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PAPER

Highly enantioselective synthesis of *syn*-aldols of cyclohexanones *via* chiral primary amine catalyzed asymmetric transfer aldol reactions in ionic liquid†

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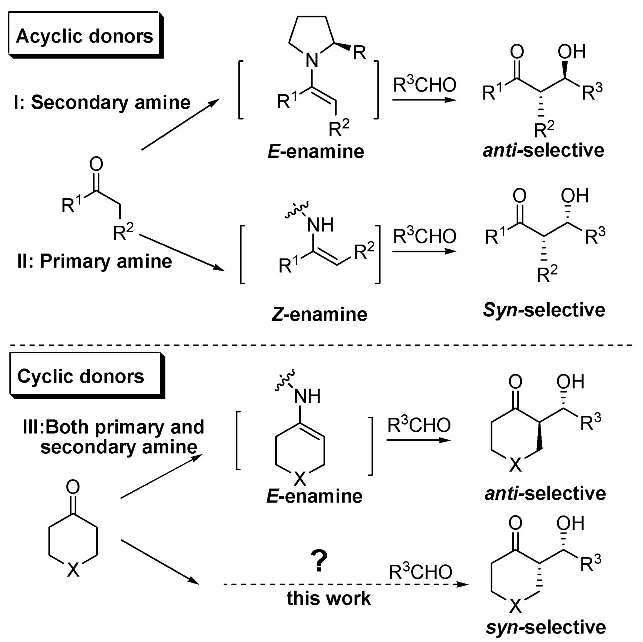
Chiral primary-tertiary diamine/TfOH was found to catalyze kinetic resolution of racemic *syn*-aldols of cyclohexanones in ionic liquid effectively, affording the chiral *syn*-aldols with up to 99 : 1 *syn*/*anti* and 99% ee.

Introduction

Asymmetric direct aldol reaction, a milestone in the evolution of aldol chemistry, is undoubtedly one of the most versatile C–C bond-forming reactions in constructing chiral molecules with promising reaction (atom, step and redox) economies.[1] Accordingly, the search for asymmetric aldol catalysts with exquisite control of chemo-, regio-, diastereo- and enantio-selectivity has been and continues to be a research focus in this field.[2]

Recently, chiral amines, exemplified by chiral pyrrolidines, have appeared as a prominent type of asymmetric direct aldol catalysts that enable effective catalysis with ketone and aldehyde donors *via* enamine intermediates (Scheme 1).[3] Specifically, secondary amine catalysts have been very successful for both cyclic and acyclic aldol donors and these reactions normally give excellent *anti*-diastereoselectivity and enantioselectivity, presumably *via* *E*-enamines (Scheme 1, **I** and **III**). However, *syn*-selective aldol reaction remains a challenging subject with the typical secondary aminocatalysis. This challenge has now been partially addressed with the identification of chiral primary amine catalysts.[4b] In particular, *syn*-selective aldol reactions of acyclic ketone and aldehyde donors have been realized *via* chiral primary aminocatalysis.[4] The success of primary aminocatalysts in these cases can be ascribed to their tendency to form thermodynamically stable *Z*-enamines (Scheme 1, **II**).[2,4b] Notwithstanding these significant advances, *syn*-selective direct aldol reactions of cyclic ketone donors have not been achieved so far. This constitutes an elusive and fundamental target in asymmetric aminocatalysis both synthetically and mechanistically as cyclic ketone donors ($n < 8$) are constrained to forming *E*-enamines due to the inherent ring strains with both primary and secondary amines (Scheme 1, **III**), which consequently leads



Scheme 1

to *anti*-diastereoselectivity as indeed observed experimentally in numerous previous studies.[3] In addition, other currently developed asymmetric direct aldol strategies also gave predominantly *anti*-selectivity for this class of substrates and examples with *syn*-selectivity were rare with only modest enantioselectivity.[5]

Recently, we established that simple chiral primary–tertiary vicinal diamines such as **1** act as effective catalysts for a series of *syn*-selective aldol reactions of acyclic donors such as linear aliphatic ketones,[6a] α-hydroxyketones,[6b] dihydroxyacetone,[6c] pyruvic acetals,[6d] acetoacetals[6e] and aliphatic aldehydes.[6f] Furthermore, the same chiral primary amines have also been found to be unprecedented asymmetric catalysts for retro-aldol reactions, enabling enantioselective synthesis of aldol products that are usually difficult to obtain through the forward process.[7] It is thus hypothesized that a facile enantioselective synthesis of *syn*-aldols of cyclic ketones would be achieved by utilizing **1** catalyzed

