Preparation of Heterocyclic Amines via a Copper(I)-Mediated Oxidative Cross-Coupling of Organozinc Reagents with Lithium Amides

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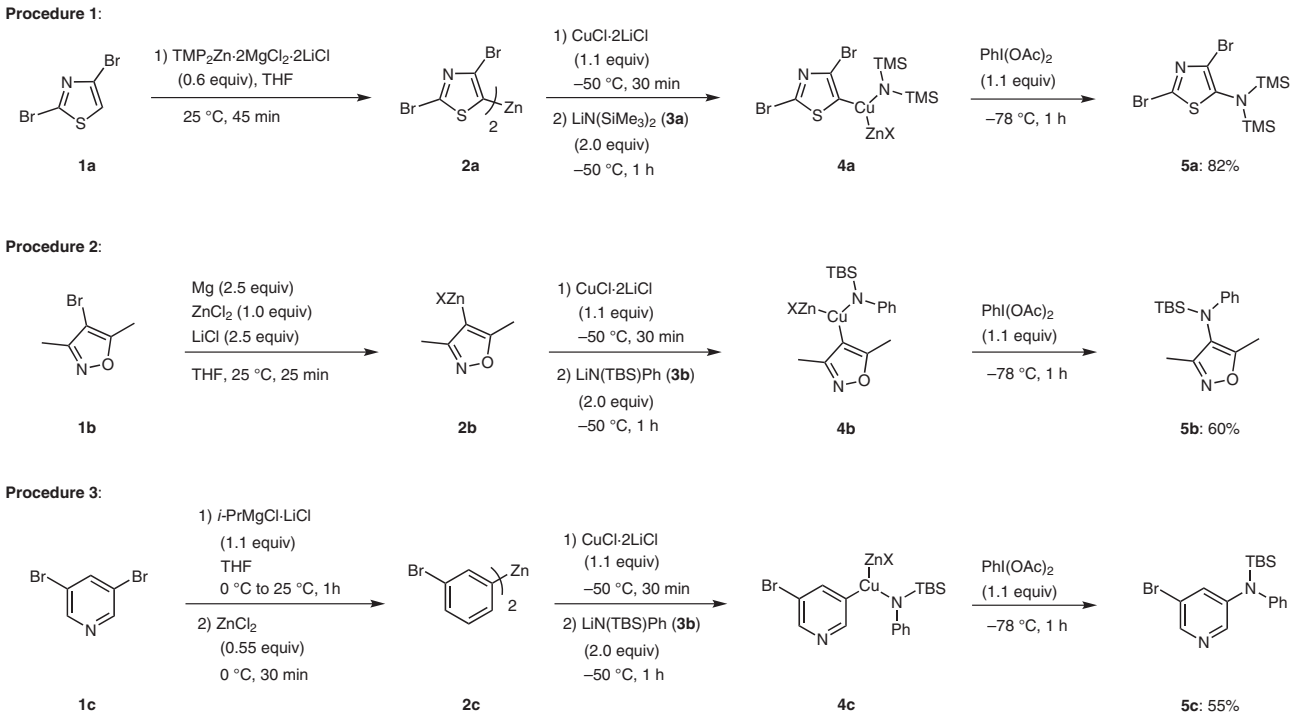
Abstract: Functionalized heteroaromatic amines are readily prepared by the oxidative coupling of polyfunctional zinc amidocuprates using $PhI(OAc)_2$ as oxidant. Various sensitive heterocyclic organometallics undergo this oxidative cross-coupling reaction furnishing aminated heteroaromatics. A high functional group tolerance and relative insensibility to steric hindrance characterize this general amination reaction. A practical procedure for the preparation of protected primary and secondary as well as tertiary heteroaryl amines is described.

