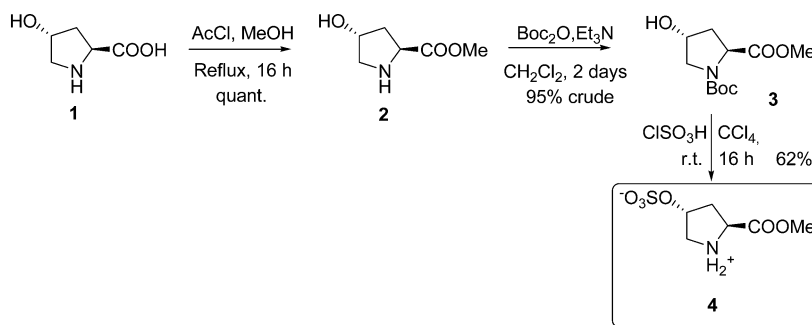
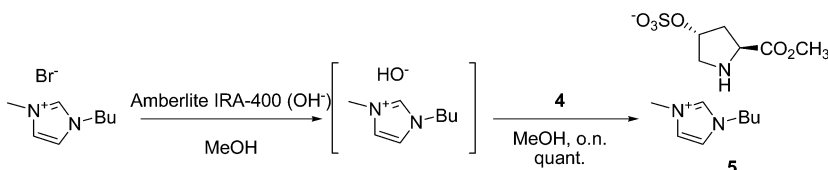


Scheme 1. Synthesis of the Anion



Scheme 2. Preparation of the Catalyst



time was required (Table 1). TLC analysis revealed that some reactions were still incomplete after 5 days.

Table 1. Solvent Screening^a

| entry | solvent | yield (%) | dr (anti/syn) ^b | ee (anti) ^c (%) |
|-------|------------------------|----------------------|----------------------------|----------------------------|
| 1 | [Bmim]BF ₄ | 37 (82) ^d | 66:34 (71:29) ^d | 46 (55) ^d |
| 2 | [Bmim]PF ₆ | 51 (82) ^d | 76:24 (73:27) ^d | 60 (52) ^d |
| 3 | [Bmim]NTf ₂ | 53 (89) ^d | 76:24 (75:25) ^d | 57 (55) ^d |
| 4 | MeOH | 53 (73) ^d | 62:38 (68:32) ^d | 22 (30) ^d |
| 5 | DCM | 41 (66) ^d | 75:25 (76:24) ^d | 40 (30) ^d |
| 6 | DMSO | 22 (73) ^d | 72:28 (64:36) ^d | 34 (40) ^d |
| 7 | DMF | 20 (16) ^d | 71:29 (73:27) ^d | 79 (75) ^d |
| 8 | neat | 82 (98) ^d | 59:41 (58:42) ^d | 44 (60) ^d |

^aConditions: A solution of cyclohexanone (0.3 mmol) and catalyst (30 mol %) in solvent (0.3 mL) was stirred for 30 min at 4 °C. *p*-Nitrobenzaldehyde (0.1 mmol) was added, and the mixture was stirred for 72 h at 4 °C. ^bDetermined by ¹H NMR. ^cDetermined by chiral HPLC. ^dResults in parentheses were obtained when acetic acid was used as an additive; reaction time was 48 h.

ILs led to better enantioselectivities than common organic solvents. As it was previously demonstrated that the formation of the enamine intermediate should be enhanced by a catalytic source of acid, a solvent screening study was performed using acetic acid (30 mol %) as an additive. As shown in Table 1, the overall trend for the addition of acid was to reduce the reaction time, though selectivity was unchanged. Increasing solvent polarity had little effect on diastereoselectivity, but generally offered a slight improvement of ee. Performing the reaction in neat conditions predictably afforded excellent yields, but poor selectivity. Within this series, the ionic liquids ([Bmim]BF₄, [Bmim]PF₆, and [Bmim]NTf₂), offered the best combination of good yields and selectivities. Best results were achieved in [Bmim]PF₆, and [Bmim]NTf₂, but since PF₆-derived ILs are known to release HF,²² we further explored the [Bmim]NTf₂ system by improving the reaction conditions and recyclability.

With the goal of optimizing the reaction conditions, various acidic additives were tested for the aldol reaction (Table 2).

Table 2. Influence of Acidic Additives

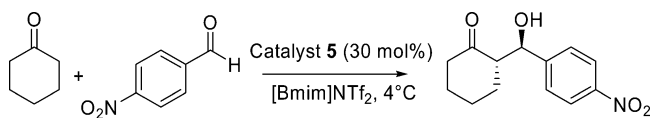
| entry | additive | yield (%) | dr (anti/syn) ^a | ee (anti) ^b (%) |
|-------|---------------|-----------|----------------------------|----------------------------|
| 1 | none | 43 | 76:24 | 57 |
| 2 | <i>p</i> -TSA | 6 | 57:43 | rac |
| 3 | TFA | 11 | 75:25 | rac |
| 4 | 3,5-DNBA | 63 | 74:26 | 47 |
| 5 | benzoic acid | 64 | 71:29 | 41 |
| 6 | acetic acid | 72 | 75:25 | 52 |

^aDetermined by ¹H NMR. ^bDetermined by chiral HPLC.

