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Proline-Histidine Dipeptide: A Suitable Template for Generating Ion-Tagged Organocatalysts for the Asymmetric Aldol Reaction

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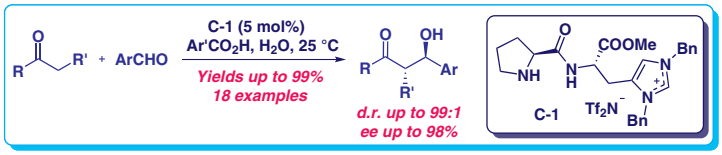

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Abstract Proline-histidine dipeptide laid the foundation for the construction of three new ion-tagged organocatalysts, utilising the imidazole moiety of histidine for generating the quaternary species. A brief comparative investigation of the catalysts in the enamine-mediated direct asymmetric aldol reaction brought out their contrasting features, particularly under aqueous conditions. The best among them was also utilised in preparing some derivatives and effecting a desymmetrisation.

Key words dipeptide, ion tag, proline, histidine, asymmetric catalysis, aldol reaction, aqueous reactions

In the realm of organocatalysis, the advantages of immobilisation of the proline scaffold with an ion tag are renowned.[1] The strategy has its genesis in the profitable use of ionic liquids as solvents in proline-catalysed reactions[2] and the successful application of solid-supported ionic liquid phases.[3] This triggered the development of new amino catalysts bearing a quaternary ammonium ion that have been employed with great success in typical organocatalytic transformations. Asymmetric aldol addition has been a huge beneficiary of the ion-tagging strategy; considerable rate acceleration of the enamine route to aldol adducts has been achieved, along with exceptional stereocontrol. The positive influence of the ion tag could be attributed to a host of factors: with regard to the enhanced efficiency, researchers have concurred upon a better electrostatic stabilisation of charged transition states along the path that leads to the iminium ion intermediate from an uncharged reactant. A high affinity of the ion tag to other ionic moieties could also be hypothesised, resulting in a more structured reaction domain; consequently, a 'tighter' transition state may be anticipated, leading to the observed enhancement in stereoselectivity. The first report of an imidazolium-tagged proline was by Miao and Chan, who demonstrated its use in asymmetric aldol addition.[4] Following this, significant contributions have come from the groups of Wang, Zlotin, Trombini and Lombardo, Liebscher, Cheng and Juaristi, to name a few.[5–11] An added advantage of ion-tagged catalysts is the ease of tuning their hydrophilicity/lipophilicity by varying the counterion, a feature that is crucial for the development of aqueous-based protocols. This has assumed significance owing to: (i) the obvious benefits of using water as a solvent, and (ii) the intriguing role that water has often played in improving the outcome of organocatalytic processes.[12,13] The research groups of Zlotin[6] and Trombini and Lombardo[7] in particular have come up with several ways of incorporating an ion tag, predominantly onto proline, to build recyclable catalysts that perform excellently under aqueous conditions. The former's ion-tagged prolinamides[6c,6e–h] and the *trans*- and *cis*-hydroxyproline-derived ion-tagged catalysts developed by the latter[7a,d] are standout examples of catalysts that have proven proficient in mediating the asymmetric aldol reaction in the presence of water.

On a parallel note, it is surprising that peptides, which form an integral part of living systems and fulfil a multitude of functions, have not been extensively explored as asymmetric organocatalysts,[14] although recent literature suggests an increase in the use of di- and tripeptide catalysts for asymmetric aldol addition, conjugate addition, the Stetter and Morita–Baylis–Hillman reactions, hydrogenations, cyanations and numerous other transformations.[15] Peptidic catalysts often have unique features such as high chemoselectivity paired with broad substrate scope, site selectivity over long distances, and chemical robustness.

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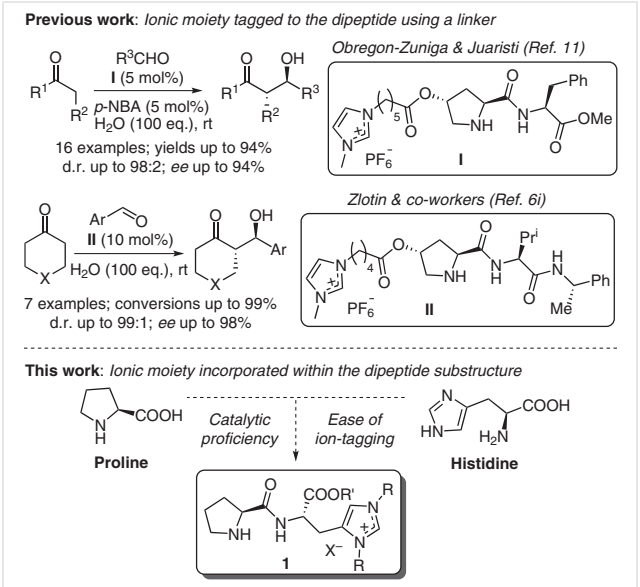
Besides, the more structured asymmetric domain of a peptide could also contribute to greater stereocontrol. Owing to these benefits, peptides are also being explored as candidates for immobilisation, as the research community strives for the design of ever more efficient catalysts and sustainable protocols.[16] A majority of known immobilised versions of peptidic organocatalysts are based on polymer supports;[17] in this context, an immobilisation strategy of ion-tagging, apart from the beneficial features discussed above, could allow for a better loading capacity than solid (polymeric) supports. However, only a couple of recent reports by Obregon-Zuniga and Juaristi[11] and Zlotin and co-workers[6i] stand out as examples of this strategy. The former synthesised a proline-based dipeptide, tagged with an imidazolium-bearing side chain at the 4-position of proline, and employed it with considerable success in the direct asymmetric aldol reaction in aqueous medium (Scheme 1, **I**).[11] Zlotin and co-workers, on the other hand, used a 4-OH-Pro-Val tagged to an imidazolium, bearing PF_6^- as the counterion, also to carry out an asymmetric aldol reaction in an aqueous environment (Scheme 1, **II**).[6i] It is worth noting that the ionic moiety in both the above catalysts did not form a part of the dipeptide substructure, necessitating a linker to tag it to the catalyst framework. We were curious to find out if the ion tag could be integrated into a dipeptide framework, thereby circumventing the use of the linker, without compromising on the efficiency of the resultant catalyst. Proline, the preeminent catalyst, would form one half of the proposed dipeptide, whereas the ion tag would evidently be borne by the other amino acid. The amino acids bearing a basic side chain present an interesting possibility in this context, since an ionic species can be produced by a simple protonation.[18] We chose histidine, which bears the imidazole moiety as a suitable platform for generating an ion tag; we envisaged that marrying the simplicity of ion-tagging in histidine to the catalytic superiority of proline would lead to a versatile ion-tagged catalyst prototype, depicted by **1** in Scheme 1. Apart from the ease of introducing an ion tag, the imidazole moiety in **1** would also allow for structural modifications to fine-tune the solubility and lipophilic properties of the catalyst. Thus, based on this strategy, we synthesised a series of proline-histidine dipeptide derived ion-tagged catalysts and studied them in asymmetric aldol addition under aqueous conditions. The results obtained from these efforts are described in the following sections.

