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Diversity-based strategy for discovery of environmentally benign organocatalyst: diamine–protonic acid catalysts for asymmetric direct aldol reaction

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Abstract—Fifteen different diamines (**4**–**18**) and potonic acids have been screened in the catalytic asymmetric direct aldol reaction of three different aldehydes in acetone. These initial studies demonstrated that the secondary–tertiary diamine series is effective with regard to reactivity. In contrast, the primary–tertiary diamines **13** and **14** were proved to be a superb structural module to avoid dehydration. Further investigation led us to a new procedure for the preparation of diamine catalysts for synthetic convenience. This involves diamine–diacid salt **22**, which acted not only as a catalyst backbone but also as a TfOH source. Salt **22**–diamine **4** catalyst thus prepared was found to exhibit higher reactivity and selectivity.

1. Introduction

Aldol reaction is a useful method for preparing β-hydroxy carbonyl compounds and has attracted a great deal of attention from synthetic organic chemists.[1] Over the last decade, rapid progress in the development of enantioselective aldol reactions has been made;[2] however, there are only a few reports on the small molecular-catalyzed direct aldol reactions.[3] Watanabe,[4a,b] Shibasaki,[4c,d,f,g] Trost[4e,h,i] and Noyori[4j] have reported several examples of direct catalytic asymmetric aldol reactions using metal-based catalysts[4] while only a few examples of the reactions using amines[5,6] have been noted in the literature. Provocative and pioneering works[7] by List,[7a–c,e] Lerner[7a] and Barbas III[7a,d] involve proline[8,9] and 5,5-dimethyl thiazolidinium-4-carboxylate (DMTC) as a catalyst and the subsequently occurring enamine[10] as a key intermediate. Each reported method has notable advantage, but problems are frequently encountered enhancing the efficiency of the aldol reaction and suppressing the dehydrated products. We recently described that diamine–protonic acids[11,12] are effective catalysts for the direct asymmetric aldol reaction.[13] This report details our full investigations of the diamine–protonic acid catalysts and survey of a more efficient catalyst.

2. Results and discussion

2.1. Diamine–protonic acid catalysts for the asymmetric aldol reaction

The most important aspect on which we focused our attention at the first stage of our research was how to obtain high catalytic efficiency in the direct aldol reaction. Several diamines were screened with protonic and Lewis acids to test their catalytic efficiency.‡ A protonic acid-1,2-diaminoethane module was found to be the best choice for the efficiency and for ready accessibility to their chiral derivatives from various α-amino acids (Scheme 1).

In a preliminary experiment, use of chiral diamine **4** gave the aldol adduct with moderate enantioselectivity. Sequential treatment of a DMF solution of *p*-nitrobenzaldehyde (**1a**) (1 equiv.) with *p*-TsOH·H_2O (3 mol%), diamine **4** (3 mol%) and acetone (27 equiv.) at room temperature, followed by stirring at 40°C for 2 h, gave aldol adduct **2a** in 19% yield with 83% ee, contaminated by dehydrated aldol adduct **3a** (4%). The use of *p*-TsOH·H_2O or the diamine **4**

Keywords: aldol reactions; asymmetric reactions; diamines; enamines.

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‡ We initiated an investigation on direct aldol reaction using *N*,*N*-dimethylethylenediamine–Lewis acid catalysts, acetone and *p*-nitrobenzaldehyde in DMF. The rate enhancement was observed, though moderate, with $Eu(OTf)_3$ and $Gd(OTf)_3$. To determine an essential catalysis that leads to high productivity, an X-ray single crystallographic study of the $Gd(OTf)_3$–diamine **4** catalyst was undertaken. Interestingly, single crystals of the Gd(III)-**4** complex were not obtained but diprotonic acid salt **22** was eventually grown at −20°C under a vapor of Et_2O (Fig. 4). This result implies that the protonic acid might play an important role in even this Lewis acid–diamine system: triflate salts should work as good TfOH sources.

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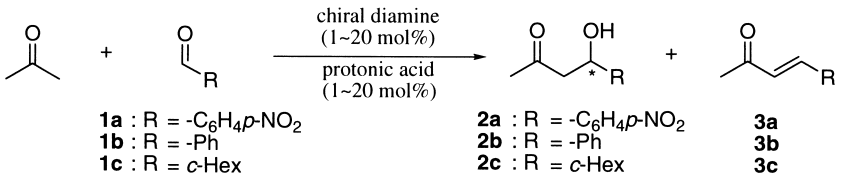
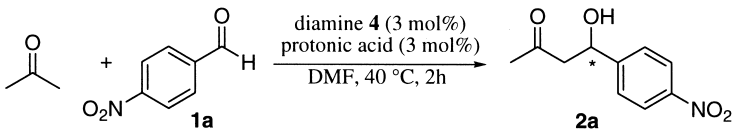
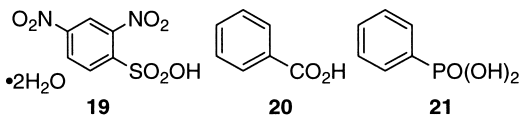


Scheme 1.

Table 1. Protonic acid variations



Acid	$TsOH{\cdot}H_2O$	Tf_3CH	**19**	**20**	**21**
% Yield	19	27	25	6	8
% ee	83	84	83	18	32



Reactions were performed using diamine **4** (3 mol%) and acid (3 mol%) in DMF at 40°C for 2 h under air in a closed system.

alone led to negligible formation of **2a** and **3a** under similar conditions. The most suitable acid–diamine ratio was found to be 1:1 for effective rate acceleration; acid–diamine ratios greater or less than 1:1 significantly reduced the reaction rate.

Diamine **4** was evaluated for catalysis of the aldol reaction with **1a** in the presence of a series of different protonic acids in DMF (Table 1). In general, the rate of the aldol reaction was enhanced as the acidity[14] of the protonic acid increased. These acid variations affected the enantioselectivity (18–84% ee). Both Tf_3CH and acid **19** emerged as superior protonic acids; we chose acid **19** for further survey due to its commercial availability. In parallel with these investigations, solvent effects were evaluated (THF: 7% yield, 79% ee; DMSO: 25%, 82% ee; MeOH: 6%, 75% ee; CH_3CN: 30%, 80% ee). Acetone was shown to be the best solvent (63% yield, 83% ee).