With the exception of acetic acid, the decrease of selectivity in spite of a shorter reaction time suggests a kinetic control of the reaction, where the formation of the racemate is favored, instead of one particular enantiomer. Another indication of kinetic control was the lower selectivity observed when performing the reaction at room temperature. Strong inhibition of the aldol reaction was observed in the presence of TFA and *p*-TSA: these acids are strong enough to protonate the counteranion of the catalyst (*p*K_a of 0.3 and −2.8, respectively), leading to anion metathesis and destruction of the catalyst, explaining the poor yields, and selectivities.

A variation of the medium concentration was also tested using [Bmim]NTf₂ as solvent with catalyst 5. As a general trend, it was observed that increasing the concentration of the reaction medium reduced the reaction time was, and led to better selectivities (Table 3). In an attempt to further decrease the reaction time, the reaction was carried out at the highest concentration tested, using acetic acid as additive, and we were surprised to observe that enantioselectivity plummeted.

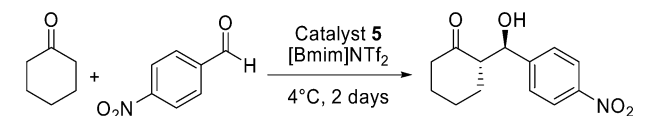
Based on reaction results in neat conditions, we observed that adding 10 equiv of cyclohexanone instead of 3 allowed the reaction to be completed in 2 days, with higher dr (86:14) and

Table 3. Concentration Studies^a


| entry | [aldehyde] (mol·L ⁻¹) | dr (anti/syn) ^b | ee (anti) ^c (%) |
|----------------|-----------------------------------|----------------------------|----------------------------|
| 1 | 0.33 | 76:24 | 57 |
| 2 | 0.40 | 75:25 | 65 |
| 3 | 0.50 | 76:24 | 71 |
| 4 | 0.66 | 81:19 | 69 |
| 5 | 1 | 89:11 | 73 |
| 6 ^d | 1 | 71:29 | 29 |
| 7 ^e | 1 | 86:14 | 86 |

^aAll reactions were arbitrarily stopped after 16 h. ^bDetermined by ¹H NMR. ^cDetermined by chiral HPLC. ^dReaction was carried out using acetic acid as a additive (30 mol %). ^e10 equiv of cyclohexanone; reaction time was 2 days

ee (86%) (entry 7). Using these optimized conditions, a lower catalyst loading only resulted in a longer reaction time and lower selectivities (Table 4).

Table 4. Influence of Catalyst Loading


| entry | catalyst loading (%) | yield (%) | dr (anti/syn) ^a | ee (anti) ^b (%) |
|-------|----------------------|-----------|----------------------------|----------------------------|
| 1 | 30 | 83 | 86:14 | 86 |
| 2 | 20 | 35 | 83:17 | 81 |
| 3 | 10 | 17 | 73:27 | 75 |

^aDetermined by ¹H NMR. ^bDetermined by chiral HPLC.

To broaden the scope of our catalyst **5**, we performed the asymmetric aldol reaction for different cyclic ketones under the optimized conditions, using *o*-, *m*-, or *p*-nitrobenzaldehydes. As shown in Table 5 (entries 1–6), apart from cycloheptanone, the reaction proceeded with good yields and generally good ee. However, when performing the aldol reaction with other aldehydes, no aldol product was observed, probably due to both the lower reactivity of these aldehydes and the steric hindrance induced by the methyl group of the catalyst.

Based on these observations, we designed another catalyst anion bearing a hydrogen bond donor functional group. Zwitterion **6** was obtained by dissolving **4** in concentrated NH₄OH, and catalyst **7** was prepared using the same conditions used for catalyst **5** (Scheme 3). We expected this new catalyst **7** to be more efficient toward less reactive aldehydes through activation by hydrogen bonding with these aldehydes and to have the properties required to participate and control the stereoselectivity of the reaction.

Carrying out the aldol reaction with less activated aldehydes and catalyst **7** gave access to aldol products that catalyst **5** could not produce, with good to excellent yields, as well as excellent selectivities (Table 5, entries 7–13). Less reactive aldehydes, such as 2-naphthaldehyde or 2-thiophenecarboxaldehyde gave only low to moderate yields, even after longer reaction times, but still led to the aldol product with excellent diastereo- and enantioselectivities. These results highlighted the assistance of the amide group in the reaction, by activating the aldehydes through hydrogen bonding. Nonetheless, when catalyst **7** was

used in our model reaction of cyclohexanone with *p*-nitrobenzaldehyde, a qualitatively faster reaction was observed, but with a lower selectivity. Catalyst **5** gave a complex mixture of regioisomers when using linear ketones, but using catalyst **7** with 2-butanone as substrate, only one regioisomer was obtained in good yields and selectivities (entry 14).

In terms of mechanism, our first hypothesis was that the steric hindrance of the methyl group of the ester moiety on the anion was the main source of the selectivity of the reaction when using catalyst **5** (Figure 1 (1)). The methyl group should be bulky enough to hinder the approach of aldehyde to the enamine intermediate, and favor the approach by the opposite face. However, catalyst **7**, able to form H-bonds with the aldehyde (Figure 1 (2)) and direct its approach, led to the same major enantiomer and a 3-fold shorter reaction time (16 h instead of 48 h). The amide group, by hydrogen bonding, may be responsible for directing the approach of the aldehyde toward the enamine while activating the aldehyde. It is reasonable to propose a similar transition state using catalyst **5**, but steric hindrance of the ester moiety may be the source of the lower reactivity. None of our experiments confirmed the implication of the imidazolium cation in the transition state, as proposed previously.²¹

As the major obtained stereoisomers are the same using either the ester or the amide catalyst, discrimination between the two faces of the reaction intermediate when approaching the aldehyde could be attributed to the position of the imidazolium cation close to the sulfonate group (Figure 1 (3)). The imidazolium cation, being localized near the negative charge on the proline derivative, may block the approach of the aldehyde on this side and allow the formation of the *anti* diastereomer.

