Preparation of Tertiary Amines via the Oxidative Coupling of Polyfunctional Aryl and Heteroaryl Amidocuprates

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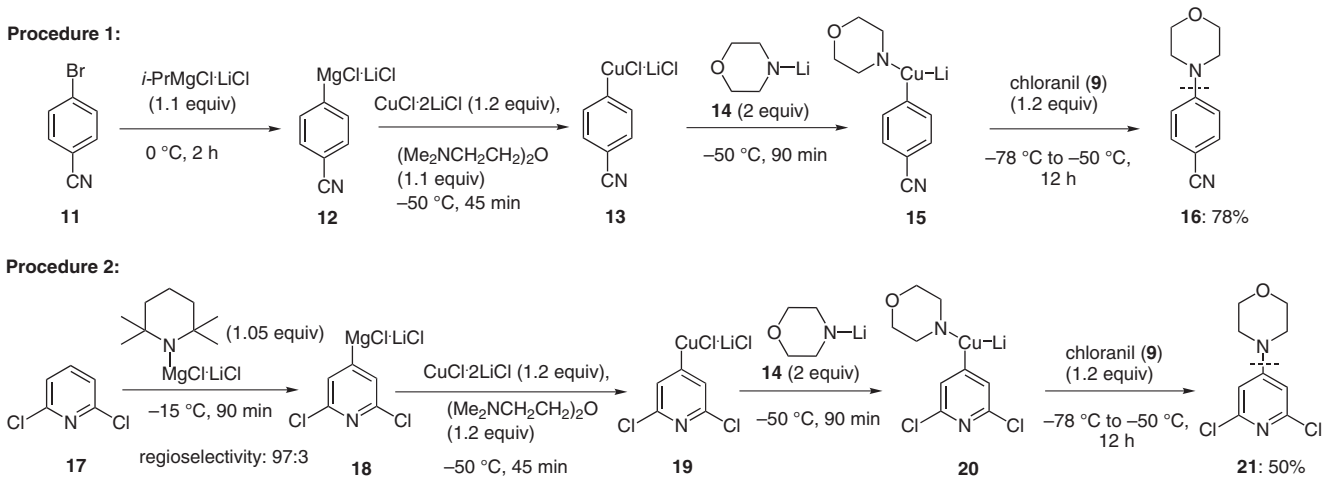
Abstract: Highly functionalized tertiary amines can be prepared by the oxidative coupling of polyfunctional lithium amidocuprates using chloranil as an oxidant. A high functional group tolerance and insensibility to steric hindrance characterize this general amination reaction. Herein, we report a practical procedure for the preparation of aryl and heteroaryl tertiary amines.

Key words: amination, amidocuprates, C–N bond formation, lithium amides, polyfunctional Grignard reagents



Scheme 1

Introduction

Aromatic and heterocyclic arylamines are important target molecules in organic synthesis due to their potential applications as pharmaceuticals,[1] xerographic and photographic materials,[2] conducting polymers, or material precursors.[3] In addition to several electrophilic amination methods,[4] the palladium-catalyzed amination of aromatic halides and related electrophiles described by Buchwald and Hartwig has become a widely used method for the preparation of arylamines.[5] However, this reaction has some limitations, such as long reaction times for sterically hindered systems and the necessity to carefully choose the appropriate phosphine or carbene ligand to obtain optimum yields. Also, triarylamines cannot always be prepared efficiently using this method.[6] Furthermore, some functional groups like iodides (and bromides) are not compatible with this palladium-catalyzed amination procedure. Some years ago Yamamoto[7] and Ricci[8] reported the oxidative coupling of amidocuprates, leading to amines, using oxygen. Recently, we reported an alternative preparation of primary, secondary, and tertiary arylamines via the oxidative coupling of polyfunctional aryl and heteroaryl amidocuprates.[9] The general approach is depicted in Scheme 2. Aryl iodides **1** or bromides **2** are the starting material for our procedure. An I/Mg-exchange reaction with isopropylmagnesium chloride,[10a,b] or a Br/Mg exchange with the more reactive isopropylmagnesium chloride–lithium chloride complex (*i*-PrMgCl·LiCl),[10c,d] lead to the corresponding Grignard reagents. Alternatively, aromatic rings bearing acidic protons **3** can be also magnesiated upon treatment with 2,2,6,6-tetramethylpiperidin-1-ylmagnesium chloride–lithium chloride complex (TMPMgCl·LiCl).[11] The so obtained organomagnesium reagents **4** are readily transmetalated with the tetrahydrofuran soluble salt copper(I) chloride–bis(lithium chloride) (CuCl·2 LiCl)[12] to provide the copper derivatives **5**, which after treatment with a lithium amide **7** (prepared from the

