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Brønsted acid catalyzed enantio- and diastereoselective one-pot three component Mannich reaction

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ABSTRACT

A chiral derivative of 1,2-benzenedisulfonimide, (−)-4,5-dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide is herein proven to be an efficient chiral catalyst in a one pot three-component Mannich protocol. Reaction conditions are mild and green, while the enantio- and diastereoselectivity are excellent.

1. Introduction

Mannich reactions[1] are among the most important carbon–carbon bond forming reactions in synthetic organic chemistry and are a standard method for the synthesis of β-amino carbonyl compounds, which are key intermediates in the production of several nitrogen containing natural products and pharmaceuticals.[2] The reaction can be conducted either via a two or three-component protocol.[2]

Three-component reactions have proven themselves to be a most useful synthetic approach, as the combination of three-components to generate new products in a single step provides simple, mild and economically valid procedures, which synthesize complex products along with the added advantages of atom efficiency and waste reduction.[3]

For these reasons, a three-component approach to the Mannich reaction which is carried out in the presence of various catalysts and which sees imines formed in situ, has gained considerable importance. A variety of catalysts have been used for this reaction including Brønsted[4] and Lewis acids[5] (organic or mineral), Lewis bases,[6] ionic liquids,[7] and many others.[2] Catalysts that allow the reaction to be carried out under mild and green conditions are obviously favoured.

Chiral catalyst promoted stereoselective Mannich reactions have also attracted considerable attention as they are a powerful protocol for the enantioselective preparation of β-amino carbonyl compounds.[8] In particular, the literature shows that L-proline[8] (first introduced by List[9a] in his seminal work), several of its derivatives,[8] other chiral amines,[8] thioureas[8,9b] and other chiral organocatalytic systems are all excellent catalysts.[8,9c,d]

It should be stressed that axially chiral Brønsted acids have also found their place as efficient catalysts, providing very good diastereo- and enantioselectivity.[8] Nevertheless, the majority of chiral Brønsted acid catalyzed Mannich reactions are still run with imine catalysis.[10] In fact the literature only contains a few examples of chiral Brønsted acid catalyzed one-pot three component Mannich reactions.

The most significant are as follows: in 2007 Gong et al.[11a] reported that an axially chiral phosphoric acid promoted an *anti*-selective direct asymmetric Mannich reaction between cyclohexanone and other heterocyclic ketones, aniline and various aldehydes (18 examples) with good diastereo- (average *anti*/*syn* ratio 87:13) and enantioselectivity (enantiomeric excess over 75%; average 85%) while acyclic ketones (6 examples) gave reasonably good enantioselectivity (enantiomeric excess over 70%; average 78%); it should be noted that to the best of our knowledge, this is the only significant example of a one-pot three component Brønsted acid catalyzed asymmetric Mannich reaction carried out in the presence of acyclic and aromatic ketones as Mannich donors.

In 2012 Zhang et al.[11b] demonstrated that a double axially chiral bisphosphorylimide was a very efficient catalyst in furnishing *syn*-β-aminoketones by reacting cyclohexanone, aniline and various aldehydes (13 examples) with excellent diastereo- (average *syn*/*anti* ratio over 99:1) and enantioselectivity (enantiomeric excess over 90%; average 97%). Furthermore, in 2012 Enders et al.[11c] synthesized a new planar chiral Brønsted acid, which was derived from [2.2]paracyclophane and tested it in a direct asymmetric Mannich reaction between cyclohexanone, 4-nitrobenzaldehyde and aniline giving poor enantiomeric excess (38%).

We have recently reported the use of *o*-benzenedisulfonimide **1** (Fig. 1) in catalytic amounts as a safe, non-volatile and non-corrosive Brønsted acid in several acid-catalyzed organic reactions, and

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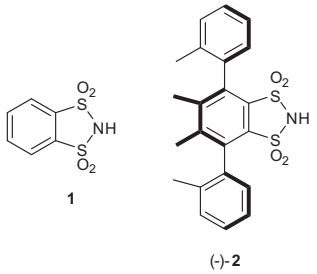
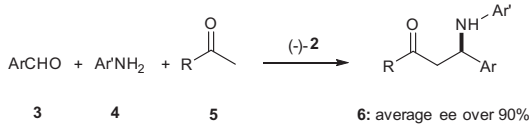


Figure 1. *o*-Benzenedisulfonimide **1** and (−)-4,5-dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide **2**.



Scheme 1. Three-component Mannich reaction catalyzed by (−)-**2**.

obtained excellent results.[12a] The results and advantages of using of *o*-benzenedisulfonimide **1** are very promising if one considers its applications in the field of asymmetric catalysis. Therefore, a chiral derivative of 1,2-benzenedisulfonimide, 4,5-dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide **2** (Fig. 1) has been synthesized and its (−)-atropisomer has been demonstrated to be an efficient chiral catalyst in Strecker reactions.[12b]

In light of this research and in order to further enhance the new chiral catalyst (−)-**2**, we herein report our studies into a stereoselective three-component Mannich reaction between aromatic aldehydes **3**, aromatic amines **4** and aromatic or aliphatic acyclic ketones **5** carried out in the presence of chiral catalyst (−)-**2** (Scheme 1).

2. Results and discussion

The model reaction between benzaldehyde **3a**, aniline **4a** and acetophenone **5a** was initially studied in the presence of a catalytic amount of (−)-**2** and under various conditions. As reported in Table 1, the best results were obtained in neat, green conditions, at rt and in the presence of 5% mol of **2**, which gave β-aminoketone **6a** in excellent yields and with excellent enantioselectivity (over 90%; entry 9).

Catalyst **2** was easily recovered and was reused in other two consecutive reactions. The results are listed in Table 2 where it can be seen that the yields and the enantioselectivity of **6a** were consistently good over the various runs.

Table 2
Consecutive runs with recovered (−)-**2**

Entry	Time (h)	Yield (%) of **6a**[a,b]	Recovery (%) of (−)-**2**	Ee (%) in **6a**
1	24	100	100, 11 mg[c]	90.2
2	24	94	91, 10 mg[d]	90.7
3	24	85	85, 8.5 mg	90.3

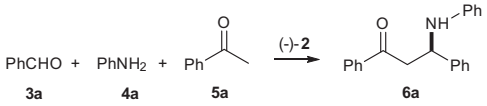
[a] Yields refer to the pure and isolated product.
[b] The reaction was performed at rt with 0.5 mmol of **3a**, **4a**, **5a** and 5 mol % of (−)-**2** (11 mg, 0.025 mmol).
[c] Recovered **2** was used as a catalyst in entry 2.
[d] Recovered **2** was used as a catalyst in entry 3.

Encouraged by these excellent results and with the optimized conditions in hand, a number of other aldehydes **3**, aromatic amines **4** and ketones **5** with electron withdrawing or electron donating groups were reacted. Target adducts **6** were always obtained in good yields and with excellent enantioselectivities (22 examples, average yield 86%; average enantiomeric excess 94%) regardless of the electronic effects of the substituents (Table 3), whereas their position was crucial: the reaction did not occur in the presence of a substituent at the *ortho*-position of **4** and **5** (Table 3; entries 10, 13 and 18), most likely due to the steric hindrance of these groups.

