Synthesis of Polyfunctional Secondary Amines by the Reaction of Functionalized Organomagnesium Reagents with Tertiary Nitroalkanes

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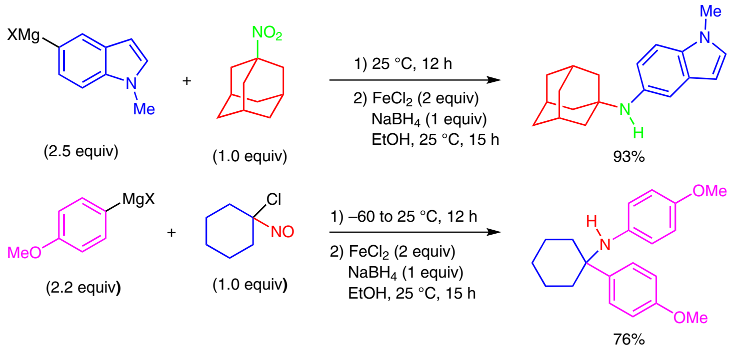

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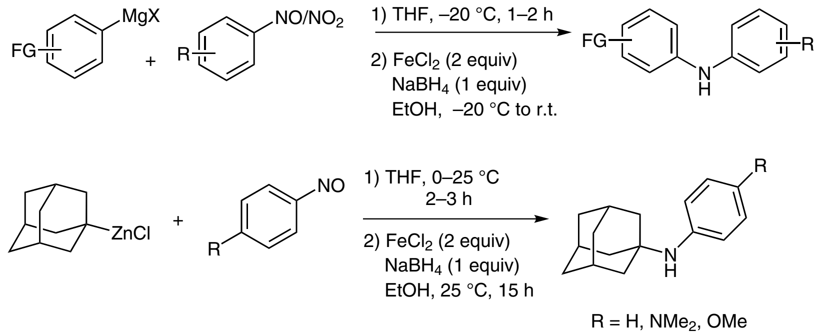
Abstract Addition of polyfunctionalized aryl, heteroaryl, and tertiary alkylmagnesium reagents to tertiary nitroalkanes at 25 °C in tetrahydrofuran produces, after reductive workup with $FeCl_2$ and $NaBH_4$ in ethanol, the corresponding polyfunctional secondary amines in high yields.

Key words secondary amines, nitroalkanes, organomagnesium reagents, amination reactions, adamantane

The synthesis of arylamines is an important synthetic goal because such amines are common functional groups with useful properties in pharmaceuticals and material science.[1] Aminoadamantane derivatives, in particular, have found several interesting applications in drug development and medicinal chemistry.[2] Palladium,[3] nickel,[4] copper,[5] and rhodium[6] catalyzed aminations are excellent amination methods, but they have the disadvantage of requiring both expensive and toxic transition metals. Recently, Buchwald and co-workers reported a palladium-catalyzed arylation of hindered primary amines with aryl halides.[7] Additionally, Cu-catalyzed C–N cross-couplings of arylboronic acids with adamantylamine have been described.[8] Alternatively, the reaction of inexpensive and less toxic main group organometallics with electrophilic nitrogen reagents have been used to prepare various amines.[9]

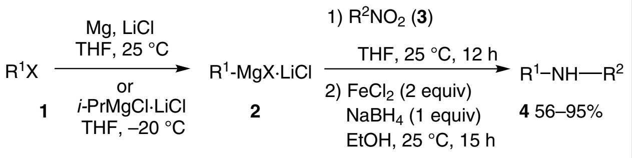
A few years ago, we reported the preparation of diarylamines through the addition of functionalized organomagnesium reagents to nitroso-arenes[10] and nitro-arenes.[11] Recently, we reported that the addition of functionalized organozinc reagents[12] to nitroso-arenes produces the corresponding polyfunctional secondary amines in high yields.[13] However, adamantylzinc chloride reacts smoothly only with electron-rich nitroso-arenes and furnishes the corresponding adamantyl(aryl)amines in good yields only with such substrates (Scheme 1). Nitroso-arenes substituted with an electron-withdrawing group do not react in satisfactory yields (less than 20%) under these conditions.

Herein, we wish to report a mild synthesis of highly sterically hindered polyfunctionalized adamantyl(aryl)- or tertiary-alkyl(aryl)-amines as well as di-adamantylamine, including aryl amines bearing electron-withdrawing substituents. Thus, we first prepared various aryl, heteroaryl,



Scheme 1 Previously reported aminations using nitroso- or nitro-arenes[10,11,13]

and tertiary alkyl magnesium reagents of type **2** from the corresponding aryl halides (R^1–X; X = Br, I) either by the direct insertion of Mg in the presence of LiCl[14] or by an I/Mg exchange using *i*PrMgCl·LiCl.[15] Thus, the reaction of Grignard reagents of type **2** with tertiary nitroalkanes **3** at 25 °C in THF produced, after reductive workup with $FeCl_2$ and $NaBH_4$ in ethanol, the corresponding polyfunctional secondary amines **4** in high yields (Scheme 2 and Table 1).



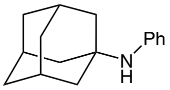
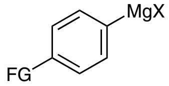
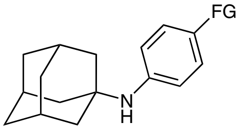
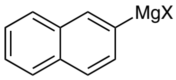
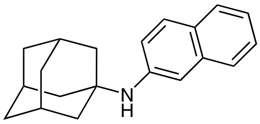
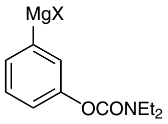
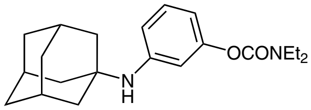
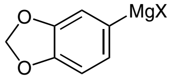
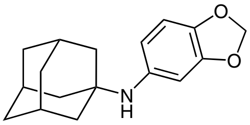
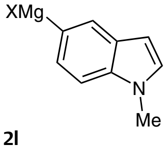
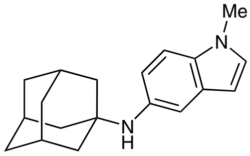
Scheme 2 Synthesis of polyfunctional secondary amines of type **4** through the addition of functionalized magnesium reagents **2** to tertiary nitroalkanes **3** followed by reductive workup

Thus, PhMgCl (**2a**; 2.5 equiv) reacted with 1-nitroadamantane (**3a**; 1.0 equiv)[16] at 25 °C for 12 hours and produced, after reductive workup with $FeCl_2$ (2.0 equiv) and $NaBH_4$ (1.0 equiv) in ethanol, the corresponding phenyladamantylamine **4a** in 95% yield (Table 1, entry 1).[8] A variety of functionalized aryl, heteroaryl, or tertiary-alkylmagnesium reagents bearing an amide, amine, silyl ether, thiomethyl ether, or fluoro substituent were prepared by the direct insertion of Mg (2.5 equiv) in the presence of LiCl (1.3 equiv) in THF at 0–25 °C for 1–3 hours.[14] Remarkably, all these Grignard reagents reacted smoothly with 1-nitroadamantane (**3a**) furnishing, after reductive workup, the corresponding adamantyl(aryl)amines in 56–93% yield, allowing the preparation of aryl(adamantyl)amines bearing electron-withdrawing substituents (entries 2–11) for the first time.[7,13] Additionally, the magnesiated indole reagent **2l** reacted smoothly with 1-nitroadamantane (**3a**) to give heteroaryl(adamantyl)amine **4l** in 93% yield (entry 12).