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



Scheme 1 Procedures for the oxidative amination of arylzinc reagents

Introduction

Functionalized aromatics and heteroaromatics are important building blocks for the synthesis of pharmaceuticals, polymers, and materials.[1] Especially, amines containing five-membered heteroaryl groups such as furans, thiophenes, thiazoles, and pyrazoles are found in various target molecules.[2] Although the Pd-catalyzed amination reaction[3]is widely used, these protocols still have some limitations such as long reaction times and the requirement of using strong bases. Furthermore, some functional groups such as iodides and bromides are not compatible with these amination procedures. Inspired by the works of Yamamoto[4] and Ricci,[5] we recently reported a Cu(I)-mediated oxidative amination of magnesium reagents with lithium amides using chloranil as oxidant.[6] However, this protocol is limited due to the low stability of some heteroarylmagnesium reagents. Furthermore, functionalized heteroaromatics bearing halides often underwent halogen-dance reactions[7] and could not be employed in this procedure. Finally, the scale-up of this reaction was difficult

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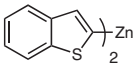
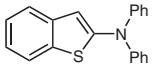
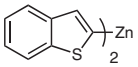
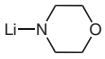
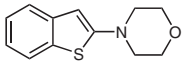
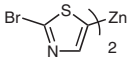
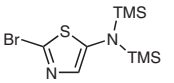
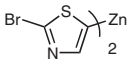
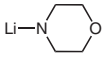
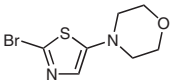
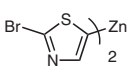
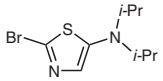
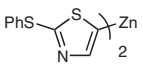
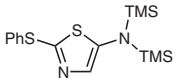
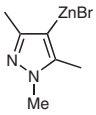
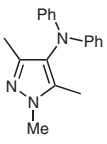
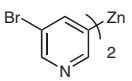
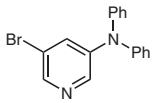
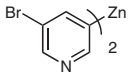
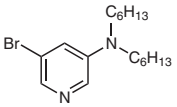
(over 10 mmol) due to the formation of the corresponding homocoupling product. Therefore, we have recently reported an extension of this work using the more stable organozinc reagents in an oxidative amination reaction, which was mediated by $PhI(OAc)_2$[8] as oxidation reagent.[9] Beside a large tolerance towards functional groups, the generated organozinc reagents showed a remarkable stability even at higher temperatures. The resulting organozinc compounds reacted in a Cu(I)-mediated oxidative cross-coupling with various lithium amides and furnished the desired amines in moderate to good yields. Herein, we wish to report typical practical procedures illustrating the preparation of functionalized organozinc reagents and subsequent reaction in an oxidative amination reaction.

Scope and Limitations

The required organozinc reagents can either by obtained by direct zincation (Procedure 1), by magnesium insertion in the presence of $ZnCl_2$ (Procedure 2) or by transmetalation of an organomagnesium reagent (Procedure 3; Scheme 1). Thus, the direct zincation of 2,4-dibromothiazole (**1a**) with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$[10] (TMP = 2,2,6,6-tetramethylpiperidyl)[11] (0.55 equiv, 25 °C, 45 min) gave the diarylzinc species **2a**. This compound was treated with the THF-soluble complex CuCl·2LiCl (1.1 equiv, –50 °C, 30 min) and $LiN(SiMe_3)_2$ (**3a**, 2.0 equiv, –50 °C, 1 h) affording the corresponding zinc amidocuprate **4a**. Subsequent oxidation of **4a** using $PhI(OAc)_2$ (1.1 equiv, –78 °C, 1 h) afforded the heterocyclic amine **5a** in 82% yield (Scheme 1, Procedure 1). The magnesium insertion[12] in the presence of LiCl and $ZnCl_2$ into the heteroaryl bromide **1b** gave the corresponding zinc reagent **2b**, which reacted with CuCl·2LiCl and secondary TBS-protected lithium amide to the amido cuprate **4b**. Subsequent oxidation with $PhI(OAc)_2$ gave the protected secondary amine **5b** in 60% yield. Finally, the organozinc reagent **2c**, obtained via a Br/Mg exchange[13] on 3,5-dibromopyridine (**1c**) and subsequent transmetalation, was reacted in the same manner furnishing the triarylamine **5c** in 82% yield (Procedure 3). The mild conditions of this oxidative ami-

Table 1 Oxidative Amination of Zinc Reagents with Various Lithium Amides[a]

