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Simple and inexpensive threonine-based organocatalysts for the highly diastereo- and enantioselective direct large-scale *syn*-aldol and *anti*-Mannich reactions of α-hydroxyacetone

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ABSTRACT

Simple and inexpensive threonine-based organocatalysts that promote *syn*-aldol reactions and three-component asymmetric *anti*-Mannich reactions of α-hydroxyacetone achieving a respectable level of enantioselectivities are reported. The *syn*-aldol products could be obtained with up to a 99:1 *syn*/*anti* ratio and >99% ee while the *anti*-Mannich products could be obtained with up to a 96:4 *anti*/*syn* ratio and >99% ee. Catalyst **1c** can be used efficiently on a large-scale with the enantioselectivities of the *syn*-aldol and *anti*-Mannich reactions being maintained at the same level, which offers a great possibility for application in industry.

1. Introduction

Chiral 1,2-diols and 1,2-amino alcohols are common structural motifs found in a vast array of natural and biologically active molecules.[1] Recently, significant efforts has been applied toward the development of direct catalytic asymmetric approaches to the construction of these units based on the addition of unmodified α-hydroxyketone to imines or aldehydes in aldol and Mannich-type reactions, respectively.[2,3] Although the studies of Shibasaki and Trost have provided routes to both *syn*-1,2-diols and *anti*-1,2-amino alcohols using metal-based catalysis,[2] highly enantioselective organocatalytic approaches have remained limited to *anti*-1,2-diols and *syn*-1,2-amino alcohols.[3] On the other hand, the aldol and Mannich reactions are some of the most powerful methods for the formation of C–C bonds in organic synthesis.[3] The classical aldol and Mannich reactions are highly atom-economic but suffer from problems with selectivity, notably, with respect to chemo- and regioselectivity. One of the most difficult challenges is the design of sustainable organocatalysis processes, which are not only more economical but also more benign toward the environment and more practicable both in industry and in practice.[4] Stimulated by this challenge, a great deal of effort is currently being made in the search for elegant and practical solutions for preparing highly stereoselective *syn*-1,2-diols and *anti*-1,2-amino alcohols. Due to the atom-economy, the direct one-pot three-component asymmetric Mannich reactions are some of the most elegant and synthetically attractive.[5] The first example of a direct organocatalytic three-component Mannich reaction was reported by List et al.,[6] and was followed by the excellent work of several other groups.[7–14] In addition to (*S*)-proline,[5–10] proline-derived tetrazoles,[11] acylic amino acids and their derivatives,[12,15a] and chiral phosphoric acids[13] have been developed as enantioselective organocatalysts for the direct one-pot three-component Mannich reactions. Although 1,2-amino alcohol and 1,2-diols can be constructed via Mannich reactions and aldol reactions of hydroxyketone to imines or aldehydes, hydroxyacetone is seldom used as a donor in the asymmetric-catalyzed direct Mannich reactions and aldol reactions.[5,11,12,14] Threonine derivatives were developed as organocatalysts for the direct one-pot three-component asymmetric *anti*-Mannich reactions and *syn*-aldol reactions of hydroxyketone to imines or aldehydes and were reported by Barbas, Lu, and our group.[12b,c,15a] The main limitation associated with *anti*-Mannich reactions and *syn*-aldol reactions is the requirement of a high catalyst loading.[6,12b,15a] This will raise a cost concern when large amounts of chiral materials are used for the large-scale synthesis. Therefore, the development of a new type of highly active organocatalysts with a natural crude chiral pool, simple preparation procedure, and inexpensive reagents is urgently needed. In our earlier studies,[15] we successfully developed simple and inexpensive threonine-based organocatalysts for a variety of reactions (including *anti*-aldol[15b,c] and three-component *anti*-Mannich[15a]) that work efficiently in both organic and aqueous media.

Given the success of threonine-based organocatalysts for *anti*-Mannich reactions and *syn*-aldol reactions pioneered by Barbas and Lu et al.,[12b,c] we herein report simple, inexpensive,

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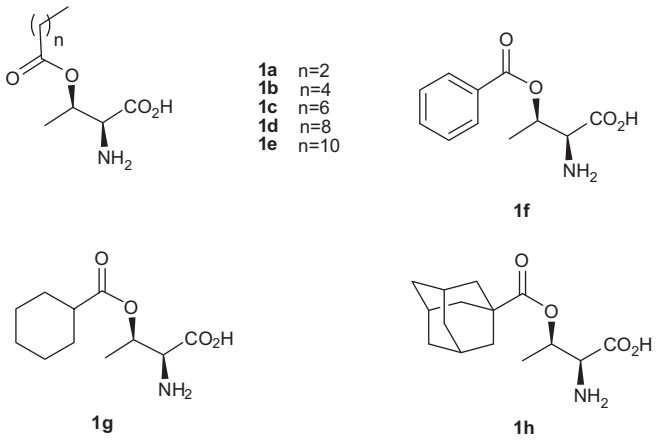


Figure 1. Threonine-based organocatalysts **1a**–**h**.

and efficient routes to not only highly enantiomerically enriched *anti*-1,2-amino alcohols but also to *syn*-1,2-diols through direct asymmetric *anti*-Mannich[15a] and *syn*-aldol reactions of unprotected hydroxyacetone catalyzed by threonine-based organocatalysts (Fig. 1). We first report that the catalyst **1c** can be used in large-scale *anti*-Mannich reactions and *syn*-aldol reactions with the enantioselectivities being maintained at the same level, which offers a great possibility for application in industry.

2. Results and discussion

On the basis of our design considerations, we first evaluated a variety of threonine-based derivatives **1a**–**h** for the *syn*-aldol reactions of hydroxyacetone in wet NMP to afford *syn*-aldol product **2a** (Fig. 1 and Table 1). In accordance with our hypothesis, threonine-based derivatives **1a**–**h** predominantly provided *syn*-aldol product **2a**, but the *syn*/*anti* ratios and ee's did vary. With all catalysts tested, the carbon-carbon formation with hydroxyacetone selectively occurred at the carbon bearing the hydroxyl group. Amongst the five synthesized threonine-based derivatives **1a**–**e** by the *O*-acylation of L-threonine with acyl chlorides, it was found that the chain length (n) dramatically affected the yields and the enantioselectivities for the *syn*-aldol reaction. Neither very long (n = 8, 10) nor very short carbon chains (n = 2, 4) were effective; the threonine-based derivative **1c** containing the *n*-octanoic group (n = 6) gave the best yield, diastereoselectivity and enantioselectivity for the *syn*-aldol reaction (Table 1, entries 3). Meanwhile, lower diastereoselectivities and enantioselectivities (Table 1, entries 6–8) were obtained using the more sterically hindered *O*-acylation of L-threonine **1f**–**h** compared to the less sterically hindered *O*-acylation of L-threonine **1c**. The results suggested that the steric hindrance of the O-acylation of L-threonine did not have an effect on the stereoselectivity. Therefore, we chose threonine-based organocatalyst **1c** as a catalyst for the *syn*-aldol reaction.

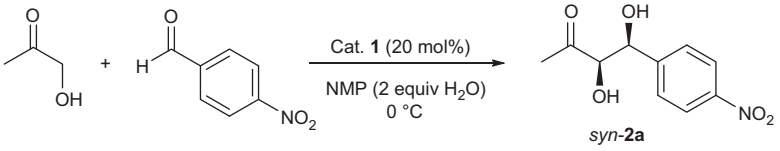
Next, NMP (2 equiv H_2O) was used as the media for the *syn*-aldol reaction of *p*-nitrobenzaldehyde and hydroxyacetone. We investigated the above reactions employing different amounts of threonine-based derivative **1c** (Table 2). When using a larger amount (20 mol %) of organocatalyst **1c**, the *syn*-aldol reaction was faster but diastereoselectivity was lower (Table 2, entry 1). The amount was changed to 3 mol %, after 48 h the yield was not good although the dr and ee values were high (Table 2, entry 5). Noticeably, when using 5 mol % of catalyst **1c** after 36 h, we obtained a good yield and excellent stereoselectivity (Table 2, entry 4).

A solvent screen was then performed at 0 °C to identify the best reaction conditions (Table 3, entries 1–5). Amongst the organic solvents tested, NMP–water was slightly better in terms of both diastereoselectivities and enantioselectivity for the *syn*-aldol reaction of *p*-nitrobenzaldehyde and hydroxyacetone, 99% ee was obtained for *syn*-aldol product **2a** (Table 3, entry 3). When the reaction was performed in DMSO, DMF, CH_3CN, or $ClCH_2CH_2Cl$, the enantioselectivity was slightly inferior to the results obtained in NMP–water. Thus, NMP (2 equiv H_2O) was selected as the solvent for the *syn*-aldol reaction.