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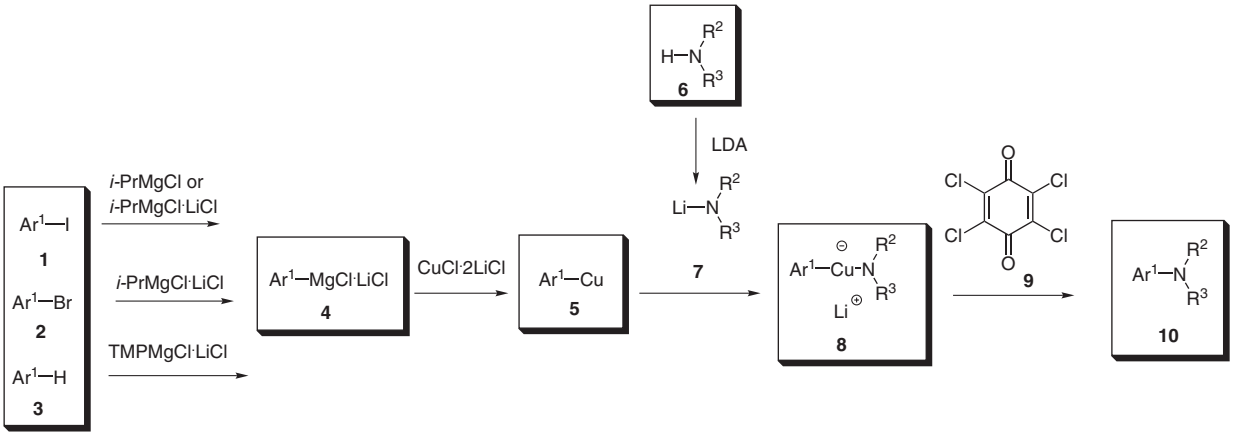


Scheme 2 General scheme for the amination reaction

corresponding amine **6** by deprotonation with butyllithium or lithium diisopropylamide) result in the lithium amidocuprates **8**. These intermediates can be oxidized with chloranil (**9**) to afford, after purification, the desired amines **10**. As a plausible mechanism for this reaction, we propose the coordination of chloranil (**9**) to the copper center of the lithium amidocuprate as outlined in Scheme 3. This coordination is supposed to trigger the oxidation process and to lead to the desired products.

We have shown that this method tolerates a broad range of functional groups and is not hampered by steric hindrance.[9] Herein, we wish to report a typical practical procedure illustrating this method.

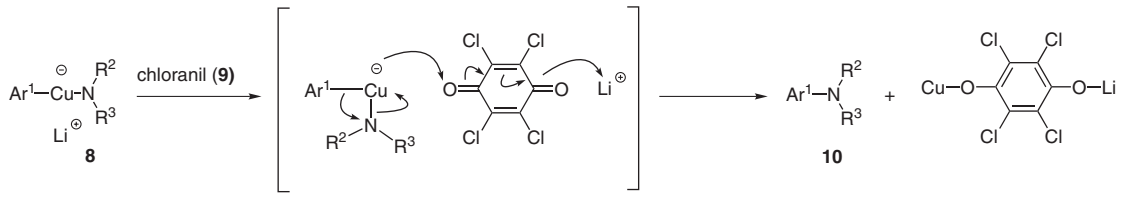
Scope and Limitations

The mild conditions of this procedure are compatible with a wide variety of functionalities (Scheme 1, Table 1). For the synthesis of tertiary aromatic amines, neat 4-bromobenzonitrile (**11**) was added to *i*-PrMgCl·LiCl (1.1 equiv, 0 °C, 2 h) leading to the arylmagnesium derivative **12**, which was added dropwise to the pale-colored mixture of CuCl·2 LiCl (1.2 equiv) and bis[2-(dimethylamino)ethyl] ether (1.2 equiv, –50 °C, 45 min) to form the copper derivative **13**. Then, further addition of lithium morpholide (**14**, 2 equiv, –50 °C, 90 min) followed by chloranil (**9**, 1.2 equiv, –78 °C to –50 °C, 12 h) afforded the tertiary aromatic amine derivative **16** in 78% yield (Scheme 1, Procedure 1).

On the other hand, a Grignard reagent like **18** can be also prepared by addition of 2,6-dichloropyridine (**17**, 1 mmol, 1 M in anhyd THF) to TMPMgCl·LiCl (1.05 mmol) at –15 °C for 90 minutes affording a 29:1 (average of three experiments) regioisomeric ratio of magnesiated products in favor of **18** as determined by capillary GC after the iodolysis of a reaction aliquot.[11b] The corresponding organocopper intermediate **19** was readily obtained from **18** and the amination reaction was further carried out as detailed above (Scheme 1, Procedure 2).

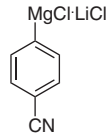
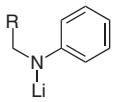
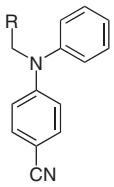
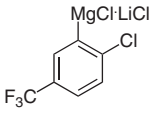
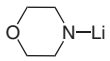
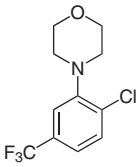
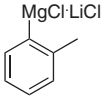
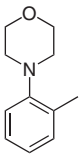
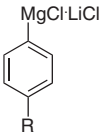
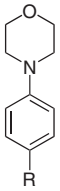
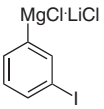
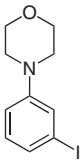
We have also applied this reaction to the preparation of *N*,*N*-diarylalkylamines **23** and **25**. Thus, the corresponding organocopper reagent **13** (readily obtained from the Grignard reagent **12**) was treated with lithium *N*-ethylanilide (**22**) or lithium *N*-benzylanilide (**24**) (2.0 mmol, prepared by adding *n*-BuLi to the corresponding secondary amine at –40 °C and stirring for 30 min, then the mixture was allowed to reach 0 °C and stirred for an additional 15 min) followed by the addition of chloranil (**9**) (1.2 equiv, –78 °C to –50 °C, 12 h) leading to the *N*,*N*-diarylalkylamines **23** and **25** (Table 1, entries 1, 2) in 69% and 71% yield, respectively. The sterically hindered tertiary amines **27** and **29** and tertiary amines **31**, **33**, **35**, and **37** (Table 1) were prepared in a similar manner. We have also scaled up this amination reaction, starting from 3–5 mmol of the Grignard reagents, although the yield of the product decreased slightly (Table 1, entry 5).