The scope of the reaction was extended to the preparation of sterically hindered[17] di-tertiary-alkylamines using tertiary alkylmagnesium reagents, such as commercially available *tert*-butylmagnesium chloride (**2m**) and 1-adamantylmagnesium bromide (**2n**).[18] Their reaction with 1-nitroadamantane (**3a**) produced the expected di-tertiary-alkylamines **4m**–**n** in 53–77% yield (Table 2, entries 1 and 2).[19] Moreover, 2-methyl-2-nitropropane (**3b**) also reacted efficiently with arylmagnesium reagents of type **2a**, **2i**, and **2f**, furnishing the corresponding *tert*-butyl(aryl)amines **4o**–**q** in 72–80% yield (entries 3–5).[20]

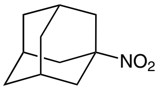
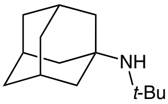
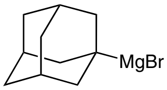
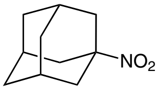
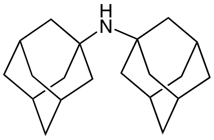
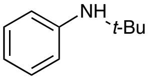
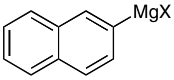
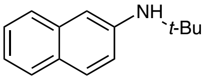
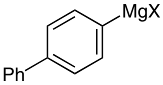
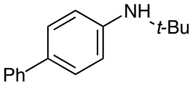
In the reaction of organomagnesium reagents with 1-nitroadamantane (**3a**) an excess of the magnesium reagent **2** (2.5 equiv) was necessary to achieve complete conversion. The first equivalent of the organomagnesium reagent **2** adds at the oxygen of the nitro group of adamantane **3a**, producing an intermediate adamantylnitroso derivative **5** after elimination of magnesium alcoholate. The tertiary alkylnitroso compound **5** reacts with a second equivalent of the magnesium reagent **2** leading to the formation of the desired C–N bond, and affords the hydroxylamine derivative **6**, which, after reductive workup, gives the corresponding secondary amines **4** in excellent yields (Scheme 3).

Table 1 Synthesis of Polyfunctional Adamantyl(aryl)amines of Type **4a**–**l** by the Addition of Arylmagnesium Reagents **2a**–**l** to 1-Nitroadamantane (**3a**) Followed by Reductive Workup[a]

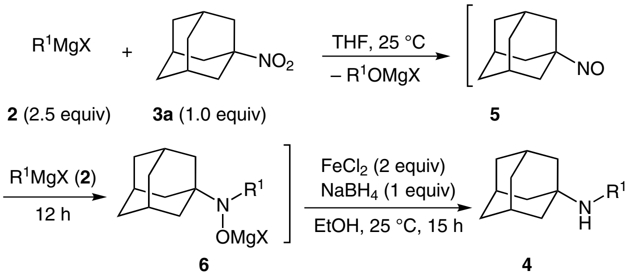
Entry	Grignard reagent (R^1)	Product	Yield (%)[b]
1	PhMgCl **2a**	 **4a**	95
			
2	**2b** FG = *n*-Bu	**4b**	85
3	**2c** FG = SMe	**4c**	81
4	**2d** FG = NMe_2	**4d**	56
5	**2e** FG = OTIPS	**4e**	93
6	**2f** FG = Ph	**4f**	79
7	**2g** FG = F	**4g**	73
8	**2h**[c] FG = CO_2Et	**4h**	60
9	 **2i**	 **4i**	90
10	 **2j**	 **4j**	82
11	 **2k**	 **4k**	70
12	 **2l**	 **4l**	93

[a] General reaction conditions: arylmagnesium reagent **2** (2.5 equiv), 1-nitroadamantane **3a** (1.0 equiv), $NaBH_4$ (1.0 equiv), $FeCl_2$ (2.0 equiv).
[b] Isolated yield after purification by flash-column chromatography.
[c] Prepared by I/Mg exchange with *i*PrMgCl·LiCl.15

Table 2 Synthesis of Polyfunctional Secondary Amines of Type **4m–q** by the Addition of Aryl- and Alkylmagnesium Reagents **2** to Tertiary Nitroalkanes **3a** and **3b** Followed by Reductive Workup[a]

Entry	Grignard reagent	Electrophile (R^2)	Product, yield[b]
1	t-BuMgCl **2m**	 **3a**	 **4m** 77%[c]
2	 **2n**	 **3a**	 **4n** 53%[c]
3	PhMgCl **2a**	*t*-BuNO$_2$ **3b**	 **4o** 72%
4	 **2i**	*t*-BuNO$_2$ **3b**	 **4p** 75%
5	 **2f**	*t*-BuNO$_2$ **3b**	 **4q** 80%

[a] General reaction conditions: organomagnesium reagent **2** (2.5 equiv), **3a** or **3b** (1.0 equiv), NaBH$_4$ (1.0 equiv), FeCl$_2$ (2.0 equiv).
[b] Isolated yield after purification by flash-column chromatography.
[c] Reaction was performed at –60 °C to room temperature.

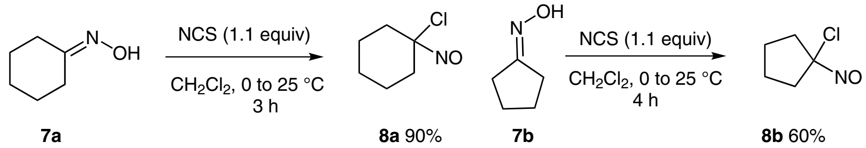


Scheme 3 Reaction pathway and mechanism for the synthesis of adamantyl(aryl)amines

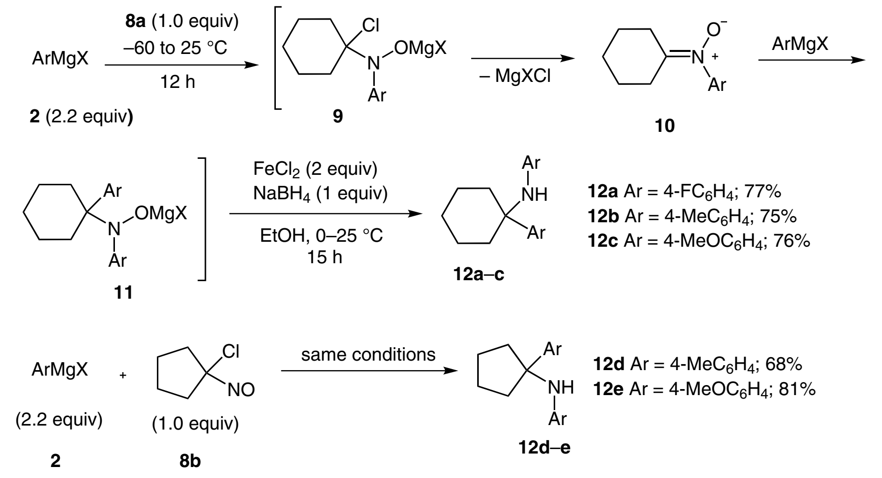
We also examined the addition of magnesium and zinc organometallics to 1-chloro-1-nitrosocycloalkanes such as **8a** and **8b**. 1-Chloro-1-nitrosocyclohexane (**8a**) was obtained by chlorination of cyclohexanone oxime with *N*-chlorosuccinimide in 90% yield. Similarly, 1-chloro-1-nitrosocyclopentane **8b** was obtained from **7b** in 60% yield (Scheme 4).[21]

Notably, an arylmagnesium reagent of type **2** (2.2 equiv) reacted smoothly with 1-chloro-1-nitrosocyclohexane (**8a**; 1.0 equiv) at –60 °C to room temperature for 12 hours, producing an intermediate nitrone **10**[22] after elimination of chloride. Nitrone **10** then reacted with a second equivalent of magnesium reagent **2**, leading to a magnesiated hydroxylamine of type **11**, which, after reductive workup, led to the corresponding double arylated amines **12a–c** in 75–77% yield. Similarly, **8b** reacted with arylmagnesium reagents **2** to produce the cyclopentyl(aryl)amines **12d–e** in 68–81% yield (Scheme 5).