Some aldol reactions have been performed under aqueous conditions, with the presence of water reported to increase the reactivity and stereoselectivity.[12b] Using catalyst **1c** (5 mol %) we investigated the effect of different amounts of water (Table 4). When in the presence of only 1 equiv of water (Table 4, entry 2), the *syn*-aldol product was obtained in good yield with good diastereo- and excellent enantioselectivity. However, using 2 or more equivalents of water (Table 4, entries 2–5) a high yield was observed. In each case, the stereoselectivity was high, but when a large amount of water (8 equiv) was employed, while we obtained excellent diastereo- and enantioselectivity, the yield decreased.

Conditions were optimized for the **1c**-catalyzed *syn*-aldol reactions. In order to test the substrate generality of this organocatalyzed direct *syn*-aldol reaction, the reactions of various aromatic

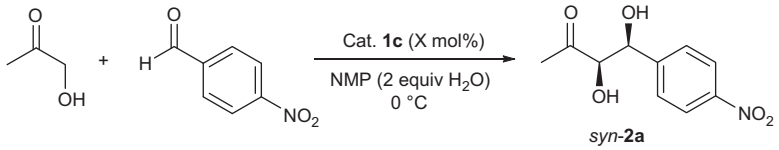
Table 1
Evaluation of catalysts for the *syn*-aldol reactions[a]



Entry	Cat.	Time (h)	Yield[b] (%)	dr (*syn:anti*)[c]	ee[d] (%)
1	**1a**	36	89	8:1	80
2	**1b**	24	91	7:3	84
3	**1c**	24	95	6:1	98
4	**1d**	36	90	7:1	84
5	**1e**	36	85	3:1	70
6	**1f**	36	83	4:1	80
7	**1g**	24	91	5:1	89
8	**1h**	24	92	5:1	93

[a] The reaction was performed with *p*-nitrobenzaldehyde (1 mmol), hydroxyacetone (3 mmol), and catalyst (0.2 mmol) in NMP–water (1 mL) at 0 °C.
[b] Isolated yield after chromatography on silica gel.
[c] The *anti* to *syn* ratio was determined by ^1H NMR analysis of the crude product.
[d] Determined by chiral HPLC analysis (AD-H).

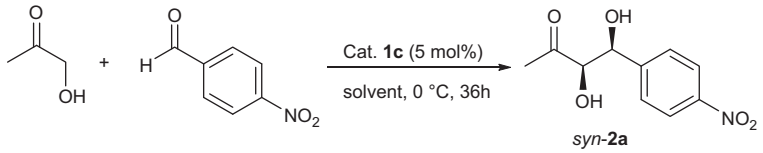
Table 2
Effects of catalyst loading on the *syn*-aldol reaction[a]



Entry	Catalyst (mol %)	Time (h)	Yield[b] (%)	dr (*syn*:*anti*)[c]	ee[d] (%)
1	20	24	95	6:1	98
2	15	24	92	20:1	98
3	10	36	94	49:1	99
4	5	36	94	49:1	99
5	3	48	83	19:1	93

[a] The reaction was performed with *p*-nitrobenzaldehyde (1 mmol), hydroxyacetone (3 mmol) and catalyst (see Table 2) in NMP–water (1 mL) at 0 °C.
[b] Isolated yield after chromatography on silica gel.
[c] The *anti* to *syn* ratio was determined by ^{1}H NMR analysis of the crude product.
[d] Determined by chiral HPLC analysis (AD-H).

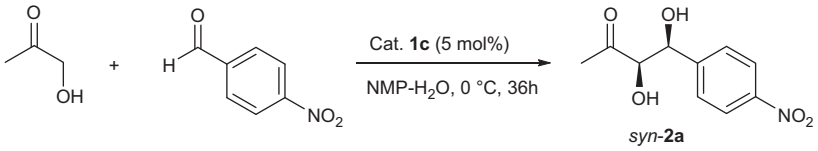
Table 3
Effects of solvent on the *syn*-aldol reaction[a]



Entry	Solvent	Yield[b] (%)	dr (*syn*:*anti*)[c]	ee[d] (%)
1	DMSO	91	4:1	78
2	DMF	89	8:1	80
3	NMP (2 equiv H_2O)	94	49:1	99
4	CH_3CN	80	4:1	80
5	$ClCH_2CH_2Cl$	85	4:1	90

[a] The reaction was performed with *p*-nitrobenzaldehyde (1 mmol), hydroxyacetone (3 mmol) and catalyst (0.05 mmol) in solvent (1 mL, see Table 3) 0 °C.
[b] Isolated yield after chromatography on silica gel.
[c] The *anti* to *syn* ratio was determined by ^{1}H NMR analysis of the crude product.
[d] Determined by chiral HPLC analysis (AD-H).

Table 4
Effects of the amount of water on the *syn*-aldol reactions[a]

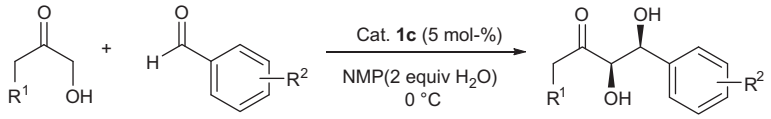


Entry	Water (equiv)	Yield[b] (%)	dr (*syn*:*anti*)[c]	ee[d] (%)
1	0	89	30:1	90
2	1	90	38:1	92
3	2	94	49:1	99
4	4	92	44:1	97
5	8	85	40:1	97

[a] The reaction was performed with *p*-nitrobenzaldehyde (1 mmol), hydroxyacetone (3 mmol) and catalyst (0.05 mmol) in NMP–water (see Table 4) 0 °C.
[b] Isolated yield after chromatography on silica gel.
[c] The *anti* to *syn* ratio was determined by ^{1}H NMR analysis of the crude product.
[d] Determined by chiral HPLC analysis (AD-H).

aldehydes with hydroxyacetone were studied. The results are summarized in Table 5. It can be seen that a wide range of aromatic aldehydes can effectively participate in the *syn*-aldol reactions. In general, the *syn*-aldol reaction between hydroxyacetone and aromatic aldehydes bearing electron-withdrawing substituents furnished β-hydroxy carbonyl aldol products in good yields (80–96%) and excellent enantioselectivities (92–>99%) within 36–72 h (Table 5, entries 1–10), especially the *p*-nitrobenzaldehyde and *m*-nitrobenzaldehyde (Table 5, entries 1 and 2, up to 99% ee). In contrast, longer reaction times (96 h) were required for aromatic aldehydes containing an electron-donating group to give comparatively lower yields (62–72%) (Table 5, entries 11, 12). This can be explained by the fact that the electron-withdrawing groups enhance the electrophilicity of the carbonyl carbons in aldehydes which facilitates the reaction, while electron-donating groups lessen the electrophilicity. Moreover, the direct

Table 5
Scope of the organocatalyzed direct *syn*-aldol reactions under optimal conditions[a]



2a-p

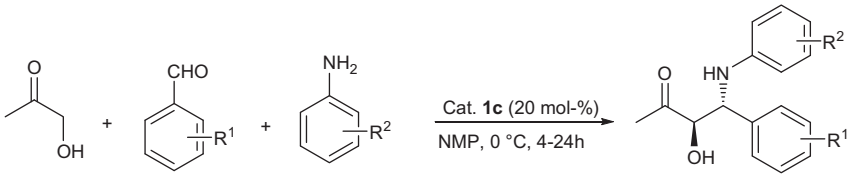
Entry	Product (R)	Time (h)	Yield [b] (%)	dr (*syn*:*anti*)[c]	ee[d] (%)
1	**2a** (R^1 = H, R^2 = 4-NO_2)	36	94	49:1	99
2	**2b** (R^1 = H, R^2 = 3-NO_2)	36	95	32:1	99
3	**2c** (R^1 = H, R^2 = 2-NO_2)	36	94	24:1	98
4	**2d** (R^1 = H, R^2 = 4-CN)	72	96	49:1	>99
5	**2e** (R^1 = H, R^2 = 4-Cl)	72	84	6:1	95
6	**2f** (R^1 = H, R^2 = 2-Cl)	72	80	32:1	96
7	**2g** (R^1 = H, R^2 = 4-Br)	72	85	6:1	97
8	**2h** (R^1 = H, R^2 = 3-Br)	72	82	4:1	93
9	**2i** (R^1 = H, R^2 = 2-Br)	72	81	16:1	96
10	**2j** (R^1 = H, R^2 = 4-F)	72	83	6:1	92
11	**2k** (R^1 = H, R^2 = 4-MeO)	96	72	4:1	96
12	**2l** (R^1 = H, R^2 = 4-CH_3)	96	62	4:1	95
13	**2m** (R^1 = H, R^2 = 1-naphthyl)	96	75	9:1	97
14	**2n** (R^1 = H, R^2 = 2-naphthyl)	96	73	6:1	94
15	**2o** (R^1 = H, R^2 = H)	96	56	4:1	90
16	**2p** (R^1 = OH, R^2 = 4-NO_2)	30	96	32:1	99

[a] The reaction was carried out using aldehyde (1.0 mmol), hydroxyacetone (3 mmol) and catalyst **1c** (0.05 mmol) in NMP–water (1 mL) at 0 °C.
[b] Isolated yield after chromatography on silica gel.
[c] The *anti* to *syn* ratio was determined by ^{1}H NMR analysis of the crude product.
[d] Determined by chiral HPLC analysis (AD-H, OD-H or OJ-H).

syn-aldol reaction of neutral aromatic aldehydes catalyzed by catalyst **1c** also afforded the products in high enantioselectivities and diastereoselectivities (Table 5, entries 13–15). Next, the direct *syn*-aldol reaction of dihydroxyacetone with 4-nitrobenzaldehyde afforded the corresponding product **2p** with excellent enantioselectivity (99% ee for *syn*-isomer) and diastereoselectivity (32:1 *syn*/*anti*) (Table 5, entry 16). All reactions of hydroxyacetone or dihydroxyacetone with aromatic aldehydes provided the corresponding products with excellent enantioselectivities (90–99% ee for *syn*-isomers) and good diastereoselectivities (*syn*/*anti* 4:1 to 49:1) (Table 5, entries 1–16).