Entry		Zinc reagent		Lithium amide		Product	Yield (%)[b]
1	**2d**		**3c**	$LiNPh_2$	**5d**		60[c]
2	**2d**		**3d**		**5e**		75[c]
3	**2e**		**3a**	$LiN(SiMe_3)_2$	**5f**		73[c]
4	**2e**		**3d**		**5g**		80[c]
5	**2e**		**3e**	LDA	**5h**		65[c]
6	**2f**		**3a**	$LiN(SiMe_3)_2$	**5i**		63[c]
7	**2g**		**3c**	$LiNPh_2$	**5j**		66[d]
8	**2c**		**3c**	$LiNPh_2$	**5k**		88[e]
9	**2c**		**3f**	$LiN(C_6H_{13})_2$	**5l**		54[e]

[a] Reactions were carried out on a 10 mmol scale.
[b] Yield of analytically pure products.
[c] Arylzinc reagent was obtained via direct metalation using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$.
[d] The arylzinc reagent was prepared by Mg insertion in the presence of LiCl and $ZnCl_2$ into the corresponding aryl bromide.
[e] The zinc reagent was prepared from the corresponding Mg reagent by transmetalation with $ZnCl_2$.

nation are compatible with a wide range of functionalized heterocycles (Scheme 1 and Table 1). Moreover, this amination reaction is also suitable for large-scale reactions, when the previously described organozinc reagents are used.

Thus, the zincation of benzothiophene (10 mmol) with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.55 equiv, 25 °C, 24 h) afforded the corresponding diarylzinc species **2d**, which was reacted with the lithium amides **3c** and **3d** under the conditions described above. The tertiary amines **5d** and **5e** were obtained in yields of 60 and 75%, respectively (Table 1, entries 1,2). 2-Bromothiazole was metalated using the same base. Thus, the reaction of 2-bromothiazole (10 mmol) with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.55 equiv, 25 °C, 2 h) furnished the zinc reagent **2e**. After transmetalation (CuCl·2LiCl, 1.1 equiv) and addition of an appropriate lithium amide such as **3a**, **3d**,**e**, the resulting amidocuprates of type **4** were treated with $PhI(OAc)_2$ to give the desired amines **5f**–**h** in 65–80% yields (entries 3–5). The zinc species **2f** was obtained by direct zincation of the corresponding thiazole derivative using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (0.55 equiv, 25 °C, 2 h). Amination with $LiN(SiMe_3)_2$ furnished the amine **5i** in a yield of 63% (entry 6). (Phenylthio)thiazoles of this type are useful intermediates since the phenylthio group can serve as a leaving group in cross-coupling reactions.[14]

Treatment of 4-bromo-1,3,5-trimethyl-1*H*-pyrazole with Mg turnings in the presence of LiCl and $ZnCl_2$ at 25 °C resulted in the formation of the zinc species **2g** after a reaction time of 25 minutes. Copper(I)-mediated oxidative amination of **2g** with lithium diphenylamide (**3c**) furnished the triaryl amine **5j** in 66% yield (entry 7).

Finally, 3,5-dibromopyridine was treated with *i*-PrMgCl·LiCl (1.1 equiv, 0 °C to 25 °C, 1 h) to give the corresponding monomagnesium reagent. Subsequent transmetalation with the THF-soluble salt $ZnCl_2$ provided the zinc species **2c**. Oxidative amination with the lithium amides **3c** and **3f** furnished the corresponding tertiary amines **5k** and **5l** in 88 and 54% yield, respectively (entries 8,9).

It has to be highlighted that this oxidative amination reaction is not very substrate-dependent and does not show sensitivity to steric hindrance. Remarkably, all the compounds reported herein were prepared according to the standardized reaction conditions.

In summary, we have extended our previous work to more heteroaromatics and optimized the scale-up for such amination reactions. These reactions could be performed with standard laboratory glassware and did not require the use of expensive chemicals or catalysts. Further studies are under way in our laboratory for extending the scope of this oxidative amination.