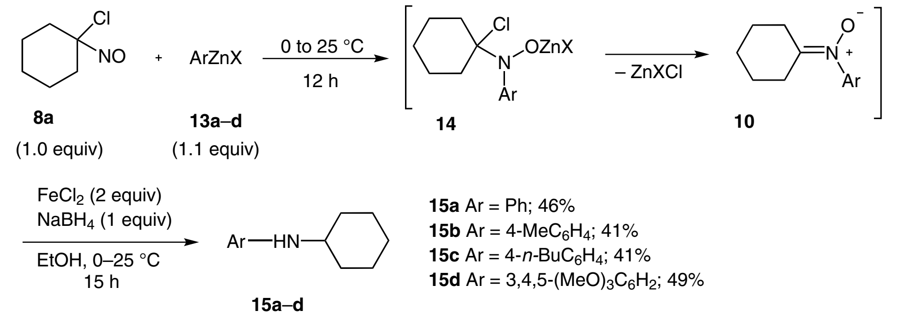
Finally, the arylzinc reagents **13a–d**[14] (1.1 equiv) reacted with 1-chloro-1-nitrosocyclohexane (**8a**; 1.0 equiv) at 0 °C to room temperature (12 h) producing an intermediary ni-



Scheme 4 Synthesis of 1-chloro-1-nitrosocycloalkanes **8a** and **8b**



Scheme 5 Synthesis of secondary amines **12a**–**e** by the reaction of arylmagnesium reagents of type **2** with 1-chloro-1-nitrosocycloalkanes **8a**,**b**



Scheme 6 Synthesis of secondary amines **15a**–**d** by the reaction of arylzinc reagents **13** with 1-chloro-1-nitrosocyclohexane (**8a**)

trone, which, under our reaction conditions, did not react further with arylzinc reagents and gave, after reductive workup (Scheme 6),[23] the corresponding secondary amines **15a**–**d** in 41–49% yield.

In summary, we have developed a practical synthesis of sterically hindered polyfunctionalized secondary amines by the reaction of aryl, heteroaryl, or tertiary alkylmagnesium reagents with 1-nitroadamantane or 2-methyl-2-nitropropane as well as 1-chloro-1-nitrosocycloalkanes. Further extensions of this work are underway in our laboratories.

All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes that were used to transfer anhydrous solvents or reagents were purged with argon prior to use. THF was continuously heated at reflux and freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^1H NMR (25 °C) and capillary GC analyses. Chemical shifts are reported as δ-values in ppm relative to the solvent peak. NMR spectra were recorded in a solution of $CDCl_3$ (residual chloroform: $\delta = 7.25$ ppm for ^1H NMR and $\delta = 77.0$ ppm for ^{13}C NMR). Signal multiplicities are abbreviated as: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of a doublet), ddd (doublet of a doublet of a doublet), dt (doublet of triplet), tt (triplet of triplet), and m (multiplet). Column chromatographic purification was performed using SiO_2 (0.040–0.063 mm, 230–400 mesh ASTM) from Merck if not indicated. All reagents were obtained from commercial sources.

Preparation of $ZnCl_2$ (1 M in THF)

A dry and argon-flushed 250 mL Schlenk flask equipped with a magnetic stirring bar and a septum was charged with $ZnCl_2$ (13.6 g, 100 mmol). The salt was heated to 140 °C under high vacuum for 10 h. After cooling to 25 °C, anhydrous THF (100 mL) was added and stirring was continued until the salt was dissolved completely (4 h).

Preparation of Functionalized Aryl and Heteroarylmagnesium Reagents (2)[14] through LiCl-Mediated Magnesium Insertion in Aryl and Heteroaryl Halides

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with LiCl (1.3 equiv) and heated to 450 °C with a heat gun under high vacuum for 5 min. After cooling to r.t., magnesium turnings (2.5 equiv) were added, followed by THF (2 mL/mmol). The magnesium turnings were activated using 1,2-dibromoethane (5 mol%) and trimethylsilyl chloride (5 mol%). The suspension was cooled to 0 °C, followed by addition of the aryl or heteroaryl halide (1.0 equiv). The reaction mixture was stirred at 0 °C to r.t. until GC analysis of hydrolyzed reaction aliquots showed full consumption of the starting material. The solids were allowed to settle or the reaction mixture was centrifuged (10 min, 2000 rpm). The yield of the insertion reaction was determined by iodometric titration[24] of the supernatant solution.

Preparation of Functionalized Aryl and Heteroarylzinc Reagents (13)[14] through LiCl-Mediated Magnesium Insertion in the Presence of Zinc Chloride in Aryl and Heteroaryl Halides

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with LiCl (1.3 equiv) and heated to 450 °C with a heat gun under high vacuum for 5 min. After cooling to r.t., magnesium turnings (2.5 equiv) were added, followed by THF (2 mL/mmol). The magnesium turnings were activated using 1,2-dibromoethane (5 mol%) and trimethylsilyl chloride (5 mol%). The suspension was cooled to 0 °C, $ZnCl_2$ solution (1 M in THF, 1.1 equiv) was added followed by addition of the aryl or heteroaryl halide (1.0 equiv). The reaction mixture was stirred until GC analysis of hydrolyzed reaction aliquots showed full consumption of the starting material. The solids were allowed to settle or the reaction mixture was centrifuged (10 min, 2000 rpm). The yield of the insertion reaction was determined by iodometric titration[24] of the supernatant solution.

Preparation of Secondary Amines (4) by the Reaction of Functionalized Magnesium Reagents (2) with Nitro-Electrophiles (3); Typical Procedure 1 (TP1)

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with freshly prepared organomagnesium reagent **2** (2.5 mmol. 2.5 equiv) in anhydrous THF (2 mL) and cooled to 0 °C. The nitro substrate **3** (1.0 mmol, 1.0 equiv) was added and the reaction mixture was stirred at 0 to 25 °C for 12 h until GC analysis of a reaction aliquot showed full consumption of the starting material. EtOH (1.0 mL), $FeCl_2$ (2.0 mmol, 2.0 equiv), and $NaBH_4$ (1.0 mmol, 1.0 equiv) were added and the reaction mixture was stirred at r.t. for 15 h. After quenching the reaction with sat. aq NH_4Cl (10 mL), the mixture was neutralized with aq NaOH (2 M) and extracted with EtOAc (6 × 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash-column chromatography to give the analytically pure amine product **4**.

