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D-Fructose-derived β-amino alcohol catalyzed direct asymmetric aldol reaction in the presence of *p*-nitrophenol†

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D-Fructose derived β-amino alcohols **2** and **3** were used as organocatalysts for direct asymmetric aldol reaction of various aromatic aldehydes with three kinds of cyclic ketones in the presence of different additives as a co-catalyst. The results showed that the combinations of β-amino alcohol **2** and *p*-nitrophenol built up a novel catalytic system. Loading of 20 mol% **2** and 15 mol% *p*-nitrophenol gave excellent yields (up to 98% with respect to aldehyde) of aldol reaction products with good enantioselectivity (up to 87% ee). Accordingly, a mechanism for the reaction was proposed by ^{1}H NMR spectrum in this paper. Furthermore, the catalysts can be reused and have the significant catalyst recovery (77–84%).

Introduction

Carbohydrate-based derivatives as chiral catalysts in direct asymmetric aldol reactions have been exploited in recent years.[1–9] Most of these catalysts, with attached other chiral moieties such as acyl groups,[1] proline,[2,4–8] or aminoacyl groups,[3] have been used as organocatalysts in the direct asymmetric aldol process. Peddinti and co-workers[9] first reported the glucosamine-based primary amine used independently as bifunctional organocatalyst in asymmetric synthesis. They proposed that glucosamine-derived organocatalyst **1** (Fig. 1) bearing a free hydroxyl group vicinal to primary amine functionality provided the best results in direct asymmetric aldol reaction through hydrogen bonding between the proton on the hydroxyl moiety and the carbonyl group of the aldehyde. More recently, Shen[10] reviewed asymmetric reactions using D-glucosamine derivatives as catalyst, highlighting the importance of D-glucosamine derivatives for applications in asymmetric aldol reactions.

D-Fructose, readily available and highly functionalized with several stereogenic centers, has been explored for numerous asymmetric transformations like asymmetric addition of diethylzinc to aldehydes,[11] 1,4-addition reactions,[12] hydrogenations,[13] oxygen transfer reactions,[14] Diels–Alder reactions[15] and epoxidation reactions.[16] As it is cheaper and has more structural flexibility than glucosamine, D-fructose was selected as the chiral pool in our studies, with the aim of widening its use in asymmetric transformations. We herein report D-fructose-derived organocatalysts **2** and **3** and their applications in direct asymmetric aldol reactions. Based on a structural difference on the carbohydrate moiety and less steric hindrance of the amino alcohol section than in **1**, D-fructose derivatives **2** and **3** were proposed as promising catalysts in the reaction. To the best of our knowledge, there are no reports about amino alcohols derived from D-fructose used as chiral catalysts for the direct asymmetric aldol reaction.

Our group has taken a long-term goal of developing novel chiral building blocks for asymmetric synthesis of drugs and their intermediates or natural products with carbohydrates as starting materials, such as the synthesis of natural product D-mannoheptulose,[17] the stereocontrolled formation of protected aminodeoxyalditols,[18] and synthesis of topiramate and its derivate from D-fructose.[19] In this context, we synthesized two kinds of D-fructose derived β-amino alcohols **2** and **3** (Fig. 1) according to our previous reports[20,21] to study their catalytic properties analogous to the reaction catalyzed by **1**. Starting with commercially available D-fructose, two types of di-*O*-isopropylidene-β-D-fructopyranoses can be conveniently prepared on a large scale in good yield with dry acetone using different ratios of H_2SO_4 as the catalyst. The final products **2** and **3** were received by esterification, hydrolysis, cyclic sulfation, azide substitution and reduction reactions. The aldol reaction was first tested in the presence of **2** and **3**; then, different additives were employed to select the most efficient cocatalyst system; finally, the optimized cocatalyst system was used to test the aldol reactions between different aromatic aldehydes and three kinds of cyclic ketones, which give excellent yields (up to 98% with respect to aldehyde) and good enantioselectivity (up to

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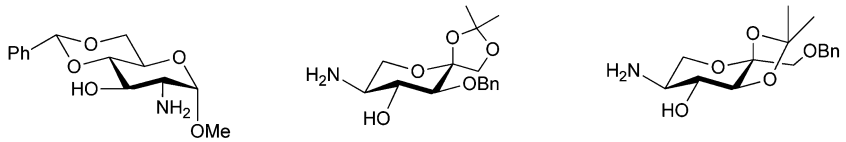


1 2 3

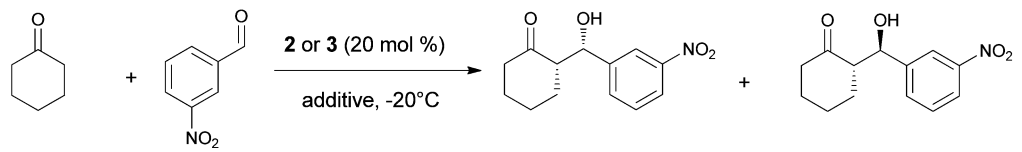
Fig. 1 The structure of β-amino alcohols **1–3**.

87% ee). A mechanism for the reaction was also proposed by ^{1}H NMR in this paper.