We further investigated threonine-based organocatalyst **1c** as a catalyst in the three-component *anti*-Mannich reactions between aromatic aldehydes, aniline, and hydroxyacetone. The catalytic results are summarized in Table 6. When using a larger amount (20 mol %) of organocatalyst **1c**, the *anti*-Mannich reaction was

Table 6
The three-component direct asymmetric *anti*-Mannich reactions of different aldehydes[a]



3a-o

Entry	Product (R^1)	Time (h)	Yield[b] (%)	dr (*anti*:*syn*)[c]	ee[d] (%)
1	3a (R^1 = 4-NO_2; R^2 = 4-OMe)	4	92	11.5:1	98
2[e]	**3a** (R^1 = 4-NO_2; R^2 = 4-OMe)	4	80	3:1	86
3	**3b** (R^1 = 3-NO_2; R^2 = 4-OMe)	4	93	4:1	90
4	**3c** (R^1 = 2-NO_2; R^2 = 4-OMe)	4	90	6:1	91
5	**3d** (R^1 = 4-CN; R^2 = 4-OMe)	4	91	4:1	>99
6	**3e** (R^1 = 4-F; R^2 = 4-OMe)	8	92	1.3:1	94
7	**3f** (R^1 = 4-Cl; R^2 = 4-OMe)	8	90	4:1	96
8	**3g** (R^1 = 2-Cl; R^2 = 4-OMe)	8	87	8:1	97
9	**3h** (R^1 = 4-Br; R^2 = 4-OMe)	8	90	9:1	98
10	**3i** (R^1 = H; R^2 = 4-OMe)	12	75	1:1	70
11	**3j** (R^1 = 4-OMe; R^2 = 4-OMe)	12	78	2:1	76
12	**3k** (R^1 = 4-NO_2; R^2 = 3-MeO)	4	91	>10:1	99
13	**3l** (R^1 = 4-NO_2; R^2 = 4-Me)	5	93	>13:1	96
14	**3m** (R^1 = 4-NO_2; R^2 = 2,4-Me_2)	5	95	24:1	96
15	**3n** (R^1 = 4-NO_2; R^2 = 4-Cl)	4	95	24:1	95
16	**3o** (R^1 = 4-NO_2; R^2 = H)	10	89	9:1	98

[a] The reaction was performed with aldehydes (1.1 mmol), hydroxyacetone (3 mmol), aniline (1 mmol), and catalyst1c (0.2 mmol) in NMP (3 mL) at 0 °C.
[b] Isolated yield.
[c] The *anti* to *syn* ratio was determined by ^{1}H NMR analysis of the crude product.
[d] Determined by chiral HPLC analysis (AD-H).
[e] The catalyst loading was 10 mol %.

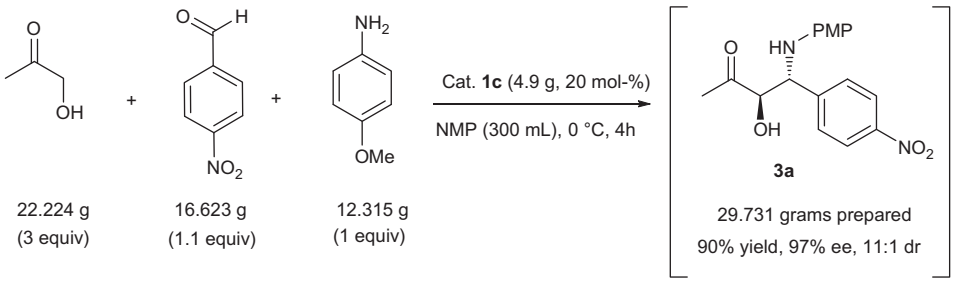


Figure 2. Large-scale example of enantioselective *anti*-Mannich reaction.

faster, the diastereoselectivity and enantioselectivity were higher than the other case (10 mol %) (Table 6, entries 1 and 2). Using the optimized conditions, the direct *anti*-Mannich reaction in *N*-methylpyrrolidone (NMP) catalyzed by catalyst **1c** was extended to a series of aromatic aldehydes to explore the generality of this catalytic system. It can be seen that a wide range of aromatic aldehydes can effectively participate in the reaction. In general, the reaction between hydroxyacetone, 4-methoxyaniline, and aromatic aldehydes bearing electron-withdrawing substituents furnished chiral 1,2-amino alcohols in excellent yields (87–92%), up to 99% ee (*anti*-isomer) and dr (*anti*/*syn*) values ranging from 1.2/1 to12/1 within 4–8 h (Table 6, entries 1–8), Moreover, the Mannich reactions of neutral and electron rich aromatic aldehydes catalyzed by the catalyst **1c** afforded the products in moderate enantioselectivities (70–76% ee) and diastereoselectivities (*anti*/*syn* = 1.3/1 to 2/1) (Table 6, entries 9, 10). The stereochemical outcome depended significantly on the electronic properties of the substituent groups on benzaldehydes. The electron-withdrawing groups had a positive effect on the enantioselectivities (Table 6, entries 1–10). In addition, different aniline components were also investigated (Table 6, entries 11–16); all of the selected aromatic amines furnished Mannich products in good yields (89–95%) with excellent diastereoselectivities (*anti*/*syn* = 9/1 to 24/1) and enantioselectivities (95–98% ee).

We first performed a large-scale asymmetric direct *anti*-Mannich reaction with 110 mmol of *p*-benzaldehydes, 4-methoxyaniline (100 mmol), and 3 equiv of hydroxyacetone (Fig. 2) using a 500 mL round-bottomed flask. Although the diastereoselectivity and enantioselectivity (88% yield, 97% ee, 98:1 dr) were maintained at the same level for the large-scale reaction, the main limitation associated with *anti*-Mannich reaction is the requirement of a high catalyst loading of **1c** (4.9 g, 20 mol %). This will raise a cost concern when large amounts of chiral materials are used for a large-scale synthesis in practical applications.

We further performed large-scale asymmetric direct *syn*-aldol reactions with 100 mmol of aromatic aldehydes and 3 equiv of hydroxyacetone using a 500 mL round-bottomed flask. The only catalyst loading of 5 mol % **1c** as in the experimental scale was used. The large-scale experiments can be easily carried out using the same procedure as for the experimental scale reactions. As can be seen from the results summarized in Table 7, delightfully, the enantioselectivity maintained at the same level for the large-scale reactions.

3. Conclusion

In conclusion, we have developed threonine-based organocatalysts, which efficiently catalyze the one-pot three-component *anti*-Mannich reactions of unprotected hydroxyacetone with high diastereo- and enantioselectivities in NMP. These catalysts also efficiently and selectively catalyze *syn*-aldol reactions of unprotected hydroxyacetone with excellent diastereo- and enantioselectivities in NMP–water. Furthermore, only 5 mol % of threonine-based organocatalyst **1c** was required to furnish the *syn*-aldol products in excellent diastereoselectivity (up to 99:1 *syn*/*anti*) and enantioselectivity (>99% for *syn*-isomers). Notably, these organocatalyzed direct asymmetric *anti*-Mannich and *syn*-aldol reactions can be performed on a large-scale with the enantioselectivity being maintained at the same level, which offers a great possibility for application in industry.

