# Simple 1,2-Diamine Ligands for Asymmetric Addition of Aryllithium Reagents to Imines

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Enantioselective addition of various aryllithium reagents to aromatic imines was catalyzed (20 mol-%) by readily accessible 1,2-diamines to afford a wide range of protected diarylmethylamines in up to 94% enantiomeric excess. Furthermore, the absolute configuration of these arylation products was determined by using X-ray crystallography.


## Introduction and Background

Chiral amines are compounds of great interest in organic synthesis since they constitute building blocks for complex structures of biologically active molecules, as well as being employed as chiral auxiliaries, ligands, or agents for kinetic resolution.[1] The addition of aliphatic organometallic compounds to the azomethine bond of activated imines is now a route of choice for synthesizing aliphatic amines and arylalkylamines in excellent yields and enantioselectivities.[2] By contrast, the asymmetric addition of aromatic compounds to imines affording diarylmethylamines has been scarcely reported, although this backbone can be found in different drugs such as cetirizine or the non-peptidic γ-opioid agonist SNC-80.[3] In 1990 Tomioka and coworkers described the first enantioselective addition of an aryllithium compound to aromatic imines promoted by an external chiral ligand, but despite this work,[4] only a few efficient examples of such arylation processes were reported in the nineties. Nevertheless, since 2000, this is a topic of growing interest. The most remarkable examples in terms of enantioselectivity include the diphenylzinc addition to *N*-formylimines reported by Bräse et al. in 2002[5] and the work of Hayashi et al.[6] They described in 2000 a highly enantioselective rhodium-catalyzed arylation of *N*-alkylidenesulfonamides with organostannanes, and very recently a more environmentally friendly procedure involving the addition of arylboroxines to different imines with enantioselectivities of up to 99%.[6] All of these procedures are indeed high yielding and selective, but they suffer from the cost of the catalysts used. We report herein a low cost and efficient catalytic arylation of aromatic imines using a wide diversity of aryllithium reagents activated by readily accessible chiral 1,2-diamines.[7] The stereochemical outcome of the reaction has been established by a single X-ray analysis of an *N*-*p*-methoxyphenyldiarylmethylamine adduct [(–)-**16**, see text].

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## Results and Discussion

Recently, we described the synthesis of new chiral tertiary 1,2-diamines **1a**–**f** (Scheme 1) and their use in the addition of organolithium compounds to *N*-*p*-methoxyphenylimines.[8] Herein, we wish to present the results obtained for the addition of aryllithium reagents to these types of imines (Table 1). Bearing in mind that only a few examples have been reported to date on this topic, our preliminary study and optimization of the conditions were carried out with imine **2**, the substrate used by Tomioka and co-workers in 1994.[9] They reported that in the presence of a stoichiometric amount of diether **4**, product **3** was obtained in 87% *ee* with the absolute configuration *S*.[9] We found that the same reaction afforded **3** in 86% *ee* (Entry 7). As also mentioned by these authors, we noticed that only toluene and diethyl ether were suitable solvents for the enantioselective version of the reaction. Indeed, in more coordinating solvents such as THF, the reaction proceeded well, but afforded a racemic product. When the reaction was carried out with our diamine ligands, poorer levels of enantioselectivity were induced, particularly with hindered ligands, in contrast with the results obtained for the previously reported addition of methyllithium to imines.[8] It has to be noted at this point that the best result (54% *ee*, Entry 1) was reached with the simplest (*R*,*R*)-(–)-*N*,*N*,*N*′,*N*′-tetramethyl-*trans*-1,2-cyclohexanediamine (**1a**), readily prepared by the Eschweiler–Clark methylation of the readily available (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate.[10]

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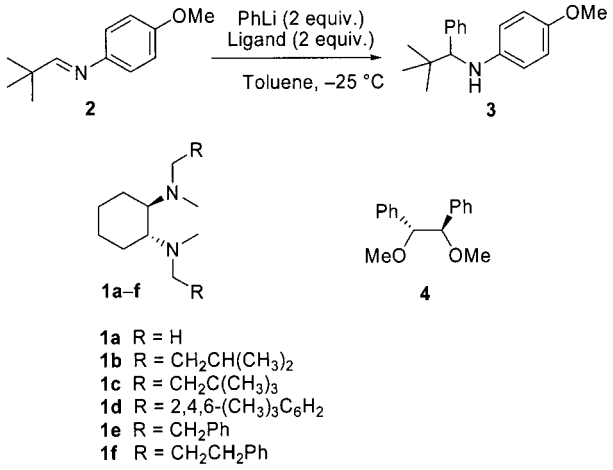


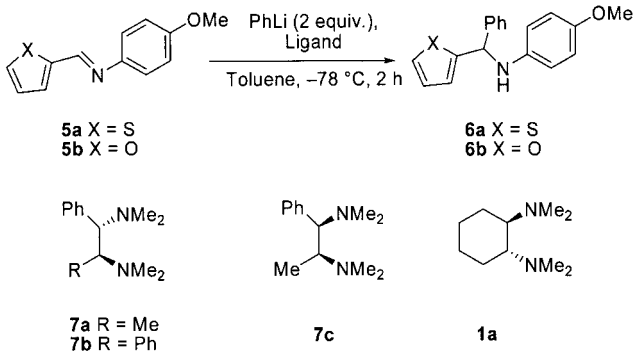

Scheme 1.

Table 1. Addition of phenyllithium to imine **2**.

| Entry | Ligand | Isolated yield (%) | *ee* (%)[a] |
|---|---|---|---|
| 1 | **1a** | 72 | 54 (*R*) |
| 2 | **1b** | 60 | 19 (*R*) |
| 3 | **1c** | 61 | 0 |
| 4 | **1d** | 34 | 11 (*R*) |
| 5 | **1e** | 44 | 43 (*R*) |
| 6 | **1f** | 79 | 19 (*R*) |
| 7 | **4** | 49 | 86 (*S*)[b] |
| 8 | (–)-sparteine | 50 | 23 (*R*) |

[a] Enantiomeric excesses were determined by supercritical fluid chromatography (SFC), column Chiralcel OB-H. The absolute configuration was established by comparison of the SFC chromatogram with the one obtained in entry 7 (see ref.[9]). [b] 87% *ee* was reported by Tomioka et al. (see ref.[9]).