To further expand upon the scope of our work, we decided to test cyclohexanone **5g** as a carbonyl partner (Scheme 2).

At first, **1** was used as a catalyst and little diastereoselectivity was found when reacting **5g** with **3a** and **4a** (Table 4, entry 2), **3b** and **4a** (Table 4, entry 4), **3a** and **4c** (Table 4, entry 8). However, total diastereoselectivity was found when using (−)-**2**. In fact the *syn*-diastereomer was formed exclusively (Table 4). The *syn*-configuration was determined by comparing the chemical shift

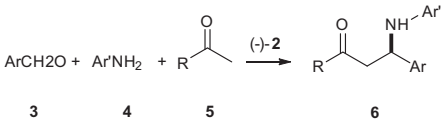
Table 1
Trial reactions



Entry	Solvent	**2**; mol %	Time (h)	Temperature (°C)	Yield (%) of **6a**[a,b]	Ee[c] (%)
1	Neat	–	24	50	–[d]	–
2	CH_2Cl_2	5	24	Reflux	48[b,d]	–
3	MeCN	5	24	50	62[b,d]	–
4	THF	5	24	50	25[b,d]	–
5	Toluene	5	24	50	51[b,d]	–
6	H_2O	5	24	50	12[b,d]	–
7	Neat	5	8	50	97[e]	53.5
8	Neat	10	6	50	94[e]	51.8
9	Neat	5	24	rt	96[e]	90.2
10	Neat	5	24	−20	45[b]	91.8
11	Neat[f]	5	24	rt	99[e]	6.7

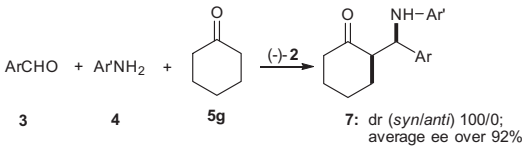
[a] Reactants **3a**, **4a** and **5a** were present in equimolar amounts (0.5 mmol).
[b] Yields refer to pure **6a**.
[c] Ee was determined by chiral analysis on GC connected to a column with a chiral stationary phase.
[d] GC–MS analyses showed the presence of starting products **3a**, **4a** and **5a**.
[e] Pure **6a** (GC, GC–MS, ^{1}H NMR) was obtained after filtering on a Büchner funnel and washing with a small amount of H_2O and petroleum ether the crude residues.
[f] The reaction was performed in the presence of 5% mol of **1** as a catalyst.

Table 3
Three-component Mannich reaction between **3**, **4**, **5** catalyzed by (−)-**2**



Entry	Ar in **3**	Ar′ in **4**	R in **5**	Products **6**	Time (h)	Yield[a] (%)	Ee (%) in **6**[b]
1	Ph; **3a**	Ph; **4a**	Ph; **5a**	**6a**	24	96[c]	90.2
2	4-MeC_6H_4; **3b**	Ph; **4a**	Ph; **5a**	**6b**	36	75[c]	92.8
3	2-MeC_6H_4; **3c**	Ph; **4a**	Ph; **5a**	**6c**	48	72[c]	92.2
4	3-MeC_6H_4; **3d**	Ph; **4a**	Ph; **5a**	**6d**	32	77[c]	93.6
5	4-$NO_2C_6H_4$; **3e**	Ph; **4a**	Ph; **5a**	**6e**	48	88[c]	96.8
6	2-$NO_2C_6H_4$; **3f**	Ph; **4a**	Ph; **5a**	**6f**	48	74[c]	96.4
7	3-$NO_2C_6H_4$; **3g**	Ph; **4a**	Ph; **5a**	**6g**	36	90[c]	97.8
8	4-ClC_6H_4; **3h**	Ph; **4a**	Ph; **5a**	**6h**	24	89[c]	97.8
9	Ph; **3a**	4-MeC_6H_4; **4b**	Ph; **5a**	**6i**	24	92[c]	90.2
10	Ph; **3a**	2-MeC_6H_4; **4c**	Ph; **5a**	—	48	—[d]	—
11	Ph; **3a**	3-MeC_6H_4; **4d**	Ph; **5a**	**6j**	32	77[c]	96.2
12	Ph; **3a**	4-$NO_2C_6H_4$; **4e**	Ph; **5a**	**6k**	28	100[c]	96.3
13	Ph; **3a**	2-$NO_2C_6H_4$; **4f**	Ph; **5a**	—	48	—[d]	—
14	Ph; **3a**	3-$NO_2C_6H_4$; **4g**	Ph; **5a**	**6l**	32	95[c]	92.0
15	Ph; **3a**	4-ClC_6H_4; **4h**	Ph; **5a**	**6m**	24	97[c]	95.0
16	Ph; **3a**	Ph; **4a**	4-MeC_6H_4; **5b**	**6n**	36	78[c]	92.2
17	Ph; **3a**	Ph; **4a**	4-ClC_6H_4; **5c**	**6o**	24	92[c]	95.4
18	Ph; **3a**	Ph; **4a**	2-MeC_6H_4; **5d**	—	48	—[d]	—
19	Ph; **3a**	Ph; **4a**	3-MeC_6H_4; **5e**	**6p**	48	81[c]	95.0
20	2-Thienyl; **3i**	Ph: **4a**	Ph; **5a**	**6q**	36	92[c]	90.6
21	Ph; **3a**	Ph; **4a**	*n*Pr; **5f**	**6r**	32	87[c]	94.2
22	4-MeC_6H_4; **3b**	Ph; **4a**	*n*Pr; **5f**	**6s**	48	71[c]	92.4
23	Ph; **3a**	4-$NO_2C_6H_4$; **4c**	*n*Pr; **5f**	**6t**	36	92[c]	90.2
24	4-$NO_2C_6H_4$; **3e**	4-MeC_6H_4; **4b**	4-ClC_6H_4; **5c**	**6u**	32	87[c]	91.8
25	3-ClC_6H_4; **3j**	3-$NO_2C_6H_4$; **4g**	3-MeC_6H_4; **5e**	**6v**	48	85[c]	91.2

[a] The reactants **3**, **4** and **5** were in equimolar amounts (0.5 mmol). The reactions were performed at rt in the presence of 5 mol % of (−)-**2**.
[b] Ee was determined by chiral analyses on GC connected to a column with a chiral stationary phase.
[c] Yields refer to the pure adducts **6** obtained after filtering on a Hirsch funnel and washing with a small amount of H_2O and petroleum ether. They were then purified in a short chromatography column (EP–EtOAc, 9:1).
[d] The reaction did not take place. The sole detected product on GC–MS analyses was the imine.