4. Experimental

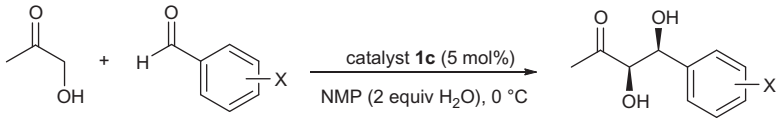
4.1. General

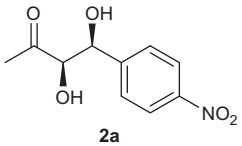
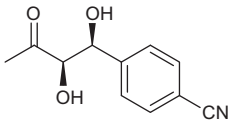
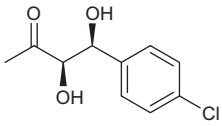
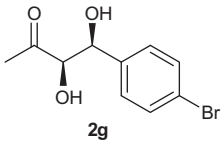
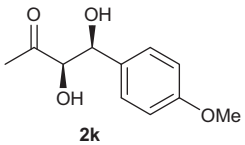
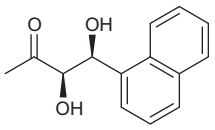
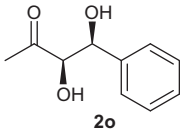
All reagents were commercial products. The reactions were monitored by TLC (thin layer chromatography). The column and preparative TLC purification were carried out using silica gel. Flash column chromatography was performed on silica gel (200–300 mesh). NMR spectra were recorded on a Bruker Avance 300 spectrometer at ambient temperature with tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on a Bruker Tenser 27 FTIR Spectrometer. Melting points were determined by differential scanning calorimetry (TAQ100) at a heating rate of 10 °C/min under an Ar atmosphere. Mass spectra (MS) were measured with a Bruker HCT Mass Spectrometer. Analytical high performance liquid chromatography (HPLC) was carried out on Agilent 1200 instrument using Chiralpak AD (4.6 mm × 250 mm), Chiralcel OD-H (4.6 mm × 250 mm), or Chiralcel OJ-H (4.6 mm × 250 mm) columns. Optical rotations were measured on a JASCO P-1010 Polarimeter at λ = 589 nm.

4.2. Typical experimental procedure for the preparation of the *O*-acylation threonine organocatalysts 1a–h[15,16]

A 500 mL round-bottomed flask was charged with CF_3CO_2H (120 mL) and placed in an ice/water bath. Powdered threonine (250 mmol) was added in small portions with vigorous stirring to give a viscous solution (leaving some small pieces of undissolved material). The reaction mixture was stirred for 15 min, and then removed from the ice/water bath. After 5 min of stirring, acyl chloride (375 mmol) was added in one portion. The reaction flask was fitted with a loose glass stopper, and the reaction mixture was stirred at room temperature without any external temperature adjustment for 12 h, giving a clear and colorless solution. The reaction flask was then cooled in an ice/water bath, and Et_2O (360 mL) was added under vigorous stirring over a period of 20 min, slowly at first. The resulting white suspension was stirred at 0 °C for 15 min, and then filtered by vacuum. The crystals were washed with two portions of Et_2O and dried at room temperature for 23 h in a ventilated hood to give the O-acylation threonine hydrochloride. This essentially pure material could be used for the next step. The O-acylation threonine hydrochloride was dissolved in water, and to it was added an equivalent amount of triethylethanamine (Et_3N). The resulting white suspension was stirred at room temperature for 10 min, and then filtered by

Table 7
Large-scale asymmetric *syn*-aldol reactions[a]



Entry	Product	Time (h)	Yield[b] (%)	dr (*syn*:*anti*)[c]	ee[d] (%)
1	 **2a**	36	93	99:1	98
2	 **2d**	72	95	99:1	>99
3	 **2e**	72	84	5:1	94
4	 **2g**	72	85	6:1	96
5	 **2k**	96	72	4:1	96
6	 **2m**	96	75	9:1	97
7	 **2o**	96	57	6:1	90

[a] The reaction was carried out using aldehyde (100 mmol), hydroxyacetone (300 mmol) and catalyst (5 mmol) in NMP–water (100 mL) at 0 °C.
[b] Isolated yield after chromatography on silica gel.
[c] The *anti* to *syn* ratio was determined by ^{1}H NMR analysis of the crude product.
[d] Determined by chiral HPLC analysis (AD-H and OD-H).

vacuum. The white crystals were washed with two portions of H_2O and dried to give O-acylation threonine-based organocatalysts **1a**–**h**. This essentially pure material was used for the next step without further purification

4.2.1. (2*S*,3*R*)-*O*-(*n*-Butyl)-L-threonine 1a

White solid; 51.17 g, yield: 96%; mp: 120–121 °C; $[\alpha]_D^{20} = +16.1$ (*c* 1, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 0.84–0.92 (m, 3H), 1.32–1.34 (d, *J* = 6.5 Hz, 3H), 1.45–1.60 (m, 2H), 2.26–2.31 (m, 2H), 4.13 (d, *J* = 2.7 Hz, 1H), 5.26–5.29 (dp, *J* = 3.5 Hz and 6.2 Hz, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ = 13.4, 16.7, 17.9, 35.4, 55.4, 67.7, 168.4, 171.7 ppm. MS (ESI) *m*/*z* calcd for ($C_8H_{15}NO_4$) 189.10. Found: 189.51. IR (KBr): *v* 2968, 1754, 1737, 1588, 1493, 1415, 1167, 1124, 1056, 747, 709 cm^{-1}.

4.2.2. (2*S*,3*R*)-*O*-(*n*-Hexanoyl)-L-threonine 1b

White solid; 61.38 g, yield: 97%; mp: 126–127 °C; $[\alpha]_D^{20} = +15.0$ (*c* 1, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6) δ = 0.84–0.88 (m, 3H), 1.05–1.26(m, 4H), 1.32–1.34 (d, *J* = 6.5 Hz, 3H), 1.45–1.60 (m, 2H), 2.27–2.32 (m, 2H), 4.13 (d, *J* = 2.7 Hz, 1H), 5.25–5.28 (dp, *J* = 3.6 Hz and 6.0 Hz, 1H)ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ = 13.9, 16.7, 21.8, 24.0, 30.6, 33.4, 55.4, 67.7, 168.5, 171.9 ppm. MS (ESI) *m*/*z* calcd for ($C_{10}H_{19}NO_4$) 217.13. Found: 217.51. IR (KBr): *v* 2959, 1759, 1737, 1413, 1340, 1166, 1125, 1057, 783, 715 cm^{-1}.

4.2.3. (2*S*,3*R*)-*O*-(*n*-Octanoyl)-L-threonine 1c

White solid; 66.77 g, yield: 95%; mp: 127–128 °C; $[\alpha]_D^{20} = +13.2$ (*c* 1, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 0.86–0.90 (m, 3H),

1.27 (br s, 8H), 1.34–1.36 (d, J = 6.6 Hz, 3H), 1.51–1.55 (m, 2H), 2.29–2.34 (m, 2H), 4.15 (d, J = 2.7 Hz, 1H), 5.27–5.30 (dp, J = 3.6 Hz and 6.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ = 14.0, 16.7, 22.1, 24.3, 28.4, 31.2, 33.5, 55.4, 67.6, 168.5, 171.8 ppm. MS (ESI) m/z calcd for ($C_{12}H_{23}NO_4$) 245.16. Found: 245.56. IR (KBr): ν 2957, 1758, 1737, 1413, 1383, 1208, 1164, 1122, 1055, 789, 635 cm^{-1}.

4.2.4. (2*S*,3*R*)-*O*-(*n*-Decanoyl)-L-threonine 1d

White solid; 74.20 g, yield: 96%; mp: 128–129 °C; $[\alpha]_D^{20} = +13.0$ (c 1, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6) δ = 0.84–0.86 (m, 3H), 1.24 (br s, 12H), 1.32–1.34 (d, J = 6.3 Hz, 3H), 1.40–1.42 (m, 2H), 2.27–2.31 (m, 2H), 4.15 (d, J = 2.7 Hz, 1H), 5.26–5.27 (dp, J = 3.6 Hz and 6.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ = 14.0, 16.7, 22.2, 24.3, 28.5, 28.8, 28.8, 28.9, 31.4, 33.5, 55.4, 67.7, 168.5, 171.8 ppm. MS (ESI) m/z calcd for ($C_{14}H_{27}NO_4$) 273.19. Found: 273.55. IR (KBr): ν = 2923, 2854, 1753, 1412, 1353, 1159, 1141, 1076, 744, 705 cm^{-1}.

4.2.5. (2*S*,3*R*)-*O*-(*n*-Dodecanoyl)-L-threonine 1e

White solid; 79.24 g, yield: 94%; mp: 127–128 °C; $[\alpha]_D^{20} = +11.6$ (c 1, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6) δ = 0.84–0.86 (m, 3H), 1.24 (br s, 16H), 1.31–1.33 (d, J = 6.6 Hz, 3H), 1.39–1.41 (m, 2H), 2.26–2.31 (m, 2H), 4.13 (d, J = 2.6 Hz, 1H), 5.25–5.28 (dq, J = 3.6 Hz and 6.3 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ = 14.1, 16.8, 22.3, 24.4, 28.5, 28.8, 28.9, 29.0, 29.2, 31.5, 33.5, 55.5, 67.7, 168.6, 171.9 ppm. MS (ESI) m/z calcd for ($C_{16}H_{31}NO_4$) 301.23. Found: 301.59. IR (KBr): ν = 2922, 2852, 1753, 1717, 1412, 1353, 1159, 1141, 1076, 744, 705 cm^{-1}.