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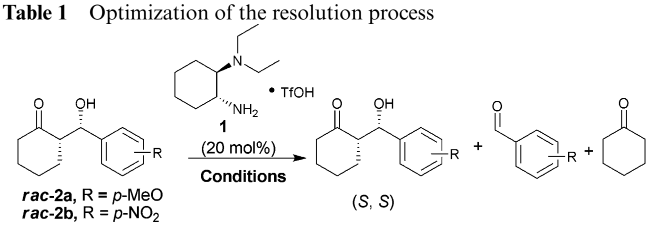
† Electronic supplementary information (ESI) available: ^{1}H NMR, ^{13}C NMR and HPLC spectrum of *syn* aldol products. See DOI: 10.1039/c0ob00682c

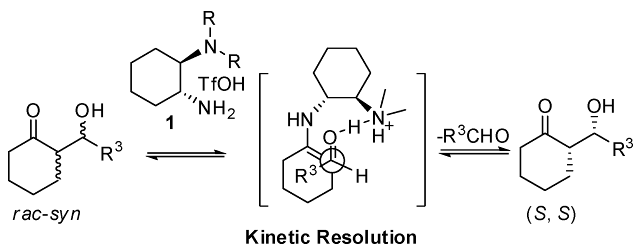
Table 1 Optimization of the resolution process



Entry[a]	Conditions		Time (h)	Yield (%)[b]	dr[c]	ee (%)[d]
1	*rac*-**2a**	DCM, rt	24	33	98 : 2	98
2	*rac*-**2b**	DCM, rt	36	86	95 : 5	18
3	*rac*-**2b**	Acetone, rt	36	70	95 : 5	27
4	*rac*-**2b**	Acetone, 50 °C	36	45	89 : 11	94
5	*rac*-**2b**	IL, rt	36	36	80 : 20	59
6	*rac*-**2b**	Acetone–IL,[e] 50 °C	36	55	97 : 3	96
7	*rac*-**2b**	Acetone–IL,[f] 50 °C	36	57	95 : 5	95
8	*rac*-**2a**	Acetone–IL,[e] 50 °C	24	55	98 : 2	78
			36	60		98

[a] Unless otherwise stated, all reactions were carried out on 0.1 mmol scale at 0.25 M in solvent using 20 mol% catalyst **1**. [b] Isolated yield. [c] The *syn*/*anti* ratios were analyzed by ^{1}H NMR of the crude product. [d] Determined by chiral HPLC. [e] IL: [BMIM]BF_4. [f] IL: [BMIM]PF_6.

retro-aldol reactions of racemic *syn*-aldols (Scheme 2). Our preliminary studies indicated that such a process was indeed possible (Table 1) and highly enantioenriched *syn*-aldols of cyclohexanone could be obtained *via* kinetic resolution of the racemic *syn*-aldols. However, the initial retro-aldol protocol suffered from the lower activity, unsatisfactory *s* factors and decreased *syn*-diastereoselectivity (Table 1, entries 1 and 2). Herein, we present a new and improved protocol for the synthesis of *syn*-aldols of cyclohexanones by the use of asymmetric transfer aldol in ionic liquids.



Scheme 2

Results and discussion

We started first to develop a convenient synthesis of racemic *syn*-aldols of cyclohexanones. The reactions between cyclohexanones and aromatic aldehydes occurred rapidly to afford the racemic aldols in the presence of NaOH. Fortunately, the *syn*- and *anti*-aldols of cyclohexanones generally demonstrate large differences in solubility. Pure diastereoisomers can be easily obtained *via* recrystallization, thus providing a practical access to the racemic *syn*-aldols.

Racemic *syn*-aldols **2a** and **2b** (*syn*/*anti*>99 : 1), bearing electron-donating MeO- and electron-withdrawing NO_2-, respectively, were chosen as the representative substrates. As expected, **2a** reacts much faster than **2b** and satisfactory enantioenrichment could be attained for **2a** at >60% conversion (Table 1, entry 1). In contrast, the retro-reaction of **2b** is very sluggish even in the presence of acetone, wherein the *in situ* generated aldehyde would be consumed *via* a forward aldol reaction (*i.e.* transfer aldol reaction) (Table 1, entries 2 and 3). In this case, good enantioselectivity (94% ee) could be obtained by increasing the reaction temperature to 50 °C, albeit with a reduction of diastereoselectivity (from 99 : 1 to 89 : 11) (Table 1, entry 4). After considerable screening, it is interesting to observe that the reaction could be significantly accelerated when conducted in an imidazolium ionic liquid, [BMIM]BF_4 (Table 1, entry 5 *vs.* entry 2). The examination with other ionic liquids such as [BMIM]PF_6 gave similar results (Table 1, entry 7). The beneficial effect of an ionic liquid may be ascribed to its polar and ionic features that are generally favorable for reactions with charged transition states or intermediates.[9a,9b] Combining the use of ionic liquids and the transfer aldol protocol, we finally reached optimal resolution of both **2a** and **2b** at 50 °C (Table 1, entries 6–8). Under the optimized conditions (in acetone–[BMIM]BF_4 at 50 °C), kinetic resolution factors of 21 and 32 were obtained for **2a** and **2b**, respectively. The acetone aldol products obtained from the transfer aldol processes are of low enantioselectivity (<20% ee) likely due to the high temperature.