Scheme 2. Three-component Mannich reaction between **3**, **4** and cyclohexanone **5g** catalyzed by (−)-**2**.

and *J* values of ^{1}H NMR peaks in adducts **7a**–**d**, **7f** with those of the literature data.[13] Indeed, the *J* value of CH(NH) in the *anti*-diastereomer was approximately 6–7 Hz, while the same value in the *syn*-diastereomer is about 4 Hz. Moreover, the CH(NH) *anti*-proton was more shielded than the CH(NH) *syn*-proton. Interestingly, the enantioselectivity was excellent: the enantiomeric excess was over 90% (Table 4; average enantiomeric excess 92%) in the presence of an electron-donating group (Table 4; entry 2). In light of these results, it can be stated that (−)-**2** is a powerful chiral catalyst for the asymmetric one-pot three component Mannich reaction.

From a mechanistic point of view, it would appear obvious that (−)-**2** promotes imine **8** formation first. Then, as demonstrated by Akiyama,[10h] **2** protonates **8** to form iminium salt **9**, which bears the chiral counteranion of **2**. The formation of this ion pair **9** is fundamental to inducing enantioselectivity and thus creating the chiral environment needed to direct the nucleophile's attack towards the iminium salt (Scheme 3). This chiral Brønsted acid catalyzed reaction could be classified as asymmetric counterion directed catalysis (ACDC) for these reasons.[14]

3. Conclusion

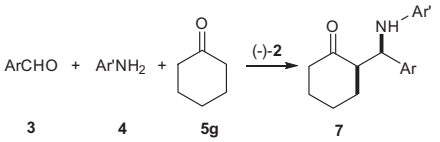
Herein we have reported on an asymmetric one pot three-component Mannich reaction catalyzed by (−)-4,5-dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide **2**. The target products β-amino ketones **6** and **7** were obtained via an efficient, mild, green and simple procedure. Enantio- (over 90%) and diastereoselectivity (dr 100:0) were always excellent and significantly better compared with those reported in the literature[11a] regarding asymmetric Mannich reactions involving acyclic and aromatic ketones.

4. Experimental

4.1. General

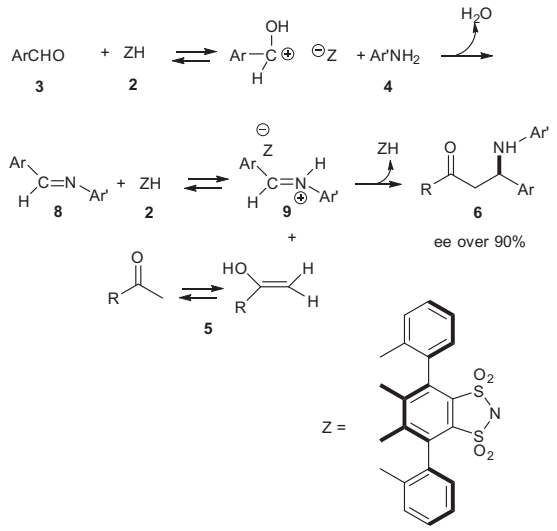
Analytical grade reagents and solvents were used and reactions were monitored by GC, GC–MS. Column chromatography and TLC were performed on Merck silica gel 60 (70–230 mesh ASTM) and GF 254, respectively. Petroleum ether (PE) refers to the fraction boiling in the range 40–70 °C. Mass spectra were recorded on an HP5989B mass selective detector connected to an HP 5890 GC with a cross-linked methyl silicone capillary column. Chiral analyses were performed on a Perkin–Elmer Autosystem GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 200 spectrometer at 200 and 50 MHz respectively. IR spectra were recorded on a IR Perkin–Elmer UATR-two spectrometer. For the determination of the optical rotations, a Jasco P-2000

Table 4
Three-component Mannich reaction between **3**, **4** and cyclohexanone **5g** catalyzed by **1** or (−)-**2**



Entry	Ar in **3**	Ar′ in **4**	Products **7**	Time (h)	Yield (%)[a,b]	dr[c] in (*syn*/*anti*) **7**	ee[c] (%) in *syn* **7**
1	Ph; **3a**	Ph; **4a**	**7a**	42	87	100:0	92.0
2	Ph; **3a**	Ph; **3a**	**7a**	40	85[d]	83:17	3.3
3	4-MeC_6H_4; **3b**	Ph; **4a**	**7b**	54	71	100:0	94.1
4	4-MeC_6H_4; **3b**	Ph; **4a**	**7b**	48	68[d]	85:15	6.0
5	4-$NO_2C_6H_4$; **3c**	Ph; **4a**	**7c**	36	89	100:0	93.8
6	4-ClC_6H_4; **3d**	Ph; **4a**	**7d**	36	91	100:0	92.6
7	Ph; **3a**	4-$NO_2C_6H_4$; **4c**	**7e**	42	87	100:0	90.0
8	Ph; **3a**	4-$NO_2C_6H_4$; **4c**	**7e**	40	87[d]	57:44	3.9
7	Ph; **3a**	4-ClC_6H_4; **4h**	**7f**	42	84	100:0	91.4

[a] The reactants **3**, **4** and **5g** were in equimolar amounts (0.5 mmol). The reactions were performed at rt.
[b] Yields refer to the pure and isolated *syn* adducts **7** obtained after filtering on a Büchner funnel and washing with a small amount of H_2O and petroleum ether.
[c] Dr and ee were determined by chiral analysis on GC connected to a column with chiral stationary phase.
[d] The reactions were carried out in the presence of **1** as a catalyst.



Scheme 3. Mechanism of enantioselective Mannich reaction catalyzed by (−)-**2**.

polarimeter was used. *o*-Benzenedisulfonimide **1**[12a,15] and chiral catalyst (−)-4,5-dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide **2**[12b] were synthesized as previously reported by us. All reagents and solvent were purchased from Sigma–Aldrich or Alfa-Aesar. The structures and purities of all products obtained were confirmed by their spectroscopic (NMR, MS, IR) data, similar to those reported in the literature. The yields and ee of the pure (GC, GC–MS and NMR) isolated β-aminoketones **6** and **7** are reported in Tables 2 and 4. Compounds **6f**, **6p** **7e** are known in the literature but no spectroscopic data were reported. Satisfactory microanalyses were obtained for new compounds **6c**, **6d**, **6s**, **6u** **6v**. The absolute configurations of the optically active compounds **6b**, **6n**, **6o**[10d] and **7a**–**7d**, **7f**[10b,11b] were determined on the basis of the measured specific rotations compared with literature values. All other absolute configurations were assigned by analogy.

4.2. Chiral sulfonimide (−)-2 as a catalyst in a Mannich reaction. General procedure

Chiral catalyst (−)-4,5-dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide **2** (5 mol %, 11 mg, 0.025 mmol) was added to a stirred mixture of aldehydes **3** (0.5 mmol), aromatic amines **4** (0.5 mmol) and ketones **5** (0.5 mmol). The mixture was stirred at rt for the times listed in Tables 2 and 4, until the GC and GC–MS analyses showed the complete disappearance of starting compounds and the complete formation of β-aminoketones **6**. Cold H_2O (2 ml) was added to the reaction mixture, under vigorous stirring. The resulting solids were filtered on a Hirsch funnel and washed with additional cold H_2O (2 × 1 ml) and a small amount of petroleum ether (1 ml). Virtually pure (TLC, GC, GC–MS, ^1H NMR, ^{13}C NMR) β-aminoketones **6** were obtained.