4.2.6. (2*S*,3*R*)-*O*-(Benzoyloxy)-L-threonine 1f

White microcrystals, yield 50.78 g (227.5 mmol, 91 %); mp 144–145 °C; $[\alpha]_D^{20} = -12.8$ (c 1.02, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.46–1.48 (d, ^3J = 6.6 Hz, 3H, CH_3), 4.35 (br s, 1H, NC*H*), 5.55–5.58 ((dq, ^3J = 3.0 Hz and 6.5 Hz, 1H, 3-H, OC*H*), 7.52–7.57(m, 2H, Ph–H), 7.67–7.71(m, 1H, Ph–H), 8.10–8.13(m, 2H, Ph–H) ppm. ^{13}C NMR (75 MHz, DMSO): δ = 16.7, 55.6, 68.9, 128.7, 129.0, 129.9, 133.9, 164.6, 168.5 ppm. MS (ESI) m/z calcd for ($C_{11}H_{13}NO_4$) 223.23. Found: 223.47. IR (KBr): ν = 2985, 1759, 1716, 1650, 1602, 1586, 1493, 1415, 1157 cm^{-1}.

4.2.7. (2*S*,3*R*)-*O*-(Cyclohexylcarbonyl)-L-threonine 1g

White microcrystals, yield 51.64 g (225 mmol, 90%); mp 97–100 °C; $[\alpha]_D^{20} = +15.7$ (c 1.1, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.27–1.38 (m, 8H, cyclo–CH_2), 1.42–1.44 (d, ^3J = 6.6 Hz, 3H, CH_3), 1.84–1.88 (m, 2H, cyclo–CH_2), 2.30–2.38 (m, 1H, cyclo–CH_2), 4.22 (br s, 1H, NC*H*), 5.30–5.33 ((dq, ^3J = 3.2 Hz and 6.5 Hz, 1H, 3-H, OC*H*) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 16.9, 25.1, 25.2, 25.7, 28.6, 28.7, 42.4, 55.8, 67.9, 168.8, 174.2 ppm. MS (ESI) m/z calcd for ($C_{11}H_{19}NO_4$) 229.27. Found: 229.50. IR (KBr): ν = 3026, 2947, 2929, 2857, 1735, 1629 cm^{-1}.

4.2.8. (2*S*,3*R*)-*O*-(1-Adamantylcarbonyl)-L-threonine 1h

White microcrystals, yield 63.34 g (225 mmol, 90%); mp 97–100 °C; $[\alpha]_D^{20} = +5.4$ (c 1.2, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.28–1.30 (d, ^3J = 6.6 Hz, 3H, CH_3), 1.66 (m, 6H, cyclo–CH_2), 1.81 (m, 6H, cyclo–CH_2), 1.95 (m, 3H, cyclo–CH), 4.19 (br s, 1H, NC*H*), 5.24–5.27 ((dq, ^3J = 2.9 Hz and 6.6 Hz, 1H, 3-H, OC*H*) ppm. ^{13}C NMR (75 MHz, D DMSO-d_6): δ = 15.6, 16.6, 27.7, 36.3, 38.2, 40.5, 55.8, 65.3, 67.8, 168.8, 175.6 ppm. MS (ESI) m/z calcd for ($C_{15}H_{23}NO_4$) 281.35. Found: 281.52. IR (KBr): ν = 3026, 2968, 1758, 1726, 1601, 1575, 1493, 1415, 1157 cm^{-1}.

4.3. General procedure for catalytic asymmetric *syn*-aldol reactions using 1c as a catalyst

To a solution of the aldehyde (1 mmol, 1 equiv) and catalyst **1c** (0.05 mmol) in NMP (2 equiv water) was added hydroxyacetone or dihydroxyacetone (3 mmol, 3 equiv). The resulting reaction mixture was stirred at room temperature until the aldehyde was consumed as monitored by TLC (30–96 h). The reaction mixture was diluted with ethyl acetate (5 mL) and poured into a half saturated NH_4Cl solution. The mixture was extracted with ethyl acetate and the organic layers were combined and washed with brine, dried (Na_2SO_4), concentrated, and purified by flash column chromatography (mixtures of hexanes/ethyl acetate) to afford the desired aldol products **2a**–**p**.

4.3.1. (3*R*,4*S*)-3,4-Dihydroxy-4-(4-nitrophenyl) butan-2-one 2a[12b]

Yield 211.7 mg (0.94 mmol, 94%), *syn:anti* = 49:1, enantiomeric excess: 99% of *syn* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 80:20), 20 °C, 254 1 nm, 0.8 mL/min; major enantiomer t_R = 21.7 min, minor enantiomer t_R = 16.2 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.36 (s, 3H, CH_3), 2.68 (d, J = 8.1 Hz, 1H), 3.71 (d, J = 4.6 Hz, 1H), 4.40–4.42 (m, 1H), 5.20–5.22 (m, 1H), 7.60–7.63 (m, 2H), 8.24–8.27 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.0, 74.4, 82.0, 124.0, 128.6, 148.5, 150.8, 211.6 ppm.

4.3.2. (3*R*,4*S*)-3,4-Dihydroxy-4-(3-nitrophenyl) butan-2-one 2b[3j]

Yield 213.9 mg (0.95 mmol, 95%), *syn:anti* = 32:1, enantiomeric excess: 99% of *syn* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 85:15), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 20.99 min, minor enantiomer t_R = 16.00 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.36 (s, 3H), 2.70 (d, J = 8.2 Hz, 1H), 3.74–3.75 (m, 1H), 4.42–4.47 (m, 1H), 5.21–5.24 (m, 1H), 7.56–7.60 (m, 1H), 7.77–7.79 (m, 1H), 8.18–8.21 (m, 1H), 8.31–8.33 (m, 1H) ppm. ^{13}C NMR (75 Hz, $CDCl_3$) δ = 26.0, 72.8, 80.0, 121.4, 123.1, 129.6, 132.4, 142.5, 148.5, 206.9 ppm.

4.3.3. (3*R*,4*S*)-3, 4-Dihydroxy-4-(2-nitrophenyl) butan-2-one 2c[3j]

Yield 211.7 mg (0.94 mmol, 94%), *syn:anti* = 24:1, enantiomeric excess: 98% of *syn* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak OJ-H column (hexane/2-propanol = 80:20), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 30.3 min, minor enantiomer t_R = 35.8 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.51 (s, 3H), 4.55–4.56 (m, 1H), 5.89 (m, 1H), 7.48–7.53 (m, 1H), 7.70–7.74 (m, 1H), 7.79–7.81 (m, 1H), 8.09–8.11 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 25.2, 68.7, 78.9, 124.9, 128.8, 129.3, 33.9, 137.1, 147.0, 207.2 ppm.

4.3.4. 4-(3*R*,4*S*)-(1,2-Dihydroxy-3-oxobutyl) benzonitrile 2d[3j,12b]

Yield 197.0 mg (0.96 mmol, 96%), *syn:anti* = 49:1, enantiomeric excess: >99% of *syn* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 80:20), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 23.4 min, minor enantiomer t_R = 26.3 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.34 (s, 3H), 2.72 (d, J = 8.0 Hz, 1H), 3.71 (d, J = 4.6 Hz, 1H), 4.38–4.39 (m, 1H), 5.13–5.16 (m, 1H), 7.54–7.56 (m, 2H), 7.67–7.70 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.0, 74.6, 81.9, 111.8, 119.9, 128.6, 132.9, 149.0, 211.6 ppm.

4.3.5. (3*R*,4*S*)-4-(4-Chlorophenyl)-3,4-dihydroxybutan-2-one 2e[3j]

Yield 171.7 mg (0.80 mmol, 80%), *syn:anti* = 6:1, enantiomeric excess: 95% of *syn* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/

2-propanol = 90:10), 20 °C, 220 nm, 1.0 mL/min; major *syn* enantiomer t_R = 45.1 min, minor *syn* enantiomer t_R = 35.2 min. ^{1}H NMR (300 MHz, CD_3OD) δ = 2.26 (s, 3H), 4.20 (d, J = 2.74 Hz, 1H). 5.06 (d, J = 2.74 Hz, 1H), 7.31–7.43 (m, 4H) ppm. ^{13}C NMR (75 MHz, CD_3OD) δ = 27.1, 74.6, 82.1, 129.1, 129.2, 134.0, 141.7, 211.9 ppm.

4.3.6. (3*R*,4*S*)-4-(2-Chlorophenyl)-3,4-dihydroxybutan-2-one 2f[3j]

Yield 180.3 mg (0.84 mmol, 84%), *syn:anti* = 32:1, enantiomeric excess: 96% of *syn* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (hexane/2-propanol = 90:10), 20 °C, 220 nm, 1.0 mL/min; major *syn* enantiomer t_R = 16.2 min, minor *syn* enantiomer t_R = 18.4 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.41 (s, 3H), 2.79 (br s, 1H), 3.71(d, J = 4.3 Hz, 1H), 4.47–4.48 (m, 1H), 5.53–5.55 (m, 1H), 7.26–7.3 (m, 1H), 7.35–7.39 (m, 2H), 7.52–7.54 (m, 1H) ppm. ^{13}C NMR (75 Hz, $CDCl_3$) δ = 25.4, 70.0, 78.5, 127.1, 128.0, 129.1, 129.7, 131.2, 137.8, 207.5 ppm.