We next examined the generality of the present protocol and the results are summarized in Table 2. The chiral primary amine **1** catalyzed transfer aldol reactions work smoothly with a range of racemic *syn*-aldols derived from cyclohexanone and aromatic aldehydes bearing either electron-donating or electron-withdrawing groups (Table 1, entries 1–13). The enantioenriched *syn*-aldols could be obtained with maintained diastereoselectivity (>97 : 3 *syn*/*anti*) and excellent enantioselectivity (83–99% ee) except in the case of 2-morpholinyl benzaldehyde (Table 1, entry 14). Decreasing diastereo- and enantiostereoselectivity were observed in this reaction, most likely due to the general base catalysis arisen from the morpholine moiety. The transfer aldol reaction also worked well with *syn* aldol derived from (*E*)-cinnamaldehyde to afford optically pure product in 40% isolated yield, 99 : 1 *syn*/*anti* and 98% ee (Table 2, entry 14). Racemic aldols derived from other substituted cyclohexanones have also been examined in the current reactions. Again, significant kinetic resolutions were achieved in these cases to afford enantioenriched products with 88–99% ee for the *syn*-diastereomers (Table 2, entries 16–18). In these cases, erosion of diastereoselectivity was observed. To the best of our knowledge, most of *syn*-aldols presented in Table 2 are firstly obtained as enantiomerically pure products.

Besides the beneficial effect on reaction rate, the use of ionic liquid as reaction medium adds further practical merit by facilitating a recyclable and reusable catalytic system as widely practised in the field of ionic liquids.[9] Bearing in mind that the catalyst **1** is itself a protonated salt, the potential of a reusable **1** in ionic liquids has also been explored in our study. After the indicated reaction time, the product is easily separated by extraction with ether and the remaining ionic liquid containing **1** could be directly used for the next run after drying briefly under vacuum. To our delight, the thus-recycled catalyst **1** could be reused 10 times without much loss of stereoselectivity (Chart 1) and over >50% conversions were consistently obtained in the subsequent reuses.

Table 2 Substrate scope

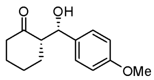
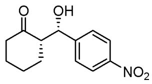
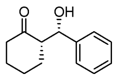
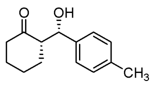
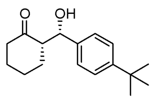
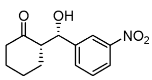
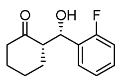
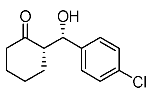
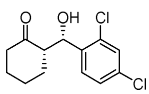
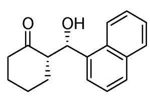
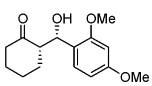
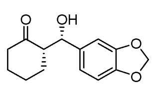
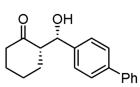
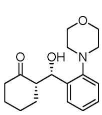
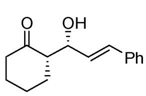
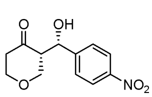
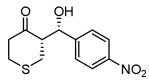
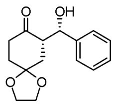
Entry[a]	Product	T (h)	Yield (%)[b]	*syn* : *anti*[c]	ee (%)[d]	*s*[e]
1	**2a** 	24 36	45 40	98 : 2	78 98	— 21
2	**2b** 	36	45	97 : 3	96	32
3	**2c** 	36	42	99 : 1	98	26
4	**2d** 	36	41	99 : 1	98	23
5	**2e** 	36 24	42 (55)[f]	99 : 1	99 (68)[f]	30 22
6	**2f** 	36	42	97 : 3	94	18
7	**2g** 	36	49	99 : 1	83	23
8	**2h** 	36	40	99 : 1	97	18
9	**2i** 	36	48	99 : 1	91	36
10	**2j** 	36	41	99 : 1	98	23
11	**2k** 	36 24	32 (42)[f]	99 : 1	95 (87)[f]	9 12
12	**2l** 	36	48	99 : 1	89	30
13	**2m** 	36	40	98 : 2	98	21
14	**2n** 	24	49	50 : 50	77/80	15
15	**2o** 	24	39	99 : 1	98	19
16	**2p** 	36	28[c]	87 : 13	89	5

Table 2 *(Contd.)*

Entry[a]	Product	T (h)	Yield (%)[b]	*syn* : *anti*[c]	ee (%)[d]	*s*[e]
17	2q 	36	30[c]	58 : 42	99	11
18	2r 	36	40[c]	93 : 7	89	11

[a] Unless otherwise noted, all reactions were carried out at 0.1 mmol scale in 0.2 mL acetone and 0.4 mL $[BMIM]BF_4$ using 20 mol% catalyst at 50 °C. [b] Isolated yield. [c] Determined by ^1H NMR. [d] Determined by chiral HPLC. [e] Calculated according to the equation developed by Kagan and Fiaud.[8] [f] Conducted in CH_2Cl_2 at 0.25 M at rt.