(3*s*,5*s*,7*s*)-*N*-Phenyladamantan-1-amine (4a)[8]

The amination reaction of freshly prepared arylmagnesium reagent **2a**[14] (1.68 M in THF, 1.48 mL, 2.5 mmol) with 1-nitroadamantane **3a**[16] (182 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP1. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 90:10] furnished **4a**.

Yield: 215 mg (95%); pale-yellow solid; mp 80.6–82.3 °C.

IR (ATR): 3408, 2904, 2847, 1598, 1502, 1305, 1130, 1096, 741, 690 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.16 (dd, *J* = 8.7, 7.3 Hz, 2 H), 6.60–6.92 (m, 3 H), 3.25 (s, 1 H), 2.04–2.21 (m, 3 H), 1.81–2.01 (m, 6 H), 1.57–1.79 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.0, 128.7, 119.2, 119.1, 52.2, 43.5, 36.5, 29.8.

MS (ESI): *m*/*z* (%) = 228 (100) $[M + H]^+$, 135 (37), 114 (1).

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{16}H_{22}N$: 228.1752; found: 228.1746.

(3*s*,5*s*,7*s*)-*N*-(4-Butylphenyl)adamantan-1-amine (4b)[7b]

The amination reaction of freshly prepared arylmagnesium reagent **2b** (0.37 M in THF, 2.5 mmol, 6.75 mL) with 1-nitroadamantane **3a** (182 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP1. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 88:12] furnished **4b**.

Yield: 240 mg (85%); pale-yellow liquid.

IR (ATR): 3400, 2903, 2848, 1614, 1511, 1452, 1308, 1092, 812 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.98 (d, *J* = 8.3 Hz, 2 H), 6.76 (d, *J* = 8.0 Hz, 2 H), 3.24 (br s, 1 H), 2.52 (t, *J* = 7.6 Hz, 2 H), 2.01–2.19 (m, 3 H), 1.75–1.99 (m, 6 H), 1.44–1.74 (m, 8 H), 1.25–1.43 (m, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.1, 134.4, 128.5, 120.5, 52.4, 43.6, 36.5, 34.8, 33.8, 29.8, 22.4, 14.0.

MS (EI): *m*/*z* (%) = 283 (100) $[M^+]$, 240 (34), 227 (20), 226 (97), 135 (87), 106 (17), 93 (21), 91 (12), 79 (21), 67 (11), 41 (13).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{29}N$: 283.2300; found: 283.2294.

(3*s*,5*s*,7*s*)-*N*-[4-(Methylthio)phenyl]adamantan-1-amine (4c)[7a]

The amination reaction of freshly prepared arylmagnesium reagent **2c** (0.34 M in THF, 7.35 mL, 2.5 mmol) with 1-nitroadamantane **3a** (182 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP1. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 80:20] furnished **4c**.

Yield: 220 mg (81%); pale-yellow solid; mp 67.1–67.5 °C.

IR (ATR): 3376, 2898, 2847, 1592, 1500, 1297, 1100, 814, 805, 671 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 8.4 Hz, 2 H), 6.72 (d, *J* = 8.6 Hz, 2 H), 3.32 (br s, 1 H), 2.40 (s, 3 H), 1.97–2.18 (m, 3 H), 1.76–1.93 (m, 6 H), 1.54–1.76 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.4, 130.0, 126.5, 119.6, 52.3, 43.3, 36.4, 29.7, 18.4.

MS (EI): *m*/*z* (%) = 273 (100) $[M^+]$, 216 (39), 169 (19), 136 (10), 135 (65), 93 (12), 79 (13).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{23}NS$: 273.1551; found: 273.1548.

*N*¹-[(3*s*,5*s*,7*s*)-adamantan-1-yl]-*N*⁴,*N*⁴-dimethylbenzene-1,4-diamine (4d)[13]

The amination reaction of freshly prepared arylmagnesium reagent **2d** (0.30 M in THF, 8.33 mL, 2.5 mmol) with 1-nitroadamantane **3a** (182 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP1. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 50:50] furnished **4d**.

Yield: 152 mg (56%); pale-yellow solid; mp 103.0–104.1 °C.

IR (ATR): 3295, 2901, 2842, 1616, 1511, 1243, 1124, 819, 689 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.83 (d, *J* = 8.3 Hz, 2 H), 6.66 (d, *J* = 8.3 Hz, 2 H), 2.89 (s, 6 H), 2.80 (br s, 1 H), 1.97–2.16 (m, 3 H), 1.50–1.85 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.6, 135.1, 125.0, 113.5, 52.6, 43.8, 41.3, 36.5, 29.8.

MS (EI): *m*/*z* (%) = 270 (100) $[M^+]$, 269 (5), 213 (14), 136 (13), 135 (34), 121 (12), 93 (7), 79 (6).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{26}N_2$: 270.2096; found: 270.2090.

(3*s*,5*s*,7*s*)-*N*-{4-[(Triisopropylsilyl)oxy]phenyl}adamantan-1-amine (4e)

The amination reaction of freshly prepared arylmagnesium reagent **2e** (0.33 M in THF, 7.57 mL, 2.5 mmol) with 1-nitroadamantane **3a** (182 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP1. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 85:15] furnished **4e**.

Yield: 372 mg (93%); pale-yellow liquid.

IR (ATR): 2904, 2866, 2849, 1503, 1463, 1240, 910, 882, 678 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.61–6.85 (m, 4 H), 2.93 (s, 1 H), 1.96–2.18 (m, 3 H), 1.42–1.92 (m, 12 H), 0.93–1.35 (m, 21 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.9, 138.4, 123.9, 119.7, 52.6, 43.7, 36.5, 29.7, 17.9, 12.6.

MS (EI): *m*/*z* (%) = 399 (100) [M^+], 356 (14), 342 (16), 135 (74), 93 (18), 86 (14), 79 (17), 59 (13), 43 (15), 41 (20).

HRMS (EI): *m*/*z* calcd for $C_{25}H_{41}NOSi$: 399.2957; found: 399.2951.

(3*s*,5*s*,7*s*)-*N*-[(1,1′-Biphenyl)-4-yl]adamantan-1-amine (4f)

The amination reaction of freshly prepared arylmagnesium reagent **2f** (0.24 M in THF, 10.41 mL, 2.5 mmol) with 1-nitroadamantane **3a** (182 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP1. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 88:12] furnished **4f**.

Yield: 240 mg (79%); pale-yellow solid; mp 117.2–117.9 °C.

IR (ATR): 3393, 2909, 1610, 1598, 1522, 1490, 1451, 1302, 1096, 813, 759, 696 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 7.5 Hz, 2 H), 7.33–7.49 (m, 4 H), 7.21–7.32 (m, 1 H), 6.87 (d, *J* = 8.3 Hz, 2 H), 3.59 (br s, 1 H), 2.0–2.23 (m, 3 H), 1.83–2.04 (m, 6 H), 1.58–1.81 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.3, 141.1, 131.6, 128.6, 127.4, 126.3, 126.2, 118.7, 52.4, 43.3, 36.5, 29.7.

MS (EI): *m*/*z* (%) = 303 (85) [M^+], 246 (78), 169 (26), 136 (26), 135 (100), 93 (29), 79 (31), 67 (19), 44 (47), 43 (41), 41 (21).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{25}N$: 303.1987; found: 303.1988.