4.3.7. (3*R*,4*S*)-4-(4-Bromophenyl)-3,4-dihydroxybutan-2-one 2g[3j,12b]

Yield 220.2 mg (0.85 mmol, 85%), *syn*:*anti* = 6:1, enantiomeric excess: 97% of *syn* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90:10), 20 °C, 220 nm, 1.0 mL/min; major *syn* enantiomer t_R = 36.2 min, minor *syn* enantiomer t_R = 38.5 min. ^{1}H NMR (300 MHz, CD_3OD) δ = 2.26 (s, 3H), 4.20 (d, J = 2.8 Hz, 1H), 5.05 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H) ppm. ^{13}C NMR (75 MHz, CD_3OD) δ = 27.1, 74.6, 82.1, 122.0, 129.6, 132.1, 142.2, 211.8 ppm.

4.3.8. (3*R*,4*S*)-4-(3-Bromophenyl)-3,4-dihydroxybutan-2-one 2h[3j]

Yield 212.4 mg (0.82 mmol, 82%), *syn:anti* = 4:1, enantiomeric excess: 93% of *syn* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90:10), 20 °C, 220 nm, 1.0 mL/min; major *syn* enantiomer t_R = 28.4 min, minor *syn* enantiomer t_R = 20.7 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3H), 2.64 (d, J = 7.1 Hz, 1H), 3.67 (d, J = 4.4 Hz, 1H), 4.36–4.38 (m, 1H), 4.99–5.01 (m, 1H), 7.24–7.28 (m, 1H), 7.34–7.36 (m, 1H), 7.45–7.47 (m, 1H), 7.59–7.60 (m, 1H) ppm. ^{13}C NMR (75 Hz, $CDCl_3$) δ = 26.2, 73.2, 80.4, 122.8, 124.9, 129.5, 130.2, 131.3, 142.5, 207.5 ppm.

4.3.9. (3*R*,4*S*)-4-(2-Bromophenyl)-3,4-dihydroxybutan-2-one 2i[3j]

Yield 209.9 mg (0.81 mmol, 81%), *syn:anti* = 16:1, enantiomeric excess: 96% of *syn* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90:10), 20 °C, 220 nm, 1.0 mL/min; major *syn* enantiomer t_R = 16.9 min, minor *syn* enantiomer t_R = 20.2 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.43 (s, 3H), 2.83 (d, J = 8.5 Hz, 1H), 3.71(d, J = 4.3 Hz, 1H), 4.48–4.50 (m, 1H), 5.49–5.51 (m, 1H), 7.18–7.22 (m, 1H), 7.37–7.40 (m, 1H), 7.50–7.53 (m, 1H), 7.56–7.58 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 25.5,72.1, 78.5, 121.4, 127.7, 128.4, 129.5, 132.7, 139.3, 207.4 ppm.

4.3.10. (3*R*,4*S*)-4-(4-Fluorophenyl)-3,4-dihydroxybutan-2-one 2j[3j]

Yield 164.5 mg (0.83 mmol, 83%), *syn:anti* = 6:1, enantiomeric excess: 92% of *syn* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90:10), 20 °C, 220 nm, 1.0 mL/min; major *syn* enantiomer t_R = 20.7 min, minor *syn* enantiomer t_R = 18.2 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.33 (s, 3H), 2.83 (d, J = 8.5 Hz, 1H), 3.71(d, J = 4.3 Hz, 1H), 4.48–4.50 (m, 1H), 5.49–5.51 (m, 1H), 7.18–7.22 (m, 1H), 7.37–7.40 (m, 1H), 7.53–7.55 (m, 1H), 7.60–7.78 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.5, 67.8, 79.6, 115.3, 124.4, 127.8, 128.2, 129.8, 159.4, 207.2 ppm.

4.3.11. (3*R*,4*S*)-4-(4-Methoxy-phenyl)-3,4-dihydroxybutan-2-one 2k[3j]

Yield 151.4 mg (0.72 mmol, 72%), *syn:anti* = 4:1, enantiomeric excess: 96% of *syn* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90:10), 20 °C, 230 nm, 0.8 mL/min; major *syn* enantiomer t_R = 34.3 min, minor *syn* enantiomer t_R = 27.6 min. ^{1}H NMR (300 MHz, CD_3OD) δ = 2.23 (s, 3H), 3.77 (s, 3H), 4.18 (d, J = 3.29 Hz, 1H), 4.95 (d, J = 3.57 Hz, 1H), 6.86–6.91 (m, 2H), 7.30–7.36 (m, 2H) ppm. ^{13}C NMR (75 Hz, CD_3OD) δ = 27.2, 75.1, 82.6, 114.5, 128.8, 129.4, 134.7, 160.6, 212.1 ppm.

4.3.12. (3*R*,4*S*)-4-(4-Tolyl)-3,4-dihydroxybutan-2-one 2l

Yield 120.4 mg (0.62 mmol, 62%), *syn:anti* = 4:1, enantiomeric excess: 95% of *syn* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 96:4), 20 °C, 220 nm, 0.8 mL/min; major *syn* enantiomer t_R = 52.0 min, minor *syn* enantiomer t_R = 37.9 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.31 (s, 3H), 2.35 (s, 3H), 4.59 (d, J = 2.6 Hz, 1H), 5.15–5.16(d, J = 2.2 Hz, 1H), 7.17–7.28 (m, 4H) ppm. ^{13}C NMR (75 Hz, $CDCl_3$) δ = 27.2, 75.1, 80.2, 114.5, 128.8, 129.4, 134.7, 161.5, 212.3 ppm.

4.3.13. (3*R*,4*S*)-4-(1-Naphthyl)-3,4-dihydroxybutan-2-one 2m[12b]

Yield 172.7 mg (0.75 mmol, 75%), *syn:anti* = 9:1, enantiomeric excess: 97% of *syn* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90:10), 20 °C, 254 nm, 1 mL/min; major *syn* enantiomer t_R = 36.6 min, minor *syn* enantiomer t_R = 28.9 min. ^{1}H NMR (300 MHz, CD_3OD) δ = 2.32 (s, 3H), 4.35 (d, J = 2.0 Hz, 1H), 5.07 (d, J = 2.0 Hz, 1H), 7.48–7.93 (m, 6H), 8.27 (d, J = 8.4 Hz, 1H) ppm. ^{13}C NMR (75 MHz, CD_3OD) δ = 27.4, 72.0, 81.1, 123.5, 125.8, 126.3, 126.4, 127.2, 128.0, 130.0, 131.3, 135.1, 138.0, 213.4 ppm.

4.3.14. (3*R*,4*S*)-4-(2-Naphthyl)-3,4-dihydroxybutan-2-one 2n[3j,12b]

Yield 168.1 mg (0.73 mmol, 73%), *syn:anti* = 6:1, enantiomeric excess: 94% of *syn* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90:10), 20 °C, 254 nm, 1 mL/min; major *syn* enantiomer t_R = 46.5 min, minor *syn* enantiomer t_R = 31.5 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.28 (s, 3H), 4.45 (d, J = 2.1 Hz, 1H), 5.05 (d, J = 2.2 Hz, 1H), 7.40–7.88 (m, 6H), 8.11 (d, J = 8.4 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.4, 72.0, 81.1, 123.5, 125.8, 126.3, 126.4, 127.2, 128.0, 130.0, 131.3, 133.1, 134.0, 211.4 ppm.

4.3.15. (3*R*,4*S*)-4-(Phenyl)-3,4-dihydroxybutan-2-one 2o[3j,12b]

Yield 100.9 mg (0.56 mmol, 56%), *syn*:*anti* = 4:1, enantiomeric excess: 90% of *syn* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90:10), 20 °C, 220 nm, 1.0 mL/min; major *syn* enantiomer t_R = 27.4 min, minor *syn* enantiomer t_R = 20.4 min. ^{1}H NMR (300 MHz, CD_3OD) δ = 2.23 (s, 3H), 4.23 (d, J = 3.29 Hz, 1H), 5.04 (d, J = 3.02 Hz, 1H), 7.23–7.27 (m, 1H), 7.33 (t, J = 7.41 Hz, 2H), 7.42 (t, J = 8.23 Hz, 2H) ppm. ^{13}C NMR (75 Hz, CD_3OD) δ = 27.2, 75.4, 82.5, 127.6, 128.5, 129.1, 142.8, 212.1 ppm.

4.3.16. (3*R*,4*S*)-1,3,4-Trihydroxy-4-(4-nitrophenyl) butan-2-one 2p[3j]

Yield 231.6 mg (0.96 mmol, 96%), *syn:anti* = 32:1, enantiomeric excess: 99% of *syn* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/

2-propanol = 80:20), 20 °C, 254 1 nm, 1.0 mL/min; major enantiomer t_R = 65.7 min, minor enantiomer t_R = 73.2 min. ^{1}H NMR (300 MHz, CD_3OD) δ = 4.42 (d, J = 2.47 Hz, 1H), 4.59 (d, J = 1.65 Hz, 2H), 5.26 (d, J = 2.20 Hz, 1H), 7.71 (d, J = 8.78 Hz, 2H), 8.23 (dt, J = 8.78 Hz, 1.92 Hz, 2H) ppm. ^{13}C NMR (75 MHz, CD_3OD) δ 68.1, 74.6, 80.6, 124.1, 128.7, 148.6, 150.8, 212.6 ppm.

