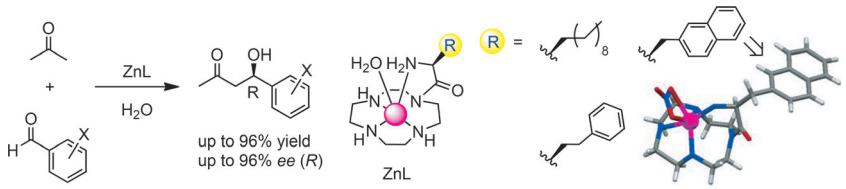
FULL PAPER



Homeward Zn-bound: New chiral Zn^{2+} complexes of amino acids that contained adequate hydrophobic and bulky side chains were synthesized as catalysts for enantioselective aldol reactions between acetone and various benzaldehydes.

Asymmetric Synthesis

*Susumu Itoh, Takuya Tokunaga, Shotaro Sonoike, Masanori Kitamura, Akihito Yamano, Shin Aoki** ____ ▮▮▮▮–▮▮▮▮

Asymmetric Aldol Reactions between Acetone and Benzaldehydes Catalyzed by Chiral Zn^{2+} Complexes of Amino-acyl 1,4,7,10-Tetraazacyclododecane: Fine-Tuning of the Amino-Acid Side Chains and a Revised Reaction Mechanism

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Asymmetric Aldol Reactions between Acetone and Benzaldehydes Catalyzed by Chiral Zn^{2+} Complexes of Aminoacyl 1,4,7,10-Tetraazacyclododecane: Fine-Tuning of the Amino-Acid Side Chains and a Revised Reaction Mechanism

Susumu Itoh,[a] Takuya Tokunaga,[b] Shotaro Sonoike,[b] Masanori Kitamura,[b, c] Akihito Yamano,[d] and Shin Aoki*[b, c]

Abstract: We previously reported that chiral Zn^{2+} complexes that were designed to mimic the actions of class-I and class-II aldolases catalyzed the enantioselective aldol reactions of acetone and its analogues thereof with benzaldehyde derivatives. Herein, we report the synthesis of new chiral Zn^{2+} complexes that contain Zn^{2+}–tetraazacyclododecane (Zn^{2+}–[12]aneN$_4$) moieties and amino acids that contain aliphatic, aromatic, anionic, cationic, and dipeptide side chains. The chemical and optical yields of the aldol reaction were improved (up to 96% *ee*) by using ZnL complexes of L-decanylglycyl-pendant [12]aneN$_4$ (L-ZnL^7), L-naphthylalanyl-pendant [12]aneN$_4$ (L-ZnL^{10}), L-biphenylalanyl-pendant [12]aneN$_4$ (L-ZnL^{11}), and L-phenylethylglycyl-pendant [12]aneN$_4$ ligands (L-ZnL^{12}). UV/Vis and circular dichroism (CD) titrations of acetylacetone (acac) with ZnL complexes confirmed that a ZnL–(acac)$^-$ complex was exclusively formed and not the enaminone of ZnL and acac, as we had previously proposed. Moreover, the results of stopped-flow experiments indicated that the complexation of (acac)$^-$ with ZnL was complete within milliseconds, whereas the formation of an enaminone required several hours. X-ray crystal-structure analysis of L-ZnL^{10} and the ZnL complex of L-diphenylalanyl-pendant [12]aneN$_4$ (L-ZnL^{13}) shows that the NH_2 groups of the amino-acid side chains of these ligands are coordinated to the Zn^{2+} center as the fourth coordination site, in addition to three nitrogen atoms of the [12]aneN$_4$ rings. The reaction mechanism of these aldol reactions is discussed and some corrections are made to our previous mechanistic hypothesis.

Keywords: aldol reaction · asymmetric catalysis · enzyme models · macrocyclic ligands · zinc

Introduction

The aldol reaction is one of the most-important C–C bond-forming reactions and a wide variety of efficient asymmetric catalysts have been developed for it.[1] To date, many excellent studies of direct aldol reactions that use artificial organocatalysts and metallocatalysts have been reported.[2] Since the direct aldol reaction by using L-proline (as an organocatalyst) was first reported by List, Barbas, and co-workers,[3] numerous additional examples of organocatalysts for aldol reactions have been reported.[4]

In natural metabolic pathways in living systems, aldol reactions are catalyzed by aldolase enzymes in a stereospecific and reversible manner.[5] For example, fructose 1,6-bis(phosphate) aldolase (FBP-aldolase, EC 4.1.2.13) catalyzes the cleavage of D-fructose 1,6-bis(phosphate) (FBP) to give dihydroxyacetone phosphate (DHAP) and D-glyceraldehyde 3-phosphate (G3P) and the reverse formation of FBP from DHAP and G3P. Natural aldolases are categorized as either class-I or class-II, based on their reaction mechanisms. In class-I aldolases, an enamine intermediate is formed between a lysine residue on the enzyme and the carbonyl group of the substrate. In class-II aldolases, a zinc(II)-ion cofactor acts as a Lewis acid, with enolates generated at the active site. The use of aldolases in organic and bio-organic synthesis have been found to be an effective method for producing aldol products with high stereoselectivities in aqueous solution.[6] In addition, catalytic antibodies that were generated by immunizing mice with a 1,3-diketone

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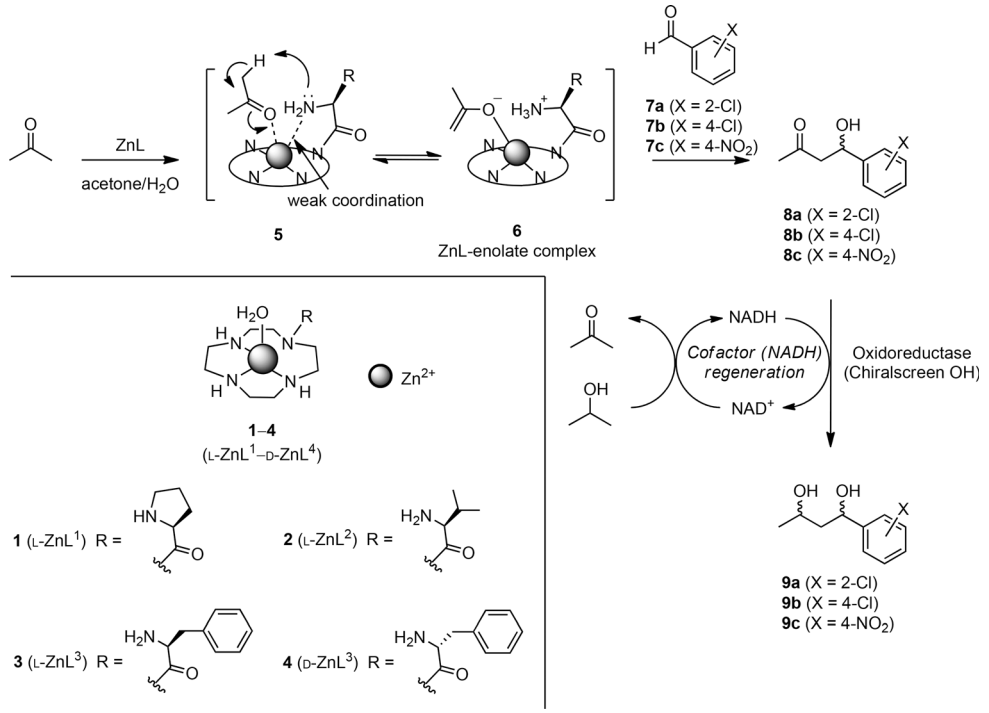


Scheme 1. Asymmetric aldol reactions of acetone catalyzed by chiral ZnL complexes and the one-pot chemoenzymatic synthesis of 1,3-diols **9a–9c** with an oxidoreductase by using a cofactor (NADH)-regenerating system. A previously proposed mechanism that proceeded through ZnL–enolate complex **6** is also presented.

hapten have been developed to catalyze aldol reactions through an enamine mechanism, analogous to class-I aldolases.[7]

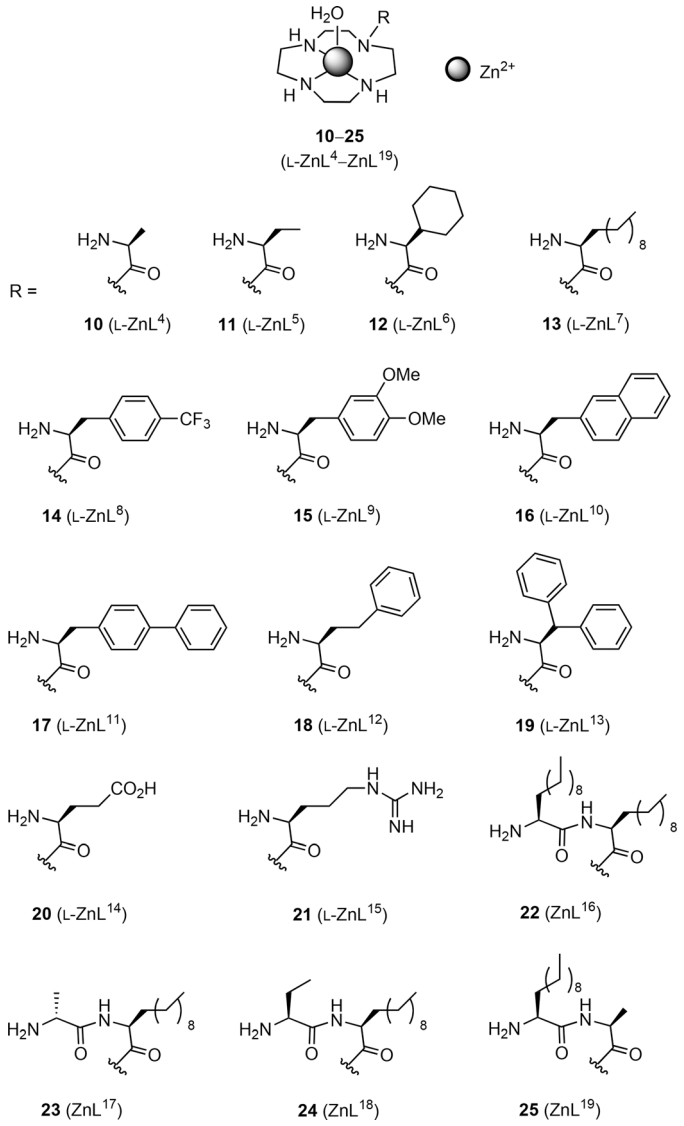
The majority of these above-described organocatalysts function as mimics of class-I aldolases. On the other hand, only several mimics of class-II aldolases have been reported.[8] For example, Mlynarski et al. reported the preparation of ZnL complexes of amino acids as chiral catalysts that were inspired by class-II and class-I aldolases.[9] These catalysts showed high reactivities and enantioselectivities for a broad range of substrates in aqueous systems.