Furthermore, for the synthesis of primary amines, the diester **38** was magnesiated with TMPMgCl·LiCl (1.1 equiv, 0 °C, 1 h) leading to the arylmagnesium derivative **39**,[11a] which was treated with CuCl·2 LiCl (1.2 equiv) at –50 °C affording the corresponding arylcopper derivative **40** followed by the addition of bis[2-(dimethylamino)ethyl] ether (1.2 equiv) and lithium hexamethyldisilazanide



Scheme 3 Plausible mechanism for the oxidation of lithium amidocuprates by chloranil

Table 1 Synthesis of Tertiary Amines by Oxidative Coupling of Aryl Amidocuprates

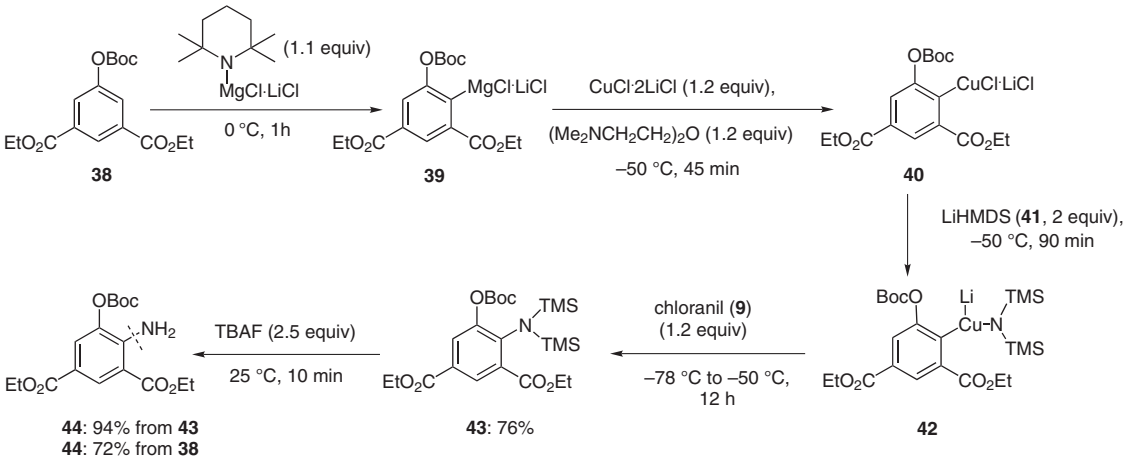
Entry	Grignard reagents		Lithium amides		Products		Yield[a] (%)
1		**12**		**22** R = Me		**23** R = Me	69[b]
2		**12**		**24** R = Ph		**25** R = Ph	71[b]
3		**26**		**14**		**27**	69[b]
4		**28**		**14**		**29**	58[c]
5		**30** R = Me		**14**		**31** R = Me	71[c] (69)[d]
6		**32** R = OMe		**14**		**33** R = OMe	55[b]
7		**34** R = I		**14**		**35** R = I	65[b]
8		**36**		**14**		**37**	59[b]

[a] Yield of analytically pure product.
[b] Arylmagnesium reagent formed through halogen–magnesium exchange reaction with *i*-PrMgCl·LiCl.
[c] The arylmagnesium reagent was prepared by Mg insertion on the corresponding aryl chloride.
[d] Reaction carried out on a 3-mmol scale.

(**41**, 2 equiv, –50 °C, 90 min) affording the amidocuprate **42**. It reacted with chloranil (**9**, 1.2 equiv, –78 °C to –50 °C, 12 h) leading to the *N*,*N*-bis(trimethylsilyl)amine derivative **43** in 76% yield. Facile desilylation was achieved with tetrabutylammonium fluoride (2.5 equiv, 25 °C, 10 min) giving the arylamine **44** in 94% yield (Scheme 4).