After the above work-up, the ee was measured. However, in order to verify the accuracy of these measurements, the crude residue of **6a**, instead of being filtered, was chromatographed in a short column (EP–EtOAc, 9:1), after which ee was determined. The ee values were identical (90.2%).

The aqueous washing was collected and evaporated under reduced pressure. Virtually pure (^1H NMR) (−)-**2a** was recovered (11 mg, 100% yield) and reused in another two consecutive runs as reported in Table 4. The same protocol was employed in the presence of *o*-benzenedisulfonimide (**1**) as a catalysts.

4.2.1. (*R*)-1,3-Diphenyl-3-(*N*-phenylamino)propan-1-one 6a

White solid (144 mg, 96% yield); mp 170–172 °C (EtOH; lit[16] 169–171 °C). R_f = 0.61. 90.2% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 6.253 min (major), t_R = 6.362 min (minor); $[\alpha]_D^{21} = -14.4$ (*c* 0.1, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.4 Hz, 2H), 7.41–7.16 (m, 10H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.78–6.65 (m, 2H), 4.98–4.92 (m, 1H), 3.62–3.58 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.2, 146.8, 142.9, 136.8, 133.6, 129.3, 129.0, 128.9, 128.4, 127.6, 126.6, 118.3, 114.3, 55.2, 46.4. MS (*m*/*z*, EI): 208 [M^+−93] (90), 207 (100), 181 (95), 180 (100). IR (neat) ν (cm^{-1}): 3335 (NH), 1684 (CO).

4.2.2. (*R*)-1-Phenyl-3-(*N*-phenylamino)-3-(4-tolyl)propan-1-one 6b

White solid (116 mg, 75% yield); mp 127–128 °C (EtOH; lit[16] 129–130 °C). R_f = 0.65. 92.8% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 7.289 min (major), t_R = 7.431 min (minor); $[\alpha]_D^{21} = -18.4$ (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.0 Hz, 2H), 7.54–7.20 (m, 6H), 7.08–7.00 (m, 4H), 6.67–6.53 (m, 2H), 4.95–4.89 (m, 1H), 3.52–3.41 (m, 2H), 2.24 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.4, 147.1, 140.0, 137.2, 136.9, 133.6, 129.7, 129.3, 128.9, 128.4, 126.5, 118.0, 114.1, 54.8, 46.9, 21.3. MS (*m*/*z*, EI): 222 [M^+−93] (45), 221 (50), 207 (100), 195 (55), 194 (60). IR (neat) ν (cm^{-1}): 3348 (NH), 1681 (CO).

4.2.3. (*R*)-1-Phenyl-3-(*N*-phenylamino)-3-(2-tolyl)propan-1-one 6c

Grey solid (114 mg, 72% yield); mp 114–115 °C (EtOH). Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.48; found: C, 83.74; H, 6.76; N, 4.47. R_f = 0.67. 92.2% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 7.196 min (major), t_R = 7.304 min (minor); $[\alpha]_D^{21} = -12.8$ (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.0 Hz, 2H), 7.58–7.39 (m, 4H), 7.17–7.05 (m, 5H), 6.70–6.50 (m, 3H), 5.26–5.20 (m, 1H), 4.92 (br s, 1H), 3.43–3.37 (m, 2H), 2.50 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.5, 147.5, 141.1, 137.1, 135.3, 133.7, 131.2, 129.6, 129.0, 128.5, 127.5, 127.0, 125.8, 118.0, 113.9, 51.2, 44.9, 19.6. MS (*m*/*z*, EI): 222 [M^+−93] (5), 221 (10), 207 (100), 195 (100), 194 (100). IR (neat) ν (cm^{-1}): 3354 (NH), 1678 (CO).

4.2.4. (*R*)-1-Phenyl-3-(*N*-phenylamino)-3-(3-tolyl)propan-1-one 6d

Pale green solid (121 mg, 77% yield). Mp 107–108 °C (EtOH). Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44; found C, 83.82; H, 6.68; N, 4.48. R_f = 0.68. 93.6% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 7.099 min (major), t_R = 7.243 min (minor); $[\alpha]_D^{21} = -14.7$ (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.2 Hz, 2H), 7.50–7.34 (m, 3H), 7.20–6.97 (m, 6H), 6.71–6.58 (m, 3H), 4.93–4.87 (m, 1H), 3.51–3.47 (m, 2H), 2.25 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.5, 147.2, 143.1, 141.7, 138.7, 136.7, 133.6, 131.7, 129.3, 128.9, 128.4, 127.3, 123.6, 118.0, 114.1, 54.8, 46.5, 21.7. MS (*m*/*z*, EI): 222 [M^+−93] (45), 221 (50), 207 (100), 195 (80), 194 (100). IR (neat) ν (cm^{-1}): 3340 (NH), 1685 (CO).

4.2.5. (*R*)-3-(4-Nitrophenyl)-1-phenyl-3-(*N*-phenylamino)propan-1-one 6e

Yellow solid (153 mg, 88% yield). Mp 170–171 °C (EtOH; lit[16] 168–169 °C). R_f = 0.44. 96.8% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 7.702 min (major), t_R = 7.910 min (minor); $[\alpha]_D^{21} = -19.5$ (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.6 Hz, 2H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.60–7.36 (m, 5H), 7.09–7.01 (m, 2H), 6.69–6.62 (m, 1H), 6.61–6.47 (m, 2H), 5.10–5.04 (m, 1H), 4.41 (br s, 1H), 3.49–3.46 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 197.4, 150.9, 147.4, 146.4, 136.5, 134.0, 129.5, 129.0, 128.3, 127.7, 124.3, 118.7, 114.1, 54.4, 45.9. MS (*m*/*z*, EI): 253 [M^+−93] (35), 236 (20), 226 (100), 225 (50), 179 (50). IR (neat) ν (cm^{-1}): 3398 (NH), 1683 (CO).

4.2.6. (*R*)-3-(2-Nitrophenyl)-1-phenyl-3-(*N*-phenylamino)propan-1-one 6f

Yellow solid (128 mg, 74% yield). Mp 160–161 °C (EtOH; lit[17] 158–162 °C). R_f = 0.42. 96.4% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 7.560 min (major), t_R = 7.756 min (minor); $[\alpha]_D^{21} = -19.9$ (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.91–7.87 (m, 3H), 7.50–7.31 (m, 6H), 7.05–6.97 (m, 2H), 6.61 (t, *J* = 7.2 Hz, 1H), 6.41 (d, *J* = 7.6 Hz, 2H), 5.52 (dd, J_1 = 8.2 Hz, J_2 = 4.0 Hz, 1H), 4.85 (br s, 1H), 5.52 (dd, J_1 = 8.0 Hz, J_2 = 4.0 Hz, 1H), 3.72 (dd, J_1 = 16.0 Hz, J_2 = 4.0 Hz, 1H), 3.34 (dd, J_1 = 16.0 Hz, J_2 = 8.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.2, 149.0, 146.4, 140.4, 138.6, 136.6, 134.0, 133.9, 129.5, 129.2, 129.0, 128.6, 125.1, 118.4, 113.8, 50.9, 45.1. MS (*m*/*z*, EI): 226 [M^+−120] (45), 209 (100), 207 (40), 179 (80), 152 (70), 105 (100), 77 (75). IR (neat) ν (cm^{-1}): 3333 (NH), 1676 (CO).