We previously reported chiral catalysts that were dually functionalized with chiral amino acids and achiral Zn^{2+} complexes of 1,4,7,10-tetraazacyclododecane ([12]aneN$_4$ or cyclen), such as L-prolyl-pendant cyclen **1** (L-ZnL^1) and L-valyl-pendant cyclen **2** (L-ZnL^2), in aqueous solution (Scheme 1).[10] A mechanistic study suggested that the carbonyl group of acetone was activated by Lewis acidic Zn^{2+} ions and that its α proton atom was deprotonated by the amine group of ZnL in a cooperative manner, as shown for compound **5** to generate ZnL–enolate complex **6**. These results were applied to the one-pot synthesis of optically active 1,3-diols (**9a–9c**) through a combination of enantioselective aldol reactions catalyzed by L- and D-phenylalanyl-pendant cyclens **3** and **4** (L-ZnL^3 and D-ZnL^3), thus affording 1,2-adducts **8a–8c** with their successive reduction by the recombinant oxidoreductase system Chiralscreeen OH.[11]

The aim of this study was to fine-tune the side chain of chiral ZnL complexes to improve the aldol reactions between acetone and various benzaldehyde derivatives. We synthesized various ZnL complexes that contained aliphatic, aromatic, anionic, cationic, and dipeptide side chains (**10–25**, L-ZnL^4–ZnL^{19}). The proposed reaction mechanism for this aldol reaction is based on data that were obtained from UV/Vis titrations, stopped-flow experiments, and CD titrations

Abstract in Japanese:
我々はキラル亜鉛錯体が室温、水溶液中でエナンチオ選択的アルドール反応を触媒することを報告している。本研究ではアミノ酸側鎖に脂肪族、芳香族、アニオン性、カチオン性及びジペプチド側鎖を有する亜鉛錯体を新たに合成した。アセトンとベンズアルデヒド誘導体のアルドール反応に用いた結果、化学収率及び光学収率の向上を達成した。アセチルアセトン(acac)との UV/Vis 及び CD 滴定の結果、亜鉛錯体–(acac)$^-$複合体が ms オーダーで形成されることが示唆された。また、亜鉛錯体の X-線結晶構造解析の結果、アミノ酸側鎖の窒素原子が亜鉛に配位した構造を有していることが明らかとなった。これらの知見からアルドール反応の反応メカニズムを議論した。

of ZnL complexes with acetylacetone (acac). Based on the X-ray crystal structures of complexes **16** (L-ZnL[10]) and **19** (L-ZnL[13]), the mechanism for these aldol reactions is discussed with some revisions to our previous hypothesis.



Results and Discussion

Synthesis of Chiral Ligands

The ligands for ZnL complexes **10**–**25** (L-ZnL[4]–ZnL[19]) were synthesized from 3Boc-cyclen (Boc = *tert*-butoxycarbonyl)[12] with *N*-Boc-protected amino-acid derivatives, as described in our previous paper.[10,11] The ZnL complexes were prepared in situ immediately before use by reacting the acid-free ligand with Zn^{2+} ions. For details, see the Supporting Information.

Enantioselective Aldol Reactions in Aqueous Media Catalyzed by Chiral ZnL Complexes

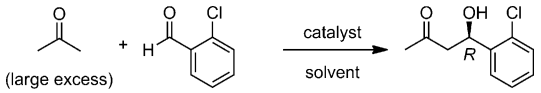
The aldol reaction between acetone and 2-chlorobenzaldehyde was performed in acetone/H_2O (4:1 or 9:1) in the presence of 50 mM ZnL complexes, a concentration at which the ZnL complexes were considered to be formed quantitatively, based on our previous results.[10,11] The results are summarized in Table 1, with our previous results by using ZnL complexes **1**–**3** (L-ZnL[1]–L-ZnL[3]).[10,11]

As shown in Table 1, entry 4, catalyst **10** (L-ZnL[4]), which contained alanine as the amino-acid unit, afforded compound (*R*)-**8a** in high optical yield. Catalysts **11** (L-ZnL[5]), **12** (L-ZnL[6]), and **13** (L-ZnL[7]), which contained aliphatic side chains, exhibited higher catalytic activities than catalysts **1**–**3** (L-ZnL[1]–L-ZnL[3]; Table 1, entries 5–7). Catalysts **14** (L-ZnL[8]) and **15** (L-ZnL[9]), which contained 4-trifluoromethylphenylalanine and 3,4-dimethoxyphenylalanine amino acids, respectively, afforded lower optical yields than catalyst **3** (L-ZnL[3]), which contained a phenylalanine group (Table 1, entries 8 and 9). Catalysts **16** (L-ZnL[10]), **17** (L-ZnL[11]), and **18** (L-ZnL[12]), which contained aromatic side chains, also afforded higher catalytic activities than catalysts **1**–**3** (L-ZnL[1]–L-ZnL[3]; Table 1, entries 10–12). On the other hand, catalyst **19** (L-ZnL[9]), which contained a bulky diphenylmethyl group, gave compound (*R*)-**8a** in moderate yield and 88% *ee* (Table 1, entry 13). These results suggest that ZnL complexes that contain sufficiently bulky side chains, such as decyl, naphthyl, biphenyl, and phenylethyl groups, can be expected to have efficient catalytic activity. As shown in Table 1, entries 14 and 15, catalyst **20** (L-ZnL[14]), which contains an anionic propanoate side chain (from Glu), and catalyst **21** (L-ZnL[15]), which contains a cationic guanidium group (from Arg), afforded compound (*R*)-**8a** in 78% *ee* and 92% *ee*, respectively, thus indicating negligible electrostatic effects on the enantioselectivity of the products. It was possible to improve the *ee* values by increasing the amount of acetone and performing the reaction at lower temperatures (Table 1, entries 16–18 versus entries 5, 7, and 12, respectively).

Next, we synthesized catalysts **22**–**25** (ZnL[16]–ZnL[19]), which contained dipeptide side chains, based on the assumption that the presence of more hydrophobic and hydrogen-bonding functionalities around the Zn^{2+} site would improve their catalytic activity. However, these ZnL complexes resulted in low chemical and optical yields (Table 1, entries 19–22), thus suggesting that one amino-acid side chain is suitable for aldol reactions catalyzed by the ZnL series.

Organic reactions in buffer systems should enable a one-pot reaction to be achieved by using a combination of enzymes that work best in aqueous solutions at optimum pH values.[14] Herein, we tested a number of buffer systems and the results are listed in Table 2. Complex **1** (L-ZnL[1]) gave compound (*R*)-**8a** in low chemical and optical yields in acetone/HEPES buffer (pH 7.0) and acetone/Tris buffer (pH 8.0), as described in our previous paper (Table 2, entries 1 and 2).[10] In contrast, complexes **3** (L-ZnL[3]) and **13** (L-ZnL[7]) afforded high enantioselectivities, such as 90% *ee*

Table 1. Asymmetric aldol reactions between acetone and 2-chlorobenzaldehyde (**7a**) catalyzed by complexes **1**–**3** (L-ZnL[1]–L-ZnL[3]) and **10**–**25** (L-ZnL[4]–ZnL[19]).