This method has been used to prepare various primary amines bearing electron-withdrawing substituents like a cyano, an ester, or a nitro group or electron-donating substituents like methoxy or iodo. In all these cases, the Grignard reagents were prepared by an I/Mg- or Br/Mg-exchange reaction.[10] This procedure can also be used for heterocyclic Grignard reagents such as polyfunctional pyridine, benzothiophene, and benzothiazole derivatives. The resulting primary amines of the type **44** are obtained, after deprotection of the corresponding *N*,*N*-bis(trimethylsilyl) group using tetrabutylammonium fluoride (2.5 equiv, 25 °C, 10 min) in good yields.[9]

Secondary amines were prepared from an aniline derivative such as **45** (Scheme 5). Its in situ protection with a *tert*-butyldimethylsilyl group was performed by lithiation with methyllithium (1.1 equiv, –50 °C, 10 min) followed by the addition of *tert*-butylchlorodimethylsilane (1.2 equiv, –50 °C to 25 °C, 0.5 h) leading to the *N*-silylaniline **46**. Further treatment with methyllithium (1.1 equiv, –50 °C, 10 min) provided the lithium amide **47**, which was treated with the arylcopper reagent **50** for two hours at –50 °C. This copper reagent was prepared from 4-iodoanisole (**48**) by an I/Mg-exchange reaction with



Scheme 4 Preparation of a primary amine[9]

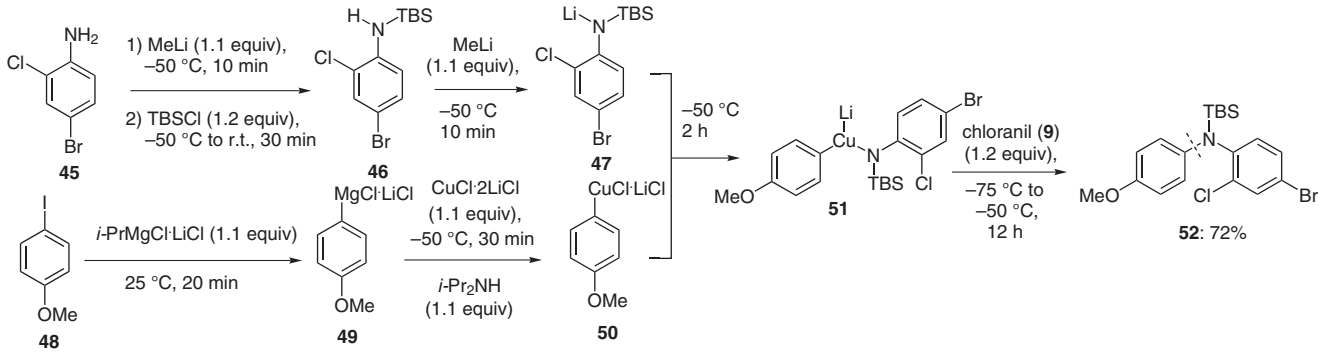
i-PrMgCl·LiCl (1.1 equiv, 25 °C, 20 min), followed by the addition of CuCl·2 LiCl (1.1 equiv, –50 °C, 30 min) in the presence of diisopropylamine (1.1 equiv). The resulting lithium amidocuprate **51** was treated with chloranil (**9**, 1.2 equiv, –78 °C to –50 °C, 12 h) providing the silyl-protected polyfunctional diarylamine **52** in 72% yield (Scheme 5). This reaction proved to be quite general and a number of functionalized aromatic and heteroaromatic Grignard reagents bearing a cyano, trifluoromethyl, or bromine substituent undergo a smooth oxidative amination with lithiated *N*-(*tert*-butyldimethylsilyl)anilines bearing various functional groups like chloro, methoxy or an ester function.[9]

Finally, the preparation of polyfunctional triarylamines can be performed using the same approach. For example, the lithiation of the secondary amine **55** with lithium diisopropylamide (1.05 equiv, –40 °C, 1 h) in the presence of an additional equivalent of diisopropylamine provides the lithium amide **56** which reacted with the copper reagent **54** affording the lithium amidocuprate **57**. This copper reagent **54** was prepared by an I/Mg exchange on 1,3-diiodobenzene (**53**) with *i*-PrMgCl·LiCl (1.1 equiv, 0 °C, 15 min) leading to the Grignard reagent **36**, followed by the transmetalation with CuCl·2 LiCl (1.1 equiv, –40 °C, 30 min). The resulting lithium amidocuprate **57** was treated with chloranil (**9**, 1.2 equiv, –78 °C to –40 °C, 12 h) providing the polyfunctional triarylamine **58** in 71% yield (Scheme 6). This sequence can be performed with several arylmagnesium reagents bearing various functional groups such as methoxy, iodo or an amide group, as well as with various lithium amides bearing functional groups like bromo or nitrile and ester groups leading to the tertiary amines in acceptable yields.[9]