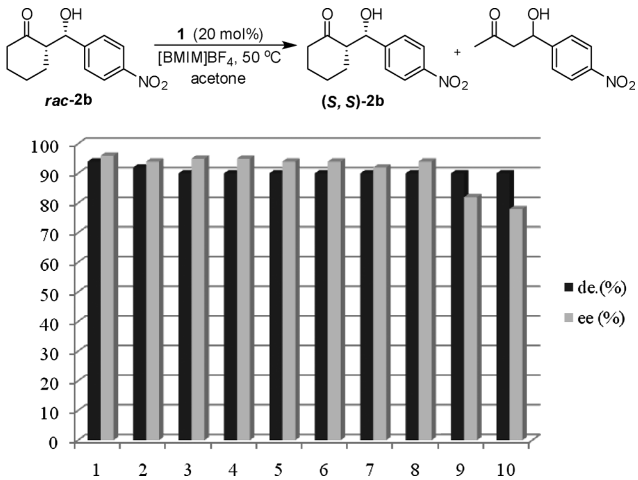


Chart 1 Catalyst **1** recovery and reuse in $[BMIM]BF_4$.

Conclusions

In summary, we have developed an effective chiral primary amine catalyzed transfer aldol reaction for the synthesis of optically pure *syn*-aldols between cyclohexanones and aromatic aldehydes,[10] which remains difficult to obtain with other methods. The catalysis of primary amine **1** has been shown to work favorably in ionic liquids, thus facilitating a recyclable and reusable catalytic system. Catalyst **1** in the ionic liquid $[BMIM]BF_4$ could be reused at least 9 times with only a little loss of activity and stereoselectivity.

Experimental section

General

Commercial reagents were used as received, unless otherwise stated. ^1H and ^{13}C NMR were recorded on either a Bruker-DPX 300 or AV-400 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Mass spectra were obtained using a fast atom bombardment (FAB) spectrometer or electron spray ionization (ESI) mass spectrometer. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Perkin–Elmer 341 digital polarimeter and are reported as follows: $[\alpha]_D^{20}$ (*c* in g per 100 mL of solvent). All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on gel F254 plates. Silica gel (200–300 mesh) was used for column chromatography, and the distillation range of petroleum was 60–90 °C. Enantiomeric excess was analyzed using ChiralPak columns on HPLC.

General procedure for the kinetic resolution of racemic aldols

To a stirred solution of the catalyst **1** (0.02 mmol, 6.4 mg) in $[BMIM]BF_4$ (0.4 mL) and acetone (0.2 mL) were added 0.1 mmol racemic aldol substrates. Then the reaction mixture was reacted at 50 °C for the given time. After cooling to room temperature, the reaction solution was extracted with diethyl ether (2 mL ×3). The combined organic layers were concentrated and purified by flash chromatography to give the pure *syn*-aldol product. The catalyst remained in the $[BMIM]BF_4$ could be directly reused in the next run after evaporating the volatile solvent. Compounds **2a**,[11] **2b**,[12] **2c**,[12] **2d**,[11] **2f**,[12d] **2h**,[12d] **2i**,[12e] **2m**,[13] **2o**,[14] **2p**[15] and **2q**[15] are known compounds.

Characterization data

***syn*-Aldol 2a**[11]**.** 98% ee; $[\alpha]_D^{20}$ = −105.6 (*c* = 1.0, $CHCl_3$); IR (KBr, cm^{-1}): 3437, 2948, 1694, 1513, 1248, 1023, 832, 534; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.32 (t, J = 2.7 Hz, 1H), 3.80 (s, 1H), 2.99 (d, J = 3.3 Hz, 1H), 2.60 –2.53 (m, 1H), 2.46–2.34 (m, 2H), 2.11–2.04 (m, 1H), 1.88 –1.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.9, 158.6, 133.6, 126.9, 113.6, 70.4, 57.3, 55.3, 42.7, 28.0, 26.2, 24.9. The ee value was determined by Chiral HPLC. [Daicel Chiralpak AS-H column, λ = 254 nm, 2-propanol : *n*-hexane = 1 : 9, flow rate = 0.8 mL min^{-1}]: t_R = 18.26 min (minor), t_R = 21.35 min (major).