Results and discussion

Since the success of L-proline as a chiral catalyst in the direct asymmetric aldol reaction, chiral amines have demonstrated their significance in asymmetric C–C or heteroatom–C bond formation.[22] There have been a great deal of successful attempts to ameliorate the efficiency of the aldol process, the most remarkable improvement was attained by employing different additives, such as Lewis acids, 2,4-dinitrophenol, (*R*)- or (*S*)-binol, D-camphorsulfonic acid, or thiourea in combination with proline.[23–27] These additives could promote aldol reactions through hydrogen bonding or bind from the carboxyl group to metals. Thus, we assumed that these additives could be also applied to the direct asymmetric aldol reaction catalyzed by D-fructose-derived β-amino alcohol. A series of additives was first screened for efficiency in the aldol reaction between cyclohexanone and 3-nitrobenzaldehyde in the presence of β-amino alcohols **2** or **3** (Table 1). As several reports suggested that chiral reagents like 1-(2-hydroxynaphthalen-1-yl)naphthalen-2-ol (BINOL) or α,α,α′,α′-tetraaryl-1,3-dioxolan-4,5-dimethanol (TADDOL) could improve the enantioselection through hydrogen bonding,[24,28] (*S*)-BINOL was first employed as an additive. Inconspicuous improvement of the enantioselectivity

Table 1 The effect of additives on yield and ee for the aldol reaction between 3-nitrobenzaldehyde and cyclohexanone catalyzed by D-fructose derivatives **2** or **3**[a]



4a **5a** *syn*-**6a** *anti*-**6a**

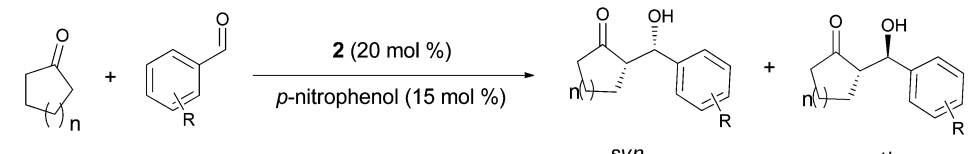
Entry	Catalyst	Additive (mol%)	Solvent	Time (h)	Yield[b] (%)	dr[c] *syn* : *anti*	ee[f] (%) *syn*	ee[f] (%) *anti*
1	**2**	No	Neat	48	38	1 : 2.70	2	73
2	**3**	No	Neat	48	60	1 : 0.59	24	50
3	**2**	(*S*)-BINOL (5)	Neat	47	40	1 : 3.80	31	73
4	**2**	(*S*)-BINOL (20)	Neat	24	19	1 : 1.71	32	68
5	**3**	(*S*)-BINOL (5)	Neat	47	67	1 : 0.55	15	46
6	**2**	*p*-Nitrophenol (10)	Neat	46	92	1 : 2.79	45	82
7	**2**	*p*-Nitrophenol (15)	Neat	23	94	1 : 2.80	59	83
8	**2**	*p*-Nitrophenol (20)	Neat	22	66	1 : 4.10	58	84
9	**3**	*p*-Nitrophenol (20)	Neat	22	73	1 : 0.80	4	31
10	**2**	F_3CCOOH (20)	Neat	75	20	1 : 4.30[e]	47	80
11	**2**	CH_3COOH (20)	Neat	23	71	1 : 0.78	33	48
12	**2**	PhCOOH (20)	Neat	46	91	1 : 0.76	26	36
13	**2**	Cl_3CCOOH (20)	Neat	94	8	1 : 3.19	73	54
14	**2**	TsOH (20)	Neat	94	Trace	1 : 1.44[e]	72	75
15	**2**	Citric acid (20)	Neat	70	80	1 : 0.68	31	74
16	**2**	$ZnCl_2$ (20)	Neat	24	31	1 : 1.73	34	3
17	**2**	$ZnCl_2$ (20)	DMSO : H_2O = 4 : 1[d]	24	Trace	1 : 1.79[e]	19	46
18	**2**	$FeSO_4$ (20)	DMSO : H_2O = 4 : 1[d]	24	Trace	1 : 0.88[e]	45	37
19	**2**	$Pb(OAc)_2$ (20)	DMSO : H_2O = 4 : 1[d]	24	Trace	1 : 2.13[e]	43	66

[a] Reactions were performed with 3-nitrobenzaldehyde (0.2 mM) and cyclohexanone (0.3 mL) in the presence of catalyst (0.04 mM) and additive. [b] Isolated yields. [c] Determined by ^{1}H NMR (400 MHz) of the crude sample. [d] **4a** : **5a** : catalyst = 5 : 1 : 0.2. [e] Determined by chiral HPLC analysis (Chiralcel AD-3). [f] Determined by chiral HPLC analysis.