4.2.7. (*R*)-3-(3-Nitrophenyl)-1-phenyl-3-(*N*-phenylamino)propan-1-one 6g

Yellow solid (155 mg, 90% yield). Mp 141–142 °C (EtOH; lit[16] 140–141 °C). R_f = 0.43. 97.8% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 7.560 min (major), t_R = 7.756 min (minor); $[\alpha]_D^{21} = -13.7$ (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.28 (s, 1H), 7.85 (d, *J* = 7.0 Hz, 2H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.56–7.36 (m, 4H), 7.09–7.02 (m, 2H), 6.65 (t, *J* = 7.2 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 2H), 5.11–5.04 (m, 1H), 4.21 (br s, 1H), 3.49–3.46 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 197.4, 148.9, 146.6, 145.8, 136.6, 133.9, 133.3, 129.9, 129.5, 129.0, 128.4, 122.7, 121.8, 118.6, 114.4, 54.2, 46.1. MS (*m*/*z*, EI): 253 [M^+−93] (100), 236 (40), 226 (100), 206 (35), 178 (45), 105 (100), 77 (50). IR (neat) ν (cm^{-1}): 3345 (NH), 1682 (CO).

4.2.8. (*R*)-3-(4-Chlorophenyl)-1-phenyl-3-(*N*-phenylamino)propan-1-one 6h

Pale brown solid (150 mg, 89% yield). Mp 115–116 °C (EtOH; lit[16] 114–115 °C). R_f = 0.74. 97.8% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 7.494 min (major), t_R = 7.683 min (minor); $[\alpha]_D^{21} = -15.2$ (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.8 Hz, 2H), 7.55–7.31 (m, 6H), 7.25–7.21 (m, 2H), 7.08–7.01 (m, 2H), 6.67–6.41 (m, 1H), 6.50 (d, *J* = 8.4 Hz, 2H), 4.96–4.90 (m, 1H), 4.53 (br s, 1H), 3.42–3.38 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.2, 146.6, 141.5, 136.7, 133.8, 133.2, 129.4, 129.1, 128.4, 128.1, 127.9, 118.4, 114.2, 54.5, 46.2. MS (*m*/*z*, EI): 242 [M^+−93] (100), 211 (90), 210 (100), 207 (65), 179 (50), 165 (60). IR (neat) ν (cm^{-1}): 3402 (NH), 1678 (CO).

4.2.9. (*R*)-1,3-Diphenyl-3-[*N*-(4-tolyl)amino]propan-1-one 6i

Grey solid (144 mg, 92% yield). Mp 111–112 °C (EtOH; lit[18] 107–110 °C). R_f = 0.64. 90.28% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 6.987 min (major), t_R = 7.110 min (minor); $[\alpha]_D^{21} = -11.7$ (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.6 Hz, 2H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.60–7.36 (m, 5H), 7.09–7.01 (m, 2H), 6.69–6.62 (m, 1H), 6.61–6.47 (m, 2H), 5.10–5.04 (m, 1H), 4.41 (br s, 1H), 3.49–3.46 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.5, 143.7, 142.4, 136.8, 133.6, 129.9, 129.1, 128.9, 128.6, 128.4, 127.7, 126.9, 115.0, 56.1, 46.1, 20.6. MS (*m*/*z*, EI): 208

[M^+−107] (85), 207 (100), 195 (100), 194 (100). IR (neat) ν (cm^{-1}): 3418 (NH), 1675 (CO).

4.2.10. (*R*)-1,3-Diphenyl-3-[*N*-(3-tolyl)amino]propan-1-one 6j

White solid (122 mg, 77% yield). Mp 136–137 °C (EtOH; lit[19] 138–140 °C). R_f = 0.65. 96.2% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 6.998 min (major), t_R = 7.126 min (minor); $[\alpha]_D^{21}$ = −5.4 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.2 Hz, 2H), 7.53–7.46 (m, 1H), 7.41–7.30 (m, 4H), 7.26–7.18 (m, 3H), 6.97–6.89 (m, 1H), 6.53–6.37 (m, 3H), 4.98–4.92 (m, 1H), 4.61 (br s, 1H), 3.52–3.49 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.5, 146.5, 142.8, 139.2, 136.8, 133.7, 129.3, 129.1, 128.9, 128.5, 127.8, 126.9, 119.2, 115.6, 111.8, 55.6, 46.2, 21.9. MS (*m*/*z*, EI): 222 [M^+−93] (35), 207 (100), 195 (100), 194 (100), 178 (60), 105 (75), 77 (80). IR (neat) ν (cm^{-1}): 3400 (NH), 1684 (CO).

4.2.11. (*R*)-1,3-Diphenyl-3-[*N*-(4-nitrophenyl)amino]propan-1-one 6k

Yellow solid (173 mg, 100% yield using (−) **2** as catalyst). Mp 186–187 °C (EtOH; lit[20] 185–186 °C). R_f = 0.39. 96.3% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 7.724 min (major), t_R = 7.934 min (minor); $[\alpha]_D^{21}$ = −13.8 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 9.2 Hz, 2H), 7.56–7.20 (m, 10H), 6.47 (d, *J* = 9.2 Hz, 2H), 5.07–5.01 (m, 1H), 4.69 (br s, 1H), 3.49–3.46 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.2, 141.8, 141.3, 136.6, 133.9, 129.3, 129.1, 128.9, 128.4, 128.1, 126.3, 120.5, 112.5, 54.7, 45.6. MS (*m*/*z*, EI): 226 [M^+−120] (100), 225 (80), 207 (100), 206 (90). IR (neat) ν (cm^{-1}): 3392 (NH), 1677 (CO).

4.2.12. (*R*)-1,3-Diphenyl-3-[*N*-(3-nitrophenyl)amino]propan-1-one 6l

Yellow solid (165 mg, 95%). Mp 144–145 °C (EtOH; lit[21] 146–147 °C). R_f = 0.41. 92.0% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 7.814 min (major), t_R = 8.014 min (minor); $[\alpha]_D^{21}$ = −12.2 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.4 Hz, 2H), 7.55–7.08 (m, 11H), 6.82–6.78 (m, 1H), 5.01–4.95 (m, 1H), 3.47–3.44 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.3, 149.2, 147.8, 141.9, 136.6, 133.9, 129.8, 129.2, 129.0, 128.4, 127.9, 126.5, 119.8, 112.5, 108.1, 54.9, 46.2. MS (*m*/*z*, EI): 226 [M^+−120] (50), 225 (40), 207 (100), 179 (25), 131 (25), 77 (50). IR (neat) ν (cm^{-1}): 3412 (NH), 1684 (CO).