(3*s*,5*s*,7*s*)-*N*-(4-Fluorophenyl)adamantan-1-amine (4g)

The amination reaction of freshly prepared arylmagnesium reagent **2g** (0.55 M in THF, 4.54 mL, 2.5 mmol) with 1-nitroadamantane **3a** (182 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP1. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 80:20] furnished **4g**.

Yield: 180 mg (73%); colorless solid; mp 64.3–65.1 °C.

IR (ATR): 3338, 2896, 1502, 1354, 1240, 1205, 1090, 836, 753, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.68–6.97 (m, 4 H), 3.19 (br s, 1 H), 1.96–2.24 (m, 3 H), 1.48–1.90 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9 (d, *J* = 237.0 Hz), 141.2, 122.6 (d, *J* = 7.5 Hz), 115.1 (d, *J* = 21.7 Hz), 52.7, 43.5, 36.4, 29.7.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –124.1 (s, 1 F).

MS (EI): *m*/*z* (%) = 245 (100) [M^+], 216 (6), 202 (10), 189 (17), 188 (97), 135 (36), 110 (6).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{20}FN$: 245.1580; found: 245.1560.

Ethyl 4-{[(3*s*,5*s*,7*s*)-Adamantan-1-yl]amino}benzoate (4h)

The amination reaction of freshly prepared arylmagnesium reagent **2h** (0.45 M in THF, 5.55 mL, 2.5 mmol) with 1-nitroadamantane **3a** (182 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP1. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 75:25] furnished **4h**.

Yield: 180 mg (60%); pale-yellow solid; mp 97.2–99.3 °C.

IR (ATR): 3372, 2903, 1680, 1598, 1525, 1273, 1170, 1094, 836, 771, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.4 Hz, 2 H), 6.70 (d, *J* = 8.2 Hz, 2 H), 4.33 (q, *J* = 7.0 Hz, 2 H), 4.02 (br s, 1 H), 2.09–2.23 (m, 3 H), 1.90–2.07 (m, 6 H), 1.62–1.82 (m, 6 H), 1.37 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 150.6, 131.1, 118.3, 114.5, 60.1, 52.1, 42.7, 36.4, 29.6, 14.5.

MS (EI): *m*/*z* (%) = 299 (27) [M^+], 242 (26), 136 (13), 135 (100), 93 (20), 79 (19), 67 (10), 41 (9).

HRMS (EI), *m*/*z* calcd for $C_{19}H_{25}NO_2$ (299.1885): 299.1877.

(3*s*,5*s*,7*s*)-*N*-(Naphthalen-2-yl)adamantan-1-amine (4i)

The amination reaction of freshly prepared arylmagnesium reagent **2i** (0.37 M in THF, 6.75 mL, 2.5 mmol) with 1-nitroadamantane **3a** (182 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP1. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 88:12] furnished **4i**.

Yield: 250 mg (90%); pale-yellow solid; mp 111.9–112.6 °C.

IR (ATR): 3396, 2903, 1629, 1525, 1399, 1226, 831, 812, 744 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.75 (m, 3 H), 7.37 (t, *J* = 7.3 Hz, 1 H), 7.19–7.29 (m, 1 H), 7.14 (s, 1 H), 6.98 (dd, *J* = 8.7, 1.8 Hz, 1 H), 3.64 (br s, 1 H), 2.08–2.25 (m, 3 H), 1.84–2.08 (m, 6 H), 1.54–1.83 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.4, 134.6, 128.4, 128.1, 127.5, 126.2, 126.1, 122.5, 122.0, 111.9, 52.6, 43.3, 36.5, 29.7.

MS (EI): *m*/*z* (%) = 277 (100) [M^+], 221 (18), 220 (86), 143 (15), 135 (61), 127 (13), 115 (17), 93 (17), 79 (17), 43 (13).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{23}N$: 277.1830; found: 277.1814.

3-{[(3*s*,5*s*,7*s*)-Adamantan-1-yl]amino}phenyl Diethylcarbamate (4j)

The amination reaction of freshly prepared arylmagnesium reagent **2j** (0.31 M in THF, 8.1 mL, 2.5 mmol) with 1-nitroadamantane **3a** (182 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP1. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 75:25] furnished **4j**.

Yield: 280 mg (82%); pale-yellow solid; mp 55.9–59.9 °C.

IR (ATR): 3363, 2904, 1698, 1613, 1421, 1269, 1176, 1156, 753, 686 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.09 (t, *J* = 8.0 Hz, 1 H), 6.34–6.74 (m, 3 H), 3.14–3.61 (m, 5 H), 2.01–2.18 (m, 3 H), 1.76–1.99 (m, 6 H), 1.54–1.76 (m, 6 H), 1.05–1.34 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.2, 152.1, 147.0, 129.0, 115.1, 111.8, 52.3, 43.2, 42.1, 41.9, 36.4, 29.7, 14.2, 13.4.

MS (EI): *m*/*z* (%) = 342 (57) [M^+], 285 (37), 135 (46), 100 (100), 79 (14), 72 (40), 44 (20).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{30}N_2O_2$: 342.2307; found: 342.2303.

N-[(3*s*,5*s*,7*s*)-Adamantan-1-yl]benzo[*d*][1,3]dioxol-5-amine (4k)

The amination reaction of freshly prepared arylmagnesium reagent **2k** (0.43 M in THF, 5.8 mL, 2.5 mmol) with 1-nitroadamantane **3a** (182 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP1. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 75:25] furnished **4k**.

Yield: 190 mg (70%); pale-yellow solid; mp 90.1–90.6 °C.

IR (ATR): 3365, 2900, 1495, 1478, 1194, 1180, 1035, 934, 821 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.63 (d, *J* = 8.0 Hz, 1 H), 6.46 (s, 1 H), 6.21–6.37 (m, 1 H), 5.88 (s, 2 H), 3.08 (br s, 1 H), 1.96–2.16 (m, 3 H), 1.49–1.84 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.5, 142.4, 139.7, 115.0, 107.8, 104.7, 100.8, 52.9, 43.6, 36.4, 29.7.

MS (EI): *m*/*z* (%) = 271 (100) [M^+], 214 (45), 184 (15), 137 (18), 135 (96), 93 (21), 79 (18), 77 (15).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{21}NO_2$: 271.1572; found: 271.1561.

N-[(3*s*,5*s*,7*s*)-Adamantan-1-yl]-1-methyl-1*H*-indol-5-amine (4l)

The amination reaction of freshly prepared heteroarylmagnesium reagent **2l** (0.25 M in THF, 10.0 mL, 2.5 mmol) with 1-nitroadamantane **3a** (182 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP1. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 50:50] furnished **4l**.

Yield: 260 mg (93%); pale-yellow solid; mp 91.4–93.0 °C.

IR (ATR): 3302, 2897, 2843, 1498, 1237, 1154, 787, 754, 717 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.09–7.21 (m, 2 H), 6.98 (d, *J* = 2.7 Hz, 1 H), 6.86 (d, *J* = 8.2 Hz, 1 H), 6.37 (d, *J* = 2.5 Hz, 1 H), 3.74 (s, 3 H), 2.88 (br s, 1 H), 1.97–2.15 (m, 3 H), 1.72–1.85 (m, 6 H), 1.52–1.70 (m, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 133.6, 128.9, 128.6, 120.4, 115.5, 108.7, 100.2, 52.9, 43.8, 36.5, 32.9, 29.8.