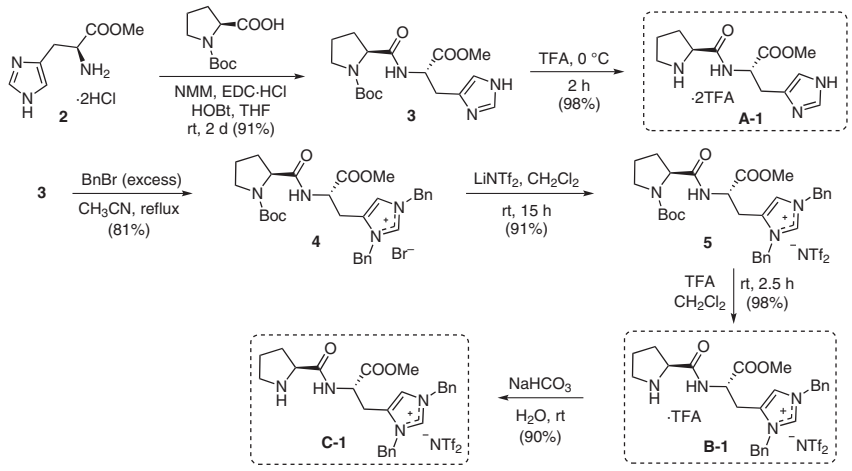
The synthesis of the proline-histidine dipeptide derivatives was carried out as illustrated in Scheme 2. At the outset, coupling of L-histidine methyl ester dihydrochloride (**2**) with Boc-L-proline under standard conditions afforded the protected dipeptide **3**.[19] Cleaving the carbamate in **3** using excess TFA delivered the first of the catalysts, the bis-TFA salt **A-1**. The protonated proline nitrogen in **A-1** is distinct from a mere depiction of the parent amino acid in a zwitterionic representation; it would therefore be interesting to



Scheme 1 Ion-tagged dipeptide organocatalysts for direct asymmetric aldol addition

check its effectiveness as an aminocatalyst. The technique used for the generation of a quaternised species in the synthesis of catalyst **A-1** is a simple protonation. On the other hand, synthesis of the ion-tagged catalysts **B-1** and **C-1** required an alkylative quaternisation protocol. To this end, imidazole **3** was treated with excess benzyl bromide to deliver the dibenzylic imidazolium species **4** as a quaternary bromide salt in good yield. It is evident from these brief results that the presence of the imidazole-bearing histidine allows for a relatively easy quaternisation, either by a simple protonation or by alkylation, resulting in the incorporation of an ion tag. Further, metathesis of the bromide salt **4** with $LiNTf_2$ gave the bis(trifluoromethanesulfonyl)imide ($[NTf_2]^-$) salt **5**, which was converted into **B-1** upon deprotection of the carbamate. Catalyst **B-1** is an interesting bisquaternary species having two counteranions of contrasting genesis and character, namely the hydrophilic trifluoroacetate ($[CF_3COO]^-$) as a consequence of protonation, and the lipophilic $[NTf_2]^-$ born out of an alkylative quaternisation; a ^{19}F NMR scan confirmed the presence of the two distinct anions. The favourable assistance of the latter in asymmetric aldol reactions under aqueous conditions has been well documented. Lastly, the protonated moiety in **B-1** was neutralised to afford **C-1**, a monoquaternary species that bears only the lipophilic $[NTf_2]^-$ as the counterion. Significantly, unlike **A-1** and **B-1**, catalyst **C-1** boasts a free NH group on the proline moiety, presumably a critical factor for catalysis.

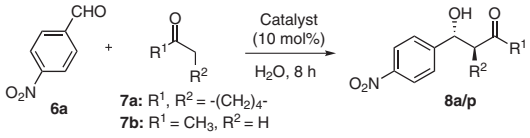
With the three catalysts possessing ion tags of varying nature in hand, we embarked upon comparing their performance in the direct asymmetric aldol reaction under aqueous conditions. A typical aldol reaction involving 4-nitro-



Scheme 2 Synthesis of the proline-histidine dipeptide derived catalysts

benzaldehyde (**6a**) and either cyclohexanone (**7a**) or acetone (**7b**) as the donor ketone was used for study under conditions that employed varying amounts of water, to account for the vastly different hydrophilic quotients of the three catalysts and the possibility of altered results arising from it. The results of these comparative studies are collected in Table 1. An initial reaction between **6a** and **7a** was carried out using 10 mol% of the bis-TFA salt **A-1** in the absence of water. The results were not very encouraging; a moderate yield of aldol **8a** was obtained along with modest enantio- and diastereoselectivity (Table 1, entry 1). The addition of water in the reaction unfortunately had a detrimental impact on the yield of the aldol, which worsened upon increasing the quantity of water; there was not much improvement in the stereoselectivity either (entries 2 and 3). On the other hand, catalyst **B-1**, having both hydrophilic ($[CF_3COO]^-$) and hydrophobic ($[NTf_2]^-$) counterions, gave a much-improved yield of the aldol along with marginally better stereoselectivity in a reaction without water. Unfortunately, as with **A-1**, a drastic drop in the yield resulted upon the addition of a small amount of water; interestingly however, the diastereo- and enantioselectivity both received a boost under these conditions, and **8a** was obtained in a 95:5 diastereomeric ratio and 95% optical purity (entry 5). The results with **A-1** and **B-1** reflect the fascinating water–counterion interplay in aldol additions mediated by ion-tagged systems. If one were to attempt to rationalise, in an aqueous reaction, the highly hydrophilic bis(trifluoroacetate) **A-1** presumably remains submerged in water, precluding any possible interaction with the lipophilic substrates; not surprisingly, a steep drop in catalytic activity ensues with increased quantities of water. On the other hand, catalyst **B-1**, bearing two counterions of contrasting nature, displays enhanced efficiency and selectivity; here, the positive impact on the stereochemical outcome upon addition of water, as with similar cases in the literature, may be thought of as a result of the reaction occurring in hydrophobic pockets that sequester the transition state from water. If the counterion indeed plays such an instrumental role in influencing the reaction outcome, the monoionic catalyst **C-1** bearing just the hydrophobic $[NTf_2]^-$ counterion loomed as a potentially superior candidate.

Table 1 Investigating Catalysts **A-1**, **B-1** and **C-1** in Direct Asymmetric Aldol Addition[a]



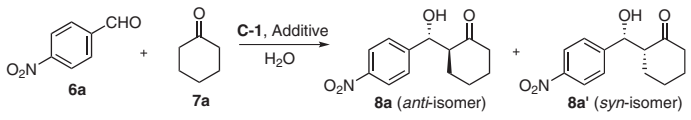
Entry	Ketone	Catalyst	H_2O (μL)	Yield (%)[b] **8a**/**p**	*anti*/*syn*[c]	*anti ee* (%)[d]
1	**7a**	**A-1**	–	55	86:14	80
2	**7a**	**A-1**	25	36	91:9	89
3	**7a**	**A-1**	100	13	84:16	88
4	**7a**	**B-1**	–	84	89:11	86
5	**7a**	**B-1**	25	42	95:5	95
6	**7a**	**C-1**	–	81	77:23	64
7	**7a**	**C-1**	25	84	82:18	84
8	**7b**	**A-1**	–	10	–	30
9	**7b**	**A-1**	25	5	–	40
10	**7b**	**A-1**	100	trace	–	47
11	**7b**	**B-1**	–	35	–	80
12	**7b**	**B-1**	25	17	–	60
13	**7b**	**C-1**	–	80	–	72
14[e]	**7b**	**C-1**	25	95	–	44

[a] Reaction conditions: **6a** (1 mmol), **7a** (5 eq.), rt (25–27 °C).
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude reaction mixture.
[d] Determined on the purified product by HPLC on a chiral stationary phase.
[e] Reaction was carried out for 6 h.

Pleasingly, the use of **C-1** instantly resulted in much better yields of the aldol in reactions carried out in the absence as well as in the presence of water (entries 6 and 7). Unfortunately, the stereoselectivity values were rather disappointing, although a significant spike was observed in the aqueous reaction. In the next study, cyclohexanone was replaced with the hydrophilic acetone (**7b**) as the donor. The dicationic catalysts **A-1** and **B-1** once again performed poorly. Using **A-1** in the absence of water, a very poor yield of aldol **8p** was obtained (entry 8), which diminished to negligible levels upon addition of water (entries 9 and 10); the stereochemical results were also rather disappointing throughout. As expected, catalyst **B-1** exhibited an improved performance with respect to both efficiency and stereoselectivity in corresponding reactions; the addition of water again had an unfavourable effect, proving the limitations of working with hydrophilic anions in aqueous organocatalysis (entries 11 and 12). In sharp contrast, further indications of the advantages of the lipophilic $[NTf_2]^-$ counterion were provided by the superior activity of the monoionic catalyst **C-1** in reactions with acetone; dramatic increase in the yields were obtained in the absence as well as in the presence of water, albeit with a huge drop in stereoselectivity for the latter (entries 13 and 14).