Molecular modeling was performed to confirm the proposed transition states and, as shown in Figure 2(2), the resulting models support the experimental results. The imidazolium cation is close to the negative charge of the sulfate group (1), which sterically hinders the approach of the aldehyde (2) on this side.

The possibility to recycle the catalyst and the ionic liquid was also proven for cyclohexanone and *p*-nitrobenzaldehyde reaction (Table 6). Up to five catalytic runs were achieved, with only a small decrease in the catalytic efficiency of our system.

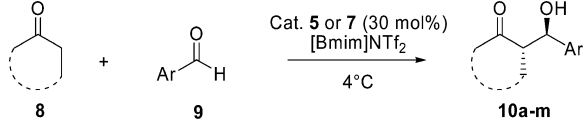
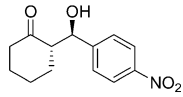
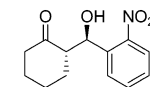
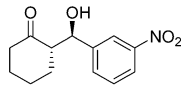
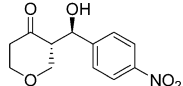
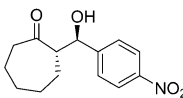
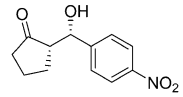
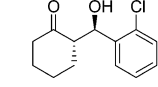
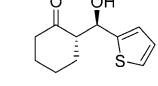
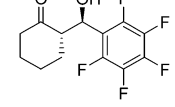
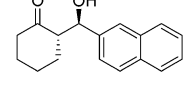
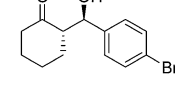
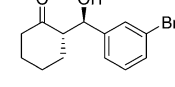
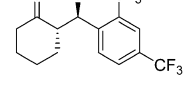
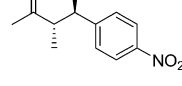
CONCLUSION

In conclusion, we report the supramolecular assistance of an imidazolium-based chiral catalyst in asymmetric organic synthesis. The mechanistic insights of the asymmetric aldol reaction allow us to propose that the same proline-based catalyst can be used in other reactions involving enamine intermediates, such as the Michael addition. Up to five catalytic cycles were performed using the same conditions, illustrating the recyclability of this setup. The ease of switching the anion encouraged us to develop a new recycling method, as well as the design of other catalytic anions are currently underway in our group.

EXPERIMENTAL SECTION

Materials. All organic compounds were obtained commercially and used without further purification. ¹H and ¹³C NMR spectra were recorded on 400, 300, 100, and 75 MHz spectrometers, respectively, in the indicated solvent. Chemical shifts are reported in ppm with internal reference to TMS, and *J* values are given in Hertz. All HPLC

Table 5. Substrate Scope

| | |  | | | | | |
|-------|----|---|----------|--------|-------|-----------------------------------|-------------------------------|
| Entry | | Product | Catalyst | Time | Yield | <i>dr</i> (anti:syn) ^a | <i>ee</i> (anti) ^b |
| 10a | 1 |  | 5 | 2 days | 83% | 84:16 | 4%/86% (syn/anti) |
| | | | 7 | 16h | 82% | 75:25 | 76% |
| 10b | 2 |  | 5 | 2 days | 82% | 97:3 | 69% |
| 10c | 3 |  | 5 | 2 days | 77% | 85:15 | 67% |
| 10d | 4 |  | 5 | 2 days | 99% | 83:17 | 56% |
| 10e | 5 |  | 5 | 5 days | 33% | 66:34 | 16% |
| 10f | 6 |  | 5 | 2 days | 71% | 37:63 | 16% |
| 10g | 7 |  | 7 | 2 days | 93% | >99:1 | 89% |
| 10h | 8 |  | 7 | 5 days | 11% | 95:5 | 85% |
| 10i | 9 |  | 7 | 2 days | 92% | >99:1 | 88% |
| 10j | 10 |  | 7 | 4 days | 38% | 84:16 | 77% |
| 10k | 11 |  | 7 | 2 days | 49% | 98:2 | 83% |
| 10l | 12 |  | 7 | 2 days | 70% | 78:22 | 75% |
| 10m | 13 |  | 7 | 2 days | 80% | >99:1 | 88% |
| 10n | 14 |  | 7 | 2 days | 58% | 62:38 | 76% |

^aDetermined by ¹H NMR. ^bDetermined by chiral HPLC.