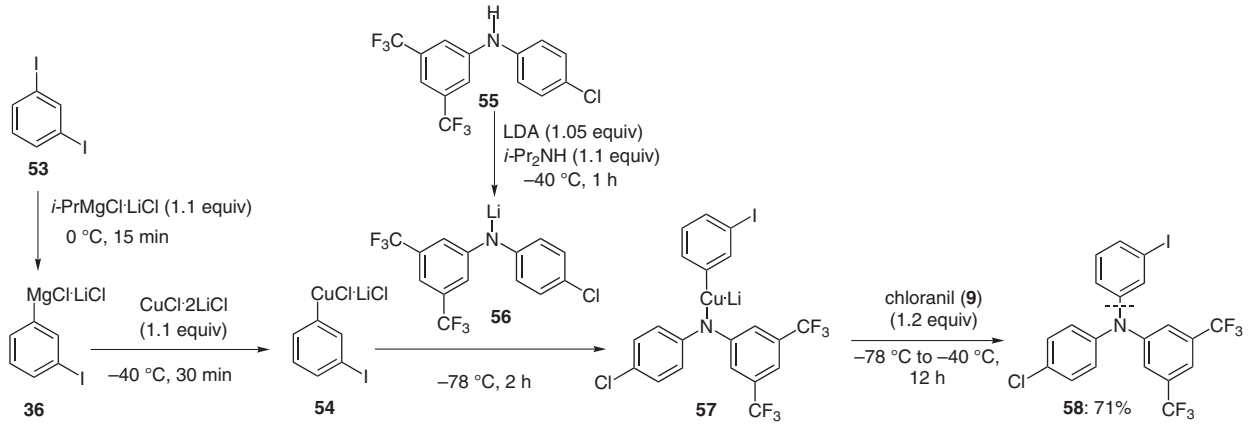
It has to be highlighted that this amination reaction is not substrate-dependent and does not show sensitivity to steric hindrance. Remarkably, all the compounds presented were prepared according to the standardized reaction conditions. In summary, we have extended our previous work to the scaled-up and optimized preparation of tertiary aromatic and heteroaromatic amines. These reactions could be performed with standard laboratory glassware and did not require the use of expensive chemicals or catalysts. We envision great acceptance and applicability for these reactions and hence further studies are underway in our laboratory.

Procedures

All reactions were carried out under argon atmosphere in dried glassware. All starting materials were purchased from commercial suppliers and used without further puri-



Scheme 5 Preparation of a secondary amine[9]



Scheme 6 Preparation of a triarylamine[9]

fication unless otherwise stated. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under N_2. *i*-Pr_2NH and bis[2-(dimethylamino)ethyl] ether were distilled from CaH_2 under N_2. Yields refer to isolated compounds estimated to be >95% pure as determined by ^1H NMR and capillary GC analysis.

Isopropylmagnesium Chloride–Lithium Chloride Complex

Mg turnings (110 mmol) and anhyd LiCl (100 mmol) were placed in an argon-flushed flask dried, and THF (50 mL) was added. A solution of *i*-PrCl (100 mmol) in THF (50 mL) was slowly added at r.t. The reaction started within a few minutes. When the addition was complete, the mixture was stirred for 12 h at r.t. The grey solution of *i*-PrMgCl·LiCl was cannulated from the excess of Mg to a different flask under argon. A yield of ca. 95–98% of *i*-PrMgCl·LiCl was obtained. The reagent was titrated prior to use by the method of Paquette,[13a] or the method developed in our laboratory.[14]

Grignard Reagents like 28 or 30; General Procedure

Mg turnings (150 mmol) and anhyd LiCl (100 mmol) were placed in an argon-flushed three-necked round-bottom flask, equipped with a magnetic stirrer, a condenser, and an addition funnel, and THF (50 mL) was added. A solution of the corresponding chloroarene (100 mmol) in anhyd THF (50 mL) was added dropwise at 50–60 °C through the addition funnel. If the reaction did not start spontaneously, 20% DIBAL-H in hexane (10 mmol) was added to the mixture. After 2 h of vigorous stirring the desired Grignard reagent was formed, as determined by GC analysis after the iodolysis of a reaction aliquot. The grey solution of the Grignard reagent was cannulated from the excess of Mg under argon to a Schlenk flask. The reagent was titrated prior to use by the method developed in our laboratory.[14]

2,2,6,6-Tetramethylpiperidin-1-ylmagnesium Chloride–Lithium Chloride Complex

A dry and N_2-flushed 250-mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with freshly titrated 1.2 M *i*-PrMgCl·LiCl in THF (100 mL, 120 mmol). 2,2,6,6-Tetramethylpiperidine (17.8 g, 126 mmol, 1.05 equiv) was added dropwise at r.t.. The mixture was stirred at r.t. until gas evolution was completed (ca. 24 h). The reagent was titrated prior to use [benzoic acid and 4-(phenylazo)diphenylamine as indicator].[13b]

Copper(I) Chloride–Bis(lithium chloride) Complex

A dry and argon-flushed 50-mL Schlenk flask, equipped with a magnetic stirrer and a glass stopper, was charged with LiCl (1.7 g, 40 mmol) and heated up to 130 °C under high vacuum for 2 h. After cooling to r.t. under argon, CuCl (1.98 g, 20 mmol, 99.5% Cu) was added under inert atmosphere inside a glove box. The Schlenk flask was further heated to 130 °C for 5 h under high vacuum, cooled to r.t. (ca. 1 h), charged with freshly distilled THF (20 mL) under argon and wrapped in aluminum foil to protect it from light. The mixture was vigorously stirred until all solid was in solution (ca. 2 h). The reagent 1 M CuCl·2 LiCl appears as a colorless or slightly pink solution.