Having established the superiority of **C-1**, our curiosity was aroused by the disparity between its activity and stereocontrol. We pondered whether the poor stereoselectivity could be attributed to the lack of a COOH group, a structural feature shared by all three catalysts. The COOH group is known to play an important role in enhancing both the efficiency and selectivity of proline-mediated aldol reactions, and the addition of a Brønsted acid, where appropriate, to enhance performance is a common practice.[20] To this end, we undertook further studies using catalyst **C-1** in combination with a Brønsted acid to check for any improvement in the stereoselectivity as an upshot of the latter; the results are collated in Table 2. It was pleasing to observe an immediate improvement in the catalytic performance of **C-1** upon adding an equivalent amount of PhCOOH (10 mol%) in the reaction of **6a** with **7a**, initially in the absence of water; in particular, the spike in the enantioselectivity was significant (Table 2, entry 1). The addition of water furthered the advantage in terms of both efficiency and selectivity (entry 2). To our delight, replacing PhCOOH with *o*-fluorobenzoic acid (OFBA) in the presence of water resulted in a marked enhancement; a near quantitative yield of aldol **8a** was obtained in just 45 minutes, accompanied by a diastereomeric ratio of 93:7 and 93% *ee* of the major adduct (entry 3) and excellent results were obtained upon increasing the amount of water (entries 4–6). The results were also reproduced in a reaction using a large quantity of water, namely 'bulk' water conditions, as it is termed (entry 6). This is a significant result, since a catalyst that performs equally well in the presence of 'micro' as well as 'bulk' quantities of water would certainly be of interest to explore a variety of transformations. This noteworthy feature of **C-1**

Table 2 Use of Brønsted Acid Additives in Conjunction with Catalyst **C-1** for the Aldol Addition of Cyclohexanone (**7a**) to 4-Nitrobenzaldehyde (**6a**) in the Presence of Water[a]

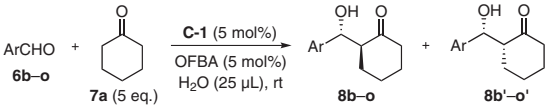


Entry	**C-1** (mol%)	**7a** (eq.)	Additive/mol%	H_2O (μL)	Time (h)	Yield (%)[b] **8a**	*anti*/*syn*[c]	*anti ee* (%)[d]
1	10	5	PhCOOH/10	–	6	95	79:21	87
2	10	5	PhCOOH/10	25	6	99	85:15	92
3	10	5	OFBA/10	25	0.75	99	93:7	93
4	10	3	OFBA/10	100	1.5	98	94:6	93
5	10	3	OFBA/10	450	1.5	99	93:7	93
6	10	3	OFBA/10	900	1.5	99	93:7	93
7	10	3	PhCOOH/10	900	6	96	89:11	94
8	20	5	OFBA/20	25	0.33	~100	91:9	94
9	5	5	OFBA/5	25	2.5	99	92:8	93
10	–[e]	5	OFBA/5	25	2.5	68	88:12	96
11	1	5	OFBA/1	25	9	97	89:11	91

[a] Reaction conditions: **6a** (0.5 mmol), rt (25–27 °C); OFBA: *o*-fluorobenzoic acid.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude reaction mixture.
[d] Determined on the purified product by HPLC on a chiral stationary phase.
[e] 2nd run.

could also be observed in a reaction using PhCOOH as the additive (entry 7). It would be pertinent here to refer to the contrast in the use of the above acid additives in the context of the TFA salts **A-1** and **B-1**. The results not only reiterate the importance of the nature of the counterion as discussed earlier, but also the significance of the choice of the Brønsted acid additive in the absence of a free COOH moiety in the catalyst.[21] Next, we varied the catalyst loading to further test the efficacy of **C-1**. By doubling the loading, a near quantitative yield of **8a** could be obtained in just 20 minutes (entry 8), whereas a commendable result could also be obtained with just 5 mol% (entry 9). Disappointingly, we were unable to achieve much success with a recycling experiment using these conditions (entry 10). Lastly, we were pleased to obtain an excellent yield of aldol **8a** using just 1 mol% of **C-1** in reasonable time (entry 11). In all these cases, it is worth noting that the stereoselectivity parameters remained consistently very good. Finally, it may be added as a footnote to the above comparative studies that the performance of catalyst **C-1** is also far superior to that of proline itself, alluding to the already well-established benefits of ion-tagged catalysts for the asymmetric aldol reaction.

Table 3 Asymmetric Aldol Addition of Cyclohexanone (**7a**) to Various Aldehydes Catalysed by **C-1**[a]



Entry	Ar	Time (h)	Yield (%)[b]	*anti*/*syn*[c]	*anti ee* (%)[d]
1	4-CNC_6H_4 (**8b**)	5	99	85:15	88
2	4-$CF_3C_6H_4$ (**8c**)	5	99	86:14	89
3[e]	4-$CF_3C_6H_4$ (**8c**)	3	99	90:10	94
4	4-BrC_6H_4 (**8d**)	5	83	89:11	93
5	4-ClC_6H_4 (**8e**)	7	90	80:20	89
6	C_6F_5 (**8f**)	2	99	>99:1	98
7	3-pyridyl (**8g**)	3	95	93:7	94
8	2-$NO_2C_6H_4$ (**8h**)	4	99	92:8	97
9	2-ClC_6H_4 (**8i**)	8	81	93:7	90
10	3-$NO_2C_6H_4$ (**8j**)	2.5	91	93:7	91
11	3-ClC_6H_4 (**8k**)	24	98	88:12	86
12	4-Cl-3-$NO_2C_6H_3$ (**8l**)	2	96	91:9	93
13	C_6H_5 (**8m**)	18	91	81:19	69
14[e]	C_6H_5 (**8m**)	16	99	85:15	80
15[e]	4-MeC_6H_4 (**8n**)	24	85	70:30	60
16[e]	4-$MeOC_6H_4$ (**8o**)	36	58	74:26	36

[a] All reactions were performed on 0.5 mmol scale of aldehyde; OFBA: *o*-fluorobenzoic acid.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude reaction mixture.
[d] Determined on the purified product by HPLC on a chiral stationary phase.
[e] 10 mol% catalyst was used.

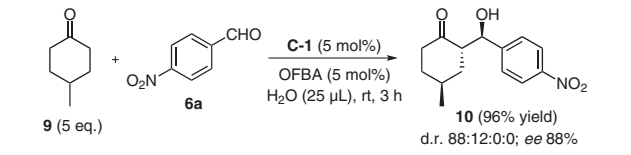
The above results with catalyst **C-1** were quite satisfying; we were especially pleased with the strategy of using an easily generated dipeptide derivative to successfully entwine enamine catalysis under aqueous conditions with the highly effective ion-tagging approach for asymmetric aldol addition. Synthesis of various aldol adducts was not pursued expansively, as the objective was rather to explore a simple route to operational ion-tagged dipeptides and using them to illustrate the peculiar interplay between the presence of water, the role of the counterion and the presence of a COOH group in enamine catalysis. Nonetheless, the scope of the reaction was extended to some other substrates under the deduced optimal conditions. Benzaldehydes bearing an electron-withdrawing group unsurprisingly afforded excellent yields of the aldols in short reaction times, along with good to excellent *ee* values (Table 3). The reaction with pentafluorobenzaldehyde was particularly rewarding as a 99% yield of the aldol was obtained in a rapid reaction accompanied by near complete diastereoselectivity and equally impressive enantiocontrol (entry 6), whereas the heteroaromatic nicotinaldehyde also afforded excellent results (entry 7). Reactions with other substituted benzaldehydes also fared impressively, including *ortho*-, *meta*- and disubstituted ones (entries 8–12). It was pleasing to observe that **C-1** was also able to deliver good yields of the aldols with two relatively poorer acceptors (entries 13–15), although the stereochemical outcome with anisaldehyde in particular was disappointing (entry 16). Next, using acetone as the donor, an excellent yield of the aldol with 4-nitrobenzaldehyde was obtained, but with a modest enantioselectivity (Table 4, entry 1). Cyclopentanone proved to be an exceptionally rapid donor, as the reaction was complete in just 30 minutes, affording a near quantitative yield of the aldol, but the diastereo- and enantioselectivity were rather modest; interestingly though, in a reversal of the usual selectivity, the *syn*-isomer was favoured over its *anti*-counterpart (entry 2), which could be worth investigating more deeply in the future.