with slightly inferior yield was observed compared with the reactions based on activation by only **2** or **3** (Table 1, entries 1–5). Hence, other additives were tested in our research. Further investigation found that strong acids like CF_3COOH, CCl_3COOH, TsOH could improve the *syn* or *anti* products with lower yields, probably due to the protonation of amine under acidic condition that lowered its nucleophilicity and therefore reduced yields of the reactions (Table 1, entries 10, 13 and 14). On the other hand, lower yields and enantioselectivity were observed by using weak acidic additives (Table 1, entries 11, 12 and 15). Several Lewis acids were also tested in our studies. Lower yields and low-to-moderate enantioselectivities were observed in both neat and DMSO–H_2O conditions (entries 16–19). Interestingly, however, *p*-nitrophenol proved to be the best additive both in terms of yield and enantioselectivity when **2** was employed as cocatalyst in the reaction (Table 1, entries 1 and 6–8). Increasing the amount of *p*-nitrophenol from 10 mol % to 15 mol% gave higher yield and enantioselectivity for both *syn* and *anti* products with less improvement for the dr (ratio of *syn* to *anti* products). In Da *et al.*'s[25] report, they explored DNP (2,4-dinitrophenol) as co-catalyst for asymmetric aldol reactions by employing 20 mol% DNP with 20 mol% amino alcohol catalysts and received excellent results. Based on their results, we increased the amount of *p*-nitrophenol from 15 mol% to 20 mol% and the reaction showed the dr increased from 1 : 2.8 to 1 : 4 (Table 1, entries 6–8) with lower yield. Finally, we found that higher enantioselectivity and near-quantitative yield were obtained by loading of 20 mol% **2** and 15 mol% *p*-nitrophenol into the reaction.

To explore the versatility of this catalytic system, further investigation between three types of cyclic ketones and several aromatic aldehydes were screened to broaden the scope of substrates in the presence of 20 mol% **2** and 15 mol% *p*-nitrophenol at −20 °C or −40 °C (Table 2). The reaction worked with aromatic aldehydes bearing both electron-donating and electron-withdrawing groups to afford aldol adducts **6a–n**. As can be seen from the results summarized in Table 2, we found that the yields of the reactions were dependent not only on the electronic nature of the substituents on the aromatic aldehyde, but also on their positions. For example, the aldol reaction between cyclohexanone and 3-nitrobezaldehyde afforded aldol product **6a** in a combined yield of 94% with 59% and 83% enantioselectivity for *syn* and *anti* products in 23 h at −20 °C (Table 2, entry 1). The 2-nitrobenzaldehyde as substrate gave rise to aldol product **6b** in 23 h with near-quantitative yield and moderate enantioselectivities (Table 2, entry 3). The halo-substituted benzaldehydes provided the corresponding products with lower yields and enantioselectivity compared with

Table 2 Direct aldol reactions between various cyclic ketones and aromatic aldehydes catalyzed by **2**/*p*-nitrophenol[a]

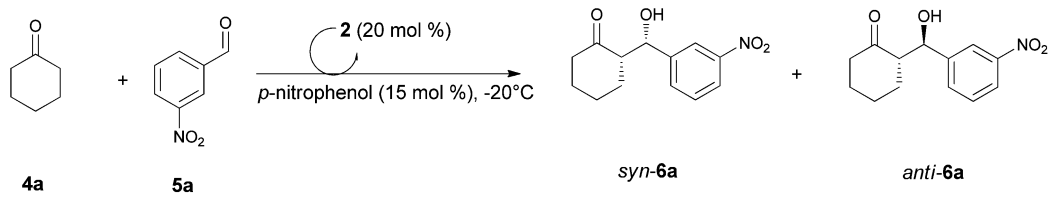


4a (n = 2) **4b** (n = 3) **4c** (n = 1) **5a-j** **6a-n**

Entry	R	*n*	Temp (°C)	Product	Time (h)	Yield[b] (%)	dr[c] *syn* : *anti*	ee[d] (%) *syn*	ee[d] (%) *anti*
1	3-NO_2	2	−20	**6a**	23	94	1 : 2.80	59	83
2	3-NO_2	2	−40	**6a**	69	67	1 : 0.89	67	73
3	2-NO_2	2	−20	**6b**	23	96	1 : 2.29	45	75
4	2-NO_2	2	−40	**6b**	69	41	1 : 6.22	6	57
5	4-NO_2	2	−20	**6c**	23	98	1 : 2.66	46	80
6	4-NO_2	2	−40	**6c**	96	71	1 : 3.07	60	87
7	2-NO_2	1	−20	**6d**	67	21	1 : 1.12	48	84
8	3-NO_2	1	−20	**6e**	72	35	1 : 3.10	39	66
9	4-NO_2	1	−20	**6f**	72	48	1 : 4.52	35	68
10	3-NO_2	3	−20	**6g**	67	37	1 : 0.92	19	16
11	3-Cl	2	−20	**6h**	68	69	1 : 1.83	14	68
12	4-Cl	2	−20	**6i**	90	68	1 : 0.61	37	25
13	3-Br	2	−20	**6j**	75	72	1 : 1.24	29	63
14	4-Br	2	−20	**6k**	68	81	1 : 2.10	45	72
15	4-F	2	−20	**6l**	64	57	1 : 0.60	41	42
16	3-NO_2-4-Cl	2	−20	**6m**	75	72	1 : 1.65	35	49
17	3-OMe	2	−20	**6n**	72	56	1 : 1.64	74	21

[a] Reactions were performed with aldehyde (0.2 mM) and cyclic ketones (0.3 mL) in the presence of catalyst (0.04 mM) and additive. [b] Isolated yields. [c] Determined by ^{1}H NMR (400 MHz) of the crude sample. [d] Determined by chiral HPLC analysis.