When employing aromatic imines **5a** and **5b** as substrates (Scheme 2),[11] with the expectation that this system is more suitable than imine **2** for our diamine ligands, a different trend was observed. We found that under stoichiometric conditions, and at –78 °C, an enantiomeric excess of 58% was obtained with the addition of phenyllithium to imine **5a** with diamine **1a** (Table 2, Entry 1), versus 44% with (–)-sparteine (Entry 7) and only 7% with diether **4** (Entry 6). Moreover, under substoichiometric conditions, the level of enantioselectivity remained unchanged with 0.2 equiv. of ligand **1a** per mol of imine (Entry 2), whereas such catalysis was not possible with (–)-sparteine (Entry 8). It should be pointed out that, in the toluene solvent, the reaction is rather sluggish in the absence of diamine. For example, the synthesis of the racemic adducts was performed at room temperature, otherwise the conversions were very low. Good induction was also obtained with ligands **7a** [prepared from readily available (1*S*,2*S*)-*N*-methylpseudoephedrine following the procedure of Dieter][12] and **7b**[13] (61% and 59% *ee*, respectively, Entries 9 and 10). In both cases, the major enantiomer was the opposite one to that obtained with ligand **1a.** The effect of the configuration of each stereocenter of the 1,2-diamine ligand on the enantioselectivity was pointed out by using **7c** [prepared from (1*R*,2*S*)-*N*-methylephedrine following the procedure of Dieter][12] as the catalyst (Entry 11).




Scheme 2.

Table 2. Addition of phenyllithium to imines **5a** and **5b**.

| Entry | Ligand (0.2 equiv.) | Product | Isolated yield (%) | *ee* (%)[a] |
|---|---|---|---|---|
| 1 | **1a** (2 equiv.) | **6a** | 69 | 58 (+) |
| 2 | **1a** | **6a** | 95 | 60 (+) |
| 3 | **1a** | **6b** | 87 | 20 (–) |
| 4 | **1c** | **6a** | 68 | 3 |
| 5 | **1e** | **6a** | 62 | 12 |
| 6 | **4** (2 equiv.) | **6a** | 62 | 7 (+) |
| 7 | (–)-sparteine (2 equiv.) | **6a** | 60 | 44 (–) |
| 8 | (–)-sparteine | **6a** | 79 | 0 |
| 9 | **7a** | **6a** | 82 | 61 (–) |
| 10 | **7b** | **6a** | 87 | 59 (–) |
| 11 | **7c** | **6a** | 81 | 28 (+) |

[a] Enantiomeric excesses were determined by SFC, columns Chiralcel OJ for **6a** and Chiralcel AD-H for **6b**. Signs in parenthesis refer to the optical rotations.

The influence of an α-heteroatom could clearly be seen from the comparison of thienyl imine **5a** and furyl imine **5b**. Thienyl imine **5a** behaves like other aryl imines (see Table 3), with 60% *ee* (Table 2, Entry 2), whereas furyl imine **5b** affords a low 20% *ee* (Table 2, Entry 3). Thus, in contrast to oxygen, sulfur does not seem to compete with the diamine catalyst for coordination to lithium. The low *ee* may be ascribed to this oxygen–lithium coordination.

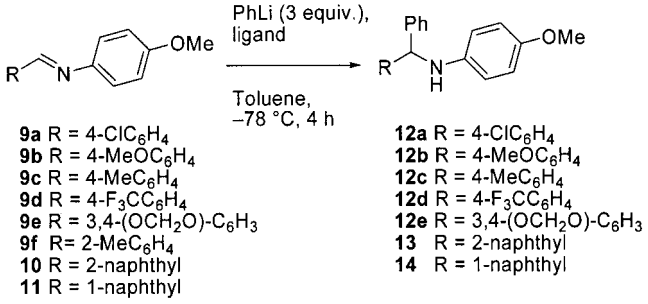
Table 3 shows the generalization of the method. With aromatic imines **9**–**11** (Scheme 3, Table 3) we could also evaluate the effect of the electronic character of the substrate. These results reveal that the electronic effect of the aromatic part of the imines **9**–**11** is low. Good yields were obtained in all cases with enantioselectivities between 60–70%. Thus, a typical electron-withdrawing group, such as trifluoromethyl (imine **9d**, Entry 9) afforded an *ee* of 60%, whereas a typical electron-donating group, such as methoxy (imine **9b**, Entry 7) gave a higher *ee* of 68%. Only product **14** presented a slightly lower *ee* of 55% (Entry 14), perhaps due to a steric hindrance of the 1-naphthyl group. Once again, an efficient catalysis with ligand **1a** was possible, while it was not with (–)-sparteine (compare Entries 2 and 4). The efficiency of the catalysis was tested further with only 10 and 5 mol-% of the diamine ligand. Despite the slightly lower conversions, the enantioselectivities remained almost unchanged (Entries 9–11).

Table 3. Addition of phenyllithium to imines **9**–**11**.[a]

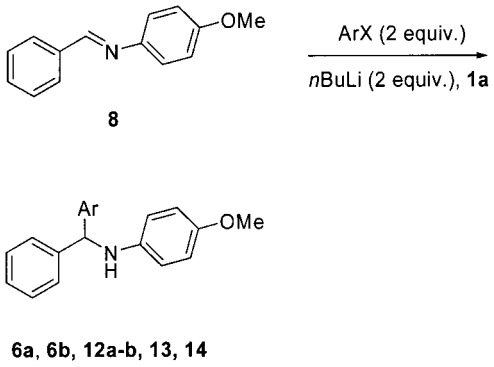
| Entry | Imine | Ligand | Product | % Conversion[b] (% isolated yield) | *ee* (%)[c] |
|---|---|---|---|---|---|
| 1 | **9a** | **1a** (3 equiv.) | **12a** | >99 (64) | 64 (+) |
| 2 | **9a** | **1a** (0.2 equiv.) | **12a** | 62 (42) | 62 (+) |
| 3 | **9a** | (–)-sparteine (3 equiv.) | **12a** | 88 (72) | 59 (–)[d] |
| 4 | **9a** | (–)-sparteine (0.2 equiv.) | **12a** | 39 (23) | 2 |
| 5 | **9a** | **4** (3 equiv.) | **12a** | >99 (72) | 28 (+) |
| 6 | **9b** | **1a** (3 equiv.) | **12b** | 79 (78) | 69 (–) |
| 7 | **9b** | **1a** (0.2 equiv.) | **12b** | 26 (14) | 68 (–) |
| 8 | **9c** | **1a** (0.2 equiv.) | **12c** | 58 (42) | 63 (–) |
| 9 | **9d** | **1a** (0.2 equiv.) | **12d** | >99 (72) | 60 (+) |
| 10 | **9d** | **1a** (0.1 equiv.) | **12d** | 97 (90) | 56 (+) |
| 11 | **9d** | **1a** (0.05 equiv.) | **12d** | 93 (86) | 53 (+) |
| 12 | **9e** | **1a** (0.2 equiv.) | **12e** | 48 (44) | 64 (–) |
| 13[e] | **10** | **1a** (0.2 equiv.) | **13** | 77 (74) | 61 (–) |
| 14 | **11** | **1a** (0.2 equiv.) | **14** | 79 (61) | 55 (+) |

[a] All reactions were carried out at –78 °C in toluene as the solvent for 4 h, unless otherwise stated. [b] Conversions evaluated by $^1$H NMR spectroscopy of the crude. [c] Enantiomeric excesses were determined by SFC, columns Chiralpak AS-H for **12a** and **12d**, Chiralcel OJ for **12b** and Chiralcel OD-H for **12c**, **12e**, **13** and **14**. Signs in parenthesis refer to the optical rotations. [d] Reported in 50% *ee* under stoichiometric conditions by Senanayake (see ref.[3b]). [e] Reaction time: 2.5 h.