7a (*R*)-**8a**

Entry	Catalyst [mM][a]	mol%	Solvent	Conditions	Yield [%][b]	CTN[c]	*ee* [%][d]
1[e]	**1** (L-ZnL[1]) (50)	5	acetone/H_2O (4:1)	24 h, 37 °C	73	15	80 (*R*)
2[e]	**2** (L-ZnL[2]) (50)	5	acetone/H_2O (4:1)	24 h, 37 °C	87	17	80 (*R*)
3[f]	**3** (L-ZnL[3]) (50)	5	acetone/H_2O (4:1)	24 h, 25 °C	85	17	91 (*R*)
4	**10** (L-ZnL[4]) (50)	5	acetone/H_2O (4:1)	24 h, 30 °C	30	6	91 (*R*)
5	**11** (L-ZnL[5]) (50)	5	acetone/H_2O (4:1)	24 h, 30 °C	89	18	94 (*R*)
6	**12** (L-ZnL[6]) (50)	5	acetone/H_2O (4:1)	24 h, 30 °C	84	17	86 (*R*)
7	**13** (L-ZnL[7]) (50)	5	acetone/H_2O (4:1)	24 h, 30 °C	91	18	94 (*R*)
8	**14** (L-ZnL[8]) (50)	5	acetone/H_2O (4:1)	24 h, 30 °C	67	13	87 (*R*)
9	**15** (L-ZnL[9]) (50)	5	acetone/H_2O (4:1)	24 h, 30 °C	86	17	78 (*R*)
10	**16** (L-ZnL[10]) (50)	5	acetone/H_2O (4:1)	24 h, 30 °C	93	19	93 (*R*)
11	**17** (L-ZnL[11]) (50)	5	acetone/H_2O (4:1)	24 h, 30 °C	92	18	92 (*R*)
12	**18** (L-ZnL[12]) (50)	5	acetone/H_2O (4:1)	24 h, 30 °C	95	19	94 (*R*)
13	**19** (L-ZnL[13]) (50)	5	acetone/H_2O (4:1)	24 h, 30 °C	54	11	88 (*R*)
14	**20** (L-ZnL[14]) (50)	5	acetone/H_2O (4:1)	24 h, 30 °C	44	9	78 (*R*)
15	**21** (L-ZnL[15]) (50)	5	acetone/H_2O (4:1)	24 h, 30 °C	79	16	92 (*R*)
16	**11** (L-ZnL[5]) (50)	5	acetone/H_2O (9:1)	24 h, 25 °C	90	18	96 (*R*)
17	**13** (L-ZnL[7]) (50)	5	acetone/H_2O (9:1)	24 h, 25 °C	85	17	95 (*R*)
18	**18** (L-ZnL[12]) (50)	5	acetone/H_2O (9:1)	24 h, 25 °C	96	19	96 (*R*)
19	**22** (ZnL[16]) (50)	5	acetone/H_2O (4:1)	24 h, 25 °C	24	5	9 (*R*)
20	**23** (ZnL[17]) (50)	5	acetone/H_2O (4:1)	24 h, 25 °C	19	4	33 (*S*)
21	**24** (ZnL[18]) (50)	5	acetone/H_2O (4:1)	24 h, 25 °C	25	5	9 (*R*)
22	**25** (ZnL[19]) (50)	5	acetone/H_2O (4:1)	24 h, 25 °C	25	5	6 (*S*)

[a] Numbers in parentheses correspond to the concentrations of the catalysts in the solvent; the ZnL complexes are formed in situ. [b] Yield of isolated product. [c] CTN = catalytic turnover number (yield/equiv of catalyst). [d] Determined by HPLC analysis on a chiral column (Ref. [13]). [e] Taken from Ref. [10]. [f] Taken from Ref. [11].

Table 2. Asymmetric aldol reactions between acetone and 2-chlorobenzaldehyde (**7a**) catalyzed by complexes **1** (L-ZnL[1]), **3** (L-ZnL[3]), and **13** (L-ZnL[7]) in buffer systems.

Entry	Catalyst [mM][a]	mol%	Solvent	Conditions	Yield [%][b]	CTN[c]	*ee* [%][d]
1[e]	**1** (L-ZnL[1]) (10)	10	acetone/HEPES buffer[f] (1:4)	20 h, 25 °C	17	2	39 (*R*)
2[e]	**1** (L-ZnL[1]) (10)	10	acetone/Tris buffer[g] (1:1)	3 h, 37 °C	15	2	20 (*R*)
3	**3** (L-ZnL[3]) (50)	5	acetone/HEPES buffer[h] (4:1)	24 h, 25 °C	91	18	90 (*R*)
4	**13** (L-ZnL[7]) (50)	5	acetone/HEPES buffer[i] (1:5)	24 h, 25 °C	20[j]	4	8 (*R*)
5	**13** (L-ZnL[7]) (50)	5	acetone/HEPES buffer[h] (4:1)	24 h, 25 °C	93	19	94 (*R*)
6	**13** (L-ZnL[7]) (50)	5	acetone/HEPES buffer[i] (4:1)	24 h, 25 °C	67	13	91 (*R*)

[a] Numbers in parentheses correspond to the concentrations of the catalysts in the solvent; the ZnL complexes are formed in situ. [b] Yield of isolated product. [c] CTN = catalytic turnover number (yield/equiv of catalyst). [d] Determined by HPLC analysis on a chiral column (Ref. [13]). [e] Taken from Ref. [10]. [f] 100 mM, pH 7.0. [g] 20 mM, pH 8.0. [h] 10 mM, pH 7.4. [i] 100 mM, pH 7.4. [j] Yield of the crude product.

Table 3. Asymmetric aldol reaction between acetone and 2-chlorobenzaldehyde in a two-phase system.

Entry	Catalyst [mM][a]	mol%	Solvent	Conditions	Yield [%][b]	CTN[c]	*ee* [%][d]
1	**3** (L-ZnL[3]) (50)	5	toluene/acetone/H_2O (4:5:1)	24 h, 30 °C	3	1	85 (*R*)
2	**11** (L-ZnL[5]) (50)	5	toluene/acetone/H_2O (4:5:1)	72 h, 25 °C	10	2	92 (*R*)
3	**19** (L-ZnL[13]) (50)	5	toluene/acetone/H_2O (4:5:1)	48 h, 30 °C	1	1	68 (*R*)
4	**13** (L-ZnL[7]) (50)	5	toluene/acetone/H_2O (4:5:1)	72 h, 25 °C	41	8	91 (*R*)
5	**13** (L-ZnL[7]) (50)	5	toluene/acetone/HEPES buffer[e] (10:8:1)	72 h, 25 °C	63	13	92 (*R*)
6	**22** (ZnL[16]) (50)	5	toluene/acetone/H_2O (4:5:1)	24 h, 25 °C	15	3	5 (*R*)

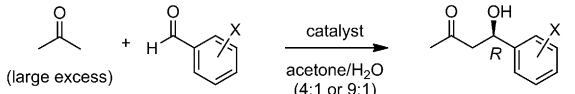
[a] Numbers in parentheses correspond to the concentrations of the catalysts in the solvent; the ZnL complexes are formed in situ. [b] Yield of isolated product. [c] CTN = catalytic turnover number (yield/equiv of catalyst). [d] Determined by HPLC analysis on a chiral column (Ref. [13]). [e] 10 mM, pH 7.6.

in acetone/HEPES buffer (pH 7.4) and 94% *ee* in acetone/HEPES buffer (pH 7.4) systems (Table 2, entries 3 and 5), which were almost the same as were obtained in non-buffer systems (Table 1, entries 3 and 7).

The use of a two-phase system for these reactions was also examined. The aldol reactions proceeded very sluggishly in the presence of catalysts **3** (L-ZnL[3]), **11** (L-ZnL[5]), and **19** (L-ZnL[13]) in a mixture of toluene/acetone/H_2O (4:5:1; Table 3, entries 1–3). In contrast, catalyst **13** (L-ZnL[7]) gave compound (*R*)-**8a** in 41% yield and 91% *ee* in toluene/H_2O and 63% yield and 92% *ee* in toluene/HEPES buffer (pH 7.4; Table 3, entries 4 and 5), thus implying that these hydrophobic ZnL complexes are effective catalysts for aldol reactions in liquid/liquid two-phase systems. For comparison, catalyst **22** (ZnL[16]), which contained two decyl groups, gave compound (*R*)-**8a** in low chemical and optical yields under the same conditions.

Table 4 summarizes the aldol reactions between acetone and various other benzaldehydes, as catalyzed by complexes **13** (L-ZnL[7]) and **18** (L-ZnL[12]) in a single-phase solution of acetone/H_2O. When 4-chlorobenzaldehyde was used, compound (*R*)-**8b** was obtained in good yield and in 93% and 92% *ee*, respectively (Table 4, entries 4 and 8) and, when 2-, 3-, and 4-nitrobenzaldehydes were used as acceptors, high chemical and optical yields were similarly observed (Table 4, entries 5–7 and 9–11).

Table 4. Asymmetric aldol reactions between acetone and various aldehydes catalyzed by complexes **13** (L-ZnL[7]) and **18** (L-ZnL[12]) in acetone/H_2O (4:1 in entries 1–3 and 9:1 in entries 4–11).



7b (X = 4-Cl)
7c (X = 4-NO_2)
7d (X = 3-NO_2)
7e (X = 2-NO_2)

(*R*)-**8b** (X = 4-Cl)
(*R*)-**8c** (X = 4-NO_2)
(*R*)-**8d** (X = 3-NO_2)
(*R*)-**8e** (X = 2-NO_2)

Entry	Catalyst [mM][a]	mol %	X	Product	Conditions	Yield [%][b]	CTN[c]	*ee* [%][d]
1[e,f]	**1** (L-ZnL[1]) (50)	5	4-NO_2	**8c**	20 h, 37 °C	78	16	63 (*R*)
2[e,f]	**2** (L-ZnL[2]) (50)	5	4-NO_2	**8c**	20 h, 37 °C	86	17	86 (*R*)
3[e,g]	**3** (L-ZnL[3]) (50)	10	4-NO_2	**8c**	24 h, 30 °C	quant.	10	90 (*R*)
4[e]	**13** (L-ZnL[7]) (50)	5	4-Cl	**8b**	72 h, 25 °C	74	15	94 (*R*)
5[e]	**13** (L-ZnL[7]) (50)	5	4-NO_2	**8c**	24 h, 25 °C	92	18	96 (*R*)
6[e]	**13** (L-ZnL[7]) (50)	5	3-NO_2	**8d**	24 h, 25 °C	92	18	95 (*R*)
7[e]	**13** (L-ZnL[7]) (50)	5	2-NO_2	**8e**	24 h, 25 °C	96	19	90 (*R*)
8[e]	**18** (L-ZnL[12]) (50)	5	4-Cl	**8b**	72 h, 25 °C	83	17	95 (*R*)
9[e]	**18** (L-ZnL[12]) (50)	5	4-NO_2	**8c**	24 h, 25 °C	92	18	95 (*R*)
10[e]	**18** (L-ZnL[12]) (50)	5	3-NO_2	**8d**	24 h, 25 °C	97	19	95 (*R*)
11[e]	**18** (L-ZnL[12]) (50)	5	2-NO_2	**8e**	24 h, 25 °C	89	18	92 (*R*)

[a] Numbers in parentheses correspond to the concentrations of the catalysts in the solvent; the ZnL complexes are formed in situ. [b] Yield of isolated product. [c] CTN = catalytic turnover number (yield/equiv of catalyst). [d] Determined by HPLC analysis on a chiral column (Ref. [13]). [e] Acetone/H_2O = 4:1 (entries 1–3), 9:1 (entries 4–11). [f] Taken from Ref. [10]. [g] Taken from Ref. [11].