MS (EI): *m*/*z* (%) = 280 (92) [M^+], 223 (100), 146 (18), 145 (18), 135 (29), 131 (20), 93 (17), 79 (17).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{24}N_2$: 280.1939; found: 280.1933.

(3*s*,5*s*,7*s*)-*N*-(*tert*-Butyl)adamantan-1-amine (4m)

The amination reaction of freshly prepared tertiary-alkylmagnesium reagent **2m** (1.18 M in THF, 2.1 mL, 2.5 mmol) with 1-nitroadamantane **3a** (182 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP1. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); EtOH] furnished **4m**.

Yield: 160 mg (77%); pale-yellow solid; mp 265–275 °C.

IR (ATR): 2912, 2850, 2781, 2441, 1497, 1375, 1189, 1073, 918, 758 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.49 (br s, 1 H), 2.22–2.47 (m, 6 H), 2.01–2.19 (m, 3 H), 1.45–1.85 (m, 15 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 62.4, 60.8, 40.9, 35.5, 29.6,

MS (EI): *m*/*z* (%) = 207 (9) [M^+], 192 (72), 150 (42), 135 (100), 94 (86), 57 (14), 41 (34).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{25}N$: 207.1987; found: 207.1993.

(3*s*,5*s*,7*s*)-Di[(3*s*,5*s*,7*s*)-adamantan-1-yl]amine (4n)[19]

The amination reaction of freshly prepared tertiary-alkylmagnesium reagent **2n** (0.10 M in THF, 25.0 mL, 2.5 mmol) with 1-nitroadamantane **3a** (182 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP1. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 60:40) furnished **4n**.

Yield: 150 mg (53%); pale-yellow solid; mp 165.5–175.1 °C.

IR (ATR): 2896, 2846, 1744, 1448, 1350, 1158, 1097, 820 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.94–2.07 (m, 6 H), 1.68–1.94 (m, 12 H), 1.40–1.66 (m, 13 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.9, 46.3, 36.6, 30.0.

MS (EI): *m*/*z* (%) = 285 (40) [M^+], 229 (21), 228 (100), 191 (17), 135 (72), 93 (20), 79 (20), 67 (11), 41 (13).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{31}N$: 285.2457; found: 285.2440.

N-(*tert*-Butyl)aniline (4o)[20a]

The amination reaction of freshly prepared arylmagnesium reagent **2a** (1.68 M in THF, 1.48 mL, 2.5 mmol) with 2-methyl-2-nitropropane **3b** (104 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP1. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); pentane–Et_2O, 80:20] furnished **4o**.

Yield: 108 mg (72%); yellow liquid.

IR (ATR): 3406, 2958, 2924, 2855, 1484, 1363, 1189, 1081, 965, 763, 685 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.05–7.25 (m, 2 H), 6.48–6.93 (m, 3 H), 3.44 (br s, 1 H), 1.36 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.8, 128.9, 118.4, 117.5, 51.5, 30.1.

MS (ESI): *m*/*z* (%) = 150 (100) [M + H]$^+$, 135 (29).

HRMS (ESI): *m*/*z* [M + H] calc. for $C_{10}H_{16}N$: 150.1283; found: 150.1277.

N-(*tert*-Butyl)naphthalen-2-amine (4p)[20b]

The amination reaction of freshly prepared arylmagnesium reagent **2i** (0.31 M in THF, 8.1 mL, 2.5 mmol) with 2-methyl-2-nitropropane **3b** (104 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP1. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 93:7] furnished **4p**.

Yield: 150 mg, (75%); red solid; mp 35.2–35.8 °C.

IR (ATR): 3408, 3328, 2960, 1628, 1596, 1360, 1213, 1184, 858, 818, 748 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.78 (m, 3 H), 7.18–7.45 (m, 2 H), 7.08 (s, 1 H), 6.94 (d, *J* = 8.8 Hz, 1 H), 3.79 (br s, 1 H), 1.46 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.3, 134.9, 128.6, 127.7, 127.5, 126.1, 122.3, 121.0, 109.6, 51.7, 29.9.

MS (EI): *m*/*z* (%) = 199 (51) [M^+], 185 (17), 184 (96), 143 (100), 127 (11), 116 (11), 115 (31), 41 (7).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{17}N$: 199.1361; found: 199.1361.

N-(*tert*-Butyl)-[1,1'-biphenyl]-4-amine (4q)[20c]

The amination reaction of freshly prepared arylmagnesium reagent **2f** (0.28 M in THF, 8.92 mL, 2.5 mmol) with 2-methyl-2-nitropropane **3b** (104 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and

$NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP1. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 90:10] furnished **4q**.

Yield: 180 mg (80%); pale-yellow solid; mp 37.1–38.3 °C.

IR (ATR): 3404, 2973, 1607, 1519, 1484, 1220, 1204, 826, 756, 694 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 7.5 Hz, 2 H), 7.35–7.49 (m, 4 H), 7.22–7.32 (m, 1 H), 6.85 (d, *J* = 8.3 Hz, 2 H), 3.99 (br s, 1 H), 1.40 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.8, 141.1, 131.2, 128.6, 127.6, 126.3, 126.2, 117.5, 51.8, 30.0, 29.9.

MS (EI): *m*/*z* (%) = 225 (52) [M^+], 211 (16), 210 (100), 170 (14), 169 (98), 168 (12), 152 (13), 115 (10), 41 (7).

HRMS (EI): *m*/*z* [M – CH_3] calcd for $C_{15}H_{16}N$: 210.1283; found: 210.1228.

1-Chloro-1-nitrosocyclohexane (8a)[21]

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with cyclohexanone oxime **7a** (20.0 g, 177.0 mmol. 1.0 equiv) in anhydrous CH_2Cl_2 (350 mL) and cooled to 0 °C. *N*-Chlorosuccinimide (26.0 g, 194.0 mmol, 1.1 equiv) was then added and the reaction mixture was stirred at 0 to 25 °C for 3 h until GC analysis of reaction aliquots showed full consumption of the starting material. Removal of the solvent followed by addition of *n*-pentane (200 mL) to the crude mixture led to the precipitation of succinimide. This succinimide was filtered off then washed with *n*-pentane (50 mL) and the filtrate was evaporated. The crude residue was purified by flash-column chromatography (silica gel; *n*-pentane) to furnish **8a**.

Yield: 23.4 g (90%); greenish blue liquid.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.29–2.74 (m, 2 H), 1.21–2.05 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 117.7, 33.4, 24.7, 21.8.

1-Chloro-1-nitrosocyclopentane (8b)[21]

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with cyclopentanone oxime **7b** (6.2 g, 62.2 mmol. 1.0 equiv) in anhydrous CH_2Cl_2 (150 mL) and cooled to 0 °C. *N*-Chlorosuccinimide (9.2 g, 68.9 mmol, 1.1 equiv) was added and the reaction mixture was stirred at 0 to 25 °C for 3 h until GC analysis of reaction aliquot showed full consumption of the starting material. Removal of solvent followed by addition of *n*-pentane (100 mL) to the crude mixture led to the precipitation of succinimide. This succinimide was filtered off then washed with *n*-pentane (50 mL) and the filtrate was evaporated. The crude residue was purified by flash-column chromatography (silica gel; *n*-pentane) to furnish **8b**.