Table 3 Recovery and reuse of **2** between 3-nitrobenzaldehyde and cyclohexanone



Cycle	Recovery of **2**[a] (%)	Time (h)	Yield[a] (%)	dr[b] *syn* : *anti*	ee[d] (%) *syn*	ee[d] (%) *anti*
1	84	24	93	1 : 2.39[c]	48	81
2	81	24	88	1 : 2.68	46	78
3	80	24	90	1 : 2.41	48	80
4	77	24	91	1 : 2.77	48	79
5	79	24	89	1 : 2.62	45	80

[a] Isolated yields. [b] Determined by HPLC analysis. [c] Determined by column chromatography. [d] Determined by chiral HPLC analysis (Chiralcel AD-3).

nitrobenzaldehydes (Table 2, entries 1, 3, 5 and 11–15); an electron-donating group like methoxy can improve the enantioselectivity of the *syn* product compared with other tested groups (Table 2, entries 1, 3, 5 and 11–17). Reaction temperature is another important impact factor. In our studies, reactions using three types of nitrobenzaldehyde were implemented at −20 °C and −40 °C, respectively. The results showed that higher enantioselectivity and dr were observed at −40 °C with lower yield and longer reaction time when nitrobenzaldehydes were tested as substrate (Table 2, entries 2, 4 and 6), the results at −20 °C were encouraging with higher yield, shorter reaction time and higher enantioselectivity for most entries (Table 2, entries 1, 3 and 5). Furthermore, the ring strain of cyclic ketones was also closely related to the yield and enantioselectivity of the reaction. As a result, cyclohexanone showed the best activity with shorter reaction time, higher yield and enantioselectivity as compared to cycloheptanone and cyclopentanone, possibly due to the stability of the six-membered ring which can reduce the energy of the transition state to reach the asymmetric procedure (Table 2, entries 1, 8 and 10).

We explored the recovery of **2** for model reactions, and found ee and dr slightly decreased. It is noteworthy that the catalyst can be reused, and has the significant catalyst recovery (77–84%) (Table 3).

As shown in Fig. 2, by comparing the ratios of proton integration between benzaldehyde and the product at 10.15 ppm and 7.52 ppm, respectively, we found the proportion of (a) is much smaller than (b), and it revealed that the reaction

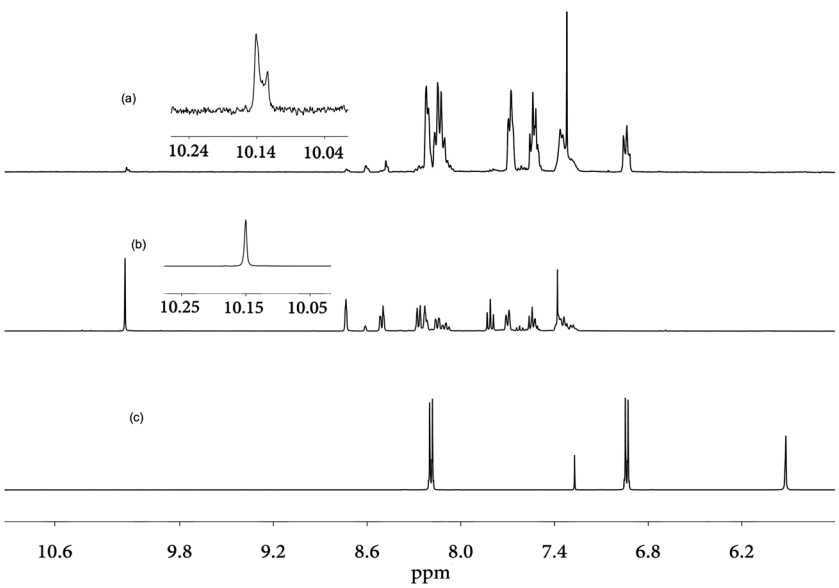


Fig. 2 ^{1}H NMR spectra for different reaction systems and *p*-nitrophenol. (a) The reaction mixture of 3-nitrobenzaldehye, cyclohexanone and organocatalyst **2** with *p*-nitrophenol as cocatalyst; (b) the same reaction conditions as (a) without *p*-nitrophenol; (c) ^{1}H NMR spectrum of *p*-nitrophenol.

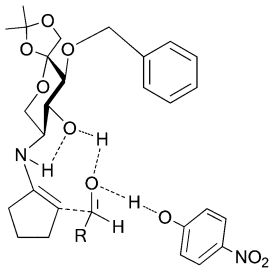


Fig. 3 Proposed transition state for the reaction.