Table 4 Asymmetric Aldol Addition of Different Donors to 4-Nitrobenzaldehyde (**6a**) Catalysed by **C-1**[a]

Entry	R^1, R^2	Time (h)	Yield (%)[b]	*anti*/*syn*[c]	*ee* (%)[d]
1	CH_3, H (**8p**)	5	95	–	65
2	-$(CH_2)_3$- (**8q**)	0.5	99	34:66	70

[a] All reactions were performed on 0.5 mmol scale of aldehyde; OFBA: *o*-fluorobenzoic acid.
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the crude reaction mixture.
[d] Determined on the purified product by HPLC on a chiral stationary phase.

To further explore the efficacy of **C-1**, we undertook the desymmetrisation of 4-methylcyclohexanone (**9**) by aldol addition. This is a challenging yet powerful reaction that can give rise to four possible diastereomeric product pairs.[21] To our delight, 5 mol% of catalyst **C-1** mediated an efficient desymmetrisation of **9** in a reaction with **6a**, and delivered aldol **10** in excellent yield accompanied by good levels of both diastereo- and enantioselectivity (Scheme 3).



Scheme 3 Desymmetrisation of 4-methylcyclohexanone by aldol addition mediated by **C-1**

Lastly, a transition state for this dipeptide-mediated aldol addition may be proposed as shown in Figure 1, depicting a possibly complex hydrogen-bonded network involving the aldehyde, benzoic acid and the counterion on the catalyst.[22] The favourable addition of the enamine to the *Re*-face of the aldehyde has been illustrated, the latter presumably activated by hydrogen-bonding to the Brønsted acid additive. The electrostatic stabilisation of such charge-distributed polar transition states by the presence of an ionic tag has been well-established in combined experimental and theoretical studies by Trombini and Bottoni and co-workers.[7,23]

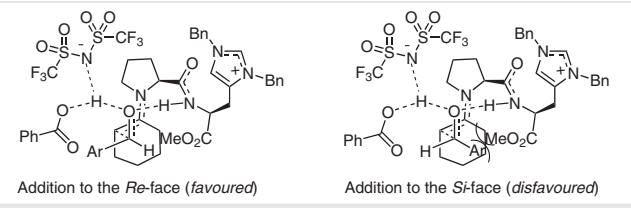


Figure 1 Plausible transition states for asymmetric aldol addition mediated by **C-1**

Thus, a thoughtfully chosen dipeptide provided a suitable platform to combine the exceptional catalytic proficiency of proline and the well-established beneficial effects of incorporating an ion tag in enamine-mediated direct asymmetric aldol addition. In the process, the endeavour provided a glimpse into the potential of ion-tagged dipeptides, minimally explored to date, as efficient catalysts in aqueous medium. This could open up an avenue for exploring more ion-tagged small peptides for mediating asymmetric transformations in water. The results also provide another illustration of the interesting interplay between the lipophilic/hydrophilic nature of the ion tag and the presence of water in enamine-mediated aldol additions.

Chemicals and solvents were purchased from commercial suppliers or purified by standard techniques. Merck 60 F_{254} precoated silica gel plates were used for TLC and compounds were visualised by irradiation with UV light and/or by treatment with a solution of $KMnO_4$ followed by heating. Column chromatography was performed using silica gel of mesh 60–120/100–200, procured from Merck. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 MHz and a JEOL ECS 400 MHz NMR spectrometers. Mass spectra were obtained using a HRMS-ESI-Q-time-of-flight LC-MS instrument (Synapt G2, Waters). Chiral HPLC studies were carried out on a Shimadzu LC-2010CHT HPLC system. Cyclohexanone, acetone, benzaldehyde and pyridine-3-/pyridine-4-carboxaldehyde were distilled before use. Commercial samples of all the other substrates were used without any purification.

Proline-Histidine Dipeptide Derivative 3[19]

To a stirred, heterogeneous mixture of *N*-(*tert*-butoxycarbonyl)-L-proline (3.22 g, 15 mmol), 1-hydroxybenzotriazole hydrate (1.77 g, 13 mmol) and L-histidine methyl ester dihydrochloride (**2**; 3.02 g, 12.5 mmol) in THF (30 mL) was added *N*-methylmorpholine (2.25 mL, 25 mmol). The resulting mixture was cooled to 0 °C and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (2.58 g, 12.5 mmol) was added. The reaction mixture was then allowed to stir in an ice bath for 2 h, following which it was allowed to warm to rt and stirred for a further 48 h. The reaction mixture was then cooled to 0 °C and stirred for 30 min. The solid urea formed was filtered off and the filtrate was concentrated under reduced pressure. The crude residue was dissolved in CH_2Cl_2 and washed with brine, saturated $NaHCO_3$ and brine once again. The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo to afford **3** (4.2 g, 91%) as a transparent yellow sticky compound. The crude product was used as such without further purification for the next step.

$[\alpha]_D^{25}$ +80.7 (*c* 0.51, $CHCl_3$).

IR (neat): 3264, 1665, 1390 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 19.0 Hz, 1 H), 6.92 (bs, 1 H), 6.75 (d, *J* = 17.0 Hz, 1 H), 4.79 (s, 1 H), 4.14 (s, 1 H), 3.69 (s, 3 H), 3.51–3.59 (m, 1 H), 3.40–3.49 (m, 1 H), 3.29–3.37 (m, 1 H), 3.11–3.20 (m, 1 H), 2.42 (bs, 1 H), 2.02–2.20 (m, 2 H), 1.80–1.91 (m, 2 H), 1.48 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.09, 171.03, 155.17, 135.73, 135.31, 80.79, 66.92, 61.08, 60.54, 55.42, 53.21, 52.64, 47.22, 46.43, 29.69, 28.49, 24.73.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{27}N_4O_5$: 367.1976; found: 367.1972.

Catalyst A-1

To dipeptide derivative **3** (500 mg, 1.36 mmol), TFA (10 mL) was added and the mixture was stirred in an ice bath. Upon consumption of the starting material (~2 h), the reaction mixture was concentrated under reduced pressure and the residue was dried under vacuum to afford bis(trifluoroacetate) **A-1** (354 mg, 98%) as a transparent light-brown sticky compound. No further purification was required and **A-1** was as such for the catalysis study.

$[\alpha]_D^{25}$ +18.6 (*c* 0.86, $CHCl_3$).

IR (neat): 3133, 1660, 1347 cm^{-1}.

^{1}H NMR (500 MHz, D_2O): δ = 8.44 (s, 1 H), 7.13 (s, 1 H), 4.65–4.68 (m, 1 H), 4.15–4.23 (m, 1 H), 3.57 (s, 3 H), 3.14–3.24 (m, 4 H), 3.01–3.09 (m, 1 H), 2.19–2.31 (m, 1 H), 1.79–1.92 (m, 3 H).