Procedures

All reactions were carried out under argon atmosphere in dried glassware. All starting materials were purchased from commercial suppliers and used without further purification unless otherwise stated. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refer to isolated compounds estimated to be >95% pure as determined by ^1H NMR and capillary GC analysis.

Reagent *i*-PrMgCl·LiCl

Mg turnings (110 mmol) and anhyd LiCl (100 mmol) were placed in a dried argon-flushed flask, 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 starts within few minutes. After the addition was complete, the reaction mixture was stirred for 12 h at r.t. The grey solution of *i*-PrMgCl·LiCl was cannulated from the excess of magnesium 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,[15] or the method developed in our laboratory.[16]

Reagent TMPMgCl·LiCl

A dry and N_2-flushed 250 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with freshly titrated *i*-PrMgCl·LiCl (1.2 M in THF) (100 mL, 120 mmol). 2,2,6,6-Tetramethylpiperidine (TMPH) (19.8 g, 126 mmol, 1.05 equiv) was added dropwise at r.t. The reaction mixture was stirred at r.t. until gas evolution was completed (ca. 24 h). The reagent was titrated with benzoic acid prior to use [4-(phenylazo)diphenylamine as indicator].[17]

Reagent $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$

In an argon-flushed Schlenk flask, $ZnCl_2$ (53.0 mmol, 7.22 g) was dried in vacuo at 140 °C for 4 h. After cooling to 25 °C, freshly titrated TMPMgCl·LiCl (100 mmol, 1.00 M, 100 mL) was added dropwise. The resulting mixture was stirred for 15 h at 25 °C. The freshly prepared $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ solution was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 1.60–1.70 M in THF (concentration of Zn) was obtained.

$ZnCl_2$ (1 M in THF)

$ZnCl_2$ (27.3 g, 200 mmol) (17.0 g, 400 mmol) was placed in a 500 mL Schlenk flask equipped with a magnetic stirring bar and a septum. The salt was heated at 150 °C in an oil bath for 4 h under high vacuum. Then, after cooling to 25 °C, absolute THF (200 mL) was added. Afterwards, the septum was replaced by a glass stopper and the suspension was left stirring overnight at 25 °C. After 12 h, the salt had completely dissolved, the stirring was stopped and the solution was left for some more time to become completely clear (little particles and insoluble impurities were allowed to settle down in that way). The solution was stored under argon upon use.

Reagent CuCl·2LiCl (1 M in THF)

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 went into solution (ca. 2 h). The reagent CuCl·2LiCl (1 M in THF) was obtained as a colorless or slightly pink solution.

Procedure 1: 2,4-Dibromo-*N*,*N*-bis(trimethylsilyl)-1,3-thiazol-5-amine (5a, Scheme 1)

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with 2,4-dibromo-1,3-thiazole (**1a**; 243 mg, 1.0 mmol) and THF (1 mL). To the resulting mix-

ture was added dropwise $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (1.30 mL, 1.68 M in THF, 0.55 mmol) and stirred for 45 min. CuCl·2LiCl (1.1 mL, 1.0 M in THF, 1.1 mmol) was added dropwise to **2a** at –50 °C under argon and the mixture was stirred for 30 min. $LiN(SiMe_3)_2$ (**3a**, 2 mmol, 1 M in THF) was added dropwise to the resulting cuprate **4a**, and the mixture was stirred for 1 h at –50 °C. The reaction mixture was cooled to –78 °C, then a solution of $PhI(OAc)_2$ (354 mg, 1.1 mmol) in anhyd THF (10 mL) was added slowly over a period of 60 min. The mixture was then warmed to –50 °C and stirred for an additional 3 h. Et_2O (100 mL) was poured into the crude reaction mixture. The organic phase was washed with aq 2 M NH_4OH (2 × 10 mL) and back-extracted with Et_2O (2 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane; Al_2O_3 III) yielded **5a** (331 mg, 80%) as a colorless oil.

IR (ATR): 2950, 1499, 1412, 1251, 1204, 1154, 1009, 909, 869, 837, 816, 790, 753, 684, 666, 632 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.17 (s, 18 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 147.3, 127.7, 119.8, 1.5.