proceeded swiftly and completely when *p*-nitrophenol was introduced to the reaction (Table 1, entries 1 and 7). Synchronously, the hydroxyl proton of *p*-nitrophenol at 5.91 ppm disappeared (Fig. 2a and c) and might be wrapped in low field, which meant that the proton of *p*-nitrophenol had probably formed a hydrogen bond in the reaction process; on the other hand, Abraham and Mobli[29] reported that the proton of CHO shifted upfield when there was an intramolecular hydrogen bond in the system. In our experiment, the proton of the aldehyde at 10.15 ppm became a double peak and shifted upfield (Fig. 2a and b), which fully confirmed that the *p*-nitrophenol activated carbonyl group of benzaldehyde through hydrogen bond. Based on the evidence discussed above and the early proposed mechanism for the amino alcohol catalyzed asymmetric aldol reaction without additives,[30–32] the probable transition state for our catalyst system is suggested and shown in Fig. 3. It is presumed that the reaction first proceeded through the dehydration of the carbinolamine intermediate, followed by the nucleophilic attack of the amine to the carbonyl groups of cyclic ketones. The C–C bond formation and hydrolysis of the amine–aldol then proceeded. The carbonyl group of the aromatic aldehyde could be activated by hydrogen bonding with *p*-nitrophenol and hydroxyl group at the C-4 position of fructose derivatives. *p*-Nitrophenol matched with amino alcohol through hydrogen bonding for higher catalytic efficiency, and this cocatalyst system is analogous to the reaction catalyzed by double hydrogen bonding,[33] which not only activated the carbonyl group of the aldehyde, but also stabilized the transition state.

Conclusions

In summary, we have demonstrated the use of amino alcohol **2** as a catalyst with *p*-nitrophenol as co-catalyst for the direct asymmetric aldol reaction between different cyclic ketones and a variety of aldehydes. Yields and enantioselectivities are moderate to good. Important features of this reaction are the following: (1) β-Amino alcohol **2** as catalyst can be synthesized from natural D-fructose by simple and high yield reactions. (2) *p*-Nitrophenol as co-catalyst is inexpensive, and readily commercial available. (3) The reactions do not require strict conditions and can be conducted neat. (4) The catalyst can be reused and has significant catalyst recovery. (5) This is the first example of a nonmetallic small-molecule catalyst, which is derived from D-fructose for direct intermolecular asymmetric aldol reaction. (6) The scope of application of this D-fructose catalyst for other related transformations could be explored in the near future.

Experimental

General information

Reagents were purchased at the highest commercial quality and used without further purification. Yields refer to chromatographically homogeneous materials, unless otherwise stated. Thin-layer chromatography (TLC) was carried out on silica gel 60 F254 (EMD Chemicals Inc.) and detection was performed by UV absorption (254 nm) where applicable, and by spraying with 50% sulfuric acid in ethanol followed by charring at ~150 °C, or by spraying with a solution of alkaline potassium permanganate followed by charring at ~100 °C.

Silica gel (particle size 200–300 mesh) was used for column chromatography. NMR spectra were recorded on a Bruker-400 (400/100 MHz) spectrometer equipped with Sun workstations. Multiplicities are quoted as singlet (s), doublet (d), doublet of doublets (dd), triplet (t), or multiplet (m). All NMR signals were assigned on the basis of ^{1}H NMR, ^{13}C NMR experiments. All chemical shifts are quoted on the δ scale in parts per million (ppm). Enantiomer ratios were determined by HPLC. HPLC was performed on an Aglient 1200 series system equipped with an autosampler, fraction-collector, UV detector, and Daicel-Chiralpak AD-3 column and Chiralpak IA-3 column (3 μm, 4.6 × 250 mm). Optical rotations were measured on a Shengguang WZZ-2B automatic polarimeter.

General procedure for direct asymmetric aldol reaction

To a solution of 0.03 mmol *p*-nitrophenol and 0.3 mL of ketone (cyclohexanone, cyclopentanone or cycloheptanone) were introduced 0.2 mmol of aldehyde and 0.04 mmol of catalyst (**2** or **3**). The mixture was stirred under the designed temperature until the completion of the reaction (monitored by TLC). The reaction mixture was directly purified by silica gel chromatography to afford the corresponding product.

General procedure for recycle experiment of 2

To a solution of 0.15 mmol *p*-nitrophenol and 1.5 mL of cyclohexanone were introduced 1.0 mmol of 3-nitrobenzaldehyde and 0.2 mmol of catalyst **2**. The mixture was stirred under −20 °C for 24 h. The reaction mixture was directly purified by silica gel chromatography to afford the corresponding product and **2**. **2** was desiccated to dryness and reused for the next recycle, the recycle experiments were performed 5 times.

2-[Hydroxy(3-nitrophenyl)methyl]cyclohexanone (6a)

2-[Hydroxy(3-nitrophenyl)methyl]cyclohexanone (**6a**): *syn* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.54–2.17 (m, 6H), 2.35–2.53 (m, 2H), 2.61–2.2.70 (m, 1H), 3.2 (d, J = 4 Hz, 1H), 5.49 (s, 1H), 7.52 (t, J = 8 Hz, 1H), 7.65 (d, J = 8 Hz, 1H), 8.12 (d, J = 8 Hz, 1H), 8.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.7, 25.9, 27.9, 42.6, 56.7, 69.9, 120.9, 122.1, 129.2, 131.9, 143.7, 148.3, 214.3; *anti* diastereomer, $[\alpha]_D^{23}$ + 23.4 (c 1, $CDCl_3$; 87% ee) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.47–2.09 (m, 6H), 2.25–2.36

(m, 1H), 2.38–2.61 (m, 2H), 4.05 (d, $J = 4$ Hz, 1H), 4.84–4.81 (dd, $J = 4$ Hz, 1H), 7.46 (t, $J = 8$ Hz, 1H), 7.60 (d, $J = 8$ Hz, 1H), 8.10 (d, $J = 8$ Hz, 1H), 8.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.7, 27.6, 30.7, 42.7, 57.1, 74.1, 122.0, 122.9, 129.3, 133.2, 143.2, 148.3, 214.9.