***syn*-Aldol 2b**[12]**.** 96% ee; $[\alpha]_D^{20}$ = −81.2 (*c* = 0.5, CH_3OH); IR (KBr, cm^{-1}): 3512, 2936, 2864, 1689, 1515, 1339, 854, 571, 538; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 5.49 (s, 1H), 3.16 (d, J = 3.3 Hz, 1H), 2.68–2.60 (m, 1H), 2.49–2.39 (m, 2H), 2.15–2.09 (m, 1H), 1.89–1.76 (m, 1H), 1.73–1.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.0, 149.0, 147.1, 126.6, 147.1, 126.6, 123.5, 70.1, 56.8, 42.6, 27.9, 25.9, 24.8. The ee value was determined by Chiral HPLC. [Daicel Chiralpak

AD-H column, λ = 254 nm, 2-propanol : *n*-hexane = 1: 4, flow rate = 0.5 mL min^{-1}]: t_R = 23.01 min (minor), t_R = 24.45 min (major).

***syn*-Aldol 2c**[12]. 98% ee; $[\alpha]_D^{20}$ = −73.4 (c = 0.5, $CHCl_3$); IR (KBr, cm^{-1}): 3545, 2943, 2862, 1444, 1312, 1059, 700, 532. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.21 (m, 5H), 5.38 (1 H, t, J = 2.7 Hz), 3.02 (d, J = 3.3 Hz, 1H), 2.61–2.55 (m, 1H), 2.44 –2.34 (m, 2H), 2.09–2.04 (m, 1H), 1.85–1.75 (m, 1H), 1.73–1.51 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.8, 141.5, 128.2, 127.0, 125.8, 70.6, 57.2, 42.7, 28.0, 26.0, 24.9. The ee value was determined by Chiral HPLC. [Daicel Chiralpak AS-H column, λ = 254 nm, 2-propanol : *n*-hexane = 1: 4, flow rate = 0.5 mL min^{-1}]: t_R = 14.12 min (major), t_R = 15.97 min (minor).

***syn*-Aldol 2d**[11]. 96% ee; $[\alpha]_D^{20}$ = −58.8 (c = 0.5, $CHCl_3$); IR (KBr, cm^{-1}): 3532, 2948, 2830, 1440, 1115, 947, 673, 542; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.13 (m, 4H), 5.35 (s, 1H), 2.99 (s, 1H), 2.61–2.54 (m, 1H), 2.44–2.41 (m, 2H), 2.34 (s, 3H), 2.10–2.04 (m, 1H), 1.87–1.53 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.9, 138.5, 136.5, 128.8, 125.7, 70.6, 57.3, 42.7, 28.0, 26.1, 24.9, 21.1. The ee value was determined by Chiral HPLC. [Daicel Chiralpak AD-H column, λ = 254 nm, 2-propanol: *n*-hexane = 1: 9, flow rate = 1.0 mL min^{-1}]: t_R = 14.12 min (major), t_R = 15.97 min (minor). The ee value was determined by Chiral HPLC. [Daicel Chiralpak AD-H column, λ = 254 nm, 2-propanol : *n*-hexane = 1: 9, flow rate = 1.0 mL min^{-1}]: t_R = 8.30 min (minor), t_R = 8.80 min (major).

***syn*-Aldol 2e.** 99% ee; $[\alpha]_D^{20}$ = −97.8 (c = 0.5, $CHCl_3$); IR (KBr, cm^{-1}): 3443, 2950, 2867, 1704, 1449, 1125, 835, 674; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 5.36 (t, J = 2.7 Hz, 1H), 2.96 (d, J = 2.1 Hz, 1H), 2.61– 2.56 (m, 1H), 2.44–2.35 (m, 2H), 2.10–2.05 (m, 1H), 1.87–1.54 (m, 5H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.9, 149.8, 138.5, 125.5, 125.1, 70.5, 57.2, 42.7, 34.5, 31.4, 28.0, 26.1, 24.9. HRMS for $C_{17}H_{24}O_2Na$: Calcd. 283.1674; Found: 283.1665 [M + Na]. The ee value was determined by Chiral HPLC. The ee value was determined by Chiral HPLC. [Daicel Chiralpak AD-H column, λ = 254 nm, 2-propanol : *n*-hexane = 1 : 4, flow rate = 0.5 mL min^{-1}]: t_R = 10.47 min (minor), t_R = 11.60 min (major).