***N*-(4-Cyanophenyl)morpholine (16); Typical Procedure for Procedure 1**

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with 1.39 M *i*-PrMgCl·LiCl in THF (0.79 mL, 1.1 mmol) and cooled to 0 °C. 4-Bromobenzonitrile (**11**, 182 mg, 1.0 mmol) was added and the mixture was stirred at 0 °C for 2 h to afford the Grignard reagent **12**. The Br/Mg exchange was completed after 2 h as determined by the GC analysis of a reaction aliquot. This reagent was added dropwise to the pale-colored mixture of 1.0 M CuCl·2 LiCl THF (1.2 mL, 1.2 equiv) and bis[2-(dimethylamino)ethyl] ether (192 mg, 1.2 mmol, distilled from CaH_2 under N_2 atmosphere) at –50 °C and the mixture was stirred for 45 min. To the so-formed arylcuprate **13**, lithium morpholide (**14**) [2 mmol; prepared by adding *n*-BuLi (2 mmol) to 0.5 M morpholine in THF (174 mg, 2 mmol) at 0 °C and stirring for 30 min] was added dropwise and the mixture was further stirred for 90 min at –50 °C. The mixture was cooled to –78 °C, then chloranil (**9** , 295 mg, 1.2 mmol), in anhyd THF (7 mL), was added slowly over a period of 45 min. The mixture was allowed to reach –50 °C and was further stirred for 12 h. Et_2O (10 mL) was added to the crude mixture and it was filtered through Celite, washed with Et_2O thoroughly, and the filtrate was washed with aq 2.0 M NH_4OH (2 × 10 mL). The organic extract was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane–Et_2O, 1:1) afforded the title amine **16** (147 mg, 78%) as an off-white solid. Spectroscopic data correspond to those given in the literature.[15]

^1H NMR (300 MHz, $CDCl_3$): δ = 7.53 (d, ^3J = 9.1 Hz, 2 H, Ar*H*), 6.88 (d, ^3J = 9.1 Hz, 2 H, Ar*H*), 3.87 (t, ^3J = 5.0 Hz, 4 H, 2 CH_2), 3.30 (t, ^3J = 5.0 Hz, 4 H, 2 CH_2).

4-(2,6-Dichloropyridin-4-yl)morpholine (21); Typical Procedure for Procedure 2

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with 1.20 M TMPMgCl·LiCl THF (0.88 mL, 1.05 mmol). 2,6-Dichloropyridine (**17**, 148 mg, 1.0 mmol) in THF (1 mL) was added dropwise at –15 °C and the mix-

ture was stirred for 90 min to afford a 29:1 (average of three experiments) regioisomeric ratio of magnesiated compounds in favor of **18**, as determined by capillary GC analysis after iodolysis of a reaction aliquot. This reagent, **18**, was added dropwise to a solution of 1.0 M CuCl·2 LiCl in THF (1.2 mL, 1.2 mmol) and bis[2-(dimethylamino)ethyl] ether (192 mg, 1.2 mmol, distilled from CaH_2 under N_2) at –50 °C and the mixture was stirred for 45 min. To the resulting arylcuprate **19**, lithium morpholide (**14**) [2 mmol; prepared by adding *n*-BuLi (2 mmol) to 0.5 M morpholine in THF (174 mg, 2 mmol), cooled to 0 °C and stirring for 30 min] was added dropwise and the mixture was further stirred at –50 °C for 90 min. The mixture was cooled to –78 °C, then chloranil (**9**, 295 mg, 1.2 mmol) in anhyd THF (7 mL) was added slowly over a period of 30 min. The mixture was allowed to reach –50 °C and was stirred for 12 h. Et_2O (10 mL) was added to the crude mixture and it was filtered through Celite, washed with Et_2O thoroughly (ca. 100 mL), and the filtrate was washed with aq 2.0 M NH_4OH (2 × 10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane–Et_2O, 6:4) afforded the title amine **21** (116 mg, 50%) as a white crystalline solid; mp 137.3–138.8 °C

IR (neat): 3118, 2971, 2919, 2855, 1585, 1542, 1428, 1234, 1170, 1118, 1040, 980, 930, 827, 808 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 6.57 (s, 2 H, Ar*H*), 3.80 (t, ^3J = 4.9 Hz, 4 H, 2 CH_2), 3.29 (t, ^3J = 4.9 Hz, 4 H, 2 CH_2).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.3, 151.5, 106.5, 77.3, 46.4.

MS (EI, 70 eV): *m*/*z* (%) = 232 (75) $[M]^+$, 231 (11), 216 (11), 177 (12), 175 (62), 173 (100), 172 (21), 146 (10).

HRMS (EI): *m*/*z* calcd for $C_9H_{10}{}^{35}Cl_2N_2O$: 232.0170; found: 232.0164.

***N*-(4-Cyanophenyl)-*N*-ethylaniline (23)**
Prepared according to Procedure 1 from 4-bromobenzonitrile (**11**, 182 mg, 1.0 mmol) and lithium *N*-ethylanilide (**22**) (2.0 mmol, prepared by adding *n*-BuLi to *N*-ethylaniline at –40 °C and stirring for 30 min, then the mixture was allowed to reach 0 °C and was stirred for additional 15 min). Purification by flash chromatography (pentane–Et_2O, 9:1) yielded **23** (153 mg, 69%) as a yellow oil. Spectroscopic data correspond to those given in the literature.[6d]

^1H NMR (300 MHz, $CDCl_3$): δ = 7.50–6.91 (m, 7 H, Ar*H*), 6.66 (d, ^3J = 9.0 Hz, 2 H, Ar*H*), 3.78 (q, ^3J = 7.2 Hz, 2 H, CH_2), 1.24 (t, ^3J = 7.2 Hz, 3 H, CH_3).