Scheme 3. Preparation of Catalyst 7

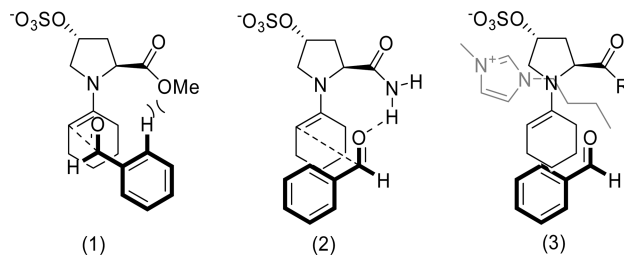
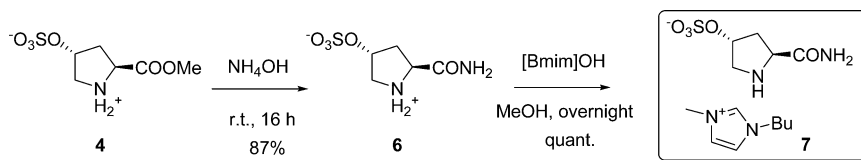


Figure 1. Proposed transition states.

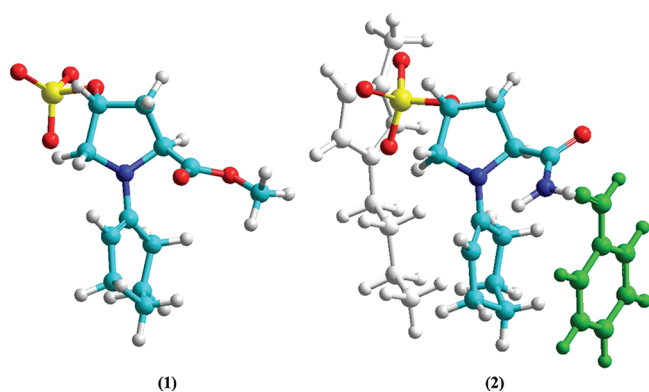


Figure 2. Theoretical calculation of the enamine intermediate obtained with MOPAC, PM6 method. Carbon atoms are represented in blue, oxygen in red, and sulfur in yellow. The aldehyde is represented in green and the imidazolium cation in gray.

Table 6. Recycling Studies

| catalytic run | reaction time (days) | conversion ^a (%) |
|---------------|----------------------|-----------------------------|
| 1 | 2 | 97 |
| 2 | 2.5 | 91 |
| 3 | 3 | 87 |
| 4 | 3 | 99 |
| 5 | 4 | 85 |

^aDetermined by chiral HPLC.

analysis were done using Chiralpak AD or OD columns and absolute configurations of the aldols products were based on previously reported literature.^{23–25} Ionic liquids used as solvents were prepared as already described.²⁶

Molecular Modeling. In order to assess the energy content for various molecules designed, semiempirical quantum calculations were undertaken using the PM6 method in gas phase or in aqueous solution (MOPAC2009TM; Stewart Computational Chemistry). All structures were optimized to a gradient inferior to 0.1 using the eigenvector following method.

(2S,4R)-Methyl-4-hydroxypyrrolidine-2-carboxylate Hydrochloride (2). *trans*-4-Hydroxy-L-proline (5.0 g) was suspended in methanol (40 mL) and cooled to 0 °C. Acetyl chloride (4.08 mL, 1.5 equiv) was slowly added, and the reaction was stirred at reflux for 16 h. The reaction mixture was then cooled to room temperature. Ether was added and the reaction medium filtered to afford compound 2 (6.92 g, quant) as white crystals. ¹H NMR (D₂O, 400 MHz): δ = 4.53–4.66

(m, 2H), 3.76 (s, 3H), 3.28–3.52 (m, 2H), 2.41 (dd, *J* = 14.1, 7.7 Hz, 1H), 2.12–2.29 (m, 1H). ¹³C NMR (D₂O, 100 MHz): δ = 171, 70.2, 58.9, 54.6, 54.2, 37.4. HRMS (ESI): calcd for C₆H₁₂NO₃ 146.08117, found 146.08111. Mp: 161.8–162.2 °C.

(2S,4R)-1-*tert*-Butyl-2-methyl-4-hydroxypyrrolidine-1,2-dicarboxylate (3). Compound 2 (4 g) was suspended in methylene chloride and cooled to 0 °C. Triethylamine (9.21 mL, 3 equiv) and di-*tert*-butyl dicarbonate (5.29 g, 1.1 equiv) were added, and the mixture was stirred at room temperature for 2 days. The solution was first washed with an aqueous solution of 1 N HCl, washed with a saturated aqueous solution of NaHCO₃, and finally washed with brine. The organic phase was dried on magnesium sulfate, filtered, and concentrated under vacuum to give the crude product 3 as a pale yellow oil (5.13 g, 95% crude). ¹H NMR (CDCl₃, 400 MHz): δ = 4.49 (bs, 1H), 4.40 (t, *J* = 8 Hz, 1H), 3.74 (s, 3H), 3.44–3.65 (m, 2H), 2.22–2.35 (m, 1H), 3.03–2.12 (m, 1H). HRMS (ESI): calcd for C₁₁H₁₉NO₅Na 268.11554, found 268.11652.