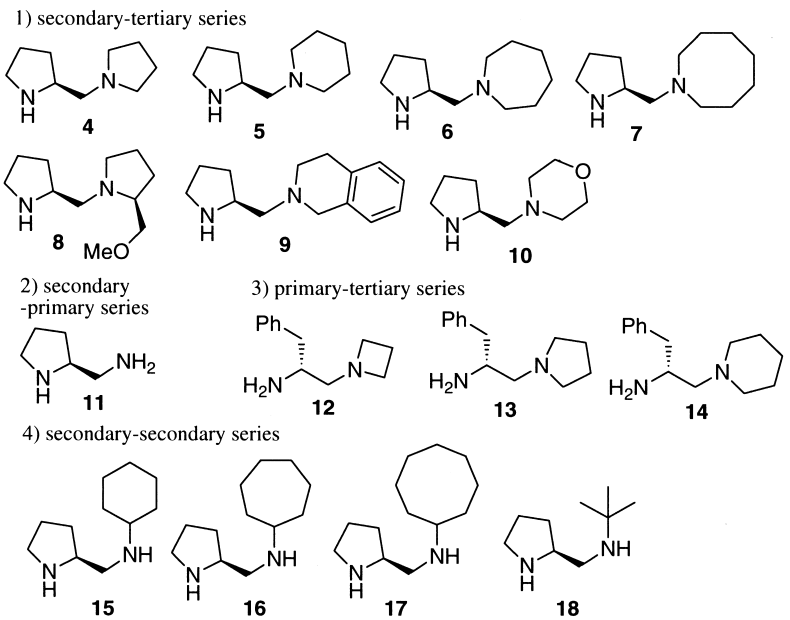


Figure 1. Diamine ligand library.

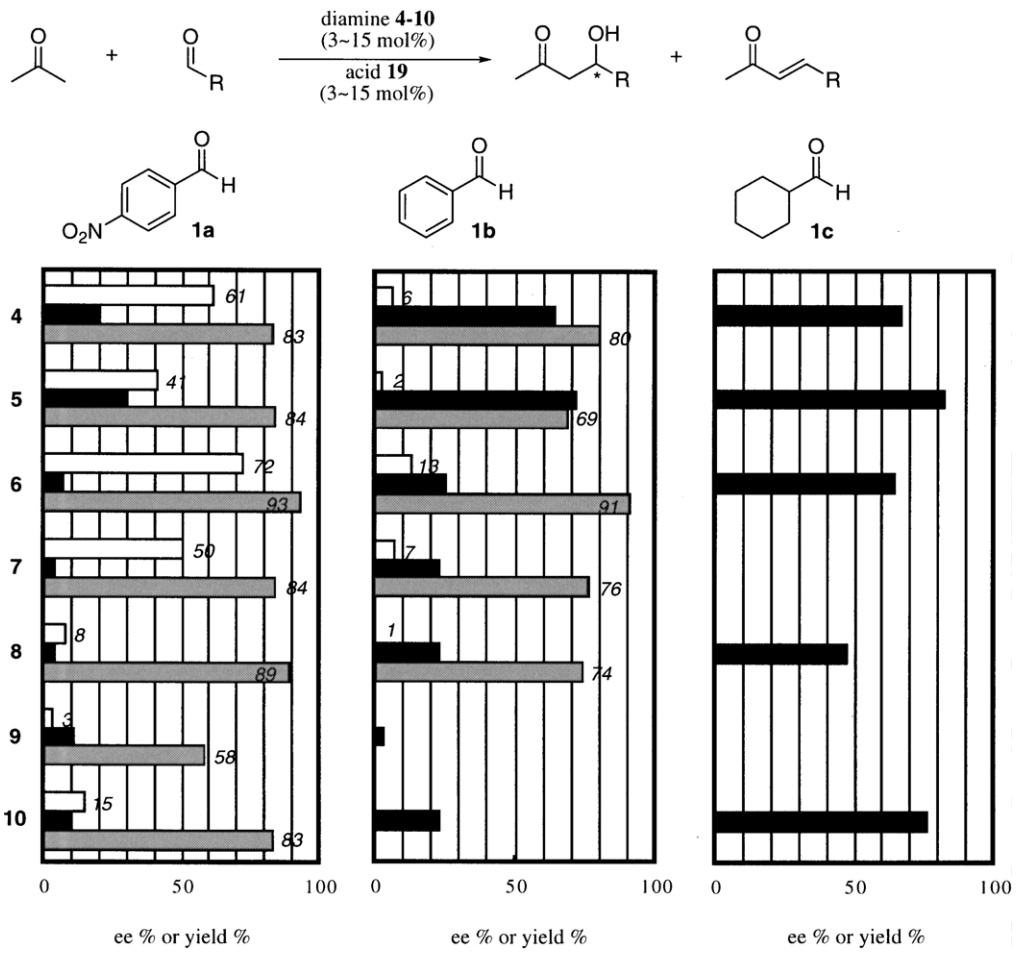


Figure 2. Library 1: Aldol reaction of **1a**–**1c** in acetone using chiral diamines and **19**. (Yield% of **2a**–**2c** (white bar); yield% of **3a**–**3c** (black bar); ee% of **2a**–**2c** (gray bar)). For the details, Section 4.

Twelve different diamines[15] (secondary–primary, secondary–secondary and secondary–tertiary diamines) with a consistent secondary amino structure derived from (L)-proline, as well as three different diamines (primary–tertiary diamines) derived from (D)-phenylalanine, were synthesized (Fig. 1) and screened with a range of aldehydes. Reactions were run at 23–40°C in acetone under conditions employing 1–20 mol% of catalyst relative to substrate.

Library 1. Based on these pioneering discoveries, our design of diamines focused on the secondary–tertiary diamine **4**–**10**. The reaction with aldehyde **1a**–**1c** was carried out using seven different diamines (Fig. 2). When **1a** was used in the direct aldol reaction, diamine **6** was the best choice for high ee (TON=24), although the reaction rate decreased in the order **4**, **6**>**5**>**7**>**8**–**10** (Fig. 2) as the tertiary amine moiety became bulkier. The turnover numbers (TON) ranged from 73 to 20 using 1–3 mol% of catalyst **4** under various conditions. **1b** and **1c** were reacted in acetone using secondary–tertiary diamines. Unfortunately, the formation of dehydrated product **3b** and **3c** posed serious limitations.