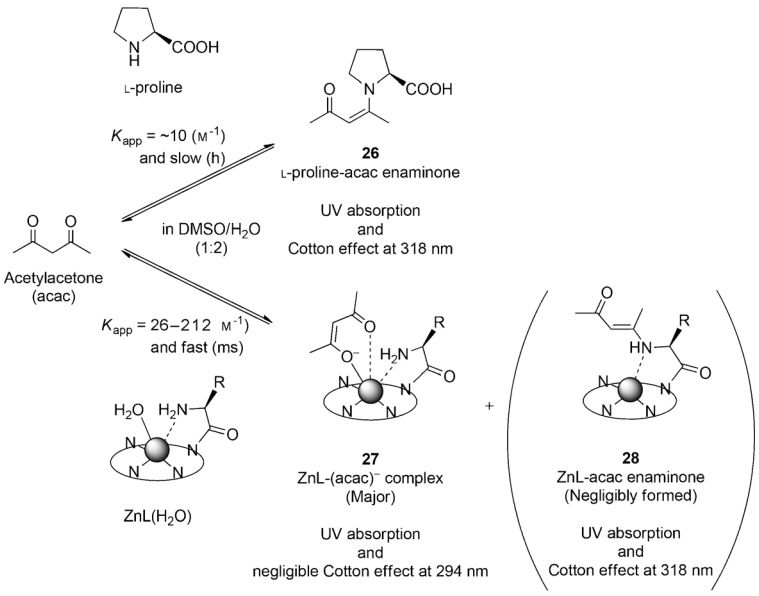
UV Titrations of Acetylacetone with ZnL Complexes 10 (L-ZnL[4]), 18 (L-ZnL[12]), and 19 (L-ZnL[13]) in a Mechanistic Study

In our previous paper, UV titrations of acetylacetone (acac) with L-proline and ZnL complexes **1** (L-ZnL[1]) and **2** (L-ZnL[2]) were conducted to characterize the major intermediates in these aldol reactions.[10] In the UV/Vis titrations of acac with L-proline (as an organocatalyst), the absorption maximum was shifted from 276 to 316 nm, thus suggesting the formation of enaminone **26** (Scheme 2). On the other hand, the UV/Vis absorption maximum was shifted from 276 to 294 nm, thus strongly suggesting the formation of ZnL–$(acac)^-$ complex **27**, with the negligible formation of enaminone **28**. The formation constants of ZnL–$(acac)^-$ complex **27** were larger than the formation constants of enaminone **26**, thus implying that complex **27** is much more thermodynamically favorable than enaminone **28**. Moreover, the catalytic activities of complexes **1** (L-ZnL[1]) and **2** (L-ZnL[2]) for aldol reactions and the K_{app} of acac with ZnL had a parallel relationship.

UV/Vis titrations of acac (0.2 mM) with ZnL complexes **10** (L-ZnL[4], 0–50 equiv), **18** (L-ZnL[12], 0–50 equiv), and **19** (L-ZnL[13], 0–50 equiv) were carried out in DMSO/H_2O (1:2) and the results are summarized in Table 5. An absorption at 287–294 nm was observed upon the addition of complexes **10** (L-ZnL[4]), **18** (L-ZnL[12]), and **19** (L-ZnL[13]), which corresponded to the ZnL–$(acac)^-$ complexes. The K_{app} values of complexes **10** (L-ZnL[4]) and **18** (L-ZnL[12]), as calculated by using the software program BIND WORKS, were 135 and 131 M^{-1}, respectively, which were almost same as that of complex **2** (L-ZnL[2], 139 M^{-1}). On the other hand, the K_{app} for complex **19** (L-ZnL[13]) with acac (26 M^{-1}) was smaller than that of complex **2** (L-ZnL[2]), possibly owing to the steric bulkiness of its amino-acid part.

CD Titrations of Acetylacetone (acac) with Complexes 2 (L-ZnL[2]), 13 (L-ZnL[7]), and 18 (L-ZnL[12])

Next, we performed individual CD titrations of acac (0.2 and 0.1 mM) with L-proline (0–500 equiv) and complex **2** (L-ZnL[2], 0–50 equiv). Figure 1 shows the changes in the CD and absorption spectra for acac with increasing concentrations of L-proline and catalyst **2** (L-ZnL[2]) in DMSO/H_2O (1:2) at 25 °C. Upon the addition of L-proline (0–500 equiv), a negative Cotton effect was observed at 318 nm (Figure 1a, top), in good agreement with the UV absorption maximum (Figure 1a, bottom), which could be assigned to optically active enaminone **26** (Scheme 2). In contrast, a negligible Cotton effect at 294 and 318 nm was observed with increasing concentrations of catalyst **2** (L-ZnL[2], 0–50 equiv; Figure 1b, bottom). These data suggest that the CD spectra of ZnL–



Scheme 2. Equilibria of acac with L-proline or Zn^{2+} complex.

Table 5. Formation constants (K_{app}) for the Zn^{2+}–enolates of complexes **1** (L-ZnL[1]), **2** (L-ZnL[2]), **10** (L-ZnL[4]), **18** (L-ZnL[12]), and **19** (L-ZnL[13]) with $(acac)^-$ in DMSO/H_2O (1:2) at 25 °C.

	1 (L-ZnL[1])	**2** (L-ZnL[2])	**10** (L-ZnL[4])	**18** (L-ZnL[12])	**19** (L-ZnL[13])
λ_{max} [nm]	294 (Zn^{2+}–enolate)	292 (Zn^{2+}–enolate)	292 (Zn^{2+}–enolate)	294 (Zn^{2+}–enolate)	287 (Zn^{2+}–enolate)
K_{app} [M^{-1}]	212[a]	139[a]	135	131	26

[a] Taken from Ref. [10].

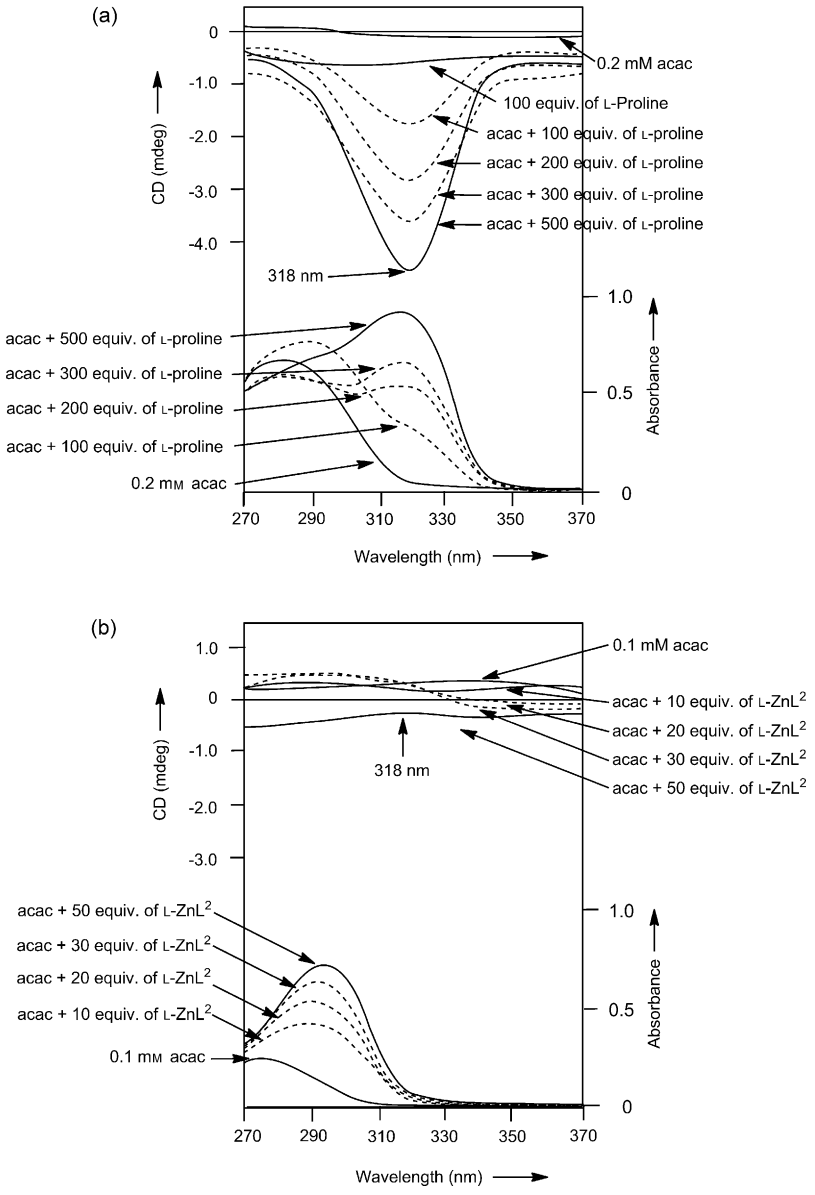


Figure 1. CD and absorption spectra of a) acac (0.2 mM) upon the addition of L-proline (0–500 equiv) and b) acac (0.1 mM) upon the addition of complex **2** (L-ZnL[2], 0–50 equiv) in DMSO/H_2O (1:2) at 25 °C.