2-[Hydroxy(2-nitrophenyl)methyl]cyclohexanone (6b)

2-[Hydroxy(2-nitrophenyl)methyl]cyclohexanone (**6b**): *syn* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.48–1.88 (m, 5H), 2.07–2.14 (m, 1H), 2.38–2.48 (m, 2H), 2.85–2.90 (m, 1H), 3.29 (br, 1H), 5.97 (s, 1H), 7.43 (t, $J = 8$ Hz, 1H), 7.65 (t, $J = 8$ Hz, 1H), 7.84 (d, $J = 8$ Hz, 1H), 8.0 (d, $J = 8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.8, 28.0, 42.5, 54.8, 66.6, 124.7, 127.9, 129.6, 133.2, 137.0, 147.1, 214.1; *anti* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.59–2.49 (m, 8H), 2.68–2.81 (m, 1H), 4.2 (brs, 1H), 5.45 (d, $J = 8$ Hz, 1H), 7.43 (t, $J = 8$ Hz, 1H), 7.64 (t, $J = 8.4$ Hz, 1H), 7.77 (d, $J = 8$ Hz, 1H), 7.85 (d, $J = 8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 25.0, 27.8, 31.1, 42.8, 57.3, 69.8, 124.1, 128.4, 129.0, 133.1, 136.6, 148.7, 215.0.

2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone (6c)

2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone (**6c**): *syn* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.57–1.77 (m, 4H), 1.81–1.90 (m, 1H), 2.08–2.16 (m, 1H), 2.34–2.45 (m, 1H), 2.59–2.67 (m, 1H), 3.18 (d, $J = 4$ Hz, 1H), 5.49 (s, 1H), 7.49 (d, $J = 8$ Hz, 2H), 8.21 (d, $J = 8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.8, 25.9, 27.9, 42.6, 56.8, 70.1, 123.5, 126.6, 147.0, 149.0, 214.1; *anti* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.52–1.74 (m, 4H), 1.79–1.87 (m, 1H), 2.07–2.17 (m, 1H), 2.31–2.42 (m, 1H), 2.54–2.64 (m, 1H), 4.08 (d, $J = 4$ Hz, 1H), 4.90 (dd, $J = 8$ Hz, 1H), 7.51 (d, $J = 8$ Hz, 2H), 8.21 (d, $J = 8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.7, 27.6, 30.7, 42.7, 57.2, 74.0, 123.6, 127.9, 147.6, 148.33, 214.8.

2-[Hydroxy(2-nitrophenyl)methyl]cyclopentanone (6d) (mix, *syn*/*anti* = 1 : 0.36)

2-[Hydroxy(2-nitrophenyl)methyl]cyclopentanone (**6d**) (mix, *syn*/*anti* = 1 : 0.36): *anti* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.68–1.74 (m, 2H), 1.94–2.15 (m, 4H), 2.36–2.50 (m, 1H), 2.65 (m, 1H), 5.85 (d, $J = 4$ Hz, 1H), 7.37 (t, $J = 8$ Hz, 1H), 7.69 (m, 1H), 7.83 (d, $J = 8$ Hz, 1H), 7.93 (d, $J = 8$ Hz, 1H); *syn* diastereomer, 4.41 (brs, 0.36H), 5.37 (d, $J = 8$ Hz, 0.36H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 20.2, 20.5, 23.0, 26.6, 38.6, 54.8, 55.5, 66.7, 69.1, 124.0, 124.6, 128.1, 128.6, 129.0, 133.2, 133.4, 136.3, 138.5, 147.0, 148.5, 218.8, 222.1.

2-[Hydroxy(3-nitrophenyl)methyl]cyclopentanone (6e) (mix, *syn*/*anti* = 1 : 0.52)

2-[Hydroxy(3-nitrophenyl)methyl]cyclopentanone (**6e**) (mix, *syn*/*anti* = 1 : 0.52): *anti* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.55–1.75 (m, 2H), 1.85–2.00 (m, 2H), 2.02–2.15 (m, 1H), 2.23–2.47 (m, 1H), 4.77 (d, $J = 8$ Hz, 0.41H), 7.52 (m, 2H), 8.02 (m, 2H); *anti* diastereomer, 3.23 (s, 0.72H), 5.34 (s, 0.78H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 20.3, 22.3, 26.8, 29.6, 38.6, 39.0, 55.0, 56.1, 70.1, 74.3, 120.5, 121.6, 122.2, 123.0, 129.3, 129.5, 131.7, 132.7, 143.6, 145.2, 148.3, 220.0, 222.5.