Scheme 3.

One of the advantages of this approach is that by simply changing the imine/organolithium partner, either enantiomer can be produced. Indeed amines **6a** and **6b** could be obtained by addition of thienyl and furyllithium to imine **8**, formed in situ by deprotonation of furane and thiophene with *n*BuLi (Scheme 4). Amines **12a**, **12b**, **13** and **14** were formed by addition of the corresponding aryllithium reagents, obtained by metal–halogen exchange of the appropriate aryl halides and *n*BuLi (for details see Exp. Sect.). In general, the enantioselectivities induced by ligand **1a** were similar to those described above, despite the higher temperatures needed in some cases, to obtain reasonable yields (Table 4). Interestingly, the *ee* of **14** reached an exceptionally good 90% *ee* with the addition of 1-naphthyllithiun to imine **8** (Entry 6).




Scheme 4.

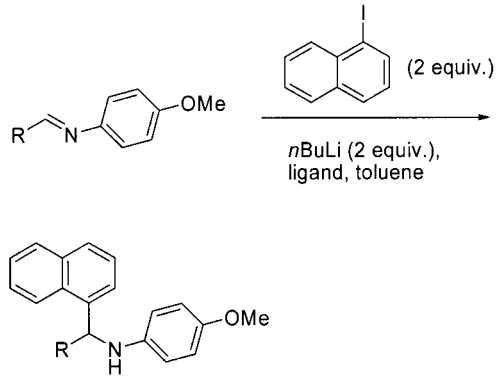
Table 4. Addition of aryllithium compounds to imine **8**.

| Entry | Conditions | Ar in ArLi | Product | Isolated yield (%) | *ee* (%)[a,b] |
|---|---|---|---|---|---|
| 1 | **1a** (2 equiv.), toluene, –20 °C, 15 h | 2-Thienyl | **6a** | 71 | 58 (–) [58 (+)] |
| 2 | **1a** (2 equiv.), $Et_2O$, –78 °C to room temp. | 2-Furyl | **6b** | 45 | 28 (+) [20 (–)] |
| 3 | **1a** (2 equiv.), toluene, –78 °C, 4 h | 4-$ClC_6H_4$ | **12a** | 76 | 69 (–) [64 (+)] |
| 4 | **1a** (2 equiv.), toluene, –78 °C, 2 h | 4-$MeOC_6H_4$ | **12b** | 93 | 62 (+) [69 (–)] |
| 5 | **1a** (2 equiv.), toluene, 78 °C, 2 h | 2-naphthyl | **13** | 98 | 67 (+) [61 (–)] |
| 6 | **1a** (2 equiv.), toluene, –78 °C, 2 h | 1-naphthyl | **14** | 98 | 90 (–) [55 (+)] |

[a] Enantiomeric excesses were determined by SFC Columns Chiralcel OJ for **6a** and **12b**, Chiralcel AD-H for **6b**, Chiralpak AS-H for **12a** and Chiralcel OD-H for **13** and **14**. Signs in parenthesis refer to the optical rotations. [b] The enantiomeric excesses of the addition of phenyllithium to imines, from Table 2 and Table 3 are indicated in brackets.

In order to study the interesting case of 1-naphthyllithium more thoroughly, the addition was carried out on other imines (Scheme 5, Table 5), as done previously for phenyllithium. However, a dramatic difference of reactivity between these two aryllithium compounds was observed. While the addition of phenyllithium to imine **9a** was complete in 4 h at –78 °C (Table 3, Entry 1), a conversion of only 15% after 6 h was reached for the addition of 1-naphthyllithium, but with a very good *ee* of 89% (Table 5, Entry 7). Similarly, with the less reactive imine **9e**, at –78 °C after 7 h, no reaction was detected. Different temperatures were tested, and good yields were obtained at temperatures near to –40 or –50 °C without any significant loss of enantioselectivity (Entries 13–15). Moreover, when (–)-sparteine was tested as the ligand, poor enantioselectivities and yields were obtained (compare Entries 10 and 8). Ligand **7a** afforded compound **14** in a 94% *ee*, one of the highest enantioselectivities reported for this kind of reaction (Entry 3). As we stated in the introduction, the achievement of a substoichiometric version of this promising asymmetric reaction would be the key to new perspectives and future improvements. Thus we tested the addition of 1-naphthyllithium to imine **8** in the presence of 0.2 equiv. of **1a** or **7a** and were gratified to obtain respectively, 84% and 80% *ee* (Entries 2 and 4). These good results with substoichiometric amounts of ligands that are so easy to prepare are providing a future for this procedure in the arylation of imines.




Scheme 5.

Since the interchange of aryl imines and aryllithiums produces opposite enantiomers, it is clear that any aryllithium attacks the same prochiral face of any aryl imine. To determine this facial selectivity, it was necessary to know the absolute stereochemistry of our adducts. Thus, the absolute configuration of the major enantiomer of (–)-**16** could be determined by X-ray crystallography. Indeed, this amine was obtained in 89% *ee* by addition of 1-naphthyllithium to imine **8** in $Et_2O$ as solvent and in the presence of 2 equiv. of **1a** (Entry 9). After usual purification by column chromatography, the amine was obtained as a white solid and crystals suitable for X-ray analysis were obtained from a mixture of pentane/$Et_2O$. We determined the configuration to be *R* [Flack parameter $x = –0.01$ (9)].[14] CD spectra of both (–)-**16** and the crystal analyzed by X-ray crystallography were of the same sign, therefore confirming the *R* configuration of (–)-**16**. 1-naphthyllithium activated by **1a** thus attacks the *Si* face of the imine. It seems reasonable to assume that the same stereochemical pathway is followed by all the other aryllithium reagents. Although the *Si* face is attacked, the actual absolute configuration may vary according to the CIP priority rules.