$(acac)^-$ complex **27** is very small and/or that the formation of ZnL–enaminone complex **28** is negligible (Scheme 2). In the cases with complexes **13** (L-ZnL[7]) and **18** (L-ZnL[12]), negligible amounts of the corresponding enaminone were also formed.

Stopped-Flow Experiments to Determine the Rates of ZnL–$(acac)^-$ Complexation

It was previously reported that the formation of the enaminone **26** between acac and L-proline reached equilibrium within 4 h in DMSO, whereas the reaction between acac and a ZnL complex was complete within a few seconds.[10] Herein, stopped-flow experiments were performed to more-precisely determine the rates of formation of ZnL–$(acac)^-$ complex **27**. The increase in the UV/Vis absorption of acac (0.2 mM) with complex **2** (L-ZnL[2], 3 mM) at 294 nm was monitored and a rate constant of $6.18(\pm0.03)\times10^{-2}\,sec^{-1}$ was calculated from the resulting curve by fitting to a single exponential equation (see the Supporting Information, Figure S1). Similar studies of the complexation between acac and complexes **13** (L-ZnL[7]) and **18** (L-ZnL[12]) afforded rate constants of $9.03(\pm0.07)\times10^{-2}$ and $7.47(\pm0.05)\times10^{-2}\,sec^{-1}$, respectively, which were almost the same as that of complex **2** (L-ZnL[2]). These formation rates of complex **27** are about 1.4×10^5 higher than that for enaminone **26**.

X-ray Crystal Structure of Complex 16 (L-ZnL[10])

We successfully crystallized complexes **16** (L-ZnL[10]) and **19** (L-ZnL[13]) as their NO_3 salts from acid-free ligands L-L[10] and L-L[13], respectively, with $Zn(NO_3)_2{\cdot}6H_2O$ in Et_2O/EtOH/H_2O. The ORTEP of complex **16** (L-ZnL[10]) is shown in Figure 2 and that of complex **19** (L-ZnL[13]) is shown in the Supporting Information, Figure S2. In our previous hypothesis, the NH_2 group of the amino-acid moiety coordinated weakly (or not at all) to the Zn^{2+} center and acted as a base to deprotonate acetone at the α position (Scheme 1). In contrast, we found that the Zn^{2+} center was not only coordinated by three nitrogen atoms (N5, N8, and N11) of the cyclen ligand and a NO_3 anion,

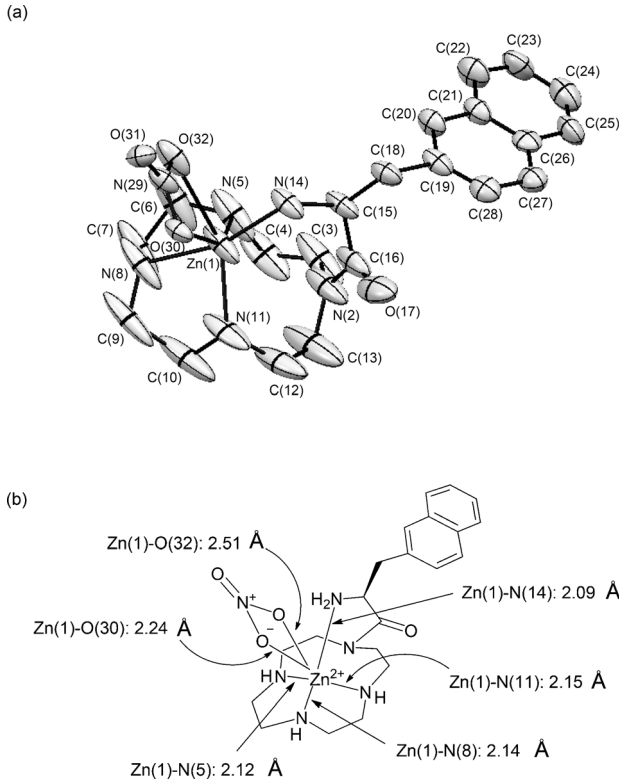


Figure 2. a) ORTEP of complex **16** (L-ZnL^{10}(NO$_3$)$_2$); thermal ellipsoids are set at 50% probability. b) Coordination-bond lengths in complex **16** (L-ZnL^{10}(NO$_3$)$_2$). A Zn^{2+} ion is 6-coordinated by these nitrogen atoms of a cyclen ring, one nitrogen atom of the side chain, and two oxygen atoms of the NO_3 anion. All of the hydrogen atoms and one NO_3 anion are omitted for clarity. Crystal data and data-collection parameters are given in the Supporting Information.

but also by the nitrogen atom (N14) of the β-naphthylalanyl moiety, as shown in Figure 2. The approximate Zn–N bond lengths are 2.12 Å for Zn–N(5), 2.14 Å for Zn–N(8), 2.15 Å for Zn–N(11), and 2.09 Å for Zn–N(14), thus implying that these Zn–N coordinate-bond lengths are almost identical. In this structure, the NO_3 anion coordinates to the Zn^{2+} atom and the bond lengths for the two Zn–O (NO_3^-) coordinate bonds are about 2.24 Å (Zn–O(30)) and about 2.51 Å (Zn–O(32)). It is very likely that this Zn^{2+}-bound NO_3 anion is replaced by a H_2O molecule in aqueous solution, based on our previous findings.[12,15] The Zn^{2+} center in complex **19** (L-ZnL^{13}) was also coordinated by the nitrogen atom of the diphenylalanyl moiety and by one water molecule (see the Supporting Information, Figure S2).

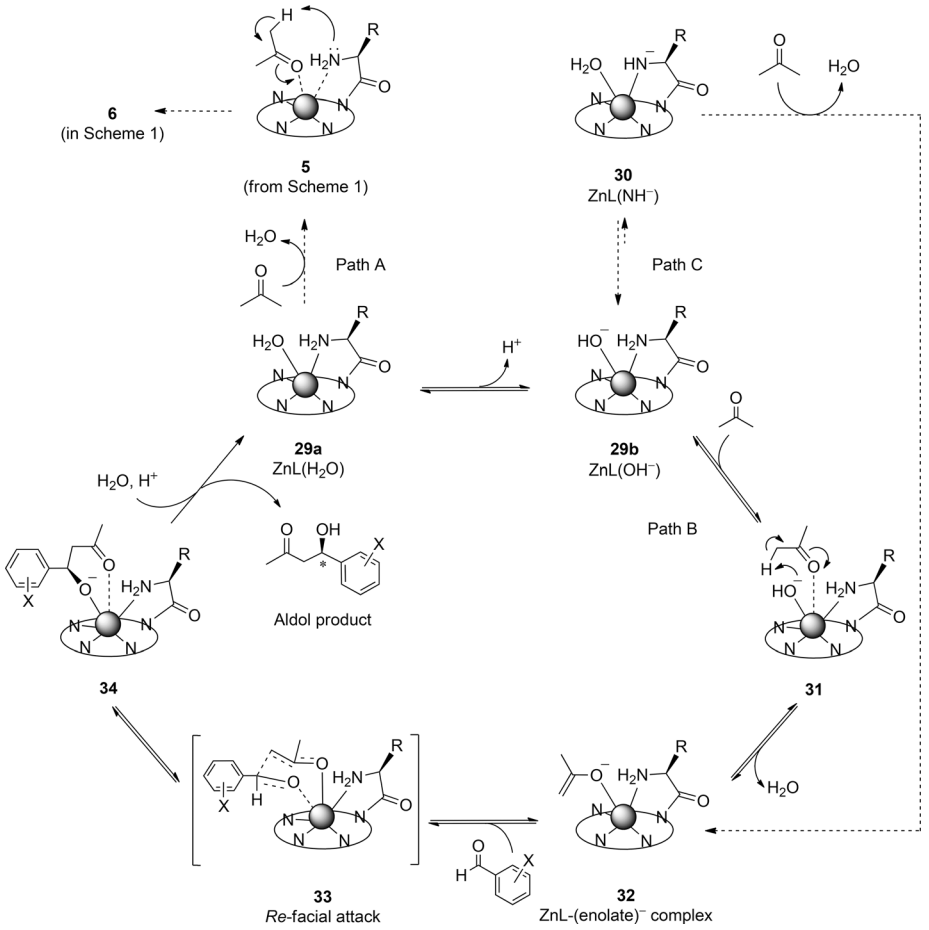
Revision of the Reaction Mechanism

Based on the information that was obtained in our previous papers and herein, we observed several key points in the enantioselective aldol reactions with chiral ZnL complexes, which are summarized as follows: 1) Reactivity and enantioselectivity are improved by fine-tuning the ZnL complexes. Appropriate hydrophobicity and bulkiness of the side chains in the ZnL complexes are necessary for producing products with high reactivities and enantioselectivities. 2) Complex **13** (L-ZnL^7), which contained a decyl side chain, catalyzed the aldol reaction of acetone with 2-chlorobenzaldehyde in a single-phase system that contained HEPES buffer and in a two-phase system that contained toluene and water, thus suggesting that hydrophobic ZnL complexes may function as catalysts in single- and two-phase systems, even in the presence of buffer solvents. 3) The UV titrations suggest that the formation of ZnL–$(acac)^-$ complexes is much preferred to the formation of an enaminone intermediate, as previously predicted. The complexation of ZnL with acac is hampered by steric hindrance of the side chain. 4) A negative Cotton effect at 318 nm was observed in the CD titrations of acac with L-proline, possibly owing to the formation of an optically active enaminone (complex **26**, Scheme 2). In contrast, Cotton effects of ZnL–$(acac)^-$ complex **27** at 294 nm and ZnL–$(acac)^-$ enaminone **28** at 318 nm were negligibly observed in the case of complexes **2** (L-ZnL^2), **13** (L-ZnL^7), and **18** (L-ZnL^{12}). 5) Stopped-flow experiments suggested that the complexation of ZnL–$(acac)^-$ was complete in the order of milliseconds. 6) The X-ray crystal structures of complexes **16** (L-ZnL^{10}) and **19** (L-ZnL^{13}) revealed that the NH_2 groups in the side chain of these ZnL complexes coordinated to the Zn^{2+} atoms. As a result, the Zn^{2+} ions were five (or six)-coordinated by three nitrogen atoms of the cyclen ligand, by one nitrogen atom of the amino-acid moiety, and by an external water molecule or NO_3 anion.