Library 2. In an effort to expand the scope of acceptable aldehyde, we examined the reaction using a number of diamines (Fig. 3). After screening diamines **11**–**18**, the primary–tertiary diamines **13** and **14** were found to be a superb structural module to avoid dehydration. Secondary–primary diamine **11** was found to be ineffective with regard to both productivity and efficiency. Secondary–secondary diamine **15** gave the most optimal result, albeit with a considerable amount of dehydrated products. The best result afforded **2b** in 58% yield with 74% ee and **2c** in 64% yield with 80% ee using **15**. Unfortunately, the rate of the aldol reaction with primary–tertiary and secondary–secondary diamine modules§ was much slower than the rates with secondary–tertiary diamines. The absolute configuration of **2a**–**2c** induced by a library of diamines derived from (L)-proline was the opposite of those obtained by (D)-phenylalanine-derived diamines.

2.2. Survey of more efficient catalyst: second generation

As demonstrated previously, the acidity[14] of the protonic acid appeared to be important to achieve high reactivity. Due to the superior reactivity exhibited by the secondary–tertiary diamine series, reinvestigation was initiated to

§ At present, we do not have a reasonable explanation for low enantioselectivity using diamine **18** and the mechanism involving secondary–secondary diamines.

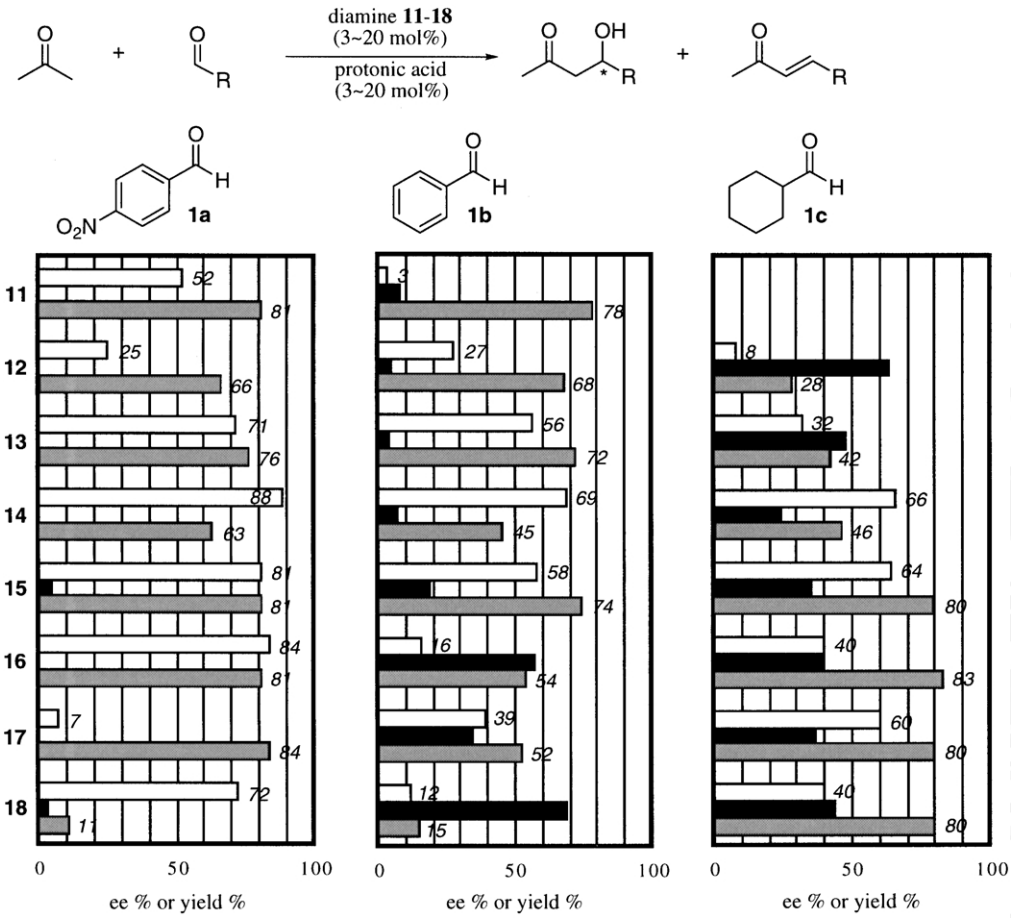
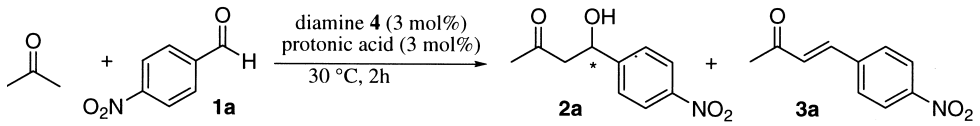


Figure 3. Library 2: Aldol reaction of **1a**–**1c** in acetone using chiral diamines and **19**. (Yield% of **2a**–**2c** (white bar); yield% of **3a**–**3c** (black bar); ee% of **2a**–**2c** (gray bar)). For the details, see Experimental section.

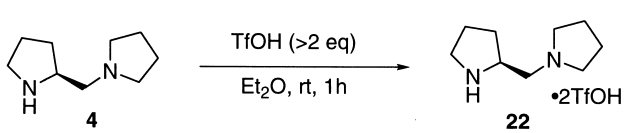
Table 2. Sulfonic acid variations



Acid	19	MsOH	$C_8F_{17}SO_3H$	TfOH
% Yield **2a** (% ee)	37 (80)	23 (77)	49 (83)	51 (82)
% Yield **3a**	18	17	16	13

Reactions were performed using diamine **4** (3 mol%) and acid (3 mol%) in acetone (27 equiv.) at 30°C for 2 h under air in a closed system.

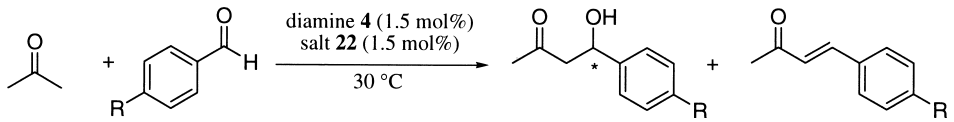
explore a more efficient catalyst involving **4** (Table 2). The acid screening revealed that TfOH was the optimal acid (**2a**, 51%, 82% ee; **3a**, 13%) with respect to both selectivity and reactivity. It is interesting to note that dehydration was relatively suppressed by using TfOH under otherwise identical conditions.



Scheme 2. Salt **22** preparation.