MS (70 eV, EI): *m*/*z* (%) = 402 (18), 399 (18), 387 (32), 385 (14), 323 (15), 321 (14), 125 (12), 123 (11), 97 (11), 83 (11), 73 (100).

HRMS (EI): *m*/*z* calcd for $C_9H_{18}{}^{79}Br_2N_2SSi_2$: 399.9096; found: 399.9086.

Procedure 2: (*tert*-Butyldimethylsilyl)-(3,5-dimethylisoxazol-4-yl)phenylamine (5b, Scheme 1)

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with LiCl (104 mg, 2.5 mmol) and dried under vacuum at 450 °C for 5 min. Then, $ZnCl_2$ (135 mg, 1.0 mmol) was added and also dried under vacuum at 450 °C for 5 min. After cooling to r.t., Mg turnings (61 mg, 2.5 mmol) and THF (5 mL) were added and activated with *i*-Bu_2AlH (0.1 mL, 0.1 M in THF, 0.01 mmol).[18] 4-Bromo-3,5-dimethylisoxazole (**1b**; 176 mg, 1.0 mmol) was added in one portion and the resulting mixture was stirred for 25 min at 25 °C and then cannulated to a new Schlenk flask for the reaction with an amine. CuCl·2LiCl (1.1 mL, 1.0 M in THF, 1.1 mmol) was added dropwise to the generated zinc species **2b** at –50 °C under argon and the mixture was stirred for 30 min. LiN(TBS)Ph [**3b**, 2.0 mmol, prepared by adding *n*-BuLi to a 0.5 M solution of HN(TBS)Ph (414 mg, 2 mmol) in THF at –20 °C and stirring for 30 min] was added dropwise to the resulting cuprate, and the mixture was stirred for 1 h at –50 °C. The reaction mixture was cooled to –78 °C, then a solution of $PhI(OAc)_2$ (354 mg, 1.1 mmol) in anhyd THF (10 mL) was added slowly over a period of 60 min. The mixture was then warmed to –50 °C and stirred for 3 h. Et_2O (100 mL) was poured into the crude reaction mixture. The organic phase was washed with aq 2 M NH_4OH (2 × 10 mL) and extracted with Et_2O (2 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane–Et_2O, 20:1) yielded **5b** (181 mg, 60%) as a yellow oil.

IR (ATR): 2928, 2855, 1594, 1490, 1472, 1440, 1419, 1276, 1260, 1249, 1241, 1215, 1030, 948, 891, 876, 858, 836, 821, 802, 772, 746, 706, 691, 681, 633 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.16–7.14 (m, 2 H, ArH), 6.88–6.83 (m, 3 H, ArH), 2.31 (s, 3 H, CH_3), 2.09 (s, 3 H, CH_3), 0.96 (s, 9 H, *t*-C_4H_9), 0.21 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.7, 160.3, 148.7, 128.8, 123.6, 120.9, 120.4, 27.9, 19.9, 11.3, 9.9, –2.1.

MS (70 eV, EI): *m*/*z* (%) = 302 (23), 246 (20), 245 (96), 204/19), 161 (17), 137 (21), 126 (15), 111 (24), 109 (17), 103 (29), 101 (58), 99 (16), 97 (35), 95 (22), 85 (40), 83 (30), 73 (100), 71 (51), 69 (28), 56 (20), 55 (24), 37 (27).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{26}N_2OSi$: 302.1814; found: 302.1822.

Procedure 3: (5-Bromopyridin-3-yl)-(*tert*-butyldimethylsilyl)phenylamine (5c, Scheme 1)