Based on these results, we considered several reaction mechanisms for the ZnL-catalyzed aldol reactions between acetone and benzaldehydes, as shown in Scheme 3. Our previous hypothesis involved path A, in which the amine group of the side chain in the ZnL complexes deprotonated the α proton of acetone, which was activated by coordination to the Lewis acidic Zn^{2+} center, as shown in structure **5**, to generate the ZnL–enolate complex (**6**, Scheme 1). However, given the data reported herein, this pathway appears to be less plausible, because the basicity of the amino side chain should be lowered by its coordination to the Zn^{2+} center, as observed in the X-ray crystal structure.

Herein, two other possibilities were considered, namely paths B and C. It has been reported that Zn^{2+}-bound HO^- and alkoxide species can act as bases and nucleophiles.[16–18] For instance, the Zn^{2+}-bound HO^- group in the class-II aldolase model complex **35b** (ZnL^{20}(OH$^-$)) is considered to deprotonate the α proton to the carbonyl group of the phenacyl side chain to give Zn^{2+}–enolate **35c** (Zn(H$_1$L^{20})) in aqueous solution (Scheme 4).[16a] Accordingly, we hypothesize that, in path B, that the OH^- moiety of complex **29b** deprotonates the α proton of acetone with the aid of the Lewis acidic Zn^{2+} center in complex **31** and generates ZnL–$(enolate)^-$ complex **32**.

Path C (Scheme 3) shows another possibility, in which the Zn^{2+}-bound OH^- group deprotonates the NH_2 group to give rise to NH^- species **30**, which deprotonates acetone, thus resulting in the formation of ZnL–$(enolate)^-$ complex **32**. However, this pathway is unlikely because the pK_a value of



Scheme 3. Proposed mechanism for the aldol reactions of acetone catalyzed by chiral ZnL complexes.

the amine group would be over 30, which is much higher than those of Zn^{2+}-bound H_2O and alcohol moieties in typical Zn^{2+}–cyclen complexes ($pK_a \approx 7$–9).[12,15,18]

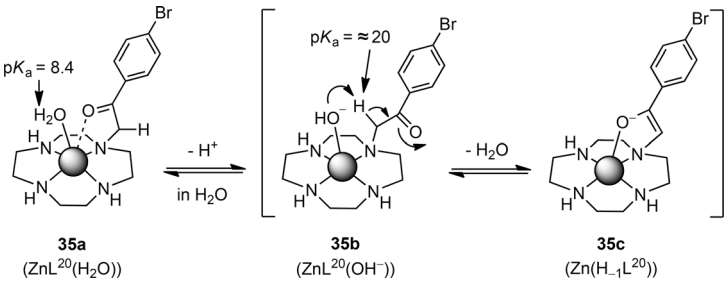
A consideration of these points allows us to conclude that path B is the most plausible among the three possibilities, although we do not completely rule out the path A scenario. Then, ZnL–(enolate)$^-$ complex **32** reacts with an acceptor aldehyde through six-membered transition state **33** to afford compound **34**, from which the aldol product is released and ZnL **29** is regenerated.

The active site and the reaction mechanism of class-II aldolases have been extensively studied.[19] In terms of the deprotonation step for the formation of a Zn^{2+}–enolate intermediate of DHAP, it has been suggested that the carboxylate group of Glu or Asp in the active site acts as a base, based on X-ray crystal structures of FBP-aldolases that are bound to DHAP, DHAP-G3P, and FBP. In those papers, it was proposed that the deprotonation of DHAP was mediated by Glu (Glu169 in FBP aldolase from *Mycobacterium tuberculosis* (MtFBA)) and/or the neighboring water molecules (Scheme 5).[20]

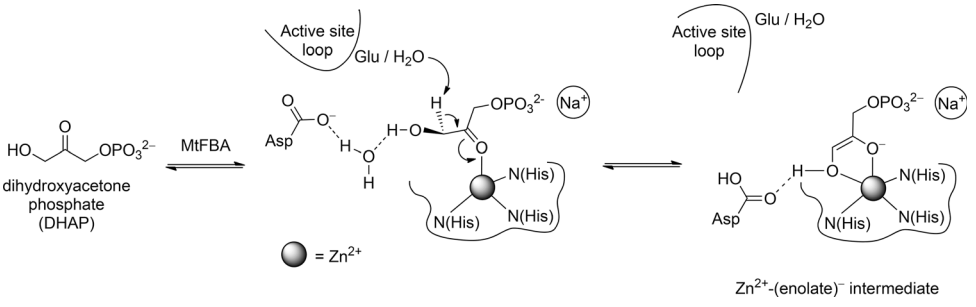
Because there are no carboxylate groups in our artificial ZnL complexes, it is not easy to speculate on the catalytic role of the carboxylate groups in class-II aldolases, such as MtFBA. However, our catalytic systems may add another possibility for consideration, that is, that Zn^{2+}-bound HO^- ligands acts as a base to deprotonate the donor substrates in aldol reactions.

Conclusions

Herein, we designed and synthesized several new chiral ZnL complexes that contained amino acids with aliphatic, aromatic, anionic, cationic, and dipeptide side chains. The chemical and optical yields of aldol reactions between acetone and various benzaldehydes im-



Scheme 4. Formation of Zn^{2+}–enolate in class-II aldolase model **35**.



Scheme 5. Proposed mechanism of deprotonation of DHAP in MtFBA.

proved when ZnL complexes **13** (L-ZnL[7]) and **16–18** (L-ZnL[10]–L-ZnL[12]) were used, which contained adequate hydrophobic and bulky side chains (up to 96% chemical and optical yields). Hydrophobic ZnL complex **13** (L-ZnL[7]), which contained a decyl side chain, catalyzed the aldol reaction in single-phase solvent systems that contained HEPES buffer and in a two-phase system that contained toluene and water. UV/Vis and CD titrations of acetylacetone (acac) with various ZnL complexes suggest the exclusive formation of a ZnL–$(acac)^-$ complex of ZnL and acac, rather than the formation of an enaminone, as we had previously proposed. Stopped-flow data suggest that the complexation of ZnL–$(acac)^-$ complexes reaches completion within milliseconds, whereas the formation of an enaminone requires several hours. X-ray crystal structures of complexes **16** (L-ZnL[10]) and **19** (L-ZnL[13]) revealed that the NH_2 groups in the side chain of these ZnL complexes were coordinated to the Zn^{2+} centers. These data indicate that the Zn^{2+}-bound OH^- groups in the ZnL complexes ($ZnL(OH^-)$) act as a base to deprotonate the α proton of acetone to generate a ZnL–$(enolate)^-$ complex (**32**) in these aldol reactions, as discussed in Scheme 3, path B, rather than our previous hypothesis (path A), in which the amine group in the side chain was hypothesized to act as the base. Aldol reactions of other substrates, such as mono- and dihydroxyacetone, with benzaldehydes and non-activated aldehydes are now underway.[21]

These results should afford useful information concerning the reaction mechanism of the aldol reaction catalyzed by artificial Zn^{2+} catalysts and should extend our knowledge of the mechanism of action of class-II aldolases.

Experimental Section

General Procedure for the Catalytic Aldol Reactions between Acetone and Various Benzaldehydes (Table 1–Table 4)

The chiral ligands (L-L^1–L-L^{13} and L^{16}–L^{19}, 0.025 mmol) were extracted from their 0.2 M NaOH aqueous solutions (1 mL) with $CHCl_3$. TFA salts of ligands L-L^{14} and L-L^{15} were deprotonated by column chromatography on NH-silica gel (MeOH) to afford ligands L-L^{14} and L-L^{15}. After drying the combined organic layer over anhydrous Na_2SO_4, the solution was filtered and concentrated under reduced pressure. The remaining residue was added to a solution of $Zn(NO_3)_2{\cdot}6H_2O$ (0.0375 mmol) in a solvent (0.1 or 0.05 mL) and acetone (0.4 or 0.45 mL) and the mixture was stirred for 10 min. The aldehyde substrate (0.5 mmol) was added and the resulting reaction mixture was stirred for 24–96 h at 25 or 30 °C. The reaction mixture was diluted with water (2 mL) and extracted with EtOAc (3× 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (hexanes/EtOAc) to provide the pure aldol product. The optical purities of the aldol products were determined by HPLC on a chiral HPLC column, as described below.[13]

*4-(2-Chlorophenyl)-4-hydroxy-2-butanone (**8a**)[10,13]*

^{1}H NMR (500 MHz, $CDCl_3$/TMS): $\delta = 2.23$ (s, 3H), 2.65–3.02 (m, 2H), 5.51 (m, 1H), 7.18–7.34 (m, 3H; ArH), 7.61–7.63 ppm (m, 1H; ArH); HPLC (Daicel Chiralpak AD-H column, 0.46ϕ×25 cm, hexanes/EtOH = 95:5, flow rate: 1 mL min^{-1}, $\lambda = 254$ nm, 25 °C): t_R (*S*) = 13.5 min, t_R (*R*) = 14.8 min.