Since TfOH is a corrosive and hygroscopic liquid that fumes copiously on exposure to moist air,[16] special care must be taken regarding its handling especially in a small-scale experiment. We thus developed a new method for the preparation of a TfOH-**4**-like catalyst for further convenience: first, acid salt **22** was prepared by treatment of **4** with excess (>2 equiv.) TfOH (Scheme 2); second, salt **22** was exposed to **4** in a 1:1 ratio to give the catalyst **22**–**4**. This procedure enabled rather a large-scale preparation of acid salt **22**, which can be stored at a low temperature without decomposition or any loss of catalytic activity over a long period of time (more than 3 months). Subsequently, an acetone solution of the **22**–**4** catalyst was easily prepared

Table 3. Aldol reaction of **1a** in acetone using diamine **4** and salt **22**



R	Time (h)	Aldol yield % (% ee)	Dehydrated product yield (%)
NO_2 (**1a**)	2	60 (88)	7
H (**1b**)	48	37 (83)	32

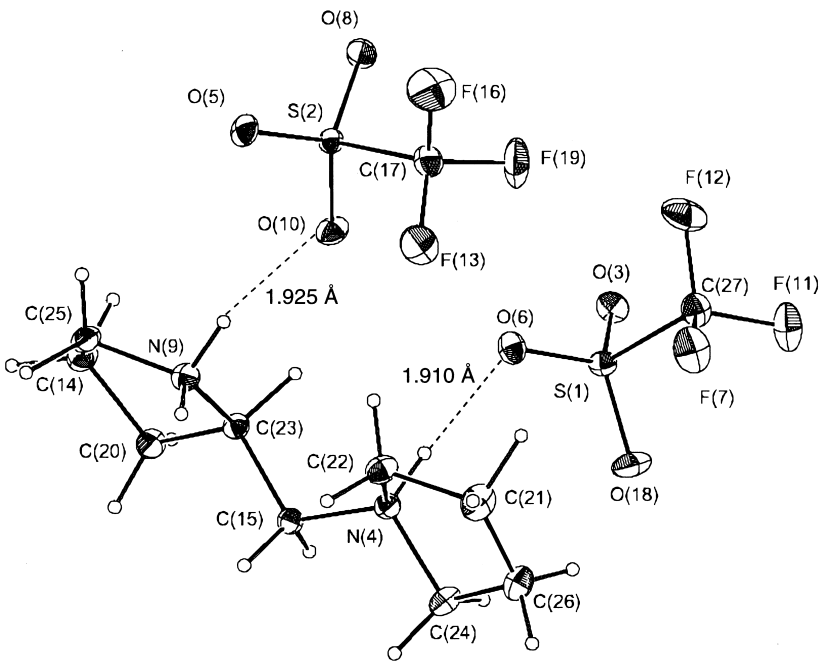
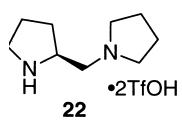


Figure 4. X-ray crystal structure of **22**.

even on a small scale (<1.0 mmol) just before use and showed reactivity and reproducibility similar to the catalyst generated by direct treatment of diamine **4** with TfOH. Slight increase in enantioselectivity was observed using the **22**–**4** catalyst compared with the **4**–TfOH catalyst (Table 3). Catalyst **22** alone had no catalytic activity.



22

The X-ray single crystal structure of **22**[17] was established by low temperature-measurement at 208 K and showed two typical hydrogen bondings (1.925 and 1.910 Å) between N^+–H and $^-$OTf (Fig. 4). Of interest for further research is that **22** could be an attractive candidate as a di-protonic acid catalyst in the termolecular double coordination system involving spontaneous activation of two functional groups by two acidic centers.[18] Both older[19] and modern investigations also highlighted that carboxylate[20] anions or carbonyl compounds bearing oxazolidinones[21] were bimolecularly recognized and/or doubly activated by guanidine derivatives.

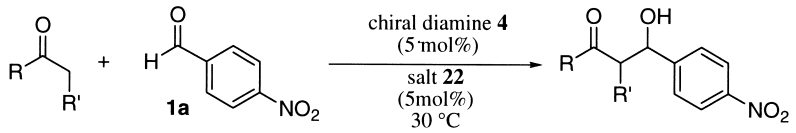
With the highest catalytic activity found so far in diamine–protonic acid catalysts, attention was next directed to the reaction of **1a** with ketones less reactive than acetone (Table 4).[‖] Both cyclopentanone and cyclohexanone exhibited good reactivity (88–97%). The cyclohexanone provided the *anti* aldol product in moderate diastereoselectivity with excellent enantioselectivity (*anti*/*syn*=74:26, ee (*anti*)=96%). Among the least reactive, diethylketone was also compatible with these conditions to give a high level of enantioselectivity as well as acceptable reactivity (81%, *anti*/*syn*=54:46, ee (*anti*)=84%).

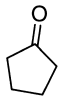
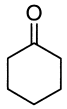
2.3. Plausible mechanism

The mechanism of the diamine–protonic acid-catalyzed aldol addition is the subject of an extensive, ongoing investigation but it remains unsolved. For the purposes of the immediate discussion, we assume that the catalytic cycle of the asymmetric aldol reaction is based on a proline-catalyzed aldol reaction[7,22] (Scheme 3) that was discovered by List,[7a–c,e] Lerner,[7a] and Barbas III.[7a,d] At the

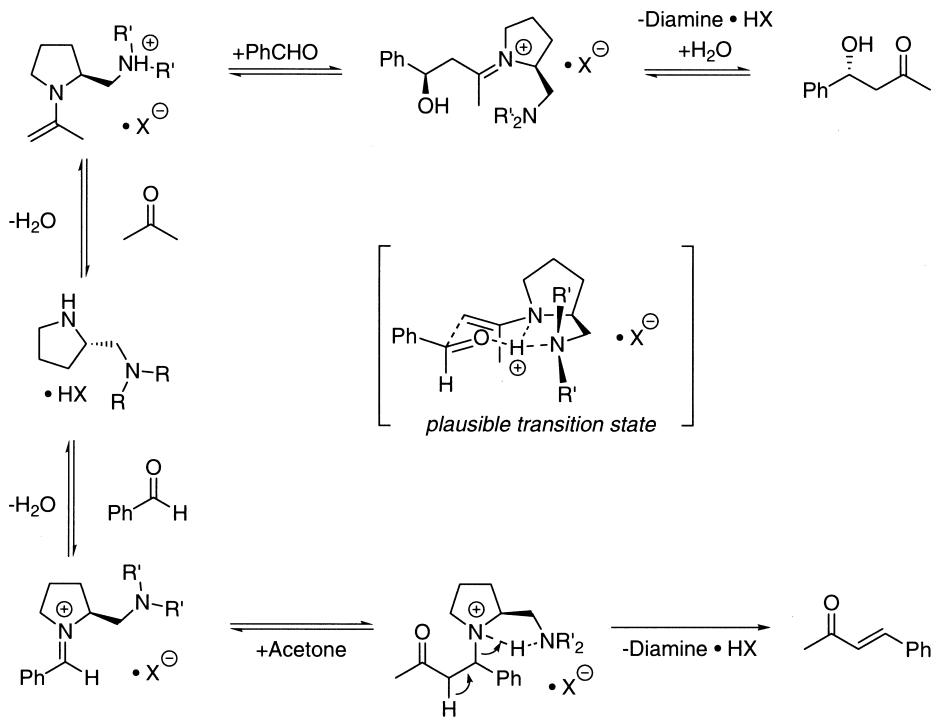
[‖] Diamine **6**–TfOH was also a good catalyst to give comparable ees: cyclopentanone, 93%, *anti*/*syn*=55:45, ee (*anti*)=85%, cyclohexanone, 99%, *anti*/*syn*=83:17, ee (*anti*)=96%.