## Conclusions

In summary, a wide variety of *N*-protected diarylmethylamines, in both enantiomeric forms, were synthesized with enantiomeric excesses of up to 94% by addition of aryl-

Table 5. Addition of 1-naphthyllithium to different imines.

| Entry | R | Imine | Product | Ligand | Conditions[a] | % Conversion[b] (% isolated yield) | *ee* (%)[c] |
|---|---|---|---|---|---|---|---|
| 1[d] | $C_6H_5$ | **8** | **14** | **1a** | –78 °C, 2 h | >99 (98) | 90 (–) |
| 2 | $C_6H_5$ | **8** | **14** | **1a** (0.2 equiv.) | –78 °C, 4 h | 19 | 84 (–)[e] |
| 3 | $C_6H_5$ | **8** | **14** | **7a** | –78 °C, 2 h | 70 (45) | 94 (+) |
| 4 | $C_6H_5$ | **8** | **14** | **7a** (0.2 equiv.) | –78 °C, 9 h | 57 | 80 (+) |
| 5 | 2-$MeC_6H_4$ | **9f** | **15** | **1a** | –41 °C, 3 d[f] | >99 | 86 (–) (>98)[g] |
| 6 | 2-$MeC_6H_4$ | **9f** | **15** | **7a** | –25 °C, 5 d[f] | >99 | 94 (+) |
| 7 | 4-$ClC_6H_4$ | **9a** | **16** | **1a** | –78 °C, 6 h | 15 | 89 (–) |
| 8 | 4-$ClC_6H_4$ | **9a** | **16** | **1a** | –65 °C, 21 h | >99 (64) | 90 (–) |
| 9 | 4-$ClC_6H_4$ | **9a** | **16** | **1a** | –65 °C, 21 h[h] | 67 | 89 (–) (*R*)[i] |
| 10 | 4-$ClC_6H_4$ | **9a** | **16** | (–)-sparteine | –67 °C, 13 h | 50 | 10 |
| 11 | 4-$MeC_6H_4$ | **9c** | **17** | **1a** | –55 °C, 3 d[f] | >99 (66) | 88 (–) |
| 12 | 4-$MeC_6H_4$ | **9c** | **17** | **7a** | –55 °C, 3 d[f] | 28 (28) | 92 (+) |
| 13 | 3,4-($OCH_2O$)-$C_6H_3$ | **9e** | **18** | **1a** | –55 °C, 3 d[f] | 20 | 90 (–) |
| 14 | 3,4-($OCH_2O$)-$C_6H_3$ | **9e** | **18** | **1a** | –41 °C, 3 d[f] | >99 (60) | 86 (–) |
| 15 | 3,4-($OCH_2O$)-$C_6H_3$ | **9e** | **18** | **7a** | –25 °C, 4 d[f] | >99 (90) | 90 (+) |

[a] Unless otherwise indicated, all reactions were carried out in toluene and in the presence of 2 equiv. of the ligand. [b] Conversions evaluated by $^1H$ NMR spectroscopy of the crude. [c] Enantiomeric excesses were determined by SFC Columns Chiralcel OD-H for **14** and **18** and OJ for **15**–**17**. Signs in parenthesis refer to the optical rotations. [d] From Table 4. [e] Average of two runs. [f] Nonoptimized reaction times. [g] In parenthesis, enantiomeric excess after recrystallization in Pentane/$Et_2O$. [h] Experiment carried out in $Et_2O$. [i] Determined by X-ray analysis.

lithium compounds to aromatic imines catalyzed by readily available 1,2-diamine ligands. The absolute configuration of one of these diarylmethylamines could be established by single-crystal X-ray analysis. Further studies on the mechanism are underway in our laboratory.

## Experimental Section

**General Techniques:** Diethyl ether and toluene were dried over Na/benzophenone and $CaH_2$, respectively, and then distilled under nitrogen. TMEDA was distilled prior to use and stored under argon. Other commercially available reagents were used without further purification, unless otherwise indicated. Imines **2**,[9] **5**,[15] **8**,[9] **9a**,[16] **9b**,[17] **9c**,[18] **9d**,[19] **9e**,[20] **9f**, **10**,[21] and **11**,[22] were generated by condensation of *p*-anisidine with the corresponding aldehyde. Ligands **1b**–**f**,[8] **7a**,[12] **7c**[12] and **7b**[13] were synthesized as described in the literature. *n*BuLi was purchased as a 1.6 M solution in hexanes and PhLi as a 1.9 M solution in cyclohexane/$Et_2O$, 70:30. All reactions were carried out under inert argon and in oven-dried glassware. Temperatures indicated in the text refer to the inner reaction mixtures. Flash column chromatography was performed using silica gel 32–63 μm, 60 Å and thin layer chromatography on silica gel plates. A 254 nm UV light and an ethanolic solution of ninhydrine are used as developing agents. $^1$H NMR and $^{13}$C NMR spectra were recorded at room temperature at 400 and 100 MHz, respectively. Chemical shift values are expressed in ppm relative to residual $CHCl_3$ calibrated to 7.26 for $^1$H NMR spectroscopy and the $CDCl_3$ signal is calibrated to 77.0 for $^{13}$C NMR spectroscopy. Enantiomeric excesses were determined by Supercritical Fluid Chromatography (capillary column, 10 psi $H_2$), using racemic mixtures as references. Temperature programs are described as follows: initial temperature (°C); initial time (min); temperature gradient (°C·min$^{-1}$); final temperature (°C). Circular dichroism spectra were recorded in acetonitrile as solvent. The measurements were carried out in the far-UV region.