(3R,5S)-5-(Methoxycarbonyl)pyrrolidin-3-yl Hydrogen Sulfate (4). Under inert atmosphere, crude 3 (4.835 g) was solubilized in 40 mL of carbon tetrachloride and then cooled to 0 °C. Chlorosulfonic acid (1.57 mL, 1.2 equiv) was added dropwise to the reaction mixture under strong stirring. The reaction medium was then stirred vigorously at room temperature overnight. The solvent was removed under vacuum, the residue was triturated in methanol and then filtered to give 4 as a white powder (2.73 g, 62%). ¹H NMR (D₂O, 400 MHz): δ = 5.12 (s, 1H), 4.65 (dd, *J* = 10.6, 7.9 Hz, 1H), 3.77 (s, 3H), 3.68 (s, 1H), 3.55–3.62 (m, 1H), 2.69–2.79 (m, 1H), 2.37 (s, 1H). ¹³C NMR (D₂O, 100 MHz): δ = 170.4, 77.83, 58.93, 54.68, 52.44, 35.64. HRMS (ESI): calcd for C₆H₁₂NO₆S 226.03798, found 226.03795.

(3R,5S)-5-Carbamoylpyrrolidin-3-yl Hydrogen Sulfate 6. Compound 4 (1 g, 4.44 mmol) was dissolved in concentrated ammonium hydroxide (10 mL), and the reaction medium was stirred overnight at room temperature. The solvent was evaporated under vacuum and the residue was suspended and triturated in methanol. Filtration of the mixture afforded compound 6 as a white powder (809.2 mg, 87%). ¹H NMR (D₂O, 400 MHz): δ = 5.12 (t, *J* = 4.2 Hz, 1H), 4.45 (dd, *J* = 10.4, 7.7 Hz, 1H), 3.45–3.66 (m, 2H), 2.74 (dd, *J* = 14.5, 7.7 Hz, 1H), 2.17–2.29 (m, 1H). ¹³C NMR (D₂O, 100 MHz): δ = 172.8, 79.1, 59.2, 52.6, 37.1. HRMS (ESI): calcd for C₅H₁₁N₂O₅S 211.03832, found 211.03886.

General Procedure for the Synthesis of the Imidazolium Catalysts. 1-Butyl-3-methylimidazolium bromide (450 mg) was dissolved in 24 mL of methanol and passed through a glass column containing 12 g of activated Amberlite IRA400 hydroxide form resin. The column was then washed twice with 15 mL of methanol. The collected fractions were assembled in a 100 mL round-bottom flask, and zwitterion 4 or 6 was added (1.15 equiv). The mixture was allowed to stir at room temperature overnight. The solvent volume was reduced under vacuum, cooled down to 0 °C for 3 h, and filtered through a Celite pad to remove excess zwitterion. The filtrate was evaporated under vacuum and dried under vacuum overnight to afford catalyst 5 or 7 as a viscous pale yellow oil (quant.).

1-Butyl-3-methylimidazolium (3R,5S)-5-(Methoxycarbonyl)pyrrolidin-3-yl Sulfate (5). ¹H NMR (D₂O, 400 MHz): δ = 8.60 (s, 1H), 7.37 (s, 1H), 7.32 (s, 1H), 4.87–4.97 (m, 1H), 4.09 (t, *J* = 7.1 Hz, 2H), 4.02 (t, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 3.00–3.20 (m, 2H), 2.33–2.48 (m, 1H), 2.03–2.18 (m, 1H), 1.64–1.81 (m, 2H), 1.21 (d, *J* = 7.7 Hz, 2H), 0.82 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (D₂O, 100 MHz): δ = 175, 135.4, 123, 121.7, 79.6, 57.5, 52.4, 51.5, 48.8, 35.8, 35.1, 30.8, 18.3, 12.1. HRMS (+ESI): calcd for C₈H₁₅N₂ 139.12297, found 139.12347; (–ESI) calcd for C₆H₁₀NO₆S 224.02343, found 224.02324.

1-Butyl-3-methylimidazolium (3*R*,5*S*)-5-Carbamoylpyrrolidin-3-yl Sulfate (7). ¹H NMR (D₂O, 400 MHz): δ = 8.63 (s, 1H), 7.38–7.43 (m, 1H), 7.36 (t, *J* = 1.7 Hz, 1H), 4.92–4.97 (m, 1H), 4.12 (t, *J* = 7.1 Hz, 2H), 3.94 (t, *J* = 8.4 Hz, 1H), 3.82 (s, 3H), 3.05–3.22 (m, 2H), 2.44 (dd, *J* = 14.5, 7.9 Hz, 1H), 2.00 (ddd, *J* = 14.3, 9.1, 5.3 Hz, 1H), 1.72–1.83 (m, 2H), 1.19–1.31 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (D₂O, 100 MHz): δ = 179.3, 136.40, 124.2, 123.0, 81.6, 59.4, 53.1, 50.0, 37.9, 36.4, 32.0, 19.5, 13.4. HRMS (+ESI): calcd for C₈H₁₅N₂ 139.12297, found 139.12323; (–ESI) calcd for C₅H₉N₂O₃S 209.02377, found 209.02279.