^{13}C NMR (125 MHz, D_2O): δ = 171.51, 169.53, 163.04, 162.75, 162.45, 162.18, 133.47, 128.26, 117.34, 117.08, 115.03, 63.75, 59.46, 53.21, 53.08, 52.04, 48.76, 46.41, 29.56, 25.70, 23.51.

^{19}F NMR (470 MHz, D_2O): δ = –75.72.

HRMS (ESI): monocationic part: *m*/*z* $[M]^+$ calcd for $C_{12}H_{19}N_4O_3^+$: 267.1452; found: 267.0896.

Bromide Salt 4

To a stirred heterogeneous mixture of dipeptide derivative **3** (1.388 g, 3.79 mmol) and $NaHCO_3$ (12.896 g, 15.35 mmol) in CH_3CN (10 mL) was added BnBr (2.26 mL, 18.95 mmol) and the reaction mixture was refluxed for 16 h. The mixture was then allowed to cool to rt, filtered and the filtrate was concentrated under reduced pressure. The crude residue was washed with Et_2O (5 × 2 mL) to remove the excess BnBr, dissolved in H_2O (5 mL) and washed with Et_2O (2 × 2 mL) again. The aqueous layer was then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford the corresponding quaternised bromide salt **4** (1.92 g, 81%) as a white solid; no further purification was required.

Mp 72 °C; $[\alpha]_D^{25}$ –17.18 (*c* 0.36, $CHCl_3$).

IR (neat): 3433, 1684, 1340 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.37 (s, 1 H), 8.30 (d, *J* = 8.0 Hz, 1 H), 7.29–7.49 (m, 11 H), 5.38–5.63 (m, 4 H), 4.85–4.89 (m, 1 H), 4.42 (d, *J* = 4.6 Hz, 1 H), 3.70 (s, 3 H), 3.45–3.58 (m, 1 H), 3.31–3.39 (m, 2 H), 3.02–3.09 (m, 1 H), 2.10–2.17 (m, 1 H), 1.83–1.97 (m, 3 H), 1.43 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.42, 170.79, 135.55, 132.96, 132.76, 131.54, 129.45, 129.20, 128.91, 128.21, 122.08, 79.61, 59.85, 53.50, 52.98, 51.30, 50.22, 47.37, 30.25, 28.51, 25.42, 24.44.

HRMS (ESI): cationic part: *m*/*z* $[M]^+$ calcd for $C_{31}H_{39}N_4O_5^+$: 547.2915; found: 547.2129.

Bis(trifluoromethanesulfonyl)imide Salt 5

To a solution of bromide **4** (1.06 g, 1.69 mmol) in CH_2Cl_2 (4 mL) was added $LiNTf_2$ (585 mg, 2 mmol). The solution was stirred overnight at rt, following which it was diluted with CH_2Cl_2 (15 mL), and washed with H_2O (3 x 15 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford bis(trifluoromethanesulfonyl)imide salt **5** (1.27 g, 91%) as a sticky yellow solid, which was used as such for the next step.

$[\alpha]_D^{25}$ –24.6 (*c* 0.32, $CHCl_3$).

IR (neat): 3379, 1677, 1348 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.34 (s, 1 H), 7.51 (s, 1 H), 7.23–7.45 (m, 10 H), 7.17 (d, *J* = 7.5 Hz, NH), 5.25–5.40 (m, 4 H), 4.72 (dd, *J* = 6.8, 13.6 Hz, 1 H), 4.15–4.28 (m, 1 H), 3.71 (s, 3 H), 3.48 (s, 1 H), 3.35–3.42 (m, 1 H), 3.18–3.23 (m, 2 H), 2.14–2.17 (m, 1 H), 1.78–1.97 (m, 3 H), 1.42 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.31, 170.28, 155.04, 134.88, 132.54, 132.20, 131.65, 129.58, 129.54, 129.47, 129.04, 128.74, 128.70, 128.42, 128.12, 128.01, 127.80, 127.02, 123.60, 122.19, 121.04, 118.49, 115.94, 79.95, 67.93, 60.13, 53.65, 53.00, 51.32, 50.57, 47.25, 29.89, 28.36, 25.53, 24.44.

^{19}F NMR (234 MHz, $CDCl_3$): δ = –78.74.

HRMS (ESI): cationic part: *m*/*z* $[M]^+$ calcd for $C_{31}H_{39}N_4O_5^+$: 547.2915; found: 547.2977.

Catalyst B-1

To a solution of bis(trifluoromethanesulfonyl)imide **5** (1.9 g, 2.29 mmol) in CH_2Cl_2 (5 mL) was added TFA (5 mL). The resulting mixture was allowed to stir at rt until complete consumption of the starting material (~2 h). The reaction mixture was then concentrated under reduced pressure, and the residue was washed with Et_2O (3 × 2 mL) and dried under vacuum to afford **B-1** (1.88 g, 98%) as a transparent light-brown sticky solid. The obtained compound was deemed to be of sufficient purity for the catalysis study.

$[\alpha]_D^{25}$ –12.68 (*c* 0.56, $CHCl_3$).

IR (neat): 3392, 1688, 1320 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.41 (s, 1 H), 8.24 (d, *J* = 8.43 Hz, NH), 8.16 (s, 1 H), 7.24–7.46 (m, 10 H), 5.28–5.32 (m, 4 H), 4.87 (s, 1 H), 4.52 (s, 1 H), 3.93 (bs, NH), 3.74 (s, 3 H), 3.39–3.55 (m, 2 H), 3.15–3.21 (m, 2 H), 2.49 (s, 1 H), 2.01–2.15 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.53, 168.83, 161.91, 134.96, 132.20, 131.55, 131.14, 129.73, 129.59, 128.87, 128.20, 122.13, 120.91, 118.36, 59.84, 53.79, 53.24, 51.42, 50.62, 46.67, 29.44, 25.45, 24.41.

^{19}F NMR (234 MHz, $CDCl_3$): δ = –75.50, –78.72.

HRMS (ESI): monocationic part: *m*/*z* $[M]^+$ calcd for $C_{26}H_{31}N_4O_3^+$: 447.2391; found: 447.2412.

Catalyst C-1

Mixed salt **B-1** (1.5 g, 2.25 mmol) was dissolved in H_2O (2 mL) and the pH was adjusted to ~8 using 10% aq $NaHCO_3$. The solution was then extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was washed with Et_2O (3 × 2 mL) and dried under vacuum to afford the bis(trifluoromethanesulfonyl)imide salt **C-1** (1.47 g, 90%) as a sticky transparent light-brown compound, which was used as such for the catalysis studies.

$[\alpha]_D^{25}$ –17.7 (*c* 0.43, $CHCl_3$).

IR (neat): 3133, 1660, 1347 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.75 (s, 1 H), 8.25 (d, *J* = 10 Hz, NH), 7.35–7.51 (m, 10 H), 7.13 (s, 1 H), 5.23–5.41 (m, 4 H), 4.58–4.69 (m, 1 H), 3.59–3.64 (m, 4 H), 3.09–3.20 (m, 1 H), 2.91–3.01 (m, 2 H), 2.72–2.78 (m, 1 H), 2.13 (bs, NH), 1.85–1.99 (m, 1 H), 1.51–1.61 (m, 1 H), 1.38–1.46 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.19, 176.16, 170.38, 135.72, 132.30, 132.12, 132.10, 131.96, 129.71, 129.62, 129.58, 128.86, 128.08, 123.62, 121.07, 120.59, 120.56, 118.51, 115.96, 65.90, 60.13, 60.09, 53.65, 53.02, 52.98, 51.34, 49.82, 49.76, 47.10, 30.74, 29.73, 26.91, 26.07.

^{19}F NMR (234 MHz, $CDCl_3$): δ = –78.73.