**Synthesis of (*R*,*R*)-(–)-*N*,*N*,*N*′,*N*′-Tetramethyl-*trans*-1,2-cyclohexanediamine (1a):** (*R*,*R*)-1,2-Diammoniumcyclohexane mono-(+)-tartrate[10] (24 g, 0.091 mol) was dissolved in formic acid 85% (36 mL) and formaldehyde 40% (44 mL) was added slowly at room temperature. The mixture was refluxed for 2 h. After cooling to room temperature, and then to 0 °C, the reaction mixture was made basic until pH 12 with solid sodium hydroxide and extracted thoroughly with diethyl ether. The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The residue was purified by distillation in a bulb-to-bulb apparatus (b.p. 50 °C/0.1 Torr) to afford a colorless liquid (11.35 g, 74%) of $[\alpha]_D^{20}$ = –62.9 (*c* = 1.05, $CHCl_3$). Spectral data were in agreement with the literature.[23]

**Synthesis of (1*S*,2*S*)-*N*,*N*,*N*′,*N*′-Tetramethyl-1-phenylpropane-1,2-diamine (7a):** Following the procedure of Dieter,[12] mesyl chloride (5.59 mL, 72.0 mmol) was added dropwise under inert conditions to a solution of (+)-(1*S*,2*S*)-*N*-methylpseudoephedrine (5.42 g, 30.0 mmol) and triethylamine (12.5 mL, 90.0 mmol) in diethylether (180 mL) at 0 °C. A white precipitate appeared and after 30 min triethylamine (16.7 mL, 120 mmol) was added once again and the temperature was raised to room temperature. Dimethylamine (96 mL, 5.6 M in EtOH) was added and the solution was stirred vigorously overnight. The solution was made basic with aqueous NaOH and organic layer was extracted with diethyl ether, washed with 5% aq. $NaHCO_3$ and water. The residue was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The product was isolated in 75% yield as a yellow oil of $[\alpha]_D^{20}$ = –31.3 (*c* = 1.01, $CHCl_3$) and was used without further purification. Spectral data were in agreement with the literature.[24]

**Synthesis of (1*R*,2*S*)-*N*,*N*,*N*′,*N*′-Tetramethyl-1-phenylpropane-1,2-diamine (7c):** The procedure was the same as described previously for **7a**, starting from (–)-(1*R*,2*S*)-*N*-methylephedrine. The product was isolated in 85% yield as a white solid of $[\alpha]_D^{20}$ = –1.5 (*c* = 0.95, $CHCl_3$) after recrystallization in diethylether. Spectral data were in agreement with the literature.[24]

**General Procedure for the Asymmetric Addition of Phenyllithium to Imines:** A solution of imine (0.5 mmol) in dry toluene (9 mL) was added to a stirred solution of ligand (0.1 mmol or 1.5 mmol) in dry toluene (1 mL) at room temperature. After cooling the medium to –78 °C, phenyllithium (0.8 mL as a 1.9 M solution in cyclohexane/$Et_2O$, 70:30) was slowly added under argon. The resulting mixture was stirred at –78 °C for 2 or 4 h (see Tables) and then quenched at low temperature with methanol and water. Layers separated and the aqueous layer was extracted three times with $Et_2O$ and once with EtOAc. The combined organic phases were dried over $K_2CO_3$, filtered and finally concentrated under reduced pressure. The resulting residue was analyzed by $^1$H NMR spectroscopy to determine the conversion of the reaction by integration of the residual peak of the aldimino proton. Then, it was purified by silica gel column chromatography to give the desired product in the *ee* indicated in tables. Spectral data were in agreement with the corresponding racemic mixture synthesized independently.

**General Procedure for the Asymmetric Addition of 2-Furyllithium, 2-Thienyllithium, 1-Naphthyllithium, 2-Naphthyllithium, 4-Chlorophenyllithium and 4-Methoxyphenyllithium to Imines:** *n*-Butyllithium (0.6 mL as a 1.6 M solution in hexanes, 1 mmol) was slowly added under argon to a stirred solution of ligand (0.1 mmol or 1.0 mmol) and the appropriate aromatic compound (1.1 mmol) in dry toluene (10 mL) cooled to –60 °C. The resulting mixture was stirred at –60 °C for 1 h, during which time the metal–halogen exchange occurred. Then, the temperature of the medium was adjusted to the one indicated in the tables and a solution of imine (0.5 mmol) in toluene (10 mL) was added carefully, so that the temperature of the medium was only raised minimally. The reaction mixture was stirred for the time indicated in the text. Quenching and workup were the same as described previously for the addition of phenyllithium, as well as the determination of conversions. Flash silica gel column chromatography afforded the pure enantioenriched compounds, whose spectroscopic data were in agreement with the corresponding racemic mixture synthesized independently.

**4-Methoxy-*N*-[phenyl(thiophen-2-yl)methyl]benzenamine (6a):** Purification by silica gel chromatography (toluene) gave (–)-**6a** as a yellow oil of $[\alpha]_D^{25}$ = –13.1 (*c* = 1.03, $CHCl_3$ for *ee* = 58% with **7b**); *ee* was determined by SFC: Chiralcel OJ, 200 bar, 2 mL·min$^{-1}$, 25% MeOH in $CO_2$ (25%, 10 min), 30 °C, $t_1$ = 7.7 min, $t_2$ = 8.6 min. $^1$H NMR: $\delta$ = 7.50–7.45 (m, 2 H), 7.39 (t, *J* = 7.3 Hz, 2 H), 7.35–7.29 (m, 1 H), 7.25 (dd, *J* = 5.0, 1.3 Hz, 1 H), 6.99–6.96 (m, 1 H), 6.94–6.91 (m, 1 H), 6.76 (d, *J* = 8.8 Hz, 2 H), 6.60 (d, *J* = 8.8 Hz, 2 H), 5.72 (s, 1 H), 4.35–4.05 (br. s, 1 H), 3.74 (s, 3 H) ppm. $^{13}$C NMR: $\delta$ = 152.5, 148.0, 142.8, 141.1, 128.8, 127.7, 127.1, 126.9, 125.0, 124.9, 115.0, 114.8, 59.6, 55.7 ppm. IR (neat): 3392, 3062, 1601, 1508, 1452, 1231, 1035, 819, 761, 698 cm$^{-1}$. MS (EI), *m*/*z* (%): 295 (M, 10), 174, 173 (100), 129 (10). HRMS calcd. for $C_{18}H_{17}NOS$ 295.1031, found 295.1027.

***N*-[(Furan-2-yl)(phenyl)methyl]-4-methoxybenzenamine (6b):** Purification by silica gel chromatography (toluene) gave (+)-**6b** as a yellow oil of $[\alpha]_D^{25}$ = +5.9 (*c* = 0.50, $CHCl_3$ for *ee* = 28% with **1a**); *ee* was determined by SFC: Chiralcel AD-H, 200 bar, 2 mL·min$^{-1}$, 5%

MeOH in $CO_2$ (5%, 5 min, 1%·min$^{-1}$, 20%, 5 min), 30 °C, $t_1$ = 6.2 min, $t_2$ = 7.7 min. $^1$H NMR: $\delta$ = 7.51–7.47 (m, 2 H), 7.45–7.39 (m, 3 H), 7.38–7.34 (m, 1 H), 6.80 (d, $J$ = 9.1 Hz, 2 H), 6.63 (d, $J$ = 8.8 Hz, 2 H), 6.77 (dd, $J$ = 3.2, 1.9 Hz, 1 H), 6.18 (br d, $J$ = 3.3 Hz, 1 H), 5.59 (s, 1 H), 4.40–4.00 (br. s, 1 H), 3.76 (s, 3 H) ppm. $^{13}$C NMR: $\delta$ = 155.4, 152.3, 142.0, 141.0, 140.6, 128.6, 127.6, 127.2, 114.8, 114.6, 110.2, 107.3, 57.6, 55.5 ppm. IR (neat): 3401, 2929, 1511, 1453, 1235, 1036, 819, 737, 699 cm$^{-1}$. MS (EI), *m*/*z* (%): 279 (M, 11), 172 (12), 158 (14), 157 (100), 128 (22), 127 (10), 105 (14), 95 (10), 77 (14). HRMS calcd. for $C_{18}H_{17}NO_2$ 279.1259, found 279.1239.