(*S*)-2-((*R*)-Hydroxy(4-nitrophenyl)methyl)cyclohexanone (10a): General Representative Procedure for the Asymmetric Aldol Reaction. Cyclohexanone (103.5 μ L, 10 equiv) was introduced in a vial containing the catalyst (10.9 mg, 30% mol) in [Bmim]NTf₂ (0.1 mL), and the mixture was stirred 30 min at 4 °C before *p*-nitrobenzaldehyde (15.12 mg, 1 equiv) was added to the reaction medium. The mixture was vigorously stirred at 4 °C until completion (monitored by TLC). The mixture was then directly purified by flash chromatography (hexanes/ethyl acetate: 9/1 then 65/35) to give the product as a white solid (20.69 mg, 83%, mp: 98–99 °C). Diastereomeric ratio (89:11) was determined by ¹H NMR spectroscopy and enantiomeric excess (syn/anti: 4%/86%) was determined by chiral HPLC (Chiralpak AD column, hexanes/2-propanol 90/10, flow rate: 1.0 mL·min^{–1}, λ = 254 nm). *t*_R (syn isomer) = 18.07 (minor), 22.24 (major); *t*_R (anti isomer) = 24.48 (minor), 32.45 min (major). ¹H NMR (CDCl₃, 400 MHz): δ = 8.19–8.27 (m, 2H), 7.47–7.58 (m, 2H), 4.92 (d, *J* = 8.4 Hz, 1H), 2.57–2.66 (m, 1H), 2.48–2.57 (m, 1H), 2.33–2.44 (m, 1H), 2.09–2.18 (m, 1H), 1.81–1.92 (m, 1H), 1.66–1.79 (m, 1H), 1.51–1.66 (m, 2H), 1.36–1.47 (m, 1H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 90/10, flow rate = 1.0 mL·min^{–1}, λ = 254 nm) *t*_R (anti isomer) = 22.01 (minor), 29.76 (major), *t*_R (syn isomer) = 16.08 (minor), 19.75 min (major). HRMS (ESI): calcd for C₁₃H₁₅NO₄Na 272.08933, found 272.08959.

(*S*)-2-((*R*)-Hydroxy(2-nitrophenyl)methyl)cyclohexanone (10b). White solid. Yield: 20.4 mg, 82%. Mp: 116–118 °C. dr (anti/syn): 97:3, ee (anti/syn): 69%/–. ¹H NMR (CDCl₃, 400 MHz): δ = 7.87 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.79 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.62–7.71 (m, 1H), 7.40–7.51 (m, 1H), 5.47 (d, *J* = 7.0 Hz, 1H), 2.72–2.84 (m, 1H), 2.43–2.53 (m, 1H), 2.30–2.42 (m, 1H), 2.07–2.20 (m, 1H), 1.83–1.94 (m, 1H), 1.48–1.83 (m, 4H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 85/15, flow rate = 0.5 mL·min^{–1}, λ = 254 nm) *t*_R (anti isomer) = 26.38 (minor), 24.52 min (major). HRMS (ESI): calcd for C₁₃H₁₅NO₄Na 272.08933, found 272.08995.

(*S*)-2-((*R*)-Hydroxy(3-nitrophenyl)methyl)cyclohexanone (10c). Pale yellow solid. Yield: 18.9 mg, 77%. Mp: 69–71 °C. dr (anti/syn): 85:15, ee (anti/syn): 67%/15%. ¹H NMR (CDCl₃, 400 MHz): δ = 8.10–8.28 (m, 2H), 7.64–7.74 (m, 1H), 7.50–7.61 (m, 1H), 4.92 (d, *J* = 8.4 Hz, 1H), 2.60–2.71 (m, 1H), 2.48–2.56 (m, 1H), 2.33–2.47 (m, 1H), 2.08–2.19 (m, 1H), 1.81–1.93 (m, 1H), 1.52–1.79 (m, 3H), 1.34–1.48 (m, 1H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 92/8, flow rate = 1.0 mL·min^{–1}, λ = 254 nm) *t*_R (anti isomer) = 27.91 (minor), 21.90 (major), *t*_R (syn isomer) = 17.87 (minor), 19.70 min (major). HRMS (ESI): calcd for C₁₃H₁₅NO₄Na 272.08933, found 272.09007.

(*S*)-Tetrahydro-3-((*R*)-hydroxy(4-nitrophenyl)methyl)pyran-4-one (10d). Pale yellow oil. Yield: 24.9 mg, 99%. dr (anti/syn): 83:17, ee (anti/syn): 67%/15%. ¹H NMR (CDCl₃, 400 MHz): δ = 8.19–8.29 (m, 2H), 7.48–7.59 (m, 2H), 5.01 (d, *J* = 8.1 Hz, 1H), 4.17–4.35 (m, 1H), 3.68–3.83 (m, 2H), 3.48 (dd, *J* = 11.3, 9.9 Hz, 1H), 2.87–3.00 (m, 1H), 2.65–2.80 (m, 1H), 2.44–2.61 (m, 1H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 90/10, flow rate = 1.0 mL·min^{–1}, λ = 254 nm) *t*_R (anti isomer) = 48.72 (minor), 57.36 (major), *t*_R (syn isomer) = 30.63 (minor), 37.60 min (major). HRMS (ESI): calcd for C₁₂H₁₃NO₃Na 274.06859, found 274.06922.

(*R*)-2-((*S*)-Hydroxy(4-nitrophenyl)methyl)cycloheptanone (10e). Colorless oil. Yield: 8.5 mg, 32%. dr (anti/syn): 66:34, ee (anti/syn): 16%/9%. ¹H NMR (CDCl₃, 400 MHz): δ = 8.24 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 5.32 (d, *J* = 2.0 Hz, 1H), 2.89 (dt, *J* = 10.5, 2.8 Hz, 1H), 2.41–2.75 (m, 2H), 1.18–2.00 (m, 8H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 80/20, flow rate = 0.5

mL·min^{–1}, λ = 254 nm) *t*_R (anti isomer) = 39.93 (minor), 19.80 (major), *t*_R (syn isomer) = 14.10 (minor), 16.57 min (major). HRMS (ESI): calcd for C₁₄H₁₇NO₄Na 286.10498, found 286.10443.