HRMS (ESI): cationic part: *m*/*z* $[M]^+$ calcd for $C_{26}H_{31}N_4O_3^+$: 447.2391; found: 447.2416.

Aldol Adduct 8a; Typical Catalysis Procedure

Cyclohexanone (**7a**; 0.26 mL, 2.5 mmol) and H_2O (25 μL, 1.4 mmol) were added to catalyst **C-1** (18.2 mg, 0.025 mmol) and the mixture was stirred for 5 min at rt. 2-Fluorobenzoic acid (3.5 mg, 0.025 mmol) was added and the resulting mixture was stirred for a further 15 min at rt. 4-Nitrobenzaldehyde (**6a**; 75.5 mg, 0.5 mmol) was then added, and the reaction mixture was stirred at rt. After 2.5 h of stirring, the mixture was charged directly onto a silica gel column and eluted with EtOAc/petroleum ether (~1:3) to isolate pure aldol adduct **8a** (123.2

mg, 99%) as a diastereomeric mixture. The absolute configuration of the major enantiomer was confirmed based on the optical rotation and HPLC traces, by comparison with literature data.

Characterisation of the Aldol Adducts[24]

2-(Hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (8a)[25]

Yellow solid; yield: 123.2 mg (99%).

$[\alpha]_D^{20}$ +13.6 (*c* 0.6, $CHCl_3$).

HPLC (Daicel Chiralpak AD-H column, hexane/2-propanol 87.5:12.5, 0.8 mL·min^{-1}, 40 °C, 254 nm): t_R = 17.1 (*syn*), 20.5 (*syn*), 22.3 (*anti* minor), 29.0 (*anti* major) min; *anti*/*syn* 92:8; 93% *ee* (*anti*).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.7 Hz, 2 H), 7.51 (d, *J* = 8.7 Hz, 2 H), 4.91 (d, *J* = 8.3 Hz, 1 H), 4.07 (m, 1 H), 2.61–2.63 (m, 1 H), 2.51–2.59 (m, 1 H), 2.34–2.49 (m, 1 H), 2.09–2.14 (m, 1 H), 1.82–1.85 (m, 1 H), 1.63–1.72 (m, 1 H), 1.59–1.60 (m, 1 H), 1.34–1.43 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 214.76, 148.35, 147.59, 127.88, 123.59, 74.03, 57.20, 42.68, 30.77, 27.64, 24.69.

2-((4-Cyanophenyl)(hydroxy)methyl)cyclohexan-1-one (8b)[26]

White solid; yield: 113.4 mg (99%).

HPLC (Daicel Chiralpak AD-H column, hexane/2-propanol 90:10, 0.5 mL·min^{-1}, 40 °C, 230 nm): t_R = 28.0 (*syn*), 33.5 (*syn*), 38.2 (*anti* minor), 47.9 (*anti* major) min; *anti*/*syn* 85:15; 88% *ee* (*anti*).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.2 Hz, 2 H), 7.44 (d, *J* = 8.2 Hz, 2 H), 4.84 (d, *J* = 8.5 Hz, 1 H), 4.09 (s, 1 H), 2.53–2.63 (m, 1 H), 2.45–2.53 (m, 1 H), 2.36 (td, *J* = 13.7, 6.3 Hz, 1 H), 2.07–2.15 (m, 1 H), 1.77–1.89 (m, 1 H), 1.52–1.72 (m, 3 H), 1.28–1.42 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 214.90, 146.34, 132.21, 127.79, 118.74, 111.72, 74.26, 57.14, 42.69, 30.75, 27.66, 24.70.

2-(Hydroxy(4-(trifluoromethyl)phenyl)methyl)cyclohexan-1-one (8c)[26]

White solid; yield: 134.6 mg (99%).

HPLC (Daicel Chiralcel OD-H column, hexane/2-propanol 95:5, 0.5 mL·min^{-1}, 40 °C, 217 nm): t_R = 14.8 (*syn*), 15.7 (*syn*), 17.7 (*anti* major), 20.9 (*anti* minor) min; *anti*/*syn* 90:10; 94% *ee* (*anti*).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.1 Hz, 2 H), 7.45 (d, *J* = 8.1 Hz, 2 H), 4.85 (d, *J* = 8.6 Hz, 1 H), 4.06 (s, 1 H), 2.55–2.64 (m, 1 H), 2.45–2.53 (m, 1 H), 2.31–2.42 (m, 1 H), 2.06–2.16 (m, 1 H), 1.78–1.86 (m, 1 H), 1.65–1.71 (m, 1 H), 1.53–1.61 (m, 2 H), 1.32–1.37 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.91, 144.83, 129.87 (q, $^2J_{C-F}$ = 32.0 Hz), 127.19, 125.12 (q, $^3J_{C-F}$ = 3.7 Hz), 123.92 (q, $^1J_{C-F}$ = 270.7 Hz), 74.06, 57.19, 42.48, 30.57, 27.52, 24.47.

2-((4-Bromophenyl)(hydroxy)methyl)cyclohexan-1-one (8d)[27]

White solid; yield: 118.2 mg (83%).

HPLC (Daicel Chiralpak AD-H column, hexane/2-propanol 90:10, 0.5 mL·min^{-1}, 40 °C, 220 nm): t_R = 15.5 (*syn*), 18.4 (*syn*), 23.1 (*anti* minor), 27.6 (*anti* major) min; *anti*/*syn* 89:11; 93% *ee* (*anti*).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 8.3 Hz, 2 H), 7.20 (d, *J* = 8.3 Hz, 2 H), 4.75 (dd, *J* = 8.7, 2.2 Hz, 1 H), 3.97 (d, *J* = 2.65 Hz, 1 H), 2.52–2.60 (m, 1 H), 2.44–2.52 (m, 1 H), 2.35 (td, *J* = 13.4, 6.1 Hz, 1 H), 2.06–2.14 (m, 1 H), 1.76–1.86 (m, 1 H), 1.64–1.74 (m, 1 H), 1.58–1.64 (m, 1 H), 1.23–1.36 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 215.40, 139.96, 131.51, 128.76, 121.75, 74.22, 57.32, 42.68, 30.77, 27.74, 24.72.

2-((4-Chlorophenyl)(hydroxy)methyl)cyclohexan-1-one (8e)[26]

White solid; yield: 107.4 mg (90%).

HPLC (Daicel Chiralpak AD-H column, hexane/2-propanol 90:10, 0.5 mL·min^{-1}, 40 °C, 220 nm): t_R = 15.8 (*syn*), 18.6 (*syn*), 23.2 (*anti* minor), 27.2 (*anti* major) min; *anti*/*syn* 80:20; 89% *ee* (*anti*).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.5 Hz, 2 H), 7.26 (d, *J* = 8.4 Hz, 2 H), 4.77 (dd, *J* = 8.7, 2.4 Hz, 1 H), 3.99 (d, *J* = 2.7 Hz, 1 H), 2.53–2.59 (m, 1 H), 2.44–2.52 (m, 1 H), 2.32–2.41 (m, 1 H), 2.07–2.14 (m, 1 H), 1.77–1.85 (m, 1 H), 1.61–1.72 (m, 1 H), 1.55–1.61 (m, 2 H), 1.25–1.35 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 215.44, 139.45, 133.61, 128.57, 128.41, 74.17, 57.37, 42.69, 30.77, 27.75, 24.72.

2-(Hydroxy(perfluorophenyl)methyl)cyclohexan-1-one (8f)[28]

Off-white solid; yield: 145.5 mg (99%); mp 82–84 °C (Lit.[28] 85–87 °C).