A dry and argon-flushed Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with 3,5-dibromopyridine (**1c**; 236 mg, 1.0 mmol). After cooling to 0 °C, *i*-PrMgCl·LiCl (0.90 mL, 1.24 M in THF, 1.1 mmol) was added dropwise and stirred for 30 min at this temperature and for a further 30 min at 25 °C. Then, THF (1 mL) was added and the resulting solution was stirred for an additional 10 min at 25 °C. After cooling to 0 °C, $ZnCl_2$ (0.55 mL, 1.0 M in THF, 0.55 mmol) was added and the mixture was stirred for 30 min at this temperature. CuCl·2LiCl (1.1 mL, 1.0 M in THF, 1.1 mmol) was added dropwise at –50 °C and the resulting mixture was stirred for an additional 30 min at –50 °C. LiN(TBS)Ph [**3b**; 2.0 mmol, prepared by adding *n*-BuLi to a 0.5 M solution of HN(TBS)Ph (414 mg, 2 mmol) in THF at –20 °C and stirring for 30 min] was added dropwise to the resulting cuprate, and the mixture was stirred for 1 h at –50 °C. The reaction mixture was cooled to –78 °C, then a solution of $PhI(OAc)_2$ (354 mg, 1.1 mmol) in anhyd THF (10 mL) was added slowly over a period of 60 min. The mixture was then warmed to –50 °C and stirred for 3 h. Et_2O (100 mL) was poured into the crude reaction mixture. The organic phase was washed with aq 2 M NH_4OH (2 × 10 mL) and extracted with Et_2O (2 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane–Et_2O; 19:1) yielded **5c** (200 mg, 55%) as a yellow solid; mp 85.5–87.1 °C.

IR (ATR): 2957, 2949, 2929, 2857, 1567, 1542, 1486, 1471, 1462, 1443, 1413, 1318, 1267, 1257, 1230, 1208, 1168, 1103, 1002, 955, 936, 911, 902, 886, 857, 842, 833, 819, 808, 788, 772, 733, 699, 676 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 8.34 (d, $^4J_{H,H}$ = 2.35 Hz, 1 H, ArH), 8.31 (d, $^4J_{H,H}$ = 1.96 Hz, 1 H, ArH), 7.20 (t, $^4J_{H,H}$ = 2.35 Hz, 1 H, ArH), 6.96–6.91 (m, 2 H, ArH), 6.85–6.81 (m, 2 H, ArH), 6.75–6.72 (m, 1 H, ArH), 0.77 (s, 9 H, *t*-C_4H_9), –0.06 [s, 6 H, $Si(CH_3)_2$].

^{13}C NMR (100 MHz, C_6D_6): δ = 147.9, 146.5, 142.5, 142.3, 130.6, 129.4, 128.9, 125.2, 120.2, 27.3, 20.0, –2.4.

MS (70 eV, EI): *m*/*z* (%) = 308 (17), 307 (98), 306 (17), 305 (100), 135 (14), 73 (12).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{23}BrN_2Si$: 362.0814; found: 362.0810.

Benzo[*b*]thiophen-2-yl-diphenylamine (5d, Table 1, entry 1)

Prepared according to Procedure 1 from benzothiophene (1.34 g, 10.0 mmol) [reaction conditions: deprotonation with $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ at 25 °C for 24 h] and $LiNPh_2$ [20.0 mmol; prepared by adding *n*-BuLi (20.0 mmol) to a 1.0 M solution of Ph_2NH in THF (3.38 g, 20.0 mmol) at –20 °C and stirring for 5 min and further stirring at 0 °C for 30 min]. Purification by flash chromatography (pentane; Al_2O_3 III) yielded **5d** (18.1 g, 60%) as a colorless solid; mp 134.0–136.3 °C.

IR (ATR): 1586, 1562, 1530, 1518, 486, 1458, 1436, 1418, 1316, 1292, 1276, 1250, 1241, 1172, 1158, 761, 750, 726, 695, 688 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 7.37–7.30 (m, 2 H, ArH), 7.16–7.10 (m, 4 H, ArH), 7.05–6.98 (m, 6 H, ArH), 6.88–6.81 (m, 2 H, ArH), 6.63 (s, 1 H, ArH).

^{13}C NMR (100 MHz, C_6D_6): δ = 151.9, 147.6, 139.4, 136.1, 129.2, 124.3, 123.6, 123.5, 123.3, 122.3, 122.0, 114.5.

MS (70 eV, EI): *m*/*z* (%) = 302 (23), 301 (100), 300 (18), 223 (12), 197 (29), 121 (13), 77 (10).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{15}NS$: 301.0925; found: 301.0919.