2-[Hydroxy(4-nitrophenyl)methyl]cyclopentanone (6f) (mix, *syn*/*anti* = 1 : 0.15)

2-[Hydroxy(4-nitrophenyl)methyl]cyclopentanone (**6f**) (mix, *syn*/*anti* = 1 : 0.15): *anti* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.63–1.83 (m, 2H), 1.88–2.09 (m, 2H), 2.09–2.34 (m, 1H), 2.34–2.55 (m, 2H), 4.78 (s, 0.13H), 4.85 (d, $J = 8$ Hz, 0.15H), 7.54 (d, $J = 8$ Hz, 2H), 8.22 (d, $J = 8$ Hz, 2H); *syn* diastereomer, 2.79 (s, 0.75H), 5.43 (s, 0.87H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 20.3, 22.3, 26.8, 38.6, 39.0, 55.1, 56.1, 70.4, 74.4, 123.6, 123.7, 126.4, 127.4, 147.1, 148.6, 150.4, 219.8, 222.3.

2-[Hydroxy(3-nitrophenyl)methyl]cycloheptanone (6g)

2-[Hydroxy(3-nitrophenyl)methyl]cycloheptanone (**6g**): *syn* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.24–1.32 (m, 2H), 1.41–1.54 (m, 1H), 1.59–1.74 (m, 2H), 1.77–1.95 (m, 3H), 2.42–2.55 (m, 1H), 2.58–2.69 (m, 1H), 2.83–2.92 (m, 1H), 3.27 (br, 1H), 5.30 (s, 1H), 7.53 (t, $J = 8$ Hz, 1H), 7.70 (d, $J = 8$ Hz, 1H), 8.12 (d, $J = 8$ Hz, 1H), 8.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 23.5, 23.9, 28.9. 29.1, 43.9, 57.1, 72.2, 121.0, 122.2, 129.2, 132.1, 144.3, 148.3, 217.6; *anti* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.27–1.39 (m, 2H), 1.47–1.57 (m, 1H), 1.59–1.75 (m, 2H), 1.76–1.82 (m, 2H), 2.18–2.59 (m, 2H), 2.80–3.01 (m, 1H), 3.63 (brs, 1H), 4.85 (d, $J = 8$ Hz, 1H), 7.63 (d, $J = 8$ Hz, 1H), 8.08 (d, $J = 8$ Hz, 1H), 8.16 (t, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 23.5, 28.2, 28.6, 44.1, 57.9, 74.7, 121.9, 122.8, 129.4, 133.1, 144.1, 148.3, 217.0.

2-[Hydroxy(3-chlorophenyl)methyl]cyclohexanone (6h)

2-[Hydroxy(3-chlorophenyl)methyl]cyclohexanone (**6h**): *syn* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.48–1.75 (m, 5H), 1.81–1.90 (m, 1H), 2.04–2.14 (m, 1H), 2.30–2.50 (m, 1H), 2.52–2.62 (m, 1H), 3.09 (d, $J = 4$ Hz, 1H), 5.36 (s, 1H), 7.13–7.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.8, 25.9, 27.9, 42.6, 57.0, 70.1, 123.8, 126.0, 127.1, 129.4, 134.2, 143.6, 214.5; *anti* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.23–1.73 (m, 5H), 1.74–1.85 (m, 1H), 2.05–2.15 (m, 1H), 2.30–2.40 (m, 1H), 2.44–2.52 (m, 1H), 2.53–2.62 (m, 1H), 3.99 (s, 1H), 4.68 (d, $J = 8$ Hz, 1H), 7.14–7.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.7, 27.7, 30.8, 42.7, 57.3, 74.3, 125.3, 127.1, 128.0, 129.6, 134.3, 143.1, 215.2.

2-[Hydroxy(4-chlorophenyl)methyl]cyclohexanone (6i) (mix, *syn*/*anti* = 1 : 1.27)

2-[Hydroxy(4-chlorophenyl)methyl]cyclohexanone (**6i**) (mix, *syn*/*anti* = 1 : 1.27): *anti* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.46–1.62 (m, 2H), 1.62–1.74 (m, 2H), 1.75–1.89 (m, 1H), 2.03–2.14 (m, 1H), 2.30–2.42 (m, 1H), 2.51–2.61 (m, 1H), 4.0 (d, $J = 4$ Hz, 0.54H), 4.77 (dd, $J = 4$ Hz, 0.56H), 7.23–7.33 (m, 4H); *syn* diastereomer, 3.08 (d, $J = 4$ Hz, 0.4H), 5.35 (s, 0.44H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.7, 24.8, 25.9, 27.7, 27.9, 30.7, 42.6, 57.0, 57.3, 70.1, 74.1, 127.2, 128.3, 128.5, 132.7, 133.5, 139.5, 139.9, 214.6, 215.3.