*4-(4-Chlorophenyl)-4-hydroxy-2-butanone (**8b**)[11,13]*

^{1}H NMR (500 MHz, $CDCl_3$/TMS): $\delta = 2.18$ (s, 3H), 2.78–2.87 (m, 2H), 3.36 (br, 1H), 5.13 (m, 1H), 7.28–7.33 ppm (m, 4H; ArH); HPLC (Daicel Chiralpak AD-H column, 0.46ϕ×25 cm, hexanes/2-propanol = 95:5, flow rate: 0.5 mL min^{-1}, $\lambda = 254$ nm, 25 °C): t_R (*R*) = 26.3 min, t_R (*S*) = 28.2 min.

*4-(4-Nitrophenyl)-4-hydroxy-2-butanone (**8c**)[10,13]*

^{1}H NMR (500 MHz, $CDCl_3$/TMS): $\delta = 2.23$ (s, 3H), 2.81–2.91 (m, 2H), 3.57 (d, $J = 3.5$ Hz, 1H), 5.27 (m, 1H), 7.54 (d, $J = 8.5$ Hz, 2H; ArH), 8.22 ppm (d, $J = 8.5$ Hz, 2H; ArH); HPLC (Daicel Chiralcel OB-H column, 0.46ϕ×25 cm, hexanes/2-propanol = 90:10, flow rate: 0.8 mL min^{-1}, $\lambda = 254$ nm, 25 °C): t_R (*R*) = 35.7 min, t_R (*S*) = 43.0 min.

*4-(3-Nitrophenyl)-4-hydroxy-2-butanone (**8d**)[13]*

^{1}H NMR (500 MHz, $CDCl_3$/TMS): $\delta = 2.24$ (s, 3H), 2.84–2.94 (m, 2H), 3.59 (d, $J = 3.5$ Hz, 1H), 5.27 (m, 1H), 7.54 (t, $J = 8.0$ Hz, 1H; ArH), 7.72 (d, $J = 8.0$ Hz, 1H; ArH), 8.14 (m, 1H; ArH), 8.25 ppm (s, 1H; ArH); HPLC (Daicel Chiralpak AD-H column, 0.46ϕ×25 cm, hexanes/2-propanol = 95:5, flow rate: 1.0 mL min^{-1}, $\lambda = 254$ nm, 25 °C): t_R (*R*) = 24.3 min, t_R (*S*) = 26.8 min.

*4-(2-Nitrophenyl)-4-hydroxy-2-butanone (**8e**)[13]*

^{1}H NMR (500 MHz, $CDCl_3$/TMS): $\delta = 2.24$ (s, 3H), 2.70–3.17 (m, 2H), 3.72 (d, $J = 3.0$ Hz, 1H), 5.68 (m, 1H), 7.45 (t, $J = 7.5$ Hz, 1H; ArH), 7.68 (t, $J = 7.5$ Hz, 1H; ArH), 7.90 (d, $J = 8.0$ Hz, 1H; ArH), 7.97 ppm (d, $J = 8.0$ Hz, 1H; ArH); HPLC (Daicel Chiralpak OB-H column, 0.46ϕ× 25 cm, hexanes/2-propanol = 95:5, flow rate: 1.0 mL min^{-1}, $\lambda = 254$ nm, 25 °C): t_R (*S*) = 24.2 min, t_R (*R*) = 26.2 min.

UV Titrations

UV spectra were recorded on a JASCO UV/Vis spectrophotometer V-550 at 25(±0.1) °C. The data for the UV titrations (increases in ε values at a given wavelength) were analyzed for apparent complexation constants, K_{app}, by using the BIND WORKS software program (Calorimetry Sciences Corp).

CD Titrations

CD and absorption spectra were recorded on a Chiralscan CD spectropolarimeter (Applied Photophysics Ltd.). All of the solutions of acac with various concentrations of L-proline and the ZnL complexes were prepared before the measurements.

Stopped-Flow Experiments

Stopped-flow spectrophotometry experiments were performed in DMSO/H_2O at 25 °C on an SX18MV stopped-flow reaction analyzer (Applied Photophysics Ltd.).

*Crystallographic Study of Complex **16** (L-ZnL[10](NO$_3$)$_2$)*

All measurements were performed on a Rigaku Saturn 724+ diffractometer by using multilayer mirror monochromated $Mo_{K\alpha}$ radiation at 93 K. The structure was solved by using direct methods and expanded by using Fourier techniques. All of the calculations were performed by using the CrystalStructure crystallographic software package except for refinements, which were performed by using SHELXL-97.

Crystallographic data: $C_{21}H_{31}N_8O_7Zn$; $M_r = 572.91$; colorless prisms; crystal size $0.16 \times 0.11 \times 0.05$ mm^3; monoclinic; space group $P2_1$(No. 4); $a = 17.756(2)$, $b = 10.8511(12)$, $c = 27.114(3)$ Å; $\beta = 95.087(3)°$; $V = 5203.5(10)$ Å^3; $Z = 8$; $\rho_{calcd} = 1.462$ g cm^{-3}; 84807 reflections measured; 19150 unique reflections ($R_{int} = 0.0000$); $2\theta_{max} = 51.0$; $R1 = 0.0994$ and $wR2 = 0.3230$; GOF = 1.247.

CCDC 916249 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystallographic Study of Complex ***19*** *(L-ZnL^{13}·$(NO_3)_2$·$(H_2O)_2$)*

All measurements were performed on a Rigaku Saturn 724+ diffractometer by using multilayer mirror monochromated $Mo_{K\alpha}$ radiation at 93 K. The structure was solved by using direct methods and expanded by using Fourier techniques. All of the calculations were performed by using the CrystalStructure crystallographic software package except for refinements, which were performed by using SHELXL-97.

Crystallographic data: $C_{23}H_{37}N_7O_9Zn$; $M_r = 620.97$; colorless blocks; crystal size $0.18 \times 0.16 \times 0.10\ mm^3$; orthorhombic; space group $P212121$; $a = 8.9542(10)$, $b = 13.8731(16)$, $c = 22.133(3)$ Å; $V = 2749.4(6)$ Å^3; $Z = 4$; $\rho_{calcd} = 1.500\ g\,cm^{-3}$; 34016 reflections measured; 6262 unique reflections ($R_{int} = 0.0394$); $2\theta_{max} = 55.0$; $R1 = 0.0310$ ($wR2 = 0.1235$); GOF = 1.255.

CCDC 916248 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

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[1] a) *Modern Aldol Reactions* (Ed.: R. Mahrwald), Wiley-VCH, Weinheim, **2004**; b) T. Mukaiyama, S. Kobayashi, H. Uchiro, I. Shiina, *Chem. Lett.* **1990**, *19*, 129–132; c) K. Furuta, T. Maruyama, H. Yamamoto, *J. Am. Chem. Soc.* **1991**, *113*, 1041–1042; d) E. R. Parmee, O. Tempkin, S. Masamune, A. Abiko, *J. Am. Chem. Soc.* **1991**, *113*, 9365–9366; e) E. J. Corey, C. L. Cywin, T. D. Roper, *Tetrahedron Lett.* **1992**, *33*, 6907–6910; f) D. A. Evans, J. A. Murry, M. C. Kozlowski, *J. Am. Chem. Soc.* **1996**, *118*, 5814–5815; g) S. E. Denmark, S. B. D. Winter, X. Su, K.-T. Wong, *J. Am. Chem. Soc.* **1996**, *118*, 7404–7405; h) S. Nagayama, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 11531–11532.

[2] For reviews, see: a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; b) D. Enders, M. Voith, A. Lenzen, *Angew. Chem.* **2005**, *117*, 1330–1351; *Angew. Chem. Int. Ed.* **2005**, *44*, 1304–1325; c) J. Mlynarski, *Eur. J. Org. Chem.* **2006**, 4779–4786; d) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; e) D. Enders, A. A. Narine, *J. Org. Chem.* **2008**, *73*, 7857–7870; f) J. Mlynarski, J. Paradowska, *Chem. Soc. Rev.* **2008**, *37*, 1502–1511; g) M. Gruttadauria, F. Giacalone, R. Noto, *Adv. Synth. Catal.* **2009**, *351*, 33–57; h) *Asymmetric Synthesis with Chemical and Biological Methods* (Eds.: D. Enders, K.-E. Jaeger), Wiley-VCH, Weinheim, **2007**. For selected examples of metal catalysts for the direct aldol reacitons: i) Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem.* **1997**, *109*, 1942–1944; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871–1873; j) N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168–4178; k) N. Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Ohshima, T. Suzuki, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2466–2467; l) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187–2209; m) M. Shibasaki, S. Matsunaga, *Chem. Soc. Rev.* **2006**, *35*, 269–279; n) M. Nakagawa, H. Nakao, K.-i. Watanabe, *Chem. Lett.* **1985**, 391–394; o) G. Lalic, A. D. Aloise, M. D. Shair, *J. Am. Chem. Soc.* **2003**, *125*, 2852–2853; p) T. Darbre, M. Machuqueiro, *Chem. Commun.* **2003**, 1090–1091; q) J. Paradowska, M. Stodulski, J. Mlynarski, *Adv. Synth. Catal.* **2007**, *349*, 1041–1046; r) Z. Lu, H. Mei, J. Han, Y. Pan, *Chem. Biol. Drug Des.* **2010**, *76*, 181–186; s) S. Kobayashi, M. Kokubo, K. Kawasumi, T. Nagano, *Chem. Asian J.* **2010**, *5*, 490–492; t) A. Karmakar, T. Maji, S. Wittmann, O. Reiser, *Chem. Eur. J.* **2011**, *17*, 11024–11029; u) L. Lin, K. Yamamoto, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2012**, *51*, 10275–10279.

[3] a) B. List, R. A. Lerner, C. F. Barbas III., *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; b) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387; c) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III., *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; d) B. List, *Acc. Chem. Res.* **2004**, *37*, 548–557; e) W. Notz, F. Tanaka, C. F. Barbas III., *Acc. Chem. Res.* **2004**, *37*, 580–591.