***N*-Benzyl-*N*-(4-cyanophenyl)aniline (25)**
Prepared according to Procedure 1 from 4-bromobenzonitrile (**11**, 182 mg, 1.0 mmol) and lithium *N*-benzylanilide (**24**) (2.0 mmol, prepared by adding *n*-BuLi to *N*-benzylaniline at –40 °C and stirring for 30 min before the mixture was allowed to reach 0 °C and was then further stirred for additional 15 min). Purification by flash chromatography (pentane–Et_2O, 5:1) yielded **25** (202 mg, 71%) as a brown oil.

IR (neat): 3059, 3028, 2924, 2853, 2215, 1603, 1591, 1509, 1495, 1452, 1378, 1350, 1259, 1222, 1176, 823, 730, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.21 (m, 12 H, Ar*H*), 6.77 (d, ^3J = 9.1 Hz, 2 H, Ar*H*), 5.02 (s, 2 H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.7, 100.2, 114.8, 120.4, 126.5, 126.6, 126.8, 127.6, 129.1, 130.4, 133.5, 137.7, 146.4, 151.6.

MS (EI, 70 eV): *m*/*z* (%) = 284 (61) $[M]^+$, 281 (14), 207 (55), 91 (100), 69 (13), 44 (13).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{16}N_2$: 284.1313; found: 284.1275.

***N*-[2-Chloro-5-(trifluoromethyl)phenyl]morpholine (27)**
Prepared according to Procedure 1 from 1-chloro-2-iodo-4-(trifluoromethyl)benzene (306 mg, 1.0 mmol) (I/Mg exchange conditions: *i*-PrMgCl·LiCl at 0 °C for 20 min) and lithium morpholide (**14**, 2 mmol; prepared as given in the typical procedure). Purification by flash chromatography (pentane–CH_2Cl_2, 4:1) yielded **27** (183 mg, 69%) as a colorless oil.

IR (neat): 2962, 2858, 1603, 1418, 1310, 1298, 1113, 1084, 1041, 956, 820 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.47 (dd, ^3J = 4.4, 4.4 Hz, 1 H, Ar*H*), 7.23–7.26 (m, 2 H, Ar*H*), 3.89 (t, ^3J = 4.4, 4 H, 2 CH_2), 3.09 (dd, ^3J = 4.4, 4 H, 2 CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.9, 131.6, 121.5, 120.8, 117.5, 67.3, 51.8.

^{19}F NMR (280 MHz, $CDCl_3$): δ = –62.9 (s, 3 F, CF_3).

MS (EI)$^+$: *m*/*z* (%) = 265 (40) $[M]^+$, 207 (100), 179 (16).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{11}NO^{35}ClF_3$: 265.0481; found: 265.0460.

***N*-(2-Methylphenyl)morpholine (29)**
Prepared according to Procedure 1 from 1.0 M 2-tolylmagnesium chloride–lithium chloride (**28**) in THF (1.0 mL, 1.0 mmol) and lithium morpholide (**14**, 2 mmol; prepared as given in the typical procedure). Purification by flash chromatography (pentane–Et_2O, 9:1) yielded **29** (103 mg, 58%) as a colorless oil. Spectroscopic data correspond to those given in the literature.[15]

^1H NMR (300 MHz, $CDCl_3$): δ = 7.27–6.96 (m, 4 H, Ar*H*), 3.86 (t, ^3J = 4.6 Hz, 4 H, 2 CH_2), 2.92 (t, ^3J = 4.6 Hz, 4 H, 2 CH_2), 2.33 (s, 3 H, CH_3).

***N*-(4-Methylphenyl)morpholine (31)**
Prepared according to Procedure 1 from 1.11 M 4-tolylmagnesium chloride–lithium chloride complex (**30**) in THF (0.9 mL, 1.0 mmol) and lithium morpholide (**14**, 2 mmol; prepared as given in the typical procedure). Purification by flash chromatography (pentane–Et_2O, 5:1) yielded **31** (125 mg, 71%) as a white solid. Spectroscopic data correspond to those given in the literature.[15]

^1H NMR (300 MHz, $CDCl_3$): δ = 7.10 (d, ^3J = 8.5 Hz, 2 H, Ar*H*), 6.84 (d, ^3J = 8.5 Hz, 2 H, Ar*H*), 3.86 (t, ^3J = 4.8 Hz, 4 H, 2 CH_2), 3.11 (t, ^3J = 4.8 Hz, 4 H, 2 CH_2), 2.28 (s, 3 H, CH_3).

***N*-(4-Methoxyphenyl)morpholine (33)**
Prepared according to Procedure 1 from 4-iodoanisole (234 mg, 1.0 mmol) (I/Mg exchange conditions: *i*-PrMgCl·LiCl at 25 °C for 1 h) and lithium morpholide (**14**, 2 mmol; prepared as given in the typical procedure). Purification by flash chromatography (pentane–Et_2O, 5:1) yielded **33** (107 mg, 55%) as a white solid. Spectroscopic data correspond to those given in the literature.[15]

^1H NMR (300 MHz, $CDCl_3$): δ = 6.99–6.85 (m, 4 H, Ar*H*), 3.90 (t, ^3J = 4.7 Hz, 4 H, 2 CH_2), 3.80 (s, 3 H, CH_3), 3.10 (t, ^3J = 4.7 Hz, 4 H, 2 CH_2).