4.2.13. (*R*)-1,3-Diphenyl-3-[*N*-(4-chlorophenyl)amino]propan-1-one 6m

White solid (163 mg, 97% yield). Mp 170–171 °C (EtOH; lit[16] 168–169 °C). R_f = 0.58. 95.0% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 7.419 min (major), t_R = 7.579 min (minor); $[\alpha]_D^{21}$ = −14.1 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 7.2 Hz, 2H), 7.51–7.18 (m, 8H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.48 (d, *J* = 8.6 Hz, 2H), 4.92–4.87 (m, 1H), 3.47–3.44 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.2, 145.1, 141.8, 136.6, 133.8, 129.4, 129.2, 128.9, 128.8, 127.9, 126.8, 121.4, 116.2, 56.1, 45.9. MS (*m*/*z*, EI): 215 [M^+−120] (100), 214 (100), 207 (100), 206 (40). IR (neat) ν (cm^{-1}): 3415 (NH), 1680 (CO).

4.2.14. (*R*)-3-Phenyl-3-(*N*-phenylamino)-1-(4-tolyl)propan-1-one 6n

White solid (123 mg, 78% yield). Mp 135–136 °C (EtOH; lit[21] 136–137 °C). R_f = 0.58. 92.2% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 6.730 min (major), t_R = 6.847 min (minor); $[\alpha]_D^{21}$ = −15.8 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.0 Hz, 2H), 7.41–7.38 (m, 2H), 7.28–7.14 (m, 5H), 7.08–7.00 (m, 2H), 6.70–6.57 (m, 3H), 4.96–4.89 (m, 1H), 3.49–3.47 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.9, 147.2, 144.5, 143.2, 134.4, 129.6, 129.3, 128.9, 128.6, 127.5, 126.7, 117.9, 114.1, 55.1, 46.3. MS (*m*/*z*, EI): 222 [M^+−93] (55), 221 (60), 181 (90), 180 (100). IR (neat) ν (cm^{-1}): 3400 (NH), 1679 (CO).

4.2.15. (*R*)-3-Phenyl-3-(*N*-phenylamino)-1-(4-chlorophenyl)propan-1-one 6o

Pale green solid (155 mg, 92% yield). Mp 123–124 °C (EtOH; lit[19] 122–124 °C). R_f = 0.58. 95.4% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 7.439 min (major), t_R = 7.512 min (minor); $[\alpha]_D^{21}$ = −13.2 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.6 Hz, 2H), 7.35–7.18 (m, 7H), 7.10–7.02 (m, 2H), 6.77–6.62 (m, 3H), 4.97–4.91 (m, 1H), 3.56–3.41 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 197.4, 146.6, 142.6, 140.1, 135.1, 129.8, 129.4, 129.2, 129.1, 127.7, 126.6, 117.9, 114.4, 55.2, 46.2. MS (*m*/*z*, EI): 242 [M^+−93] (40), 241 (60), 181 (90), 180 (100). IR (neat) ν (cm^{-1}): 3377 (NH), 1683 (CO).

4.2.16. (*R*)-3-Phenyl-3-(*N*-phenylamino)-1-(3-tolyl)propan-1-one 6p

Grey solid (128 mg, 81% yield). Mp 172–173 °C (EtOH; lit[22] 172 °C). R_f = 0.69. 95.0% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 6.727 min (major), t_R = 6.820 min (minor); $[\alpha]_D^{21}$ = −13.2 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.65 (s, 2H), 7.41–7.14 (m, 7H), 7.08–7.01 (m, 2H), 6.69–6.54 (m, 3H), 4.98–4.91 (m, 1H), 3.47–3.44 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.6, 146.7, 142.7, 138.7, 136.9, 134.4, 129.3, 129.0, 128.8, 127.7, 126.7, 125.6, 121.4, 118.4, 114.5, 55.4, 46.3, 21.5. MS (*m*/*z*, EI): 222 [M^+−93] (85), 221 (100), 181 (90), 180 (100). IR (neat) ν (cm^{-1}): 3365 (NH), 1684 (CO).

4.2.17. (*R*)-1-Phenyl-3-(*N*-phenylamino)-3-(2-thienyl)propan-1-one 6q

Pale brown solid (141 mg, 92% yield). Mp 114–115 °C (EtOH; lit[18] 116–117 °C). R_f = 0.57. 90.6% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 6.289 min (major), t_R = 6.338 min (minor); $[\alpha]_D^{21}$ = −10.4 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.0 Hz, 2H), 7.51–7.32 (m, 5H), 7.13–7.04 (m, 3H), 6.96–6.94 (m, 1H), 6.69–6.62 (m, 2H), 5.35–5.29 (m, 1H), 3.56–3.53 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.0, 147.8, 146.8, 136.9, 133.7, 129.5, 128.9, 128.4, 127.1, 124.4, 124.2, 118.6, 114.3, 50.9, 46.1. MS (*m*/*z*, EI): 214 [M^+−93] (100), 187 (90), 186 (100), 185 (40), 137 (40). IR (neat) ν (cm^{-1}): 3375 (NH), 1677 (CO).

4.2.18. (*R*)-1-Phenyl-1-(*N*-phenylamino)hexan-3-one 6r

Pale yellow solid (116 mg, 87% yield). Mp 89–90 °C (EtOH; lit[23] 87–88 °C). R_f = 0.72. 94.2% ee (GC connected to a J&W Scientific

Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 6.596 min (major), t_R = 6.701 min (minor); $[\alpha]_D^{21}$ = −9.4 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.29–7.20 (m, 5H), 7.08–7.00 (m, 2H), 6.65–6.48 (m, 3H), 4.81–4.74 (m, 1H), 2.87–2.84 (m, 2H), 2.25 (t, *J* = 7.4 Hz, 2H), 1.55–1.37 (m, 2H), 0.77 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 209.9, 147.1, 142.9, 129.4, 129.0, 127.6, 126.6, 118.0, 114.0, 54.7, 50.5, 45.8, 17.1, 13.9. MS (*m*/*z*, EI): 267 [M^+] (25), 182 (100), 180 (55). IR (neat) *ν* (cm^{-1}): 3375 (NH), 1677 (CO).

4.2.19. (*R*)-1-(*N*-phenylamino)-1-(4-tolyl)hexan-3-one 6s

Pale brown solid (100 mg, 71% yield). Mp 100–101 °C (EtOH). Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98; found: C, 81.03; H, 8.27; N, 5.04. R_f = 0.75. 92.4% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 6.805 min (major), t_R = 6.929 min (minor); $[\alpha]_D^{21}$ = −10.7 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.20–6.92 (m, 6H), 6.69–6.47 (m, 3H), 4.78–4.91 (m, 1H), 2.84–2.80 (m, 2H), 2.32–2.21 (m, 5H), 1.52–1.38 (m, 2H), 0.78 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 209.8, 147.1, 142.6, 129.9, 129.7, 129.3, 126.4, 117.9, 113.9, 54.4, 50.5, 45.7, 21.3, 17.6, 13.8. MS (*m*/*z*, EI): 281 [M^+] (15), 196 (80), 195 (80), 194 (100), 145 (50). IR (neat) *ν* (cm^{-1}): 3400 (NH), 1681 (CO).