***N*-[(4-Chlorophenyl)(phenyl)methyl]-4-methoxybenzenamine (12a):** Purification by silica gel chromatography (toluene) gave **12a** as a yellow oil of $[\alpha]_D^{25}$ = –13.6 [*c* = 0.97, $CHCl_3$ for *ee* = 59% with (–)-sparteine], +12.3 (*c* = 0.38, $CHCl_3$ for *ee* = 64% with **1a**); *ee* was determined by SFC: Chiralpak AS-H, 200 bar, 2 mL·min$^{-1}$, 25% MeOH in $CO_2$ (25%, 15 min), 30 °C, $t_1$ = 3.3 min, $t_2$ = 3.7 min. $^1$H NMR: $\delta$ = 7.24–7.16 (m, 9 H), 6.70–6.58 (m, 2 H), 6.47–6.32 (m, 2 H), 5.30 (s, 1 H), 3.88 (br. s, 1 H), 3.63 (s, 3 H) ppm. $^{13}$C NMR: $\delta$ = 152.4, 142.8, 141.6, 141.4, 133.0, 128.9, 128.7, 127.6, 127.5, 114.8, 114.7, 63.3, 55.8 ppm. IR (neat): 3402, 3028, 1602, 1509, 1452, 1241, 1035, 819, 750, 700 cm$^{-1}$. MS (EI), *m*/*z* (%): 324 (M + H, 14), 323 (M, 64), 321 (82), 292 (M, 4), 244 (21), 216 (53), 201 (93), 165 (47), 139 (84), 111 (40), 105 (100), 77 (94), 51 (35). HRMS calcd. for $C_{20}H_{18}{}^{35}ClNO$ 323.1077, found 323.1059 and for $C_{20}H_{18}{}^{37}ClNO$ 325.1047, found 325.1071.

**4-Methoxy-*N*-[(4-methoxyphenyl)(phenyl)methyl]benzenamine (12b):** Purification by silica gel chromatography (pentane/$Et_2O$: 8:1.5) gave (–)-**12b** as a yellow oil of $[\alpha]_D^{25}$ = –23.2 (*c* = 0.77, $CHCl_3$ for *ee* = 69% with **1a**); *ee* was determined by SFC: Chiralcel OJ, 200 bar, 2 mL·min$^{-1}$, 2% MeOH in $CO_2$ (2%, 15 min), 30 °C, $t_1$ = 11.3 min, $t_2$ = 13.2 min. $^1$H NMR: $\delta$ = 7.29–7.16 (m, 7 H), 6.80–6.75 (m, 2 H), 6.65–6.61 (m, 2 H), 6.42 (d, $J$ = 8.0 Hz, 2 H), 5.29 (s, 1 H), 3.88 (br. s, 1 H), 3.70 (s, 3 H), 3.63 (s, 3 H) ppm. $^{13}$C NMR: $\delta$ = 158.8, 152.1, 143.4, 141.8, 135.5, 128.7, 128.6, 127.3, 127.2, 114.7, 114.1, 63.2, 55.8, 55.3 ppm. IR (neat): 3398, 3000, 1610, 1509, 1452, 1243, 1034, 819, 761, 700 cm$^{-1}$. MS (EI), *m*/*z* (%): 319 (M, 10), 197 (100), 165 (9), 153 (9). HRMS calcd. for $C_{21}H_{21}NO_2$ 319.1572, found 319.1580.

**4-Methoxy-*N*-[phenyl(*p*-tolyl)methyl]benzenamine (12c):** Purification by silica gel chromatography (pentane/$Et_2O$, 10:1) gave (–)-**12c** as a yellow oil of $[\alpha]_D^{25}$ = –17.3 (*c* = 0.96, $CHCl_3$ for *ee* = 63% with **1a**); *ee* was determined by SFC: Chiralcel OD-H, 200 bar, 2 mL·min$^{-1}$, 2% MeOH in $CO_2$ (2%, 5 min, 1%·min$^{-1}$, 15%), 30 °C, $t_1$ = 13.0 min, $t_2$ = 13.5 min. $^1$H NMR: $\delta$ = 7.30–7.15 (m, 7 H), 7.04 (d, $J$ = 7.8 Hz, 2 H), 6.63 (d, $J$ = 8.8 Hz, 2 H), 6.42 (d, $J$ = 9.0 Hz, 2 H), 5.30 (s, 1 H), 3.90 (br. s, 1 H), 3.63 (s, 3 H), 2.24 (s, 3 H) ppm. $^{13}$C NMR: $\delta$ = 152.1, 143.3, 141.7, 140.3, 136.9, 129.4, 128.7, 127.3, 127.2, 114.7, 63.6, 55.7, 21.1 ppm. IR (neat): 3403, 3026, 1602, 1509, 1452, 1242, 1037, 819, 732, 700 cm$^{-1}$. MS (EI), *m*/*z* (%): 304 (M + H, 5), 303 (M, 26), 182 (14), 181 (100), 166 (20), 165 (18), 152 (6), 77 (5). HRMS calcd. for $C_{21}H_{21}NO$ 303.1623, found 303.1602.