Table 4. Aldol reactions of **1a** with ketones less reactive than acetone using **22**–**4** catalyst



Entry	Ketone	Time (h)	Yield (%)[a]	*anti* (% ee)/*syn* (% ee)[b]
1		29	88	43 (84)/57 (5)
2		29	97	74 (96)/26 (61)
3[c]		144	81	54 (84)/46 (16)

Unless otherwise noted, reaction were using **22** (5 mol%) and **4** (5 mol%) in a ketone solvent (18–22 equiv.)
[a] Isolated yields.
[b] *anti*/*syn* Ratios were determined by ^{1}H NMR. Enantiomeric ratios were determined by chiral HPLC analysis.
[c] 10 mol% of **22** and **4** were used, respectively.



Scheme 3. Proposed mechanism of the diamine–protonic acid catalyzed aldol reaction with **1b** and acetone.

current level of understanding, the dominant catalytic pathway to aldol adducts likely involves the intermediacy of an enamine derived from acetone. The reaction should proceed through a six-membered chair-like transition structure adopting the Ph-group of PhCHO at the equatorial position. Furthermore, a pathway to dehydration might involve an aldimine species, which undergoes Mannich-type reaction with the acetone enamine to give the β-aminoketone, followed by subsequent elimination.[7c,11k]

3. Conclusion

We demonstrated that a 1:1 mixture of chiral diamine–protonic acid could be an alternative to previously reported

methods for the catalytic asymmetric aldol reaction. Further, the diversity-based strategy was found to be of potential importance for the discovery of an appropriate catalyst for each carbonyl couple. Indeed, the screening using diamine libraries facilitated the characterization of an effective structure of diamine that leads to high catalytic activity and efficiency. In addition, the use of salt **22** offers the advantages of stability toward moisture and its handling. These initial results will be helpful to design novel chiral catalysts in the further improvement of the direct aldol reaction. Studies toward this end are now in progress.

4. Experimental

4.1. General

^{1}H NMR spectra were measured on a Varian Gemini-300 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (b=broad, s=singlet, d=doublet, t=triplet, and m=multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were recorded on a Varian Gemini-300 (75 MHz) spectrometer at ambient temperature. Chemical shifts are recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.07 ppm). All aldol reactions were carried out under an atmosphere of air in a closed system. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254 0.25 mm) were used. In some instances, the products were purified by preparative column chromatography on silica gel (E. Merck Art. 9385).

Organic substrates *p*-nitrobenzaldehyde (**1a**), benzaldehyde (**1b**), cyclohexanecaboxaldehyde (**1c**), cyclohexanone, cyclopentanone, diethylketone, **3b**, acids **19**–**21**, diamines **4** and **11** were all commercially available. **1a** was used without any purification. **1b**, **1c**, cyclohexanone, cyclopentanone and diethylketone were used after bulb-to-bulb distillation. Acetone was purchased from Nacalai Tesque (99% grade) and used without purification. Diamines **5**–**10** and **11**–**18** were prepared by the methods previously described.[15] Diamines **5**,[15g] **8**,[15g] **10**,[15g] **13**,[23] **14**[15a] and **15**[15b], Tf_3CH,[24] aldol adducts **2a**,[7d] **2b**,[7d] **2c**[25] and aldol adducts (Table 4, entries 1[7d] and 2[7d]), as well as dehydrated products **3a**[26] are all known compounds.

4.2. Typical procedure for the aldol reaction using a protonic acid and a diamine in acetone

The following procedure for the reaction of *p*-nitrobenzaldehyde (**1a**) in acetone using acid **19** and diamine **4** is representative. To a mixture of diamine **4** (3.3 μL, 0.02 mmol) and acid **19** (5.4 mg, 0.02 mmol) in acetone (4.0 mL) was added **1a** (2.0 mmol) at 23°C under air in a closed system. The reaction mixture was stirred at 43°C for 30 h. *n*-Oct_3SiMe (47.1 μL, 0.1 mmol) was added as an internal standard just before quenching. The reaction mixture was quenched with aq. NaCl. The organic layer was extracted with EtOAc, dried over Na_2SO_4, and concentrated. The residue was analyzed by ^{1}H NMR to give **2a** in a NMR yield of 73%, together with **3a** in 12% yield. After purification by column chromatography on silica gel (EtOAc/hexane=1/1 as the eluent), the enantiomeric excess (ee) of **2a** was determined to be 77% ee by chiral HPLC analysis. The chiral HPLC analytical data (column OB-H) of **2a**: retention times: t_R=28.49 min ((*R*)-isomer: minor isomer using (D)-phenylalanine-derived diamines; major isomer using (L)-proline-derived diamines) and t_R=33.39 min ((*S*)-isomer: major isomer using (D)-phenylalanine-derived diamines; minor isomer using (L)-proline-derived diamines) using *i*-PrOH/hexane (1/6) as eluent at a flow rate of 1.0 mL/min.

The ee of **2b** was similarly determined by chiral HPLC analysis. The chiral HPLC analytical data (column OB-H) of **2b**: retention times: t_R=37.32 min ((*S*)-isomer: major isomer using (D)-phenylalanine-derived diamines; minor isomer using (L)-proline-derived diamines) and t_R=42.26 min ((*R*)-isomer: minor isomer using (D)-phenylalanine-derived diamines; major isomer using (L)-proline-derived diamines) using *i*-PrOH/hexane (1/40) as eluent at a flow rate of 1.0 mL/min.