***syn*-Aldol 2f**[12d]. 94% ee; $[\alpha]_D^{20}$ = −41.3 (c = 0.5, $CHCl_3$); IR (KBr, cm^{-1}): 3437, 2954, 2867, 1690, 1538, 1134, 1067, 695; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.08 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 5.45 (s, 1H), 3.25 (s, 1H), 2.67–2.61 (m, 1H), 2.43– 2.37 (m, 2H), 2.11–2.06 (m, 1H), 2.06–1.82 (m, 1H), 1.75–1.49 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.5, 146.8, 142.2, 130.5, 127.6, 120.5, 119.4, 68.4, 55.2, 41.1, 25.3, 24.4, 23.2. The ee value was determined by Chiral HPLC. [Daicel Chiralpak AD-H column, λ = 254 nm, 2-propanol : *n*-hexane = 1: 9, flow rate = 1.0 mL min^{-1}]: t_R = 15.44 min (minor), t_R = 16.34 min (major).

***syn*-Aldol 2g.** 83% ee; $[\alpha]_D^{20}$ = −41.1 (c = 0.5, $CHCl_3$). IR (KBr, cm^{-1}): 3423, 2937, 2873, 1694, 1479, 1452, 759, 517; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.50 (m, 1H), 7.25–7.20 (m, 1H), 7.18–7.13 (m, 1H), 7.03 –6.97 (m, 1H), 5.66 (s, 1H), 3.19 (d, J = 3.3 Hz), 2.78–2.62 (m, 1H), 2.46–2.38 (m, 2H), 2.08–2.00 (m, 1H), 1.82–1.55 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.8, 157.3, 128.4, 128.3, 128.3, 128.2, 124.0, 123.9, 115.0, 114.7, 65.3, 65.3, 55.0, 42.6, 28.0, 26.2, 24.9. HRMS for $C_{13}H_{15}FO_2$: Calcd. 222.1056; found: 222.1059. The ee value was determined by Chiral HPLC. [Daicel Chiralpak AS-H column, λ = 254 nm, 2-propanol : *n*-hexane = 1: 9, flow rate = 0.8 mL min^{-1}]: t_R = 10.84 min (major), t_R = 13.60 min (minor).

***syn*-Aldol 2h**[12d]. 97% ee; $[\alpha]_D^{20}$ = −76.0 (c = 0.5, $CHCl_3$); IR (KBr, cm^{-1}): 3537, 3470, 2928, 2875, 1711, 1459, 1115, 996, 823, 664; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.22 (m, 4H), 5.35 (t, J = 5.4, 2.7 Hz, 1H), 3.06 (d, J = 3.3 Hz, 1H), 2.59–2.31 (m, 3H), 2.12–2.06 (m, 1H), 1.88–1.82 (m, 1H), 1.74–1.45(m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.5, 140.0, 132.7, 128.3, 127.2, 70.1, 57.0, 42.6, 27.9, 26.0, 24.8. The ee value was determined by Chiral HPLC. [Daicel Chiralpak AD-H column, λ = 254 nm, 2-propanol : *n*-hexane = 1: 4, flow rate = 0.5 mL min^{-1}]: t_R = 11.89 min (minor), t_R = 13.06 min (major).

***syn*-Aldol 2i**[12e]. 91% ee; $[\alpha]_D^{20}$ = −76.7 (c = 0.5, $CHCl_3$); IR (KBr, cm^{-1}): 3484, 2941, 2848, 1697, 1498, 1062, 982, 823; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.26 (m, 3H), 5.28 (dd, J = 8.1, 3.9 Hz, 1H), 4.04 (d, J = 4.2 Hz, 1H), 2.64–2.60 (m, 1H), 2.49–2.12 (m, 2H), 2.10–2.07 (m, 1H), 1.85–1.81 (m, 1H), 1.71–1.55 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.1, 137.8, 133.8, 133.5, 129.3, 128.9, 127.6, 70.1, 57.5, 42.7, 30.4, 27.8, 24.9. The ee value was determined by Chiral HPLC. [Daicel Chiralpak AD-H column, λ = 254 nm, 2-propanol : *n*-hexane = 1: 9, flow rate = 1.0 mL min^{-1}]: t_R = 8.18 min (minor), t_R = 9.33 min (major).

***syn*-Aldol 2j.** 93% ee; $[\alpha]_D^{20}$ = −81.2 (c = 0.5, $CHCl_3$); IR (KBr, cm^{-1}): 3497, 2954, 2862, 1711, 1128, 995, 823; ^{1}H NMR (300 MHz, $CDCl_3$) 7.83–7.80 (m, 4H), 7.50–7.43 (m, 2H), 7.38–7.34 (m, 1H), 5.57 (s, 1H), 3.16 (d, J = 3.3 Hz, 1H), 2.73–2.68 (m, 1H), 2.51–2.34 (m, 2H), 2.11–2.06 (m, 1H), 1.84–1.62 (m, 4H), 1.54–1.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.9, 138.9, 133.3, 132.5, 128.0, 127.8, 127.6, 126.1, 125.7, 124.5, 123.9, 70.7, 57.1, 42.7, 28.0, 26.1, 24.9. HRMS for $C_{17}H_{18}O_2$: Calcd. 254.1307; Found: 254.1310. The ee value was determined by Chiral HPLC. [Daicel Chiralpak AD-H column, λ = 254 nm, 2-propanol : *n*-hexane = 1: 9, flow rate = 1.0 mL min^{-1}]: t_R = 10.97 min (minor), t_R = 11.80 min (major).