2-[Hydroxy(3-bromophenyl)methyl]cyclohexanone (6j)

2-[Hydroxy(3-bromophenyl)methyl]cyclohexanone (**6j**): *syn* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.51–1.75 (m, 4H), 1.80–1.90 (m, 1H), 2.04–2.14 (m, 1H), 2.32–2.49 (m, 1H), 2.52–2.64 (m, 1H), 3.10 (d, $J = 4$ Hz, 1H), 5.35 (s, 1H), 7.21 (m, 2H), 7.37 (m, 1H), 7.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.8, 25.9, 27.9, 42.6, 57.0, 70.0, 122.5, 124.4, 129.0, 129.8, 130.1, 143.9, 214.5; *anti* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.24–1.36 (m, 1H), 1.52–1.74 (m, 3H), 1.76–1.84 (m, 1H), 2.01–2.13 (m, 1H), 2.29–2.40 (m, 1H), 2.42–2.51 (m, 1H), 2.52–2.62 (m, 1H), 4.02 (s, 1H), 4.74 (d, $J = 8$ Hz, 1H), 7.22 (m, 2H), 7.42 (m, 1H), 7.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.8, 27.7, 30.8, 42.7, 57.3, 74.2, 122.6, 125.8, 129.9, 130.0, 143.3, 215.2.

2-[Hydroxy(4-bromophenyl)methyl]cyclohexanone (6k) (mix, *syn*/*anti* = 1.26 : 1)

2-[Hydroxy(4-bromophenyl)methyl]cyclohexanone (**6k**) (mix, *syn*/*anti* = 1.26 : 1): *anti* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.47–1.73 (m, 4H), 1.75–1.88 (m, 1H), 2.04–1.13 (m, 1H), 2.30–2.41 (m, 1H), 2.42–2.50 (m, 1H), 2.51–2.90 (m, 1H), 3.99 (s, 0.41H), 4.75 (dd, $J = 8$ Hz, 0.42H), 7.19 (m, 2H), 7.46 (m, 2H); *syn* diastereomer, 3.08 (s, 0.53H), 5.33 (s, 0.56H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.7, 24.8, 25.9, 27.7, 27.9, 30.7, 42.6, 57.0, 57.3, 70.1, 74.2, 120.8, 121.7, 127.5, 128.7, 131.2, 131.5, 140.0, 140.5, 214.6, 215.3.

2-[Hydroxy(4-flourophenyl)methyl]cyclohexanone (6l) (mix, *syn*/*anti* = 1.41 : 1)

2-[Hydroxy(4-flourophenyl)methyl]cyclohexanone (**6l**) (mix, *syn*/*anti* = 1.41 : 1): *anti* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.52–1.89 (m, 5H), 2.04–2.14 (m, 1H), 2.29–2.49 (m, 2H), 2.52–2.62 (m, 1H), 4.0 (d, $J = 4$ Hz, 0.42H), 4.77 (d, $J = 8$ Hz, 0.41H), 7.02 (m, 2H), 7.29 (m, 2H); *syn* diastereomer, 3.06 (d, $J =$ 4 Hz, 0.53H), 5.36 (s, 0.59H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.7, 24.8, 26.0, 27.7, 28.0, 30.8, 42.7, 57.2, 57.5, 70.2, 74.1, 115.1, 115.3, 127.4, 128.6, 136.7, 137.1, 160.7, 163.1, 214.8, 215.1.

2-[Hydroxy(4-chloro-3-nitrophenyl)methyl]cyclohexanone (6m) (mix, *syn*/*anti* = 1.1 : 1)

2-[Hydroxy(4-chloro-3-nitrophenyl)methyl]cyclohexanone (**6m**) (mix, *syn*/*anti* = 1.1 : 1): *anti* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.48–1.78 (m, 4H), 1.81–1.92 (m, 1H), 2.07–2.17 (m, 1H), 2.31–2.44 (m, 1H), 2.44–2.52 (m, 1H), 2.53–2.66 (m, 1H), 4.10 (d, $J = 4$ Hz, 0.45H), 4.85 (dd, $J = 4$ Hz, 0.46H); *syn* diastereomer, 3.23 (s, 0.48H), 5.41 (s, 0.51H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.6, 24.7, 25.9, 27.5, 27.8, 30.6, 40.5, 40.6, 56.5, 57.0, 69.4, 73.4, 123.0, 124.0, 125.3, 126.1, 130.5, 131.5, 131.6, 131.7, 141.8, 142.4, 147.8, 213.9, 214.6.

2-[Hydroxy(3-methoxyphenyl)methyl]cyclohexanone (6n)

2-[Hydroxy(3-methoxyphenyl)methyl]cyclohexanone (**6n**): *syn* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.61–1.92 (m, 4H), 2.00–2.19 (m, 1H), 2.28–2.51 (m, 1H), 2.53–2.71 (m, 1H), 3.01 (s, 1H), 3.81 (s, 3H), 5.37 (s, 1H), 6.83 (m, 3H), 7.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.9, 26.0, 27.9, 42.7, 55.2, 57.2, 70.1, 111.5, 112.4, 118.0, 129.2, 143.2, 159.6, 214.8; *anti* diastereomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.49–1.72 (m, 4H), 1.74–1.84 (m, 1H), 2.03–2.13 (m, 1H), 2.31–2.40 (m, 1H), 2.44–2.51 (m, 1H), 2.55–2.65 (m, 1H), 3.81 (s, 3H), 3.93 (s, 3H), 4.76 (d, $J = 8$ Hz, 1H), 6.86 (m, 3H), 7.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.7, 27.8, 30.9, 42.7, 55.2, 57.4, 74.7, 112.4, 113.4, 119.5, 129.3, 142.5, 159.7, 215.5.

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