4.2.20. (*R*)-1-[*N*-(4-nitrophenyl)amino]-1-phenylhexan-3-one 6t

Yellow solid (144 mg, 92% yield). Mp 103–104 °C (EtOH; lit[24] 104–106 °C). R_f = 0.51. 90.1% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 6.884 min (major), t_R = 6.991 min (minor); $[\alpha]_D^{21}$ = −10.0 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 9.2 Hz, 2H), 7.24–7.15 (m, 5H), 6.42 (d, *J* = 9.2 Hz, 2H), 5.28 (br s, 1H), 4.89–4.83 (m, 1H), 2.93–2.87 (m, 2H), 2.23 (t, *J* = 7.4 Hz, 2H), 1.49–1.34 (m, 2H), 0.74 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 209.5, 152.6, 141.1, 138.3, 129.2, 128.0, 126.4, 126.3, 112.3, 54.1, 49.4, 46.1, 16.9, 13.7. MS (*m*/*z*, EI): 312 [M^+] (25), 227 (100), 131 (75). IR (neat) *ν* (cm^{-1}): 3398 (NH), 1684 (CO).

4.2.21. (*R*)-1-(4-Chlorophenyl)-3-(4-nitrophenyl)-3-[*N*-(4-tolyl)-amino]propan-1-one 6u

Pale brown solid (171 mg, 87% yield). Mp 143–144 °C (EtOH). Calcd for $C_{22}H_{19}ClN_2O_3$: C, 66.92; H, 4.85; Cl, 8.98; N, 7.09; found: C, 66.83; H, 4.88; Cl, 8.91; N, 7.12. R_f = 0.48. 91.8% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 7.909 min (major), t_R = 8.118 min (minor); $[\alpha]_D^{21}$ = −18.3 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.09 (d *J* = 8.6 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 6.40 (d, *J* = 8.2 Hz, 2H), 5.05–4.99 (m, 1H), 4.12 (br s, 1H), 3.44–3.40 (m, 2H), 2.13 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 196.3, 151.1, 147.3, 144.1, 140.4, 134.9, 130.2, 130.0, 129.8, 129.3, 127.8, 124.2, 114.3, 54.5, 45.9, 20.6. MS (*m*/*z*, EI): 287 [M^+−107] (25), 270 (30), 252 (100), 240 (100), 193 (45), 176 (30), 139 (65). IR (neat) *ν* (cm^{-1}): 3325 (NH), 1688 (CO).

4.2.22. (*R*)-3-(3-Chlorophenyl)-3-[*N*-(3-nitrophenyl)amino]-1-(3-tolyl)propan-1-one 6v

Brown solid (168 mg, 85% yield). Mp 136–137 °C (EtOH). Calcd for $C_{22}H_{19}ClN_2O_3$: C, 66.92; H, 4.85; Cl, 8.98; N, 7.09; found: C, 66.85; H, 4.90; Cl, 9.05; N, 7.00. R_f = 0.44. 91.2% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 7.925 min (major), t_R = 8.123 min (minor); $[\alpha]_D^{21}$ = −16.9 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.65 (s, 2H), 7.49–7.10 (m, 9H), 6.78–6.74 (m, 1H), 4.97–4.91 (m, 1H), 3.42–3.39 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 198.0, 149.3, 147.7, 144.3, 138.9, 136.5, 135.1, 134.8, 130.6, 130.1, 129.9, 128.9, 128.2, 126.5, 125.6, 124.8, 119.6, 112.9, 108.1, 54.4, 46.1, 21.5. MS (*m*/*z*, EI): 257 [M^+−137] (25), 256 (100), 221 (75), 138 (100). IR (neat) *ν* (cm^{-1}): 3341 (NH), 1682 (CO).

4.2.23. *syn*/*anti*-2-[Phenyl(*N*-phenylamino)methyl]cyclohexanone 7a

White solid (0.48 g, 85% yield, using **1** as a catalyst). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.36–6.98 (m, 7H), 6.72–6.49 (m, 3H), 4.77 (d, J_{syn} = 4.6 Hz) and 4.60 (d, J_{anti} = 7.0 Hz; 1H in total; ratio *syn*/*anti* 72:28), 3.95 (br s, 1H), 2.81–2.67 (m, 1H), 2.43–2.21 (m, 2H), 1.84–1.54 (m, 6H). Ratio between *syn* and *anti* diastereomers, determined by chiral analysis, is 83.3:16.7. Four peaks are detected: t_R = 5.536 min (*syn*), t_R = 5.742 min (*syn*), t_R = 6.343 min (*anti*), t_R = 6.406 min (*anti*).

4.2.24. (*R*)-2-[(*R*)-Phenyl(*N*-phenylamino)methyl]cyclohexanone 7a

White solid (121 mg, 87% yield, using (−) **2** as a catalyst). Mp 140–141 °C (EtOH; lit[25] 138–140 °C). R_f = 0.68. 92.0% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 5.419 min (major), t_R = 5.652 - min (minor); $[\alpha]_D^{21}$ = +35.9 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.34–6.98 (m, 7H), 6.62–6.48 (m, 3H), 4.77 (d, J_{syn} = 4.6 Hz, 1H), 4.30 (br s, 1H), 2.82–2.67 (m, 1H), 2.42–2.24 (m, 2H), 1.87–1.53 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 213.1, 146.7, 142.0, 130.7, 129.3, 128.7, 127.5, 127.4, 113.9, 58.2, 57.7, 40.6, 31.5, 28.7, 24.1. MS (*m*/*z*, EI): 186 [M^+−93] (75), 185 (100), 181 (75), 180 (100). IR (neat) *ν* (cm^{-1}): 3376 (NH), 1692 (CO).

4.2.25. *syn*/*anti*-2-[4-Tolyl(*N*-phenylamino)methyl]cyclohexanone 7b

Pale green solid (0.40 g, 68% yield, using **1** as a catalyst). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.15 (m, 2H), 7.12–6.98 (m, 4H), 6.75–6.47 (m, 3H), 4.72 (d, J_{syn} = 4.6 Hz) and 4.56 (d, J_{anti} = 7.2 Hz; 1H in total; ratio *syn*/*anti* 72:28), 4.03 (br s, 1H), 2.76–2.64 (m, 1H), 2.38–2.18 (m, 2H), 2.26 (s, 3H), 1.84–1.53 (m, 6H). Ratio between *syn* and *anti* diastereomers, determined by chiral analysis, is 84.6:16.4. Four peaks are detected: t_R = 6.592 min (*syn*), t_R = 6.816 min (*syn*), t_R = 7.445 min (*anti*), t_R = 7.517 min (*anti*).