The ee of **2c** was determined by converting it to the trifluoroacetate derivative (trifluoroacetic anhydride, Py, cat. DMAP, $ClCH_2CH_2Cl$, rt) and subsequently by chiral GC analysis using the chiral column γ-TA (astec). The chiral GC analytical data (column γ-TA) of **2c**: retention times: t_R=33.26 min ((*S*)-isomer. major isomer using (D)-phenylalanine-derived diamines; minor isomer using (L)-proline-derived diamines) and t_R=36.07 min ((*R*)-isomer: minor isomer using (D)-phenylalanine-derived diamines; major isomer using (L)-proline-derived diamines) at the column temperature of 92°C (injection temperature: 150°C) at a carrier gas (N_2) pressure of 75 hPa.

4.2.1. 1-(2-Pyrrolidinylmethyl)hexamethyleneimine (6). IR (neat) 3308, 2946, 1450, 1132, 1093, 804 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4 05 (bs, 1H), 3.32–3.20 (m, 1H), 3.10–2.87 (m, 2H), 2.75–2.35 (m, 6H), 1.93–1.30 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.3, 56.3, 55.7 (two peaks are overlapped), 45.5, 29.4, 28.1 (two peaks are overlapped), 27.0 (two peaks are overlapped), 24.7; HRMS (FAB): exact mass calcd for $C_{11}H_{22}N_2$+H$^+$: 183.1861. Found: 183.1821. $[\alpha]_D^{25}$=+18.8° (*c* 2.00, $CHCl_3$).

4.2.2. 1-(2-Pyrrolidinylmethyl)heptamethyleneimine (7). IR (film) 3390, 2921, 2853, 1539, 1406, 1159, 1093, 1060, 814 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.20–3.12 (m, 1H), 2.98–2.78 (m, 2H), 2.60–2.26 (m, 7H), 1.86–1.27 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.9, 56.6, 54.8 (two peaks are overlapped), 45.7, 29.3, 28.1 (two peaks are overlapped), 27.5, 26.1 (two peaks are overlapped), 24.8; HRMS (EI): exact mass calcd for $C_{12}H_{24}N_2$: 196.1939. Found: 196.1982. $[\alpha]_D^{28}$=+12.5° (*c* 1.00, $CHCl_3$).

4.2.3. 2-(2-Pyrrolidinylmethyl)-1,2,3,4-tetrahydroisoquinoline (9). IR (film) 3330, 2951, 2788, 1399, 1093, 938, 810, 741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13–6.96 (m, 4H), 3.74 (d, 1H, *J*=14.7 Hz), 3.59 (d, 1H, *J*=14.7 Hz), 3.42–3.33 (m, 1H), 3.02–2.40 (m, 9H), 1.90 (m, 1H), 1.75 (m, 2H), 1.38 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 134.3, 128.6, 126.5, 126.0, 125.5, 63.6, 56.4, 55.5, 51.2, 45.9, 29.8, 29.0, 24.9; Anal. calcd for

$C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.62; H, 9.58; N, 12,83. $[\alpha]_D^{28}=+27.4°$ (*c* 1.00, $CHCl_3$).

4.2.4. α-Phenylmethyl-1-trimethyleneimineethaneamine (12). IR (neat) 3366, 2921, 2822, 1593, 1451, 1194, 905, 833, 747, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.14 (m, 5H), 3.23–2.87 (m, 5H), 2.70 (dd, 1H, *J*=4.5, 13.2 Hz), 2.44–2.32 (m, 3H), 2.02 (tt, 2H, *J*=6.9, 6.9 Hz), 1.42 (bs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 129.1 (two peaks are overlapped), 128.2 (two peaks are overlapped), 126.0, 66.6, 55.7 (two peaks are overlapped), 50.8, 42.2, 17.8; HRMS (EI): exact mass calcd for $C_{12}H_{18}N_2$: 190.1470. Found: 190.1483. $[\alpha]_D^{27}=-13.7°$ (*c* 1.14, $CHCl_3$).

4.2.5. α-Phenylmethyl-1-pyrrolidineethaneamine (13). IR (film) 3300, 2965, 2803, 1580, 1455, 1308, 1144, 1078, 748, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.20 (m, 5H), 3.16 (tt, 1H, *J*=4.2, 8.7 Hz), 2.77 (dd, 1H, *J*=4.5, 13.2 Hz), 2.59–2.43 (m, 6H), 2.31 (dd, 1H, *J*=4.2, 12.0 Hz), 1.99 (bs, 2H), 1.71–1.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 129.3 (two peaks are overlapped), 128.4 (two peaks are overlapped), 126.1, 63.2, 54.4 (two peaks are overlapped), 51.3, 42.5, 23.5 (two peaks are overlapped); Anal. calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.3; H, 10.07; N, 13.59. $[\alpha]_D^{27}=-14.1°$ (*c* 1.00, $CHCl_3$).

4.2.6. α-Phenylmethyl-1-piperidineethaneamine (14). IR (film) 3372, 2934, 1495, 1455, 1156, 1119, 779, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.18 (m, 5H), 3.18 (tt, 1H, *J*=4.8, 8.7 Hz), 2.71 (dd, 1H, *J*=4.2, 13.2 Hz), 2.51–2.43 (m, 3H), 2.27–2.16 (m, 4H), 1.79 (bs, 2H), 1.59–1.38 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 129.3 (two peaks are overlapped), 128.3 (two peaks are overlapped), 126.1, 65.8, 55.1 (two peaks are overlapped), 49.4, 42.4, 26.2 (two peaks are overlapped), 24.5; HRMS (FAB): exact mass calcd for $C_{14}H_{22}N_2+H^+$: 219.1861. Found: 219.1898. $[\alpha]_D^{28}=-23.5°$ (*c* 0.525, $CHCl_3$).

4.2.7. *N*-Cyclohexyl-*N*-(2-pyrrolidinylmethyl)amine (15). ^1H NMR (300 MHz, $CDCl_3$) δ 3.23–2.86 (m, 3H), 2.66 (dd, 1H, *J*=4.8, 11.1 Hz), 2.52–2.35 (m, 2H), 1.94–0.97 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.5, 56.9, 52.2, 46.4, 33.55, 33.49, 29.7, 26.1, 25.6, 24.98, 24.95.

4.2.8. *N*-Cycloheptyl-*N*-(2-pyrrolidinylmethyl)amine (16). IR (neat) 3293, 2924, 2857, 1646, 1460, 1116, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.36 (bs, 2H), 3.26–3.20 (m, 1H), 2.90 (t, 2H, *J*=6.9 Hz), 2.66–2.42 (m, 3H), 1.93–1.33 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 59.2, 58.3, 51.9, 46.1, 34.6, 34.5, 29.5, 28.07, 28.04, 25.4, 24.28, 24.25; HRMS (FAB): exact mass calcd for $C_{12}H_{25}N_2+H^+$: 197.2018. Found: 197.1985. $[\alpha]_D^{25}=+6.4°$ (*c* 1.00, $CHCl_3$).