***syn*-Aldol 2k.** 95% ee; $[\alpha]_D^{20}$ = −134.4 (c = 0.5, $CHCl_3$); IR (KBr, cm^{-1}): 3507, 2937, 2857, 1690, 1617, 1503, 1036, 822, 518. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J = 8.4 Hz, 1H), 6.51–6.42 (m, 2H), 5.54 (t, J = 3.0 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.06 (d, J = 3.3 Hz, 1H), 2.74–2.68 (m, 1H), 2.41–2.35 (m, 2H), 2.09–2.04 (m, 1H), 1.86–1.52 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.5, 159.8, 156.4, 128.0, 122.0, 103.8, 98.2, 65.9, 55.3, 55.2, 54.6, 42.7, 28.1, 26.5, 24.9; HRMS for $C_{15}H_{20}O_4Na$: Calcd. 287.1159; Found: 287.1256 [M + Na]. The ee value was determined by Chiral HPLC. [Daicel Chiralpak AD-H column, λ = 254 nm, 2-propanol : *n*-hexane = 1 : 4, flow rate = 0.5 mL min^{-1}]: t_R = 17.54 min (minor), t_R = 19.01 min (major).

***syn*-Aldol 2l.** 89% ee; $[\alpha]_D^{20}$ = −73.8 (c = 0.5, $CHCl_3$); IR (KBr, cm^{-1}): 3441, 2941, 2880, 1697, 1486, 1231, 933, 809; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (s, 1H), 6.75 (d, J = 2.1 Hz, 2H), 5.93 (s, 2H), 5.28 (s, 1H), 3.00 (d, J = 2.7 Hz, 1H), 2.56–2.30 (m, 3H), 2.10–2.05 (m, 1H), 1.88–1.61 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.8, 147.6, 146.4, 135.5, 118.8, 108.0, 106.6, 100.9, 70.5, 57.3, 42.7, 28.0, 26.2, 24.9. HRMS for $C_{14}H_{16}O_4Na$: Calcd. 271.0946; Found: 271.0959 [M + Na]. The ee value was determined by Chiral

HPLC. [Daicel Chiralpak AS-H column, $\lambda = 254$ nm, 2-propanol : n-hexane = 1: 4, flow rate = 0.5 mL min^{-1}]: t_R = 26.35 min (minor), t_R = 28.63 min (major).

***syn*-Aldol 2m[13].** 98% ee; $[\alpha]_D^{20}$ = −58.2 (c = 0.5, $CHCl_3$); IR (KBr, cm^{-1}): 3444, 2922, 2862, 1693, 1093, 986, 844, 689. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61–7.56 (m, 4H), 7.46–7.33 (m, 5H), 5.43 (t, J = 2.7 Hz, 1H), 3.03 (d, J = 2.7 Hz, 1H), 2.64–2.2.62 (m, 1H), 2.47–2.38 (m, 2H), 2.09–2.08 (m, 1H), 1.85–1.67 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.7, 140.9, 140.6, 139.9, 128.7, 127.2, 127.0, 126.9, 126.2, 70.5, 57.2, 42.7, 27.9, 26.1, 24.9. HRMS for $C_{19}H_{20}O_2$: Calcd. 280.1463; Found: 280.1468. The ee value was determined by Chiral HPLC. [Daicel Chiralpak OD-H column, $\lambda = 254$ nm, 2-propanol : n-hexane = 1 : 4, flow rate = 1.0 mL min^{-1}]: t_R = 7.81 min (minor), t_R = 8.65 min (major).

***syn*-Aldol 2n.** IR (KBr, cm^{-1}): 3475, 2956, 2858, 1696, 1447, 1111, 932,552;^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.15 (m, 4H), 5.68 (t, J = 3.0 Hz, 1H), 4.46 (d, J = 3.9 Hz, 1H), 3.81–3.76 (m, 4H), 3.05–2.98 (m, 2H), 2.85–2.76 (m, 3H), 2.51–2.45 (m, 1H), 2.37–2.33 (m, 1H), 2.04–2.03 (m, 1H), 1.90–1.68 (m, 4H), 1.53–1.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.8, 149.6, 137.5, 127.9, 127.7, 125.6, 122.0, 68.4, 67.5, 56.3, 53.6, 42.5, 27.6, 26.4, 24.8. HRMS for $C_{17}H_{23}NO_3$: Calcd. 289.1678; Found: 289.1682. After reactions, the product was isolated as a mixture of diastereoisomers ($syn/anti$ = 50 : 50), 77% ee for *syn* and 80% ee for *anti*; the ee value was determined by Chiral HPLC. [Daicel Chiralpak AD-H column, λ = 254 nm, 2-propanol : n-hexane = 1: 9, flow rate = 1.0 mL min^{-1}]: t_R = 16.86 min (major), t_R = 19.76 min (minor) for *syn* diastereoisomers; t_R = 27.45 min (major), t_R = 31.94 min (minor) for *anti* diastereoisomers.