4.2.26. (*R*) 2-[(*R*)-4-Tolyl(*N*-phenylamino)methyl]cyclohexanone 7b

Pale green solid (104 mg, 71% yield, using **2** as a catalyst). Mp 120–121 °C (EtOH; lit[26] 118–119 °C). R_f = 0.74. 94.1% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 6.406 min (major), t_R = 6.649 min (minor); $[\alpha]_D^{21}$ = +24.2 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.23–7.15 (m, 2H), 7.11–6.98 (m, 4H), 6.66–6.47 (m, 3H), 4.72 (d, J_{syn} = 4.6 Hz, 1H), 2.77–2.64 (m, 1H), 2.38–2.29 (m, 2H), 2.26 (s, 3H), 1.91–1.75 (m, 3H), 1.69–1.53 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 212.5, 147.6, 139.0, 136.1, 130.0, 129.7, 129.3, 118.8, 115.4, 58.3, 57.7, 40.5, 31.4, 29.2, 23.5, 21.6. MS (*m*/*z*, EI): 200 [M^+−93] (15), 199 (20), 195 (85), 194 (100), 185 (100). IR (neat) *ν* (cm^{-1}): 3385 (NH), 1695 (CO).

4.2.27. (*R*)-2-[(*R*)-4-Nitrophenyl(*N*-phenylamino)methyl]cyclohexanone 7c

Yellow solid (144 mg, 89% yield, using **2** as a catalyst). Mp 122–123 °C (EtOH; lit[27] 123–125 °C). R_f = 0.49. 93.8% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 6.875 min (major), t_R = 7.128 min (minor); $[\alpha]_D^{21}$ = +27.7 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.8 Hz, 2H), 7.53–7.49 (m, 2H), 7.07–6.96 (m, 2H), 6.65–6.54 (m, 1H), 6.44 (d, *J* = 8.8 Hz, 2H), 4.76 (d, J_{syn} = 4.6 Hz, 1H), 4.04 (br s, 1H), 2.92–2.72 (m, 1H), 2.34–2.23 (m, 2H), 1.98–1.86 (m, 3H), 1.77–1.56 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 212.0, 150.2, 147.0, 146.8, 130.9, 129.4, 123.8, 118.9, 113.7, 57.7, 57.1, 40.6, 32.1, 29.2, 23.9. MS (*m*/*z*, EI): 231 [M^+−93] (15), 230 (20), 226 (100), 214 (100), 179 (35), 184 (45), 128 (40), 116 (45). IR (neat) ν (cm^{-1}): 3394 (NH), 1698 (CO).

4.2.28. (*R*)-[(*R*)-4-Chlorophenyl(*N*-phenylamino)methyl]cyclohexanone 7d

Grey solid (142 mg, 91% yield, using **2** as a catalyst). Mp 132–133 °C (EtOH; lit[28] 134–135 °C). 92.6% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 6.121 min (major), t_R = 6.334 min (minor); $[\alpha]_D^{21}$ = +29.8 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.27–7.22 (m, 4H), 7.15–6.99 (m, 2H), 6.65–6.60 (m, 1H), 6.49–6.44 (m, 2H), 4.69 (d, J_{syn} = 4.6 Hz, 1H), 2.77–2.64 (m, 1H), 2.36–2.29 (m, 2H), 1.87–1.82 (m, 3H), 1.67–1.54 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 212.7, 146.6, 140.3, 129.4, 129.2, 128.8, 118.7, 115.3, 113.9, 57.7, 57.5, 42.2, 31.7, 27.2, 23.5. MS (*m*/*z*, EI): 220 [M^+−93] (75), 219 (80), 215 (90), 214 (100), 185 (70), 129 (100), 115 (75). IR (neat) ν (cm^{-1}): 3399 (NH), 1705 (CO).

4.2.29. *syn*/*anti*-2-{Phenyl[*N*-(4-nitrophenylamino)]methyl}cyclohexanone 7e

Yellow solid (0.57 g, 87% yield, using **1** as a catalyst). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 9.2 Hz, 2H), 7.89 (d, *J* = 9.2 Hz, 2H), 7.27–7.25 (m, 5H), 6.53 (d, *J* = 9.2 Hz, 2H), 6.43 (d, *J* = 9.2 Hz, 2H), 4.82 (d, J_{cis} = 4.4 Hz) and 4.60 (d, J_{anti} = 6.2 Hz; 1H in total; ratio *syn*/*anti* 52:48), 2.84–2.77 (m, 1H), 2.46–2.24 (m, 2H), 1.97–1.83 (m, 3H), 1.65–1.45 (m, 3H). Ratio between *syn* and *anti* diastereomers, determined by chiral analysis, is 56.5:43.5. Four peaks are detected: t_R = 6.447 min (*syn*), t_R = 6.658 min (*syn*), t_R = 7.242 min (*anti*), t_R = 7.295 min (*anti*).

4.2.30. (*R*)-2-{(*R*)-Phenyl[*N*-(4-nitrophenylamino)]methyl}cyclohexanone 7e

Yellow solid (142 mg, 87% yield). Mp 123–124 °C (EtOH; lit[29] 121–123 °C). 90.0% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 6.437 min (major), t_R = 6.683 min (minor); $[\alpha]_D^{21}$ = +25.1 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 9.2 Hz, 2H), 7.27–7.25 (m, 5H), 6.43 (d, *J* = 9.2 Hz, 2H), 4.82 (d, J_{syn} = 4.4 Hz, 1H), 2.92–2.78 (m, 1H), 2.46–2.24 (m, 2H), 2.00–1.75 (m, 3H), 1.65–1.51 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 212.5, 153.9, 153.4, 140.4, 130.5, 128.9, 126.5, 126.3, 113.4, 57.6, 56.8, 42.1, 32.3, 27.2, 25.0. MS (*m*/*z*, EI): 226 [M^+−98] (100), 225 (35), 186 (50), 185 (100). IR (neat) ν (cm^{-1}): 3390 (NH), 1702 (CO).

4.2.31. (*R*) 2-{(*R*)-Phenyl[*N*-(4-chlorophenylamino)]methyl}cyclohexanone 7f

Brown solid (132 mg, 84% yield, using **2** as a catalyst). Mp 135–136 °C (EtOH; lit[20] 137–138 °C). 91.4% ee (GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-*O*-methyl-6-*O*-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701), t_R = 6.122 min (major), t_R = 6.321 min (minor); $[\alpha]_D^{21}$ = +32.3 (*c* 0.1, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.36–7.18 (m, 4H), 7.03–6.94 (m, 3H), 6.52–6.42 (m, 2H), 4.87 (d, J_{syn} = 3.4 Hz), 2.93–2.81 (m, 1H), 2.49–2.23 (m, 2H), 1.88–1.55 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 213.5, 146.5, 142.3, 130.6, 129.3, 128.8, 128.6, 124.9, 116.5, 58.9, 58.5, 40.9, 32.2, 28.7, 23.2. MS (*m*/*z*, EI): 216 [M^+−98] (100), 215 (100), 186 (80), 185 (100). IR (neat) ν (cm^{-1}): 3346 (NH), 1695 (CO).

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