4.2.9. *N*-Cyclooctyl-*N*-(2-pyrrolidinylmethyl)amine (17). IR (film) 3393, 2928, 1549, 1404, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.23–3.14 (m, 1H), 2.90 (td, 2H, *J*=2.7, 6.6 Hz), 2.63 (dd, 2H, *J*=4.5, 11.1 Hz), 2.45 (dd, 1H, *J*=8.4, 11.1 Hz), 1.21–1.93 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.6, 58.1, 53.0, 46.5, 33.0, 32.7, 29.8, 27.23, 27.19, 25.74, 25.73, 24.2, 24.1; HRMS (EI): exact mass calcd for $C_{13}H_{26}N_2$: 210.2096. Found: 210.2101. $[\alpha]_D^{23}=+10.2°$ (*c* 2.04, $CHCl_3$).

4.2.10. *N*-*t*-Butyl-*N*-(2-pyrrolidinylmethyl)amine (18). IR (neat) 3293, 2964, 2870, 1570, 1478, 1389, 1364, 1223, 1115, 797 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.75 (bs, 2H), 3.25–3.16 (m, 1H), 2.90 (t, 2H, *J*=6.9 Hz), 2.61–2.43 (m, 2H), 1.95–1.28 (m, 4H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.8, 50.5, 47.1, 46.1, 29.6, 28.7 (three peaks are overlapped), 25.4; HRMS (FAB): exact mass calcd for $C_9H_{20}N_2+H^+$: 157.1705. Found: 157.1705. $[\alpha]_D^{25}=+12.0°$ (*c* 1.98, $CHCl_3$).

4.2.11. 4-Cylohexyl-3-buten-2-one (3c). IR (neat) 2928, 2855, 1728, 1676, 1624, 1451, 1358, 1254, 980, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.71 (dd, 1H, *J*=6.9, 16.2 Hz), 6.48 (dd, 1H, *J*=1.2, 16.2 Hz), 2.21 (s, 3H), 2.21–1.60 (m, 6H), 1.25–1.12 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 153.4, 128.7, 40.5, 31.7, 26.8, 25.8 (two peaks are overlapped), 25.6 (two peaks are overlapped); Anal. calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.81; H, 10.77.

4.2.12. Conditions of library 1 and 2.

Diamine	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
p-Nitrobenzaldehyde (*3 mol% of a catalyst was used*)															
Temperature (°C)	23	23	23	23	40	40	23	23	23	23	23	23	23	23	23
Time (h)	10	10	10	111	2	2	72	72	72	72	36	36	36	36	24
Benzaldehyde															
Cat. (mol%)	10	3	10	10	3	3	10	10	10	10	10	10	10	10	3
Temperature (°C)	40	23	23	23	23	23	23	23	23	23	23	23	30	30	23
Time (h)	2	120	33	111	84	84	24	72	72	84	60	144	72	96	120
Cyclohexacarboxaldehyde															
Cat. (mol%)	15	15	15	15	15	15	15	15	20	20	20	15	15	15	15
Temperature (°C)	40	40	40	40	40	40	40	40	23	23	23	40	40	40	40
Time (h)	17	17	17	17	17	17	17	17	71	61	61	36	36	36	36

4.2.13. Results of library 1 and 2.

Diamine	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
p-Nitrobenzaldehyde															
Yield (**2a**)	61	41	72	50	8	3	15	52	25	71	88	81	84	7	72
Yield (**3a**)	19	30	7	4	4	11	10	1	<1	<1	<1	5	<1	1	3
ee % (**2a**)	83	84	93	84	89	58	83	81	66	76	63	81	81	84	11
Benzaldehyde															
Yield (**2b**)	6	2	13	7	1	<1	<1	3	27	56	69	58	16	39	12
Yield (**3b**)	64	72	25	23	23	3	23	8	5	4	7	19	57	34	69
ee % (**2b**)	80	69	91	76	74	–	–	78	68	72	45	74	54	52	15
Cyclohexacarboxaldehyde															
Yield (**2c**)	<1	<1	<1	<1	<1	<1	<1	<1	8	32	66	64	40	60	40
Yield (**3c**)	67	82	64	1	47	1	76	<1	63	48	24	35	39	37	44
ee % (**2c**)	–	–	–	–	–	–	–	–	28	42	46	80	83	80	80

4.2.14. Preparation of salt 22. To a solution of diamine **4** (410 μL, 2.5 mmol) in Et_2O (5 mL) was added trifluoromethanesulfonic acid (>443 μL, >5 mmol) with stirring. The salt **22** was immediately precipitated then was filtered and washed with Et_2O. The salt **22** showed the following data: IR (KBr) 3141, 3065, 2780, 2368, 1565, 1460, 1418, 1275, 1244, 1167, 1073, 1034, 841, 635, 577, 521 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 8.74 (bs, 1H), 8.61 (bs, 1H), 8.35 (bs, 1H), 4.38 (bs, 1H), 4.08–3.64 (m, 4H), 3.64 (bs, 2H), 3.45 (bs, 2H), 2.59–1.94 (m, 8H); ^{13}C NMR (75 MHz, acetone-d_6) δ 121.4 (q, J_{CF}=317.3 Hz: two peaks are overlapped), 58.1, 56.4, 56.0, 55.9, 47.7, 29.7, 23.7, 23.5 (two peaks are overlapped); Anal. calcd for $C_{13}H_{24}F_6N_2O_6S_2$: C, 29.07; H, 4.44; N, 6.16. Found: C, 29.08; H, 4.41; N, 6.08. $[\alpha]_D^{25}=-3.1°$ (*c* 1.03, EtOH).