(*S*)-2-((*S*)-Hydroxy(4-nitrophenyl)methyl)cyclopentanone (10f). Yellow solid. Yield: 8.5 mg, 71%. Mp: 88–90 °C. dr (anti/syn): 37:63, ee (anti/syn): 16%/rac. ¹H NMR (CDCl₃, 400 MHz): δ = 8.18–8.28 (m, 2H), 7.49–7.61 (m, 2H), 5.44 (d, *J* = 2.9 Hz, 1H), 2.35–2.54 (m, 2H), 2.10–2.23 (m, 1H), 1.92–2.09 (m, 1H), 1.68–1.80 (m, 2H), 1.50–1.63 (m, 1H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 95/5, flow rate = 1.0 mL·min^{–1}, λ = 254 nm) *t*_R (anti isomer) = 42.35 (minor), 45.73 (major), *t*_R (syn isomer) = 33.70 (minor), 23.90 min (major). HRMS (ESI): calcd for C₁₂H₁₃NO₄Ag 341.989, found 341.98983.

(*S*)-2-((*R*)-2-Chlorophenyl(hydroxy)methyl)cyclohexanone (10g). Colorless oil. Yield: 22.1 mg, 93%. dr (anti/syn): >99:1, ee (anti/syn): 89%/–. ¹H NMR (CDCl₃, 400 MHz): δ = 7.54–7.60 (m, 1H), 7.30–7.39 (m, 2H), 7.19–7.27 (m, 1H), 5.37 (d, *J* = 8.2 Hz, 1H), 2.65–2.75 (m, 1H), 2.45–2.54 (m, 1H), 2.31–2.42 (m, 1H), 2.06–2.16 (m, 1H), 1.80–1.88 (m, 1H), 1.51–1.78 (m, 4H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 90/10, flow rate = 1.0 mL·min^{–1}, λ = 215 nm) *t*_R (anti isomer) = 11.92 (minor), 10.49 min (major). HRMS (ESI): calcd for C₁₃H₁₅ClO₂Na 261.06528, found 261.0649.

(*S*)-2-((*R*)-Hydroxy(thiophene-2-yl)methyl)cyclohexanone (10h). Pale yellow oil. Yield: 2.4 mg, 11%. dr (anti/syn): 95:5, ee (anti/syn): 85%/–. ¹H NMR (CDCl₃, 400 MHz): δ = 7.27–7.33 (m, 1H), 6.96–7.01 (m, 2H), 5.10 (d, *J* = 8.4 Hz, 1H), 2.64–2.73 (m, 1H), 2.47–2.55 (m, 1H), 2.33–2.44 (m, 1H), 2.09–2.18 (m, 1H), 1.56–1.89 (m, 4H), 1.37 (qd, *J* = 12.8, 3.7 Hz, 1H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 90/10, flow rate = 1.0 mL·min^{–1}, λ = 215 nm) *t*_R (anti isomer) = 15.18 (minor), 13.75 min (major). HRMS (ESI): calcd for C₁₁H₁₄O₂SNa 233.06067, found 233.06033.

(*S*)-2-((*R*)-Hydroxy(perfluorophenyl)methyl)cyclohexanone (10i). White solid. Yield: 27 mg, 92%. Mp: 85–87 °C. dr (anti/syn): >99:1, ee (anti/syn): 88%/–. ¹H NMR (CDCl₃, 400 MHz): δ = 5.34 (d, *J* = 9.7 Hz, 1H), 2.96–3.08 (m, 1H), 2.50–2.59 (m, 1H), 2.42 (td, *J* = 13.0, 6.2 Hz, 1H), 2.09–2.25 (m, 1H), 1.82–1.96 (m, 1H), 1.55–1.77 (m, 3H), 1.35 (qd, *J* = 12.6, 3.7 Hz, 1H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 90/10, flow rate = 0.5 mL·min^{–1}, λ = 215 nm) *t*_R (anti isomer) = 18.74 (minor), 14.86 min (major). HRMS (ESI): calcd for C₁₃H₁₁F₅O₂Na 317.05714, found 317.0561.

(*S*)-2-((*R*)-Hydroxy(naphthalen-3-yl)methyl)cyclohexanone (10j). Colorless oil. Yield: 9.6 mg, 38%. dr (anti/syn): 84:16, ee (anti/syn): 77%/17%. ¹H NMR (CDCl₃, 400 MHz): δ = 7.82–7.90 (m, 3H), 7.78 (s, 1H), 7.46–7.54 (m, 3H), 4.99 (d, *J* = 8.8 Hz, 1H), 2.75 (dd, *J* = 13.1, 7.9, 5.1 Hz, 1H), 2.50–2.57 (m, 1H), 2.35–2.47 (m, 1H), 2.06–2.16 (m, 1H), 1.49–1.84 (m, 4H), 1.32–1.43 (m, 1H). HPLC: (Chiralpak OD column, hexanes/2-propanol = 85/15, flow rate = 1.0 mL·min^{–1}, λ = 210 nm) *t*_R (anti isomer) = 15.18 (minor), 12.10 (major), *t*_R (syn isomer) = 6.67 (minor), 10.62 min (major). HRMS (ESI): calcd for C₁₇H₁₈O₂Na 277.1199, found 277.11917.

