lett.* **2003**, *44*, 5699–5701; (g) Darbre, T.; Machuqueiro, M. *Chem. Commun.* **2003**, 1090–1091; (h) Kofoed, J.; Darbre, T.; Reymond, J.-L. *Chem. Commun.* **2006**, 1482–1484; (i) Pradowska, J.; Pasternak, M.; Gut, B.; Gryzlo, B.; Mlynarski, J. *J. Org. Chem.* **2012**, *77*, 173–187.
8. For recent reviews: (a) List, B. *Acc. Chem. Res.* **2004**, *37*, 548–557; (b) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558–569; (c) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580–591; (d) Dalco, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (e) Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1304–1325; (f) Mlynarski, J. *Eur. J. Org. Chem.* **2006**, 4779–4786; (g) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569; (h) Enders, D.; Narine, A. A. *J. Org. Chem.* **2008**, *73*, 7857–7870; (i) Mlynarski, J.; Paradowska, J. *Chem. Soc. Rev.* **2008**, *37*, 1502–1511; (j) Maruoka, K. *Org. Process Res. Dev.* **2008**, *12*, 679–697; (k) Kotsuki, H.; Ikishima, H.; Okuyama, A. *Heterocycles* **2008**, *75*, 493–529; (l) Kotsuki, H.; Ikishima, H.; Okuyama, A. *Heterocycles* **2008**, *75*, 757–797; (m) Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33–57.
9. For selected examples of organocatalysts: (a) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; (b) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167–8177; (c) Dickerson, T. J.; Janda, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 3220–3221; (d) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799; (e) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055–3057; (f) Akagawa, K.; Sakamoto, S.; Kudo, K. *Tetrahedron Lett.* **2005**, *46*, 8185–8187; (g) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5527–5529; (h) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2007**, *129*, 288–289; (i) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Tanaka, F.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2007**, *46*, 5572–5575; (j) Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2082–2084; (k) Terada, M.; Tanaka, H.; Sorimachi, K. *J. Am. Chem. Soc.* **2009**, *131*, 3430–3431; (l) Kano, T.; Sugimoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 18130–18133.
10. (a) Gijsen, H. J. M.; Qiao, L.; Fitz, W.; Wong, C.-H. *Chem. Rev.* **1996**, *96*, 443–473; (b) Takayama, S.; McGarvey, G. J.; Wong, C.-H. *Chem. Soc. Rev.* **1997**, *26*, 407–415; (c) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352–1374; (d) Wong, C.-H.; Bryan, M. C.; Nyffeler, P. T.; Liu, H.; Chapman, E. *Pure Appl. Chem.* **2003**, *75*, 179–186; (e) Dean, S. M.; Greenberg, W. A.; Wong, C.-H. *Adv. Synth. Catal.* **2007**, *349*, 1308–1320; (f) Sugiyama, M.; Hong, Z.; Liang, P.-H.; Dean, S. M.; Whalen, L. J.; Greenberg, W. A.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 14811–14817.
11. For selected examples of *anti* selective aldol reactions of cyclic ketones: (a) Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210–1212; (b) Suri, J. T.; Ramachary, D. B.; Barbas, C. F., III *Org. Lett.* **2005**, *7*, 1383–1385; (c) Grondal, C.; Enders, D. *Tetrahedron* **2006**, *62*, 329–337; (d) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 734–735; (e) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958–961; (f) Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, A. *Tetrahedron* **2006**, *62*, 317–328; (g) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801–2803; (h) Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem. Eur. J.* **2006**, *12*, 5383–5397; (i) Chen, J.-R.; Li, X.-Y.; Xing, X.-N.; Xiao, W.-J. *J. Org. Chem.* **2006**, *71*, 8198–8202; (j) Wu, X.; Jiang, Z.; Shen, H.-M.; Lu, X. *Adv. Synth. Catal.* **2007**, *349*, 812–816; (k) Paradowska, J.; Stodulski, M.; Mlynarski, J. *Adv. Synth. Catal.* **2007**, *349*, 1041–1046; (l) Lu, Z.; Mei, H.; Han, J.; Pan, Y. *Chem. Biol. Drug Des.* **2010**, *76*, 181–186.
12. For selected examples of *syn* selective aldol reactions of cyclic ketone: (a) Pousse, G.; Cavelier, F. L.; Humphreys, L.; Rouden, J.; Blanchert, J. *Org. Lett.* **2010**, *12*, 3582–3585; (b) Zhou, P.; Luo, S.; Cheng, J. P. *Org. Biomol. Chem.* **2011**, *9*, 1784–1790; (c) Gao, J.; Bai, S.; Gao, Q.; Liu, Y.; Yang, Q. *Chem. Commun.* **2011**, 6716–6718; (d) Kanemitsu, T.; Umehara, A.; Miyazaki, M.; Nagata, K.; Itoh, T. *Eur. J. Org. Chem.* **2011**, 993–997.