[4] For selected examples of direct aldol reactions, see: a) S. Saito, M. Nakadai, H. Yamamoto, *Synlett* **2001**, 1245–1248; b) T. J. Dickerson, K. D. Janda, *J. Am. Chem. Soc.* **2002**, *124*, 3220–3221; c) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799; d) T. Kano, J. Takai, O. Tokuda, K. Maruoka, *Angew. Chem.* **2005**, *117*, 3115–3117; *Angew. Chem. Int. Ed.* **2005**, *44*, 3055–3057; e) K. Akagawa, S. Sakamoto, K. Kudo, *Tetrahedron Lett.* **2005**, *46*, 8185–8187; f) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III., *J. Am. Chem. Soc.* **2006**, *128*, 734–735; g) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem.* **2006**, *118*, 972–975; *Angew. Chem. Int. Ed.* **2006**, *45*, 958–961; h) A. Córdova, W. Zou, P. Dziedzic, I. Ibrahem, E. Reyes, Y. Xu, *Chem. Eur. J.* **2006**, *12*, 5383–5397; i) S. S. V. Ramasastry, H. Zhang, F. Tanaka, C. F. Barbas III., *J. Am. Chem. Soc.* **2007**, *129*, 288–289; j) S. S. V. Ramasastry, K. Albertshofer, N. Utsumi, F. Tanaka, C. F. Barbas III., *Angew. Chem.* **2007**, *119*, 5668–5671; *Angew. Chem. Int. Ed.* **2007**, *46*, 5572–5575; k) K. Nakayama, K. Maruoka, *J. Am. Chem. Soc.* **2008**, *130*, 17666–17667; l) M. Terada, H. Tanaka, K. Sorimachi, *J. Am. Chem. Soc.* **2009**, *131*, 3430–3431; m) T. Kano, H. Sugimoto, K. Maruoka, *J. Am. Chem. Soc.* **2011**, *133*, 18130–18133.

[5] a) C. Walsh, *Enzymatic Reaction Mechanisms*, Freeman and Company, New York, **1979**; b) D. Voet, J. G. Voet, *Biochemistry*, Wiley & Sons, New York, **1990**; c) C.-H. Wong, G. M. Whitesides, *Enzymes in Synthetic Organic Chemistry*, Pergamon, Oxford, **1994**; d) J. McMurry, *Organic Chemistry, A Biological Approach*, Thomson Books/Cole, Belmont, **2007**.

[6] a) H. J. M. Gijsen, L. Qiao, W. Fitz, C.-H. Wong, *Chem. Rev.* **1996**, *96*, 443–473; b) S. Takayama, G. J. McGarvey, C.-H. Wong, *Chem. Soc. Rev.* **1997**, *26*, 407–415; c) T. D. Machajewski, C.-H. Wong, *Angew. Chem.* **2000**, *112*, 1406–1430; *Angew. Chem. Int. Ed.* **2000**, *39*, 1352–1374; d) C.-H. Wong, M. C. Bryan, P. T. Nyffeler, H. Liu, E. Chapman, *Pure Appl. Chem.* **2003**, *75*, 179–186; e) S. M. Dean, W. A. Greenberg, C.-H. Wong, *Adv. Synth. Catal.* **2007**, *349*, 1308–1320; f) M. Sugiyama, Z. Hong, P.-H. Liang, S. M. Dean, L. J. Whalen, W. A. Greenberg, C.-H. Wong, *J. Am. Chem. Soc.* **2007**, *129*, 14811–14817.

[7] a) J. Wagner, R. A. Lerner, C. F. Barbas III., *Science* **1995**, *270*, 1797–1800; b) C. F. Barbas III., A. Heine, G. Zhong, T. Hoffmann, S. Gramatikova, R. Björnestedt, B. List, J. Anderson, E. A. Stura, I. A. Wilson, R. A. Lerner, *Science* **1997**, *278*, 2085–2092.

[8] For selected examples of Zn^{2+}–enolate catalysts for direct aldol reactions, see: a) N. Kumagai, S. Matsunaga, N. Yoshikawa, T. Ohshima, M. Shibasaki, *Org. Lett.* **2001**, *3*, 1539–1542; b) N. Kumagai, S. Matsunaga, T. Kinoshita, S. Harada, S. Okada, S. Sakamoto, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 2169–2178; c) B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003–12004; d) B. M. Trost, S. Shin, J. A. Sclafani, *J. Am. Chem. Soc.* **2005**, *127*, 8602–8603; e) J. Kofoed, T. Darbre, J.-L. Reymond, *Chem. Commun.* **2006**, 1482–1484.

[9] J. Paradowska, M. Pasternak, B. Gut, B. Gryzlo, J. Mlynarski, *J. Org. Chem.* **2012**, *77*, 173–187.

[10] S. Itoh, M. Kitamura, Y. Yamada, S. Aoki, *Chem. Eur. J.* **2009**, *15*, 10570–10584.

[11] S. Sonoike, T. Itakura, M. Kitamura, S. Aoki, *Chem. Asian J.* **2012**, *7*, 64–74.

[12] E. Kimura, S. Aoki, T. Koike, M. Shiro, *J. Am. Chem. Soc.* **1997**, *119*, 3068–3076.

[13] The absolute configurations of aldol products **8a**–**8e** were determined by comparison with the following references: a) Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263; b) C. Andreu, G. Asensio, *Tetrahedron* **2011**, *67*, 7050–7056.

[14] Aldol reactions with the Zn(L-Pro)$_2$ complex in buffer systems were reported by Reymond, Darbre, and co-workers; see Ref. [8e].

[15] a) S. Aoki, D. Kagata, M. Shiro, K. Takeda, E. Kimura, *J. Am. Chem. Soc.* **2004**, *126*, 13377–13390; b) S. Aoki, Y. Tomiyama, Y. Kageyama, Y. Yamada, M. Shiro, E. Kimura, *Chem. Asian J.* **2009**, *4*, 561–573.

[16] For examples of Zn^{2+}-bound OH^- species that function as bases, see: a) E. Kimura, T. Gotoh, T. Koike, M. Shiro, *J. Am. Chem. Soc.* **1999**, *121*, 1267–1274; b) S. Aoki, K. Iwaida, N. Hanamoto, M. Shiro, E. Kimura, *J. Am. Chem. Soc.* **2002**, *124*, 5256–5257.

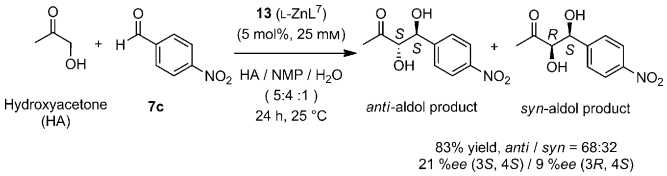
[17] For examples of Zn^{2+}-bound OH^- species that function as nucleophiles, see: a) T. Koike, S. Kajitani, I. Nakamura, E. Kimura, M. Shiro, *J. Am. Chem. Soc.* **1995**, *117*, 1210–1219; b) S. Aoki, K. Sakurama, N. Matsuo, Y. Yamada, R. Takasawa, S. Tanuma, M. Shiro, K. Takeda, E. Kimura, *Chem. Eur. J.* **2006**, *12*, 9066–9080; c) R. Ohshima, M. Kitamura, A. Morita, M. Shiro, Y. Yamada, M. Ikekita, E. Kimura, S. Aoki, *Inorg. Chem.* **2010**, *49*, 888–899; d) M. Kitamura, T. Suzuki, R. Abe, T. Ueno, S. Aoki, *Inorg. Chem.* **2011**, *50*, 11568–11580.

[18] a) S. Aoki, E. Kimura in *Comprehensive Coordination Chemistry II*, *Vol. 8* (Eds.: L. Que, Jr., W. B. Tolman), Elsevier, Amsterdam, **2004**, pp. 601–640; b) E. Kimura, *Bull. Jpn. Soc. Coord. Chem.* **2012**, *59*, 26–47.

[19] a) B. S. Szwergold, K. Ugurbil, T. R. Brown, *Arch. Biochem. Biophys.* **1995**, *317*, 244–252; b) M. K. Dreyer, G. E. Schulz, *J. Mol. Biol.* **1996**, *259*, 458–466; c) A. R. Plater, S. M. Zgiby, G. J. Thomson, S. Qamar, C. W. Wharton, A. Berry, *J. Mol. Biol.* **1999**, *285*, 843–855; d) D. R. Hall, G. A. Leonard, C. D. Reed, C. I. Watt, A. Berry, W. N. Hunter, *J. Mol. Biol.* **1999**, *287*, 383–394; e) S. Zgiby, A. R. Plater, M. A. Bates, G. J. Thomson, A. Berry, *J. Mol. Biol.* **2002**, *315*, 131–140; f) A. Galkin, Z. Li, L. Li, L. Kulakova, L. R. Pal, D. D. Mariano, O. Herzberg, *Biochemistry* **2009**, *48*, 3186–3196.

[20] a) S. D. Pegan, K. Rukseree, S. G. Franzblau, A. D. Mesecar, *J. Mol. Biol.* **2009**, *386*, 1038–1053; b) S. D. Pegan, K. Rukseree, G. C. Capodagli, E. A. Baker, O. Krasnykh, S. G. Franzblau, A. D. Mesecar, *Biochemistry* **2013**, *52*, 912–925.

[21] The aldol reaction of hydroxyacetone (HA) with 4-nitrobenzaldehyde **7c** by using complex **13** (L-ZnL^7) as the catalyst in HA/NMP (*N*-methylpyrrolidone)/H_2O (5:4:1) at 25 °C for 24 h gave the aldol products in 83% yield with *anti* selectively (*anti*/*syn*, 68:32) and 21% *ee* (3*S*,4*S*) for the *anti* product.



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