**4-Methoxy-*N*-{[4-(trifluoromethyl)phenyl](phenyl)methyl}benzenamine (12d):** Purification by silica gel chromatography (pentane/$Et_2O$, 10:1) gave (+)-**12d** as a yellow oil of $[\alpha]_D^{25}$ = +33.7 (*c* = 1.01, $CHCl_3$ for *ee* = 60% with **1a**); *ee* was determined by SFC: Chiralpak AS-H, 200 bar, 2 mL·min$^{-1}$, 5% MeOH in $CO_2$ (5%, 6 min, 2%·min$^{-1}$, 15%), 30 °C, $t_1$ = 3.0 min, $t_2$ = 4.0 min. $^1$H NMR: $\delta$ = 7.48 (d, $J$ = 8.4 Hz, 2 H), 7.42 (d, $J$ = 8.4 Hz, 2 H) 7.24–7.12 (m, 5 H), 6.63 (d, $J$ = 9.1 Hz, 2 H), 6.39 (d, $J$ = 8.8 Hz, 2 H), 5.36 (s, 1 H), 3.91 (br. s, 1 H), 3.61 (s, 3 H) ppm. $^{13}$C NMR: $\delta$ = 152.5, 147.1, 142.5, 141.2, 129.5 (q, $^2J_{C,F}$ = 32.6 Hz), 129.0, 127.8, 127.6, 127.5, 125.7 (q, $^3J_{C,F}$ = 3.9 Hz), 124.2 (q, $^1J_{C,F}$ = 272.0 Hz), 114.8, 63.6, 55.7 ppm. IR (neat): 3397, 3030, 1618, 1509, 1416, 1322, 1242, 1109, 1065, 1035, 817, 740, 700 cm$^{-1}$. MS (EI), *m*/*z* (%): 358 (M + H, 16), 357 (M, 67), 250 (15), 236 (18), 235 (87), 215 (9), 173 (10), 166 (17), 165 (32), 145 (9), 123 (11), 122 (100), 105 (26), 95 (10), 77 (13). HRMS calcd. for $C_{21}H_{18}F_3NO$ 357.1340, found 357.1358.

***N*-[(Benzo[*d*][1,3]dioxol-6-yl)(phenyl)methyl]-4-methoxybenzenamine (12e):** Purification by silica gel chromatography (toluene) gave (–)-**12e** as a yellow oil of $[\alpha]_D^{25}$–1.7 (*c* = 0.99, $CHCl_3$ for *ee* = 64% with **1a**); *ee* was determined by SFC: Chiralcel OD-H, 175 bar, 1.8 mL·min$^{-1}$, 5% MeOH in $CO_2$ (5%, 5 min, 1%·min$^{-1}$, 20%), 30 °C, $t_1$ = 15.8 min, $t_2$ = 16.2 min. $^1$H NMR: $\delta$ = 7.30–7.22 (m, 3 H), 7.19 (br. s, 2 H), 6.90–6.72 (m, 2 H), 6.70–6.58 (m, 3 H), 6.43 (d, $J$ = 8.8 Hz, 2 H), 5.85 (s, 2 H), 5.25 (s, 1 H), 3.90 (br. s, 1 H), 3.64 (s, 3 H) ppm. $^{13}$C NMR: $\delta$ = 152.2, 147.9, 146.7, 143.3, 141.6, 137.3, 128.7, 127.3, 127.2, 120.5, 114.7, 114.6, 108.3, 107.8, 101.0, 63.6, 55.7 ppm. IR (neat): 3397, 3027, 1610, 1509, 1231, 1035, 931, 818, 761, 700 cm$^{-1}$. MS (EI), *m*/*z* (%): 333 (M, 11), 331 (19), 255 (37), 254 (11), 240 (35), 226 (63), 212 (15), 211 (70), 153 (12), 152 (15), 150 (10), 149 (100), 121 (11), 105 (31), 77 (53), 63 (14), 51 (13). HRMS calcd. for $C_{21}H_{19}NO_3$ 333.1365, found 333.1379.

**4-Methoxy-*N*-[(naphthalen-2-yl)(phenyl)methyl]benzenamine (13):** Purification by silica gel chromatography (toluene) gave (–)-**13** as a yellow oil of $[\alpha]_D^{25}$ = –1.6 (*c* = 1.01, $CHCl_3$ for *ee* = 64% with **1a**); *ee* was determined by SFC: Chiralcel OD-H, 200 bar, 2 mL·min$^{-1}$, 25% MeOH in $CO_2$ (25%, 15 min), 30 °C, $t_1$ = 10.4 min, $t_2$ = 11.5 min. $^1$HNMR (400 MHz, $CDCl_3$): $\delta$ = 7.85–7.72 (m, 3 H), 7.50–7.20 (m, 9 H), 6.71 (d, $J$ = 8.8 Hz, 2 H), 6.57 (d, $J$ = 8.8 Hz, 2 H), 5.58 (s, 1 H), 3.71 (s, 3 H), 1.55 (br. s, 1 H) ppm. $^{13}$CNMR (100 MHz, $CDCl_3$): $\delta$ = 134.5, 133.4, 132.8, 130.1, 129.5, 129.1, 128.8, 128.5, 128.0, 127.6, 127.4, 126.1, 125.9, 125.8, 125.6, 114.7, 55.7 ppm. MS (EI), *m*/*z* (%) 339 (M, 18), 218 (15), 217 (100), 216 (11), 215 (21), 212 (11), 202 (23). HRMS calcd. for $C_{24}H_{21}NO$ 339.1623, found 339.1646.

**4-Methoxy-*N*-[(naphthalen-1-yl)(phenyl)methyl]benzenamine[22] (14):** Purification by silica gel chromatography (pentane/$Et_2O$, 10:1) gave **14** as a colorless oil of $[\alpha]_D^{25}$ = –40.7 (*c* = 3.57, $CHCl_3$ for *ee* = 90% with **1a**), + 60.1 (*c* = 0.32, $CHCl_3$ for *ee* = 94% with **7a**); *ee* was determined by SFC: Chiralcel OD-H, 175 bar, 1.8 mL·min$^{-1}$, 20% MeOH in $CO_2$ (20%, 15 min), 30 °C, $t_1$ = 9.6 min, $t_2$ = 12.2 min.

**4-Methoxy-*N*-[(naphthalen-1-yl)(*o*-tolyl)methyl]benzenamine (15):** Purification by silica gel chromatography (toluene) gave **15** as a white solid. M.p. 86–87 °C (pentane/diethyl ether). $[\alpha]_D^{25}$ = –22.3 (*c* = 0.18, $CHCl_3$ for *ee* = 86% with **1a**), +36.6 (*c* = 0.40, $CHCl_3$ for *ee* = 94% with **7a**); *ee* was determined by SFC: Chiralcel OJ, 170 bar, 2 mL·min$^{-1}$, 10% MeOH in $CO_2$ (10%, 5 min, 2%·min$^{-1}$, 25%, 5 min), 30 °C, $t_1$ = 10.0 min, $t_2$ = 10.9 min. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.95–7.75 (m, 4 H), 7.55–7.10 (m, 7 H), 6.73 (d, $J$ = 8.8 Hz, 2 H), 6.49 (d, $J$ = 7.4 Hz, 2 H), 6.25 (s, 1 H), 3.73 (s, 3 H), 2.31 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 136.4, 134.3, 131.6, 131.0, 129.1, 128.4, 127.8, 127.6, 126.7, 126.5, 125.8, 125.8, 125.7, 123.6, 115.0, 55.9, 19.4 ppm. IR (neat): 3400, 2928, 1750, 1510, 1242, 1038, 819, 791, 758 cm$^{-1}$. MS (EI), *m*/*z* (%): 353 (29), 232 (22), 231 (100), 216 (28), 215 (30). HRMS: ESI (positive) calcd. for $[M - H]^+$ $C_{25}H_{22}NO$ 352.1701, found 352.1713.