***N*-(4-Iodophenyl)morpholine (35)**
Prepared according to Procedure 1 from 1,4-diiodobenzene (330 mg, 1.0 mmol) (I/Mg exchange conditions: *i*-PrMgCl·LiCl at –20 °C for 2 h) and lithium morpholide (**14**, 2 mmol; prepared as given in the typical procedure). Purification by flash chromatography (pentane–Et_2O, 5:1) yielded **35** (188 mg, 65%) as a white solid. Spectroscopic data correspond to those given in the literature.[16]

^1H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, ^3J = 8.2 Hz, 2 H, Ar*H*), 6.70 (d, ^3J = 8.2 Hz, 2 H, Ar*H*), 3.88 (t, ^3J = 4.7 Hz, 4 H, 2 CH_2), 3.15 (t, ^3J = 4.7 Hz, 4 H, 2 CH_2).

***N*-(3-Iodophenyl)morpholine (37)**

Prepared according to Procedure 1 from 1,3-diiodobenzene (330 mg, 1.0 mmol) (I/Mg exchange conditions: *i*-PrMgCl·LiCl at 0 °C for 15 min) and lithium morpholide (**14**, 2 mmol; prepared as given in the typical procedure). Purification by flash chromatography (pentane–Et_2O, 5:1) yielded **37** (170 mg, 59%) as a yellow oil.

IR (neat): 2961, 2853, 2822, 1585, 1555, 1479, 1448, 1262, 1234, 1121, 982, 937, 768 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.27–6.86 (m, 4 H, Ar*H*), 3.87 (t, ^3J = 4.8 Hz, 4 H, 2 CH_2), 3.17 (t, ^3J = 4.8 Hz, 4 H, 2 CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.7, 130.8, 129.0, 124.8, 115.1, 95.5, 67.0, 49.2.

MS (EI, 70 eV): *m*/*z* (%) = 289 (100) $[M]^+$, 231 (79), 104 (15), 77 (17), 76 (10).

HRMS (EI): *m*/*z* calcd for $C_{10}H_{12}INO$: 288.9964; found: 288.9936.

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References

(1) Czarnik, A. W. *Acc. Chem. Res.* **1996**, *29*, 112; and references therein.
(2) Law, K. Y. *Chem. Rev.* **1993**, *93*, 449.
(3) (a) MacDiarmid, A. G. *Synth. Met.* **1997**, *84*, 27. (b) Gospodinova, N.; Terlemezyan, L. *Prog. Polym. Sci.* **1998**, *23*, 1443.
(4) Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 897.
(5) For selected reviews, see: (a) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (b) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *67*, 805. (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (d) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (e) Blaser, H.-U.; Indolese, A.; Naud, F.; Nettekoven, U.; Schnyder, A. *Adv. Synth. Catal.* **2004**, *346*, 1583. (f) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599. (g) Hartwig, J. F. *Synlett* **2006**, 1283.
(6) For the synthesis of nonfunctionalized triarylamines, see: (a) Thayumanavan, S.; Barlow, S.; Marder, S. R. *Chem. Mater.* **1997**, *9*, 3231. (b) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367. (c) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 11695. (d) Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019. (e) Tew, G. N.; Pralle, M. U.; Stupp, S. I. *Angew. Chem. Int. Ed.* **2000**, *39*, 517. (f) Braig, T.; Muller, D. C.; Gross, M.; Meerholz, K.; Nuyken, O. *Macromol. Rapid Commun.* **2000**, *21*, 583. (g) Thelakkhat, M.; Hagen, J.; Haarer, D.; Schmidt, H.-W. *Synth. Met.* **1999**, *102*, 1125.
(7) Yamamoto, H.; Maruoka, K. *J. Org. Chem.* **1980**, *45*, 2739.
(8) (a) Casarini, A.; Dembech, P.; Lazzari, D.; Marini, E.; Reginato, G.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1993**, *58*, 5620. (b) Alberti, A.; Canè, F.; Dembech, P.; Lazzari, D.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1996**, *61*, 1677. (c) Canè, F.; Brancaleoni, D.; Dembech, P.; Ricci, A.; Seconi, G. *Synthesis* **1997**, 545. (d) Bernardi, P.; Dembech, P.; Fabbri, G.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1999**, *64*, 641.
(9) del Amo, V.; Dubbaka, S. R.; Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 7838.
(10) I/Mg exchange: (a) Sapountzis, I.; Knochel, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 1610. (b) Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, 565. Br/Mg exchange: (c) Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333. (d) Krasovskiy, A.; Straub, B.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 159.
(11) (a) Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5683. (b) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.
(12) Knochel, P.; Yeh, M. C. P.; Berk, C. S.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.
(13) (a) Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503. (b) Hammett, L. P.; Walden, G. H.; Edmonds, S. M. *J. Am. Chem. Soc.* **1934**, *56*, 1092.
(14) Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, 890.
(15) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.
(16) Xu, G.; Wang, Y.-G. *Org. Lett.* **2004**, *6*, 985.