***syn*-Aldol 2o[14].** 98% ee; $[\alpha]_D^{20}$ = −27.1 (c = 0.5, $CHCl_3$); IR (KBr, cm^{-1}): 3458, 2936, 2858, 1693, 1118, 969, 743, 696; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.23 (m, 5H), 6.63 (dd, J = 16.0, 0.6 Hz, 1H), 6.19 (dd, J = 15.9, 6.0 Hz, 1H), 4.76 (dd, J = 3.0, 1.5 Hz, 1H), 2.97 (d, J = 4.8 Hz, 1H), 2.56–2.43 (m, 3H), 2.13–2.07 (m, 2H), 1.94–.92 (m, 1H), 1.69–1.63 (m, 3H), 1.38–1.58 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.3, 136.8, 130.9, 129.0, 128.6, 127.6, 126.4, 70.6, 55.6, 42.6, 27.6, 27.4, 24.9. The ee value was determined by Chiral HPLC. [Daicel Chiralpak OJ-H column, λ = 254 nm, 2-propanol : n-hexane = 1: 9, flow rate = 0.8 mL min^{-1}]: t_R = 16.77 min (major), t_R = 20.28 min (minor).

***syn*-Aldol 2p[15].** IR (KBr, cm^{-1}): 3497, 2884, 1716, 1522, 1716, 1522, 1091, 707. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.7 Hz, 2H), 5.52 (s, 1H), 4.25–4.19 (m, 1H), 3.88–3.66 (m, 3H), 2.98 (d, J = 3.9 Hz, 1H), 2.95–2.88 (m, 1H), 2.76–2.65 (m, 1H), 2.48–2.43 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 148.0, 126.3, 123.7, 68.8, 68.3, 67.5, 57.2, 43.1. HRMS for $C_{12}H_{13}NO_5$: Calcd. 251.0794; Found: 251.0790. After the reaction, the product was isolated as a mixture of diastereoisomers ($syn/anti$ = 87 : 13). 89% ee for *syn* isomer; the ee value was determined by Chiral HPLC. [Daicel Chiralpak AD-H column, λ = 254 nm, 2-propanol : n-hexane = 1: 4, flow rate = 1.0 mL min^{-1}]: t_R = 13.39 min (minor), t_R = 15.11 min (major).

***syn*-Aldol 2q[15].** IR (KBr, cm^{-1}): 3404, 2875, 1689, 1131, 1003, 734, 703. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 5.51(1H, s), 3.10–2.81(m, 5H), 2.81–2.77(m, 2H), 2.53–2.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 210.9, 148.1, 147.3, 126.7, 123.7, 70.2, 59.2, 45.0, 30.8, 29.5. After the reaction, the product was isolated as a mixture of diastereoisomers ($syn/anti$ = 58 : 42). 99% ee for *syn* isomer; the ee for the *anti* isomer was not determined. The ee value was determined by Chiral HPLC. [Daicel Chiralpak AD-H column, $\lambda = 254$ nm, 2-propanol : n-hexane = 1 : 4, flow rate = 1.0 mL min^{-1}]: t_R = 15.13 min (major), t_R = 25.26 min (minor).

***syn*-Aldol 2r.** IR (KBr, cm^{-1}): 3408, 2959, 2869, 1693, 1222, 1134, 996, 734, 696. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H), 5.44 (s, 1H), 3.95–3.84 (m, 4H), 2.97–2.71 (m, 2H), 2.48–2.42 (m, 1H), 2.12–1.97 (m, 3H), 1.71–1.65(m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.7, 141.1, 128.3, 127.0, 125.6, 107.6, 70.1, 64.7, 64.5, 53.2, 38.6, 34.4, 32.9. HRMS for $C_{15}H_{18}O_4$: Calcd. 262.1205; Found: 262.1208. After the reaction, the product was isolated as a mixture of diastereoisomers ($syn/anti$ = 93 : 7). 89% ee for *syn* isomer; the ee value was determined by Chiral HPLC. [Daicel Chiralpak AD-H column, λ = 254 nm, 2-propanol : n-hexane = 1 : 4, flow rate = 1.0 mL min^{-1}]: t_R = 13.02 min (minor), t_R = 14.53 min (major).

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