HPLC (Daicel Chiralpak AD-H column, hexane/2-propanol 91.5:8.5, 0.5 mL·min^{-1}, 20 °C, 254 nm): t_R = 13.0 (*syn*), 14.1 (*syn*), 16.0 (*anti* major), 21.2 (*anti* minor) min; *anti*/*syn* >99:1; 98% *ee* (*anti*).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.32 (d, *J* = 9.4 Hz, 1 H), 3.93 (s, 1 H), 2.94–3.08 (m, 1 H), 2.47–2.57 (m, 1 H), 2.32–2.46 (m, 1 H), 2.08–2.21 (m, 1 H), 1.81–1.95 (m, 1 H), 1.60–1.71 (m, 3 H), 1.28–1.39 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 214.14, 146.69, 144.32, 142.37, 139.99, 138.32, 136.78, 66.05, 54.21, 42.37, 30.16, 27.47, 24.51; note: C-F coupling could not be assigned from the ^{13}C NMR spectrum.

2-(Hydroxy(pyridin-3-yl)methyl)cyclohexan-1-one (8g)[18]

Brown sticky solid; yield: 98.1 mg (95%).

HPLC (Daicel Chiralpak AD-H column, hexane/2-propanol 92:8, 0.8 mL·min^{-1}, 20 °C, 254 nm): t_R = 39.8 (*syn*), 63.8 (*syn*), 56.8 (*anti* major), 67.1 (*anti* minor) min; *anti*/*syn* 93:7; 94% *ee* (*anti*).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 14.0 Hz, 2 H), 7.70 (d, *J* = 7.2 Hz, 1 H), 7.27 (s, 1 H), 6.93 (s, 1 H), 4.85 (d, *J* = 8.1 Hz, 1 H), 2.53–2.68 (m, 1 H), 2.23–2.46 (m, 2 H), 1.94–2.08 (m, 1 H), 1.72–1.85 (m, 1 H), 1.47–1.72 (m, 3 H), 1.18–1.34 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 215.10, 149.08, 148.55, 136.61, 134.79, 123.65, 72.61, 57.12, 42.66, 30.69, 27.69, 24.66.

2-(Hydroxy(2-nitrophenyl)methyl)cyclohexan-1-one (8h)[25]

Brown sticky solid; yield: 123.2 mg (99%).

HPLC (Daicel Chiralpak AD-H column, hexane/2-propanol 95:5, 0.5 mL·min^{-1}, 40 °C, 254 nm): t_R = 30.5 (*syn*), 32.4 (*syn*), 52.6 (*anti* major), 54.1 (*anti* minor) min; *anti*/*syn* 92:8; 97% *ee* (*anti*).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.1 Hz, 1 H), 7.76 (d, *J* = 7.8 Hz, 1 H), 7.63 (t, *J* = 7.5 Hz, 1 H), 7.42 (t, *J* = 7.5 Hz, 1 H), 5.96 (s, 1 H), 5.44 (d, *J* = 7.8 Hz, 1 H), 2.70–2.82 (m, 1 H), 2.41–2.51 (m, 1 H), 2.33 (td, *J* = 13.4, 5.95 Hz, 1 H), 2.04–2.15 (m, 1 H), 1.82–1.90 (m, 1 H), 1.72–1.79 (m, 1 H), 1.56–1.72 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 214.87, 148.77, 136.62, 133.04, 129.02, 128.39, 124.06, 69.77, 57.32, 42.82, 31.11, 27.76, 24.98.

2-((2-Chlorophenyl)(hydroxy)methyl)cyclohexan-1-one (8i)[27]

White solid; yield: 96.3 mg (81%).

HPLC (Daicel Chiralcel OD-H column, hexane/2-propanol 95:5, 1 mL·min^{-1}, 20 °C, 220 nm): t_R = 7.7 (*anti* major), 8.9 (*anti* minor), 11.0 (*syn*), 12.1 (*syn*) min; *anti*/*syn* 93:7; 90% *ee* (*anti*).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 6.9 Hz, 1 H), 7.28–7.36 (m, 2 H), 7.21 (t, *J* = 7.6 Hz, 1 H), 5.35 (d, *J* = 8.1 Hz, 1 H), 4.04 (s, 1 H), 2.62–2.74 (m, 1 H), 2.43–2.52 (m, 1 H), 2.35 (td, *J* = 13.5, 6.1 Hz, 1 H), 2.03–2.16 (m, 1 H), 1.77–1.88 (m, 1 H), 1.62–1.72 (m, 2 H), 1.53–1.62 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 215.33, 139.08, 132.97, 129.22, 128.77, 128.25, 127.27, 70.45, 57.61, 42.75, 30.40, 27.83, 24.93.

2-(Hydroxy(3-nitrophenyl)methyl)cyclohexan-1-one (8j)[25]

White solid; yield: 113 mg (91%).

HPLC (Daicel Chiralpak AD-H column, hexane/2-propanol 90:10, 1 mL·min^{-1}, 20 °C, 254 nm): t_R = 17.7 (*syn*), 19.5 (*syn*), 20.9 (*anti* major), 26.5 (*anti* minor) min; *anti*/*syn* 93:7; 91% *ee* (*anti*).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.21 (s, 1 H), 8.17 (d, *J* = 8.2 Hz, 1 H), 7.67 (d, *J* = 7.6 Hz, 1 H), 7.53 (t, *J* = 7.9 Hz, 1 H), 4.90 (d, *J* = 8.5 Hz, 1 H), 4.15 (s, 1 H), 2.57–2.68 (m, 1 H), 2.46–2.54 (m, 1 H), 2.38 (td, *J* = 13.5, 6.0 Hz, 1 H), 2.07–2.18 (m, 1 H), 1.79–1.88 (m, 1 H), 1.63–1.75 (m, 3 H), 1.36–1.45 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 215.00, 148.27, 143.21, 133.24, 129.35, 122.92, 122.05, 74.07, 57.14, 42.69, 30.76, 27.65, 24.67.

2-((3-Chlorophenyl)(hydroxy)methyl)cyclohexan-1-one (8k)[27]

Pale yellow solid; yield: 117 mg (98%).

HPLC (Daicel Chiralcel OD-H column, hexane/2-propanol 97:3, 0.8 mL·min^{-1}, 40 °C, 210 nm): t_R = 12.8 (*syn*), 14.5 (*syn*), 15.9 (*anti* major), 18.6 (*anti* minor) min; *anti*/*syn* 88:12; 86% *ee* (*anti*).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (s, 1 H), 7.29 (m, 2 H), 7.20 (t, *J* = 4.3 Hz, 1 H), 4.77 (d, *J* = 8.7 Hz, 1 H), 4.76 (s, 1 H), 2.56–2.64 (m, 1 H), 2.46–2.54 (m, 1 H), 2.37 (td, *J* = 13.4, 6.0 Hz, 1 H), 2.07–2.16 (m, 1 H), 1.79–1.88 (m, 1 H), 1.53–1.74 (m, 3 H), 1.26–1.39 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 215.38, 143.00, 134.35, 129.64, 128.09, 127.16, 125.32, 74.31, 57.27, 42.70, 30.80, 27.75, 24.71.

2-((4-Chloro-3-nitrophenyl)(hydroxy)methyl)cyclohexan-1-one (8l)[29]

Pale yellow solid; yield: 136 mg (96%).

HPLC (Daicel Chiralpak IC column, hexane/2-propanol 90:10, 1.5 mL·min^{-1}, 20 °C, 210 nm): t_R = 9.6 (*syn*), 10.8 (*syn*), 15.7 (*anti* major), 16.5 (*anti* minor) min; *anti*/*syn* 91:9; 93% *ee* (*anti*).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85–7.89 (m, 1 H), 7.52 (d, *J* = 8.2 Hz, 1 H), 7.46–7.50 (m, 1 H), 4.84 (d, *J* = 8.3 Hz, 1 H), 4.10 (s, 1 H), 2.53–2.64 (m, 1 H), 2.45–2.53 (m, 1 H), 2.36 (td, *J* = 13.7, 6.0 Hz, 1 H), 2.07–2.18 (m, 1 H), 1.80–1.92 (m, 1 H), 1.53–1.72 (m, 3 H), 1.32–1.46 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 214.68, 147.81, 141.78, 131.72, 131.69, 126.17, 124.08, 73.43, 57.05, 42.65, 30.68, 27.60, 24.64.