4.2.15. Typical procedure for the aldol reaction using salt 22 and diamine 4. The following procedure for the reaction of *p*-nitrobenzaldehyde (**1a**) in diethylketone is representative. To a mixture of diamine **4** (8.2 μL, 0.05 mmol) and salt **22** (22.7 mg, 0.05 mmol) in diethylketone (1.0 mL) was added **1a** (0.5 mmol) at 23°C under air in a closed system. The reaction mixture was stirred at 30°C for 144 h, then was quenched with aq. NaCl. The organic layer was extracted with EtOAc, dried over Na_2SO_4, and concentrated. The residual crude product was purified by column chromatography on silica gel to afford a mixture of aldol adducts (96.4 mg, 81% yield). The *anti*/*syn* ratio[27] was determined to be 54/46 by ^1H NMR analysis. The enantioselectivities of the *anti* and *syn* isomers were determined to be 84 and 16% ee by HPLC analysis. The chiral HPLC analytical data (column AD-H) of aldol adducts: retention times: t_R=92.8 (*syn*, minor), 98.6 (*syn*, major), 105.7 (*anti*, major) and 115.6 (*anti*, minor) min using hexane/*i*-PrOH (50/1) as the eluent at a flow rate of 1.0 mL/min. Spectral data of the *anti* isomer: IR (film) 3461, 2977, 2361, 1705, 1605, 1522, 1458, 1348, 1109, 1034, 853, 750, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, 2H, *J*=8.7 Hz), 7.52 (d, 2H, *J*=8.7 Hz), 4.89 (dd, 1H, *J*=7.5, 5.7 Hz), 3.33 (d, 1H, *J*=5.4 Hz), 2.93 (dq, 1H, *J*=7.2, 7.5 Hz), 2.58 (dq, 1H, *J*=18.0, 7.2 Hz), 2.38 (dq, 1H, *J*=18.0, 7.2 Hz), 1.04 (d, 3H, *J*=7.2 Hz), 1.03 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.7, 149.5, 147.5, 127.3 (two peaks are overlapped), 123.7 (two peaks are overlapped), 75.6, 52.2, 36.4, 14.5, 7.4; HRMS (FAB): exact mass calcd for $C_{12}H_{15}NO_4$: 237.1001. Found: 237.0991. $[\alpha]_D^{25}=+39.6°$ (*c* 0.22, $CHCl_3$). Spectral data of the *syn* isomer: IR (film) 3486, 2980, 2940, 2363, 1705, 1603, 1520, 1458, 1348, 1109, 1019, 978, 857, 820, 747, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, 2H, *J*=8.7 Hz), 7.52 (d, 2H, *J*=8.7 Hz), 5.25 (dd, 1H, *J*=3.0, 2.1 Hz), 3.60 (d, 1H, *J*=2.1 Hz), 2.84 (qd, 1H, *J*=7.2, 3.0 Hz), 2.63 (dq, 1H, *J*=18.0, 7.2 Hz), 2.47 (dq, 1H, *J*=18.0, 7.2 Hz), 1.08 (t, 3H, *J*=7.2 Hz), 1.04 (d, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.3, 149.0, 147.1, 126.7 (two peaks are overlapped), 123.5 (two peaks are overlapped), 71.9, 51.3, 35.1, 9.8, 7.5; HRMS (FAB): exact mass calcd for $C_{12}H_{15}NO_4$: 237.1001. Found: 237.0956.

4.2.16. 2-[Hydroxy(4-nitrophenyl)methyl]-cycropentanone. Spectral data of the *anti* isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, 2H, *J*=8.7 Hz), 7.54 (d, 2H, *J*=8.7 Hz), 4.85 (d, 1H, *J*=9.3 Hz), 4.79 (s, 1H), 2.53–1.51 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 239.6, 148.6, 147.6, 127.3 (two peaks are overlapped), 123.7 (two peaks are overlapped), 74.4, 55.1, 38.6, 26.9, 20.4; $[\alpha]_D^{29}=-95.3°$ (*c* 0.73, $CHCl_3$). Spectral data of the *syn* isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, 2H, *J*=9.0 Hz), 7.53 (d, 2H, *J*=8.7 Hz), 5.43 (dd, 1H, *J*=3.9, 3.6 Hz), 2.81 (d, 1H, *J*=4.8 Hz), 2.52–1.69 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.6, 150.1, 147.1, 126.3 (two peaks are overlapped), 123.6 (two peaks are overlapped), 70.4, 56.1, 38.9, 22.4, 20.3; $[\alpha]_D^{27}=+18.2°$ (*c* 0.66, $CHCl_3$).

4.2.17. 2-[Hydroxy(4-nitrophenyl)methyl]-cycrohexanone. Spectral data of the *anti* isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, 2H, *J*=8.7 Hz), 7.51 (d, 2H, *J*=8.7 Hz), 4.90 (dd, 1H, *J*=8.4, 3.0 Hz), 4.10 (d, 1H, *J*=3.3 Hz), 2.64–1.35 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.8, 148.3, 147.5, 127.8 (two peaks are overlapped), 123.5 (two peaks are overlapped), 74.0, 57.1, 42.6, 30.7, 27.6, 24.6; $[\alpha]_D^{29}=+12.0°$ (*c* 1.00, $CHCl_3$). Spectral data of the *syn* isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, 2H, *J*=9.0 Hz), 7.49 (d, 2H, *J*=9.0 Hz), 5.49 (dd, 1H, *J*=2.4, 2.4 Hz), 3.20 (d, 1H, *J*=3.3 Hz), 2.70–1.50 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.2, 149.0, 147.0, 126.6 (two peaks are overlapped), 123.4 (two peaks are overlapped),

70.7, 56.7, 42.6, 27.9, 25.9, 24.7; $[\alpha]_D^{26}=-59.9°$ (*c* 1.00, $CHCl_3$).

4.3. Preparation of a single crystal of salt 22 for X-ray analysis

To a mixture of diamine **4** (2 equiv.) and $Gd(OTf)_3$ (1 equiv.) was added acetone (453 equiv.) at 23°C. The crystal of salt **22** was grown at −20°C under Et_2O vapor.

4.4. X-ray crystallographic determination of 22

A single crystal of the **22** complex suitable for X-ray diffraction analysis was transferred to a glass capillary tube as quickly as possible under air atmosphere, and the glass capillary was mounted with a sticky compound on a goniometer for measurement. Diffraction data were obtained with graphite-monochromated Mo Kα radiation on a MAC Science DIP2030 diffractometer at 208 K. Standard reflections for each data set showed no significant decrease in intensity throughout the acquisition. The structure was solved by direct method and refined by full-matrix least-squares on *F*. All non-hydrogen atoms were refined anisotropically, and hydrogens were found by Fourier synthesis, using isotropic temperature factors. Crystallographic computations were performed on a Silicon Graphics INDY computer using the maXus program for data reduction, determining the structure, refining the structure, and molecular graphics. MAC DENZO software was used for cell refinement. Crystal data: a=8.3460 (5), b=11.0070 (8), c=19.920 (2) Å, V=1829.90 (2) Å^3, orthorhombic, $P212121$, Z=4, μ(Mo)=0.0676 mm^{-1}, R=0.038, R_w=0.040, GOF=1.619, 2388 unique reflections with $I>3.0(I)$.

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