Yield: 5.0 g (60%); greenish blue liquid.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.64–3.12 (m, 2 H), 1.57–2.33 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 122.9, 38.2, 25.5.

Preparation of Secondary Amines (12a–e) by the Reaction of Functionalized Arylmagnesium Reagents (2) with 1-Chloro-1-nitrosocycloalkanes (8); Typical Procedure 2 (TP2)

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with nitroso substrate **8** (1.0 mmol, 1.0 equiv) in anhydrous THF (4 mL) and cooled to –60 °C. Freshly prepared arylmagnesium reagent **2** (2.2 mmol. 2.2 equiv) was then added and the reaction mixture was stirred at –60 to 25 °C for 12 h until GC analysis of reaction aliquots showed full consumption of the starting material. The reaction mixture was cooled to 0 °C, then EtOH (1.0 mL), $FeCl_2$ (2.0 mmol, 2.0 equiv), and $NaBH_4$ (1.0 mmol, 1.0 equiv) were added and the reaction mixture was stirred at 0 °C to r.t. for 15 h. After quenching the reaction with sat. aq NH_4Cl (10 mL), the mixture was neutralized with aq NaOH (2 M) solution and extracted with EtOAc (6 × 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash-column chromatography to give the analytically pure amine product **12a**–**e**.

4-Fluoro-*N*-[1-(4-fluorophenyl)cyclohexyl]aniline (12a)

The amination reaction of freshly prepared arylmagnesium reagent **2g** (0.49 M in THF, 4.48 mL, 2.2 mmol) with 1-chloro-1-nitrosocyclohexane **8a** (148 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP2. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–Et_2O, 85:15] furnished **12a**.

Yield: 220 mg (77%); pale-yellow liquid.

IR (ATR): 3436, 2936, 2859, 1606, 1506, 1221, 1159, 905, 822, 727 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.50 (m, 2 H), 6.95 (t, *J* = 8.6 Hz, 2 H), 6.65 (t, *J* = 8.6 Hz, 2 H), 6.21 (dd, *J* = 8.1, 4.2 Hz, 2 H), 4.02 (br s, 1 H), 1.89–2.16 (m, 2 H), 1.39–1.82 (m, 7 H), 1.09–1.36 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5 (d, *J* = 244.0 Hz), 155.8 (d, *J* = 231.0 Hz), 144.0, 141.4, 127.5 (d, *J* = 8.0 Hz), 116.5, 115.4 (d, *J* = 8.0 Hz), 115.1 (d, *J* = 10.0 Hz), 57.5, 36.2, 25.4, 21.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –117.1 (s, 1 F), –128.0 (s, 1 F).

MS (EI): *m*/*z* (%) = 287 (6) [M^+], 177 (26), 135 (7), 111 (56), 109 (100), 81 (8), 55 (8).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{19}F_2N$: 287.1486; found: 287.1469.

4-Methyl-*N*-[1-(*p*-tolyl)cyclohexyl]aniline (12b)

The amination reaction of freshly prepared arylmagnesium reagent **2o** (0.51 M in THF, 4.31 mL, 2.2 mmol) with 1-chloro-1-nitrosocyclohexane **8a** (148 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP2. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–Et_2O, 99:1] furnished **12b**.

Yield: 210 mg (75%); pale-yellow liquid.

IR (ATR): 3425, 2928, 2855, 1615, 1513, 1448, 1300, 1252, 806, 720 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.0 Hz, 2 H), 7.08 (d, *J* = 7.8 Hz, 2 H), 6.77 (d, *J* = 8.2 Hz, 2 H), 6.25 (d, *J* = 7.4 Hz, 2 H), 4.01 (br s, 1 H), 2.28 (s, 3 H), 1.97–2.18 (m, 5 H), 1.4–1.87 (m, 7 H), 1.15–1.36 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 143.2, 135.8, 129.2, 129.2, 125.8, 115.7, 57.4, 36.2, 25.6, 22.0, 21.0, 20.4.

MS (EI): *m*/*z* (%) = 279 (31) [M^+], 236 (17), 173 (38), 157 (19), 129 (17), 115 (15), 107 (85), 105 (100).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{25}N$: 279.1987; found: 279.1973.

4-Methoxy-*N*-[1-(4-methoxyphenyl)cyclohexyl]aniline (12c)

The amination reaction of freshly prepared arylmagnesium reagent **2p** (0.51 M in THF, 4.31 mL, 2.2 mmol) with 1-chloro-1-nitrosocyclohexane **8a** (148 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP2. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 60:40] furnished **12c**.

Yield: 236 mg (76%); pale-yellow solid; mp 59.3–62.2 °C.

IR (ATR): 3428, 2933, 2857, 1605, 1504, 1215, 1158, 819, 770 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.8 Hz, 2 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 6.54 (d, *J* = 8.9 Hz, 2 H), 6.25 (d, *J* = 8.8 Hz, 2 H), 3.84 (br s, 1 H), 3.74 (s, 3 H), 3.61 (s, 3 H), 2.02 (d, *J* = 13.1 Hz, 2 H), 1.60–1.78 (m, 3 H), 1.42–1.59 (m, 4 H), 1.21–1.31 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 151.9, 140.9, 139.6, 127.0, 117.1, 114.3, 113.8, 57.2, 55.6, 55.2, 36.3, 25.6, 22.1.

MS (EI): *m*/*z* (%) = 311 (10) [M$^+$], 189 (82), 188 (21), 160 (10), 123 (51), 121 (100), 108 (18).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{25}NO_2$: 311.1885; found: 311.1884.

4-Methyl-*N*-[1-(*p*-tolyl)cyclopentyl]aniline (12d)

The amination reaction of freshly prepared arylmagnesium reagent **2o** (0.47 M in THF, 4.68 mL, 2.2 mmol) with 1-chloro-1-nitrosocyclopentane **8b** (134 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP2. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 99:1] furnished **12d**.

Yield: 180 mg (68%); pale-yellow liquid.

IR (ATR): 3414, 2953, 2869, 1615, 1512, 1448, 1302, 1256, 1183, 1019, 806 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 7.8 Hz, 2 H), 7.07 (d, *J* = 7.8 Hz, 2 H), 6.79 (d, *J* = 8.0 Hz, 2 H), 6.26 (d, *J* = 8.2 Hz, 2 H), 3.91 (br s, 1 H), 2.28 (s, 3 H), 1.94–2.19 (m, 7 H), 1.70–1.89 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8, 143.7, 135.6, 129.2, 129.1, 126.0, 125.9, 115.3, 66.9, 40.8, 24.2, 21.0, 20.4.

MS (EI): *m*/*z* (%) = 265 (17) [M$^+$], 159 (85), 143 (12), 115 (11), 107 (100), 105 (74), 67 (10).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{23}N$: 265.1830; found: 265.1817.

4-Methoxy-*N*-[1-(4-methoxyphenyl)cyclopentyl]aniline (12e)

The amination reaction of freshly prepared arylmagnesium reagent **2p** (0.48 M in THF, 4.58 mL, 2.2 mmol) with 1-chloro-1-nitrosocyclopentane **8b** (134 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP2. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 70:30] furnished **12e**.