2-(Hydroxy(phenyl)methyl)cyclohexan-1-one (8m)[25]

Pale yellow sticky solid; yield: 101 mg (99%).

HPLC (Daicel Chiralcel OD-H column, hexane/2-propanol 90:10, 0.5 mL·min^{-1}, 20 °C, 220 nm): t_R = 14.0 (*syn*), 15.5 (*syn*), 17.2 (*anti* major), 22.0 (*anti* minor) min; *anti*/*syn* 85:15; 80% *ee* (*anti*).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24–7.38 (m, 5 H), 4.79 (d, *J* = 8.8 Hz, 1 H), 4.10 (s, 1 H), 2.57–2.67 (m, 1 H), 2.46–2.52 (m, 1 H), 2.36 (td, *J* = 13.4, 7.0 Hz, 1 H), 2.05–2.14 (m, 1 H), 1.74–1.84 (m, 1 H), 1.62–1.73 (m, 1 H), 1.49–1.61 (m, 2 H), 1.23–1.36 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 215.49, 141.03, 128.37, 127.88, 127.05, 74.67, 57.43, 42.62, 30.83, 27.82, 24.66.

2-(Hydroxy(4-methylphenyl)methyl)cyclohexan-1-one (8n)[26]

Off-white solid; yield: 92.7 mg (85%).

HPLC (Daicel Chiralpak AD-H column, hexane/2-propanol 93:7, 1 mL·min^{-1}, 20 °C, 254 nm): t_R = 10.2 (*syn*), 11.3 (*syn*), 13.8 (*anti* major), 16.2 (*anti* minor) min; *anti*/*syn* 70:30; 60% *ee* (*anti*).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 7.9 Hz, 2 H), 7.15 (d, *J* = 7.9 Hz, 2 H), 4.76 (d, *J* = 8.7 Hz, 1 H), 3.92 (s, 1 H), 2.56–2.66 (m, 1 H), 2.42–2.52 (m, 1 H), 2.36–2.41 (m, 1 H), 2.34 (s, 3 H), 2.04–2.13 (m, 1 H), 1.75–1.89 (m, 1 H), 1.48–1.74 (m, 3 H), 1.24–1.35 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 215.64, 138.00, 137.55, 129.06, 126.94, 74.53, 57.45, 42.68, 30.88, 27.84, 24.73, 21.16.

2-(Hydroxy(4-methoxyphenyl)methyl)cyclohexan-1-one (8o)[26]

Yellow solid; yield: 68.2 mg (58%).

HPLC (Daicel Chiralpak AD-H column, hexane/2-propanol 95:5, 1 mL·min^{-1}, 20 °C, 254 nm): t_R = 18.9 (*syn*), 22.1 (*syn*), 31.6 (*anti* minor), 33.6 (*anti* major) min; *anti*/*syn* 74:26; 36% *ee* (*anti*).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (t, *J* = 8.8 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 4.74 (d, *J* = 8.8 Hz, 1 H), 3.93 (bs, 1 H), 3.80 (s, 3 H), 2.54–2.64 (m, 1 H), 2.42–2.51 (m, 1 H), 2.36 (td, *J* = 13.5, 6.0 Hz, 1 H), 2.04–2.12 (m, 1 H), 1.75–1.82 (m, 1 H), 1.55–1.70 (m, 3 H), 1.27–1.32 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 214.88, 158.64, 133.62, 126.93, 113.59, 70.42, 57.29, 55.26, 42.70, 27.99, 26.20, 24.90.

4-Hydroxy-4-(4-nitrophenyl)butan-2-one (8p)[25]

Yellow solid; yield: 99.3 mg (95%).

HPLC (Daicel Chiralpak IC column, hexane/2-propanol 92.5:7.5, 0.8 mL·min^{-1}, 40 °C, 254 nm): t_R = 23.8 (minor), 25.1 (major) min; 65% *ee*.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.7 Hz, 2 H), 7.54 (d, *J* = 8.1 Hz, 2 H), 5.24–5.30 (m, 1 H), 3.68 (s, 1 H), 2.83–2.89 (m, 1 H), 2.22 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.61, 149.98, 147.32, 126.44, 123.80, 68.91, 51.53, 30.75.

2-(Hydroxy(4-nitrophenyl)methyl)cyclopentan-1-one (8q)[26]

Yellow solid; yield: 116.3 mg (99%).

HPLC (Daicel Chiralpak AD-H column, hexane/2-propanol 95:5, 0.5 mL·min^{-1}, 40 °C, 254 nm): t_R = 49.4 (*syn*), 66.1 (*syn*), 80.2 (*anti* minor), 84.4 (*anti* major) min; *anti*/*syn* 34:66; 70% *ee* (*syn*).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18–8.25 (m, 2 H), 7.52 (t, *J* = 8.8 Hz, 2 H), 4.84 (d, *J* = 9.2 Hz, 1 H), 4.78 (s, 1 H), 2.43–2.52 (m, 1 H), 2.34–2.43 (m, 1 H), 2.10–2.33 (m, 1 H), 1.98–2.07 (m, 1 H), 1.66–1.76 (m, 2 H), 1.49–1.61 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (characteristic peaks of both diastereomers) = 222.30, 219.52, 150.17, 148.64, 147.65, 147.18, 127.37, 126.38, 123.75, 123.67, 74.44, 70.48, 56.09, 55.10, 38.95, 38.62, 26.86, 22.42, 20.38, 20.34.

2-(Hydroxy(4-nitrophenyl)methyl)-4-methylcyclohexan-1-one (10)[21]

White solid; yield: 125.8 mg (96%).

HPLC (Daicel Chiralpak IC column, hexane/2-propanol 80:20, 1 mL·min^{-1}, 40 °C, 254 nm): t_R = 16.7 (major), 18.6 (minor) min; d.r. 88:12:0:0; 88% *ee*.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.6 Hz, 2 H), 7.50 (d, *J* = 8.6 Hz, 2 H), 4.92 (d, *J* = 8.4 Hz, 1 H), 3.89 (s, 1 H), 2.71–2.79 (m, 1 H), 2.50–2.60 (m, 1 H), 2.36–2.44 (m, 1 H), 2.01–2.15 (m, 1 H), 1.89–2.0 (m, 1 H), 1.75–1.85 (m, 1 H), 1.55–1.66 (m, 1 H), 1.24–1.37 (m, 1 H), 1.06 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 214.85, 148.39, 147.68, 127.82, 123.66, 74.17, 52.82, 38.15, 36.06, 32.87, 26.65, 18.17.

Recycling Procedure for the Aldol Reaction between 4-Nitrobenzaldehyde (6a) and Cyclohexanone (7a)

Cyclohexanone (**7a**; 0.50 mL, 5 mmol) and H_2O (50 μL, 2.78 mmol) were added to catalyst **C-1** (36.3 mg, 0.05 mmol) and the mixture was stirred at rt for 5 min. To this biphasic mixture, 2-fluorobenzoic acid (7 mg, 0.05 mmol) was added and the resulting mixture was stirred for 15 min at rt. 4-Nitrobenzaldehyde (**6a**; 151 mg, 1.0 mmol) was then added and the reaction mixture was stirred at rt for 2.5 h. The reaction mixture was then extracted with Et_2O (4 × 2 mL). The combined organic extract was concentrated under reduced pressure and the residue was purified by silica gel column chromatography EtOAc/petroleum ether (~1:3) to afford pure aldol adduct **8a** (246 mg, 99%). The reaction flask containing catalyst **C-1** was dried under vacuum for 1 h and then charged with the reactants again in identical amounts and order as above.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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