4.4. General procedure for three-component *anti*-Mannich reaction using 1c as a catalyst

A mixture of 1-methyl-2-pyrrolidinone (NMP, 3 mL), *p*-anisidine (1 mmol), aldehyde (1.1 mmol), hydroxyacetone (3 mmol), and catalyst **1c** (0.2 mmol) was vigorously stirred at 0 °C (monitored by TLC). Next, the mixture was diluted with AcOEt and a half saturated ammonium chloride solution was added. The mixture was extracted with AcOEt (three or four times). The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated *in vacuo*, and purified by flash column chromatography (hexanes/ethyl acetate) to afford the desired Mannich addition products **3a**–**n**.

4.4.1. (3*R*,4*R*)-3-Hydroxy-4-(*p*-methoxyphenyamino)-4-(*p*-nitrophenyl) butan-2-one 3a[12b]

Yield 303.9 mg (0.92 mmol, 92%), *anti:syn* = 11.5:1, enantiomeric excess: 98% of *anti* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 80:20), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 28.0 min, minor enantiomer t_R = 22.8 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.23 (s, 3H), 3.55 (br s, 1H), 3.69 (s, 3H), 4.56 (br s, 1H), 4.71 (d, J = 3.5 Hz, 1H), 4.88 (d, J = 3.5 Hz, 1H), 6.53 (d, J = 9.0 Hz, 2H), 6.70 (d, J = 9.0 Hz, 2H), 7.46 (d, J = 9.0 Hz, 2H), 8.13 (d, J = 9.0 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.6, 55.6, 60.1, 79.5, 114.9, 115.6, 123.7, 128.5, 139.4, 145.1, 147.6, 153.0, 206.4 ppm.

4.4.2. (3*R*,4*R*)-3-Hydroxyl-4-(4-methoxyanilino)-4-(3-nitrophenyl) butan-2-one 3b[11e]

Yield 307.2 mg (0.93 mmol, 93%), *anti*:*syn* = 4:1, enantiomeric excess: 90% of *anti* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90:10), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 23.9 min, minor enantiomer t_R = 19.6 min. ^{1}H NMR (300 Hz, CD_3OD) δ = 2.30 (s, 3H), 3.60 (s, 3H), 4.36 (d, J = 2.2 Hz, 1H), 4.95 (d, J = 2.2 Hz, 1H), 6.41 (d, J = 9.0 Hz, 2H), 6.61 (d, J = 9.0 Hz, 1H), 7.44–7.41 (m, 1H), 7.63 (d, J = 8.2 Hz, 1H), 8.04 (d, J = 8.2 Hz, 1H), 8.20 (s, 2H) ppm. ^{13}C NMR (75 Hz, CD_3OD): δ = 27.2, 75.1, 82.6, 114.5, 128.8, 129.4, 134.7, 160.6, 212.1 ppm.

4.4.3. (3*R*,4*R*)-3-Hydroxyl-4-(4-methoxyanilino)-4-(2-nitrophenyl) butan-2-one 3c[11e]

Yield 397.3 mg (0.90 mmol, 90%), *anti:syn* = 6:1, enantiomeric excess: 91% of *anti* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 80:20), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 25.3 min, minor enantiomer t_R = 14.5 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.44 (s, 3H), 3.67 (s, 3H), 4.64 (d, J = 1.1 Hz, 1H), 5.80 (d, J = 1.1 Hz, 1H), 6.41 (d, J = 8.9 Hz, 2H), 6.67 (d, J = 8.9 Hz, 2H), 7.41–7.45 (m, 1H), 7.54–7.59 (m, 2H), 8.09 (d, J = 8.3 Hz, 1H) ppm. ^{13}C NMR (75 Hz, $CDCl_3$) δ = 24.6, 53.7, 55.6, 78.6, 114.8, 115.0, 125.3, 128.5, 129.8, 133.7, 135.8, 139.0, 148.9, 152.7, 207.1 ppm.

4.4.4. (3*R*,4*R*)-3-Hydroxyl-4-(4-methoxyanilino)-4-(4-cyanophenyl) butan-2-one 3d[12b]

Yield 282.4 mg (0.91 mmol, 91%), *anti*:*syn* = 4:1, enantiomeric excess: >99% of *anti* diastereomer; Enantiomeric excess was determined *by* HPLC with a Chiralpak AD-H column (hexane/2-propanol = 80:20), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 31.4 min, minor enantiomer t_R = 38.4 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.20 (s, 3H), 3.55 (br s, 1H), 3.69 (s, 3H), 3.54 (br s, 1H), 4.68 (d, J = 3.5 Hz, 1H), 4.82 (d, J = 3.5 Hz, 1H), 6.52(d, J = 9.0 Hz, 2H), 6.70 (d, J = 9.0 Hz, 2H), 7.40 (d, J = 9.0 Hz, 2H), 7.57 (d, J = 9.0 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.6, 55.6, 60.2, 79.5, 111.9, 114.9, 115.6, 118.4, 128.3, 132.3, 139.4, 143.1, 152.9, 206.6 ppm.

4.4.5. (3*R*,4*R*)-3-Hydroxyl-4-(4-methoxyanilino)-4-(4-fluorophenyl) butan-2-one 3e[11e]

Yield 279.1 mg (0.92 mmol, 92%), *anti:syn* = 1.3:1, enantiomeric excess: 94% of *anti* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 85:15), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 20.4 min, minor enantiomer t_R = 15.3 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.09 (s, 3H), 3.62 (s, 3H), 4.31 (d, J = 2.5 Hz, 1H), 4.80 (d, J = 2.5 Hz, 1H), 6.39–6.41 (m, 1H), 6.48–6.50 (m, 1H), 6.60–6.65 (m, 2H), 6.84–6.97 (m, 2H), 7.18–7.19 (m, 1H), 7.21–7.27 (m, 1H) ppm. ^{13}C NMR (75 Hz, $CDCl_3$) δ = 25.2, 55.6, 58.6, 80.7, 114.9, 115.3, 115.4, 115.6, 128.7, 128.8, 140.0, 152.6, 207.4 ppm.

4.4.6. (3*R*,4*R*)-3-Hydroxyl-4-(4-methoxyanilino)-4-(4-chlorophenyl) butan-2-one 3f[12b]

Yield 287.8 mg (0.90 mmol, 90%), *anti:syn* = 4:1, enantiomeric excess: 96% of *anti* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90:10), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 30.3 min, minor enantiomer t_R = 46.8 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.15 (s, 3H), 3.54 (br s, 1H), 3.69 (s, 3H), 3.54 (br s, 1H), 4.64 (d, J = 3.5 Hz, 1H), 4.75 (d, J = 3.5 Hz, 1H), 6.54 (d, J = 9.0 Hz, 2H), 6.70 (d, J = 9.0 Hz, 2H), 7.21–7.26 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.6, 55.6, 59.9, 79.6, 114.8, 115.6, 128.7, 128.8, 133.8, 135.9, 139.9, 152.7, 207.0 ppm.

4.4.7. (3*R*,4*R*)-3-Hydroxyl-4-(4-methoxyanilino)-4-(2-chlorophenyl) butan-2-one 3g[11e]

Yield 278.2 mg (0.87 mmol, 87%), *anti:syn* = 8:1, enantiomeric excess: 97% of *anti* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90:10), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 23.7 min, minor enantiomer t_R = 21.8 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.28 (s, 3H), 3.67 (s, 3H), 4.40 (d, J = 2.4 Hz, 1H), 4.86 (d, J = 2.4 Hz, 1H), 6.49–6.51 (m, 1H), 6.57–6.58 (m, 1H), 6.66–6.73 (m, 2H), 7.07–7.09 (m, 1H), 7.13–7.17 (m, 2H), 7.21–7.27 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7, 54.9, 55.6, 78.1, 114.8, 114.9, 127.2, 128.7, 128.8, 129.6, 132.8, 136.3, 139.5, 152.5, 207.1 ppm.

4.4.8. (3*R*,4*R*)-3-Hydroxyl-4-(4-methoxyanilino)-4-(4-bromophenyl) butan-2-one 3h[12b]

Yield 327.8 mg (0.90 mmol, 90%), *anti:syn* = 9:1, enantiomeric excess: 98% of *anti* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 90:10), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 30.5 min, minor enantiomer t_R = 27.3 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.26 (s, 3H), 3.61(s, 3H), 4.32 (d, J = 2.3 Hz, 1H), 4.79 (d, J = 2.3 Hz, 1H), 6.40 (d, J = 8.9 Hz, 2H), 6.61 (d, J = 8.9 Hz, 2H), 7.17 (d, J = 8.4 Hz,2H), 7.39 (d, J = 8.4 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.7, 55.6, 60.0, 79.6, 114.8, 115.6, 122.0, 129.1, 131.7, 136.4, 139.8, 152.7, 206.9 ppm.