Yield: 240 mg (81%); pale-yellow solid; mp 90.9–91.2 °C.

IR (ATR): 3407, 2966, 1606, 1508, 1243, 1170, 1024, 821, 799 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 8.6 Hz, 2 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 6.56 (d, *J* = 8.8 Hz, 2 H), 6.28 (d, *J* = 8.6 Hz, 2 H), 3.73 (s, 4 H), 3.62 (s, 3 H), 1.91–2.10 (m, 4 H), 1.67–1.85 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 151.9, 140.1, 138.9, 127.1, 116.8, 114.3, 113.6, 67.0, 55.7, 55.2, 40.4, 23.9.

MS (EI): *m*/*z* (%) = 297 (9) [M$^+$], 176 (12), 175 (100), 134 (8), 123 (41), 121 (43), 108 (10).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{23}NO_2$: 297.1729; found: 297.1725.

Preparation of Secondary Amines 15a–d by the Reaction of Functionalized Arylzinc Reagents 13a–d with 1-Chloro-1-nitrosocyclohexane (8a): Typical Procedure 3 (TP3)

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with freshly prepared arylzinc reagent **13a**–**d** (1.1 mmol. 1.1 equiv) in anhydrous THF (2 mL) and cooled to 0 °C. Then 1-chloro-1-nitrosocyclohexane **8a** (1.0 mmol, 1.0 equiv) was added and the reaction mixture was stirred at 0 to 25 °C for 12 h until GC analysis of reaction aliquots showed full consumption of the starting material. The reaction mixture was cooled to 0 °C, then EtOH (1.0 mL), $FeCl_2$ (2.0 mmol, 2.0 equiv), and $NaBH_4$ (1.0 mmol, 1.0 equiv) were added and the reaction mixture was stirred at 0 °C to r.t. for 15 h. After quenching with sat. aq NH_4Cl (10 mL), the mixture was neutralized with aq NaOH (2 M) solution and extracted with EtOAc (6 × 25 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude residue obtained was purified by flash-column chromatography to give the analytically pure amine product **15a**–**d**.

N-Cyclohexylaniline (15a)[23a]

The amination reaction of freshly prepared arylzinc reagent **13a** (1.68 M in THF, 0.65 mL, 1.1 mmol) with 1-chloro-1-nitrosocyclohexane **8a** (148 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP3. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–Et_2O, 96:4] furnished **15a**.

Yield: 80 mg (46%); pale-yellow liquid.

IR (ATR): 3401, 2926, 2852, 1600, 1502, 1319, 1255, 744, 690 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09–7.22 (m, 2 H), 6.66 (tt, *J* = 7.3, 1.1 Hz, 1 H), 6.55–6.62 (m, 2 H), 3.52 (br s, 1 H), 3.21–3.31 (m, 1 H), 2.02–2.11 (m, 2 H), 1.73–1.81 (m, 2 H), 1.62–1.69 (m, 1 H), 1.32–1.42 (m, 2 H), 1.11–1.27 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.4, 129.2, 116.8, 113.1, 51.7, 33.5, 25.9, 25.0.

MS (EI): *m*/*z* (%) = 175 (41) [M$^+$], 132 (100), 118 (11), 77 (17), 61 (12), 44 (43), 43 (92).

HRMS (EI): *m*/*z* calcd for $C_{12}H_{17}N$: 175.1361; found: 175.1355.

N-Cyclohexyl-4-methylaniline (15b)[23b]

The amination reaction of freshly prepared arylzinc reagent **13b** (0.51 M in THF, 2.15 mL, 1.1 mmol) with 1-chloro-1-nitrosocyclohexane **8a** (148 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP3. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–Et_2O, 70:30] furnished **15b**.

Yield: 78 mg (41%); pale-yellow liquid.

IR (ATR): 3382, 2924, 2854, 2480, 2429, 1618, 1515, 1464, 1021, 809, 788 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (d, *J* = 8.2 Hz, 2 H), 6.52 (d, *J* = 8.2 Hz, 2 H), 3.01–3.26 (m, 1 H), 2.17 (s, 3 H), 1.89–2.06 (m, 2 H), 1.47–1.78 (m, 3 H), 0.95–1.38 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.2, 129.8, 127.0, 114.2, 52.8, 33.3, 25.9, 25.1, 20.4.

MS (EI): *m*/*z* (%) = 189 (49) [M$^+$], 147 (17), 146 (100), 133 (16), 131 (13), 120 (13), 106 (14), 91 (15), 77 (11).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{19}N$: 189.1517; found: 189.1506.

4-Butyl-*N*-cyclohexylaniline (15c)

The amination reaction of freshly prepared arylzinc reagent **13c** (0.27 M in THF, 4.07 mL, 1.1 mmol) with 1-chloro-1-nitrosocyclohexane **8a** (148 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP3. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–Et_2O, 96:4] furnished **15c**.

Yield: 95 mg (41%); pale-yellow liquid.

IR (ATR): 3399, 2925, 2852, 1616, 1515, 1450, 1316, 1304, 1254, 816 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92 (d, *J* = 8.2 Hz, 2 H), 6.49 (d, *J* = 8.20 Hz, 2 H), 3.46 (br s, 1 H), 3.06–3.25 (m, 1 H), 2.43 (t, *J* = 7.7 Hz, 2 H), 1.87–2.10 (m, 2 H), 1.42–1.76 (m, 5 H), 1.00–1.40 (m, 7 H), 0.86 (t, *J* = 7.32 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.1, 131.6, 129.1, 113.5, 52.2, 34.8, 34.1, 33.6, 26.0, 25.1, 22.4, 14.0,

MS (EI): *m*/*z* (%) = 231 (46) [M$^+$], 230 (9), 189 (17), 188 (100), 132 (15), 106 (18).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{25}N$: 231.1987; found: 231.1967.

N-Cyclohexyl-3,4,5-trimethoxyaniline (15d)[23c]

The amination reaction of freshly prepared arylzinc reagent **13d** (0.23 M in THF, 4.78 mL, 1.1 mmol) with 1-chloro-1-nitrosocyclohexane **8a** (148 mg, 1.0 mmol), EtOH (1.0 mL), $FeCl_2$ (254 mg, 2.0 mmol), and $NaBH_4$ (38 mg, 1.0 mmol) was performed according to TP3. Flash-column chromatographic purification [silica gel (pre-neutralized with Et_3N); *i*-hexane–EtOAc, 50:50] furnished **15d**.

Yield: 130 mg (49%); greenish liquid.

IR (ATR): 3377, 2927, 2851, 1609, 1594, 1506, 1231, 1123, 1012, 801, 776 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.81 (s, 2 H), 3.80 (s, 6 H), 3.74 (s, 3 H), 3.40 (br s, 1 H), 3.13–3.22 (m, 1 H), 1.99–2.09 (m, 2 H), 1.71–1.79 (m, 2 H), 1.59–1.67 (m, 1 H), 1.30–1.40 (m, 2 H), 1.09–1.26 (m, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 154.0, 144.1, 129.8, 90.8, 61.1, 55.9, 52.1, 33.6, 25.9, 25.0.

MS (EI): *m*/*z* (%) = 265 (34) [M$^+$], 251 (16), 250 (100), 168 (41), 140 (9), 55 (8), 43 (16).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{23}NO_3$: 265.1678; found: 265.1669.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378871.

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