13. For recent reviews: (a) Sibi, M. P.; Liu, M. *Curr. Org. Chem.* **2001**, *5*, 719–755; (b) Zanoni, G.; Castronovo, F.; Franzini, M.; Vidari, G.; Giannini, E. *Chem. Soc. Rev.* **2003**, *32*, 115–129; (c) Tanaka, T.; Hayashi, M. *Synthesis* **2008**, 3361–3376; (d) Bartók, M. *Chem. Rev.* **2010**, *110*, 1663–1705.
14. For selected examples: (a) Kanai, M.; Koga, K.; Tomioka, K. *J. Chem. Soc. Chem. Commun.* **1993**, 1248–1249; (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545–4554; (c) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908–9909; (d) Nakayama, K.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 17666–17667; (e) Nojiri, A.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3779–3784; (f) Sohtome, Y.; Tanaka, S.; Tanaka, K.; Yamaguchi, T.; Nagasawa, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 9254–9257; (g) Moteki, S. A.; Han, J.; Arimitsu, S.; Akakura, M.; Nakayama, K.; Maruoka, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 1187–1190; (h) Martinez-Castañeda, A.; Rodriguez-Solla, H.;

Concellón, C.; del Amo, V. *J. Org. Chem.* **2012**, *77*, 10375–10381; (i) Nagata, Y.; Yamada, T.; Adachi, T.; Akai, Y.; Yamamoto, T.; Suginome, M. *J. Am. Chem. Soc.* **2013**, *135*, 10104–10113.
15. (a) Itoh, S.; Kitamura, M.; Yamada, Y.; Aoki, S. *Chem. Eur. J.* **2009**, *15*, 10570–10584; (b) Itoh, S.; Tokunaga, T.; Sonoike, S.; Kitamura, M.; Yamano, A.; Aoki, S. *Chem. Asian J.* **2013**, *8*, 2125–2135.
16. Sonoike, S.; Itakura, T.; Kitamura, M.; Aoki, S. *Chem. Asian J.* **2012**, *7*, 64–74.
17. (a) Dimroth, K.; Reichardt, C.; Siepmann, T.; Bohlmann, F. *Liebigs Ann. Chem.* **1963**, *661*, 1–37; (b) Reichardt, C.; Harbusch-Görnert, E. *Liebigs Ann. Chem.* **1983**, 721–743; (c) Reichardt, C. *Chem. Rev.* **1994**, *94*, 2319–2358; (d) Reichardt, C.; Welton, T. *Solvents and Solvent Effects in Organic Chemistry*, 4th ed.; Wiley-VCH: Weinheim, 2011.
18. The absolute configuration of the aldol products *anti*-**12** and **13** was determined based on the following references: (a) Martinez-Castañeda, A.; Poladura, B.; Rodriguez-Solla, H.; Concellón, C.; del Amo, V. *Org. Lett.* **2011**, *13*, 3032–3035; (b) Da, C.-S.; Che, L.-P.; Guo, Q.-P.; Wu, F.-C.; Ma, X.; Jia, Y.-N. *J. Org. Chem.* **2009**, *74*, 2541–2546.
19. (a) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; (b) Gao, J.; Liu, J.; Jiang, D.; Xiao, B.; Yang, Q. *J. Mol. Catal. A: Chem.* **2009**, *313*, 79–89.
20. Solvent-dependent switch of the stereochemistry of the products in asymmetric synthesis catalysed by a single chiral catalyst has been reported previously.[14a,14b,14f,14g,14i]
21. Shibasaki et al. reported that the addition of a catalytic amount of H_2O enhances the rate of aldol reactions and improves the enantioselectivities. See: Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420. and Chapter 6 of Ref. 2 (Vol. 2) (Shibasaki, M.; Matsunaga, S.; Kumagai, N.).
22. (a) Aoki, S.; Kimura, E. In *Comprehensive Coordination Chemistry*; Que, L., Jr, Tolman, W. B., Eds.; Elsevier: Amsterdam, 2004; Vol. 8, pp 601–640; (b) Kimura, E. *Bull. Jpn. Soc. Coord. Chem.* **2012**, *59*, 26–47; (c) Aoki, S.; Kagata, D.; Shiro, M.; Takeda, K.; Kimura, E. *J. Am. Chem. Soc.* **2004**, *126*, 13377–13390; (d) Aoki, S.; Tomiyama, Y.; Kageyama, Y.; Yamada, Y.; Shiro, M.; Kimura, E. *Chem. Asian J.* **2009**, *4*, 561–573.
23. Denmark, S. E.; Stavenger, R. A.; Wong, K-T.; Su, X. *J. Am. Chem. Soc.* **1999**, *121*, 4982–4991.
24. Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.