***N*-[(4-Chlorophenyl)(naphthalen-1-yl)methyl]-4-methoxybenzenamine (16):** Purification by silica gel chromatography (pentane/$Et_2O$, 20:1) gave (–)-**16** as a colorless oil of $[\alpha]_D^{25}$ = –36.9 (*c* = 0.38, $CHCl_3$ for *ee* = 90% with **1a**); *ee* was determined by SFC: Chiralcel OJ, 170 bar, 2 mL·min$^{-1}$, 10% MeOH in $CO_2$ (10%, 5 min, 2%·min$^{-1}$, 25%, 10 min), 30 °C, $t_1$ = 23.0 min, $t_2$ = 24.7 min. $^1$H

NMR: $\delta$ = 8.04 (d, $J$ = 7.3 Hz, 1 H), 7.94 (d, $J$ = 7.6 Hz, 1 H), 7.84 (d, $J$ = 7.8 Hz, 1 H), 7.55–7.22 (m, 8 H), 6.76 (d, $J$ = 8.6 Hz, 2 H), 6.53 (d, $J$ = 8.1 Hz, 2 H), 6.16 (s. 1 H), 4.07 (br. s, 1 H), 3.76 (s, 3 H) ppm. $^{13}$C NMR: $\delta$ = 152.3, 141.4, 141.0, 137.6, 134.1, 133.2, 131.1, 129.4, 129.0, 128.9, 128.4, 126.6, 125.8, 125.7, 125.5, 123.4, 114.9, 114.3, 59.5, 55.7 ppm. IR (neat): 3403, 3051, 1597, 1508, 1240, 1014, 781, 735, 699 cm$^{-1}$. MS (EI), *m*/*z* (%): 374 (11), 373 (46), 372 (34), 371 (63), 370 (55), 260 (20), 253 (34), 252 (18), 251 (100), 249 (14), 217 (14), 216 (70), 215 (73), 127 (14), 92 (15), 77 (24), 64 (10). HRMS calcd. for $C_{24}H_{20}{}^{35}ClNO$ 373.1233, found 373.1234.

**4-Methoxy-*N*-[(naphthalen-1-yl)(*p*-tolyl)methyl]benzenamine (17):** Purification by silica gel chromatography (toluene) gave **17** as a yellow oil of $[\alpha]_D^{25}$ = –86.6 ($c$ = 0.30, $CHCl_3$ for *ee* = 88% with **1a**), +47.9 ($c$ = 0.14, $CHCl_3$ for *ee* = 92% with **7a**); *ee* was determined by SFC: Chiralcel OJ, 170 bar, 2 mL·min$^{-1}$, 10% MeOH in $CO_2$ (10%, 5 min, 2%·min$^{-1}$, 25%, 10 min), 30 °C, $t_1$ = 14.5 min, $t_2$ = 16.0 min. $^1$H NMR: $\delta$ = 7.96 (d, $J$ = 7.1 Hz, 1 H), 7.80 (d, $J$ = 7.1 Hz, 1 H), 7.70 (d, $J$ = 8.3 Hz, 1 H), 7.48–7.30 (m, 4 H), 7.28–7.20 (m, 3 H), 7.12–7.03 (m, 1 H), 6.63 (d, $J$ = 6.8 Hz, 2 H), 6.40 (d, $J$ = 8.8 Hz, 2 H), 6.04 (s, 1 H), 3.97 (br. s, 1 H), 3.62 (s, 3 H), 2.25 (s, 3 H) ppm. $^{13}$C NMR: $\delta$ = 152.0, 141.7, 139.5, 137.9, 137.1, 134.1, 131.1, 129.4, 128.9, 128.0, 126.3, 125.5, 125.3, 123.6, 114.8, 114.2, 59.8, 55.7, 21.1 ppm. IR (neat): 3400, 3000, 1510, 1242, 1030, 800, 785 cm$^{-1}$. MS (EI), *m*/*z* (%): 353 (M, 18), 232 (26), 231 (100), 230 (22), 229 (17), 217 (11), 216 (33), 215 (44), 123 (17), 108 (24), 80 (8). HRMS calcd. for $C_{25}H_{23}NO$ 353.1780, found 353.1773.

***N*-{[Benzo[*d*][1,3]dioxol-6-yl](naphthalen-1-yl)methyl}-4-methoxybenzenamine (18):** Purification by silica gel chromatography (toluene) gave **18** as a yellow oil of $[\alpha]_D^{25}$ = –59.1 ($c$ = 0.80, $CHCl_3$ for *ee* = 86% with **1a**), +35.0 ($c$ = 0.85, $CHCl_3$ for *ee* = 90% with **7a**); *ee* was determined by SFC: Chiralcel OD-H, 170 bar, 2 mL·min$^{-1}$, 20% MeOH in $CO_2$ (20%, 30 min), 30 °C, $t_1$ = 15.3 min, $t_2$ = 18.1 min. $^1$H NMR: $\delta$ = 8.10–8.00 (m, 1 H), 8.00–7.75 (m, 2 H), 7.58–7.40 (m, 5 H), 6.98–6.85 (m, 2 H), 6.80–6.67 (m, 3 H), 6.53 (d, $J$ = 8.6 Hz, 1 H), 6.07 (s, 1 H), 6.00–5.90 (m, 2 H), 3.72 (s, 3 H), 1.55 (br. s, 1 H) ppm. $^{13}$C NMR: $\delta$ = 148.2, 147.1, 134.3, 131.3, 129.1, 128.4, 126.6, 125.8, 125.7, 125.6, 123.7, 121.6, 115.0, 108.7, 108.6, 101.3, 55.9 ppm. IR (neat): 3400, 3000, 1750, 1511, 1237, 1038, 800 cm$^{-1}$. MS (EI), *m*/*z* (%): 383 (M, 12), 373 (46), 262 (25), 261 (100), 231 (29), 203 (34), 202 (32), 201 (8), 77 (4), 65 (4). HRMS calcd. for $C_{25}H_{21}NO_3$ 383.1521, found 383.1516.

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