(*S*)-2-((*R*)-4-Bromophenyl(hydroxymethyl)cyclohexanone (10k). Colorless oil. Yield: 13.9 mg, 49%. dr (anti/syn): 98:2, ee (anti/syn): 83%/–. ¹H NMR (CDCl₃, 400 MHz): δ = 7.46–7.52 (m, 2H), 7.19–7.25 (m, 2H), 4.77 (d, *J* = 8.8 Hz, 1H), 2.54–2.63 (m, 1H), 2.47–2.54 (m, 1H), 2.32–2.43 (m, 1H), 2.07–2.16 (m, 1H), 1.78–1.87 (m, 1H), 1.50–1.75 (m, 3H), 1.27–1.38 (m, 1H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 90/10, flow rate = 0.8 mL·min^{–1}, λ = 215 nm) *t*_R (anti isomer) = 18.64 (minor), 22.70 min (major). HRMS (ESI): calcd for C₁₃H₁₃BrO₂Na 305.01476, found 305.01351.

(*S*)-2-((*R*)-3-Bromophenyl(hydroxymethyl)cyclohexanone (10l). Colorless oil. Yield: 19.8 mg, 70%. dr (anti/syn): 78:22, ee (anti/syn): 75%/13%. ¹H NMR (CDCl₃, 400 MHz): δ = 7.51 (d, *J* = 1.8 Hz, 1H), 7.44 (dt, *J* = 7.1, 1.9 Hz, 1H), 7.21–7.26 (m, 2H), 4.76 (d, *J* = 8.8 Hz, 1H), 2.55–2.64 (m, 1H), 2.47–2.54 (m, 1H), 2.32–2.44 (m, 1H), 2.08–2.16 (m, 1H), 1.79–1.88 (m, 1H), 1.51–1.77 (m, 4H), 1.29–1.39 (m, 1H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 98/2, flow rate = 0.5 mL·min^{–1}, λ = 215 nm) *t*_R (anti isomer) = 74.51 (minor), 69.73 (major), *t*_R (syn isomer) = 47.75 (minor), 39.50 min

(major). HRMS (ESI): calcd for $C_{13}H_{15}BrO_2Na$ 305.01476, found 305.01424.

(5*S*)-2-((*R*)-(2,4-Bis(trifluoromethyl)phenyl)(hydroxymethyl)-cyclohexanone (**10m**). Colorless oil. Yield: 27.1 mg, 80%. dr (*anti/syn*): >99:1. ee (*anti/syn*): 88%/. 1H NMR ($CDCl_3$, 400 MHz): δ = 7.85–7.95 (m, 3H), 5.32–5.39 (m, 1H), 2.70–2.81 (m, 1H), 2.50–2.59 (m, 1H), 2.34–2.46 (m, 1H), 2.08–2.19 (m, 1H), 1.82 (dd, J = 13.2, 1.3 Hz, 1H), 1.70 (qt, J = 13.0, 3.9 Hz, 1H), 1.50–1.63 (m, 1H), 1.36–1.48 (m, 2H). ^{13}C NMR (CD_3OD , 100 MHz): δ = 212.6, 146.6, 130.7, 130.3–130 (d, J = 24.7 Hz), 129.4 (d, J = 2.3 Hz), 128.9–128.6 (d, J = 23.2 Hz), 125.3–125.2 (d, J = 7.7 Hz), 122.6–122.5 (d, J = 6.1 Hz), 122.3, 67.4, 57.9, 42.6, 31.5, 28.7, 24.8. HPLC: (Chiralpak AD column, hexanes/2-propanol = 90/10, flow rate = 1.0 mL·min⁻¹, λ = 215 nm) t_R (*anti* isomer) = 6.92 (minor), 8.08 min (major). HRMS (ESI): calcd for $C_{15}H_{14}F_6O_2Na$ 363.07902, found 363.07848.

(3*S*,4*R*)-4-Hydroxy-3-methyl-4-(4-nitrophenyl)butan-2-one (**10n**). Colorless oil. Yield: 12.9 mg, 58%. dr (*anti/syn*): 62:38. ee (*anti/syn*): 76%/42%. 1H NMR ($CDCl_3$, 400 MHz): δ = 8.22–8.25 (m, 2H), 7.53–7.57 (m, 2H), 4.89 (d, J = 7.8 Hz, 1H), 2.93 (qt, 1H), 2.83–2.85 (m, 1H), 2.49–2.51 (m, 1H), 2.23 (s, 3H), 1.05 (t, J = 7.4 Hz, 3H), HPLC: (Chiralpak AD column, hexanes/2-propanol = 70/30, flow rate = 0.5 mL·min⁻¹, λ = 215 nm) t_R (*anti* isomer) = 22.01 (minor), 18.19 (major), t_R (*syn* isomer) = 16.78 (minor), 20.83 min (major). HRMS (ESI): calcd for $C_{11}H_{13}NO_4Na$ 246.07368, found 246.07356.

■ ASSOCIATED CONTENT

● Supporting Information

1H and ^{13}C NMR spectra, HPLC traces, and crystallographic data for compound 4. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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