4.4.9. (3*R*,4*R*)-3-Hydroxy-4-(*p*-methoxyphenyamino)-4-phenylbutan-2-one 3i[11e]

Yield 214.0 mg (0.75 mmol, 75%), *anti:syn* = 1:1, enantiomeric excess: 70% of *anti* diastereomer; Enantiomeric excess was

determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 95:5), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 58.5 min, minor enantiomer t_R = 51.7 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.24 (s, 3H), 3.60 (s, 3H), 4.34 (d, J = 2.6 Hz, 1H), 4.81 (d, J = 2.6 Hz,1H), 6.60 (d, J = 8.9 Hz, 2H), 6.42 (d, J = 8.9 Hz, 2H), 7.20–7.16 (m, 1H), 7.29–7.24 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.7, 55.6, 60.5, 79.8, 114.7, 115.6, 127.4, 128.0, 128.5, 137.3, 140.2, 152.6, 207.4 ppm.

4.4.10. (3*R*,4*R*)-3-Hydroxy-4-(*p*-methoxyphenyamino)-4-(*p*-methoxyphenyl)butan-2-one 3j[11e]

Yield 246.0 mg (0.78 mmol, 78%), *anti:syn* = 2:1, enantiomeric excess: 76% of *anti* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 95:5), 20 °C, 254 nm, 0.8 mL/min; major enantiomer t_R = 60.5 min, minor enantiomer t_R = 53.3 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.12 (s, 3H), 3.68 (s, 3H), 3.74 (s, 3H), 4.62 (d, 1H, J = 3.6 Hz), 4.73 (d, 1H, J = 3.6 Hz), 6.57 (d, 2H, J = 8.8 Hz), 6.70 (d, 2H, J = 8.8 Hz), 6.79 (d, 2H, J = 8.8 Hz), 7.19 (d, 2H, J = 8.8 Hz) ppm. 13C NMR (75 MHz, $CDCl_3$): mixture of diastereomers δ = 25.27, 26.66, 55.08, 55.15, 55.56, 58.62, 59.83, 79.77, 80.81, 113.90, 11404, 114.71, 115.16, 115.63, 128.03, 128.44, 129.15, 131.17, 140.15, 14028, 152.32, 152.51, 158.90, 159.17, 207.52, 207.55 ppm.

4.4.11. (3*R*,4*R*)-3-Hydroxyl-4-(3-methoxyanilino)-4-(4-nitrophenyl) butan-2-one 3k[11e]

Yield 330.6 mg (0.91 mmol, 91%), *anti:syn* >10:1, enantiomeric excess: 99% of *anti* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 85:15), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 38.1 min, minor enantiomer t_R = 47.6 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.38 (s, 3H), 3.71 (s, 3H), 4.46 (d, J = 2.0 Hz, 1H), 5.08 (d, J = 2.0 Hz, 1H), 6.05–6.07 (m, 1H), 6.12–6.15 b(m, 1H), 6.26–6.29 (m, 1H), 7.00–7.02 (m, 1H), 7.58–7.57 (m, 2H), 8.12–8.19 (m, 2H) ppm. ^{13}C NMR (75 Hz, $CDCl_3$) δ = 25.5, 55.6, 58.4, 80.5, 100.8, 104.1, 107.3, 124.4, 128.6, 130.8, 147.3, 147.9, 148.0, 161.3, 207.2 ppm.

4.4.12. (3*R*,4*R*)-3-Hydroxyl-4-(4-methyanilino)-4-(4-nitrophenyl) butan-2-one 3l[11e]

Yield 292.3 mg (0.93 mmol, 93%), *anti:syn* >13:1, enantiomeric excess: 96% of *anti* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 85:15), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 29.7 min, minor enantiomer t_R = 34.7 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.17 (s, 3H), 2.36 (s, 3H), 4.45 (d, J = 2.3 Hz, 1H), 5.07 (d, J = 2.3 Hz, 1H), 6.42 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.1 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2H), 8.17 (d, J = 8.7 Hz, 2H) ppm. ^{13}C NMR (75 Hz, $CDCl_3$) δ = 20.9, 25.5, 58.7, 80.6, 114.5, 124.5, 128.7, 130.6, 143.5, 148.0, 207.1 ppm.

4.4.13. (3*R*,4*R*)-3-Hydroxyl-4-(2,4-dimethyanilino)-4-(4-nitrophenyl) butan-2-one 3m[11e]

Yield 311.9 mg (0.95 mmol, 95%), *anti:syn* = 24:1, enantiomeric excess: 96% of *anti* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 85:15), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 48.8 min, minor enantiomer t_R = 34.5 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.18 (s, 6H), 2.37 (s, 3H), 4.49 (d, J = 2.4 Hz, 1H), 5.11 (d, J = 2.4 Hz, 1H), 6.19 (d, J = 10.0 Hz, 1H), 6.75 (d, J = 10.0 Hz, 1H), 6.90 (s, 1H), 7.54 (d, J = 11.0 Hz, 2H), 8.20 (d, J = 11.0 Hz, 2H) ppm. ^{13}C NMR (75 Hz, $CDCl_3$) δ = 17.9, 20.9, 25.6, 58.7, 80.8, 111.9, 123.6, 124.6, 128.0, 128.3, 128.6, 132.1, 141.4, 148.0, 148.1, 207.1 ppm.

4.4.14. (3*R*,4*R*)-3-Hydroxyl-4-(4-chloroanilino)-4-(4-nitrophenyl) butan-2-one 3n[11e]

Yield 318.0 mg (0.95 mmol, 95%), *anti:syn* = 24:1, enantiomeric excess: 95% of *anti* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 80:20), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 19.4 min, minor enantiomer t_R = 17.7 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.37 (s, 3H), 4.45 (d, J = 2.5 Hz, 1H), 5.04 (s, 1H), 6.44 (d, J = 11.0 Hz, 2H), 7.04 (d, J = 11.0 Hz, 2H), 7.54 (d, J = 10.5 Hz, 2H), 8.18 (d, J = 10.5 Hz, 2H) ppm. ^{13}C NMR (75 Hz, $CDCl_3$) δ = 25.6, 58.6, 80.5, 115.6, 124.1, 124.6, 128.7, 129.2, 144.5, 147.3, 148.1, 207.0 ppm.

4.4.15. (3*R*,4*R*)-3-Hydroxyl-4-anilino-4-(4-nitrophenyl) butan-2-one 3o

Yield 267.3 mg (0.89 mmol, 89%), *anti:syn* = 9:1, enantiomeric excess: 98% of *anti* diastereomer; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane/2-propanol = 85:15), 20 °C, 254 nm, 1.0 mL/min; major enantiomer t_R = 23.6 min, minor enantiomer t_R = 35.8 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.31 (s, 3H), 4.40 (d, J = 2.0 Hz, 1H), 5.02 (d, J = 2.0 Hz, 1H), 6.43 (d, J = 7.8 Hz, 2H), 6.65–6.62 (m, 1H), 7.05–7.01 (m, 2H), 7.49 (d, J = 8.7 Hz, 2H), 8.13 (d, J = 8.7 Hz, 2H) ppm. ^{13}C NMR (75 Hz, $CDCl_3$) δ = 25.5, 58.4, 80.5, 114.3, 119.3, 124.4, 128.7, 130.0, 145.9, 147.9, 207.3 ppm.

4.5. General procedure for large-scale *anti*-Mannich and *syn*-aldol reactions

4.5.1. *anti*-Mannich reaction

A mixture of 1-methyl-2-pyrrolidinone (NMP, 300 mL), *p*-methoxyaniline (100 mmol), *p*-nitrobenzaldehyde (110 mmol), hydroxyacetone (300 mmol) and catalyst **1c** (4.9 g, 20 mol %) using a 1 L round-bottomed flask. The resulting mixture was vigorously stirred at 0 °C (monitored by TLC). Then, the mixture was diluted with AcOEt (200 mL) and a half saturated ammonium chloride solution was added. The mixture was extracted with AcOEt (3 × 300 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated *in vacuo*, and purified by flash column chromatography (hexanes/ethyl acetate) to afford the desired *anti*-Mannich addition products **3a** (29.731 g).

4.5.2. *syn*-Aldol reactions

To a mixture of catalyst **1c** (5 mmol) and ketone (300 mmol) were added aromatic aldehyde (100 mmol) and NMP (2 equiv water) (100 mL) using a 250 mL round-bottomed flask. The resulting mixture was stirred at 0 °C. The reaction was monitored by TLC. It was then quenched with 80 mL saturated NH_4Cl solution, extracted with EtOAc(3 × 200 mL), and dried over Na_2SO_4. Purification by flash chromatography afforded the corresponding pure products **2a** (20.943 g), **2d** (19.494 g), **2e** (18.301 g), **2g** (22.023 g), **2k** (15.136 g), **2m** (17.269 g), **2o** (10.271 g).

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