4-Benzo[*b*]thiophen-2-ylmorpholine (5e, Table 1, entry 2)
Prepared according to Procedure 1 from benzothiophene (1.34 g, 10.0 mmol) [reaction conditions: deprotonation with $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ at 25 °C for 24 h] and *N*-lithium morpholide [20.0 mmol; prepared by adding *n*-BuLi (20.0 mmol) to a 0.5 M solution of morpholine in THF (1.74 g, 20.0 mmol) at 0 °C and stirring for 30 min]. Purification by flash chromatography (pentane–Et_2O; 20:1; Al_2O_3 III) yielded **5e** (1.65 g, 75%) as a colorless solid; mp 180.1–181.5 °C.

IR (ATR): 1556, 1528, 1454, 1437, 1375, 1316, 1303, 1264, 1250, 1220, 1211, 1187, 1166, 1117, 1065, 1032, 1024, 1013, 933, 901, 869, 781, 744, 723, 653 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 7.44–7.40 (m, 2 H, ArH), 7.18–7.14 (m, 1 H, ArH), 6.97–6.93 (m, 1 H, ArH), 5.90 (s, 1 H, ArH), 3.33 (t, $^3J_{H,H}$ = 4.89 Hz, 4 H, CH_2CH_2), 2.70 (t, $^3J_{H,H}$ = 4.89 Hz, 4 H, CH_2CH_2).

^{13}C NMR (100MHz, C_6D_6): δ = 157.7, 140.7, 132.9, 124.5, 121.6, 121.5, 121.0, 99.4, 65.7, 50.6.

MS (70 eV, EI): *m*/*z* (%) = 220 (12), 219 (100), 161 (50), 160 (14).

HRMS (EI): *m*/*z* calcd for $C_{12}H_{13}NOS$: 219.0718; found: 219.0712.

2-Bromo-*N*,*N*-bis(trimethylsilyl)-1,3-thiazol-5-amine (5f, Table 1, entry 3)
Prepared according to Procedure 1 from 2-bromothiazole (1.64 g, 10.0 mmol) [reaction conditions: deprotonation with $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ at 25 °C for 60 min] and LiHMDS (20 mmol, 20 mL, 1 M in THF). Purification by flash chromatography (pentane; Al_2O_3 III) yielded **5f** (2.44 g, 75%) as a colorless oil.

IR (ATR): 2956, 1517, 1436, 1412, 1251, 1185, 1148, 1132, 1001, 919, 874, 840, 818, 756, 699, 686 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 6.76 (s, 1 H, ArH), –0.02 (s, 18 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 152.3, 137.1, 128.0, 1.3.

MS (70 eV, EI): *m*/*z* (%) = 324 (13), 322 (22), 309 (17), 307 (14), 244 (10), 243 (44), 227 (15), 116 (20), 73 (100).

HRMS (EI): *m*/*z* calcd for $C_9H_{19}{}^{79}BrN_2SSi_2$: 321.9991; found: 321.9977.

4-(2-Bromo-1,3-thiazol-5-yl)morpholine (5g, Table 1, entry 4)
Prepared according to Procedure 1 from 2-bromothiazole (1.64 g, 10.0 mmol) [reaction conditions: deprotonation with $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ at 25 °C for 60 min] and *N*-lithium morpholide [20.0 mmol; prepared by adding *n*-BuLi (20.0 mmol) to a 0.5 M solution of morpholine in THF (1.74 g, 20.0 mmol) at 0 °C and stirring for 30 min]. Purification by flash chromatography (pentane–Et_2O; 9:1; Al_2O_3 III) yielded **5g** (1.99 g, 80%) as a colorless solid; mp 145.3–147.0 °C.

IR (ATR): 1512, 1448, 1430, 1368, 1336, 1308, 1293, 1272, 1257, 1220, 1211, 1168, 1143, 1112, 1071, 1038, 991, 929, 893, 855, 842, 758, 728 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 6.51 (s, 1 H, ArH), 3.23 (t, $^3J_{H,H}$ = 4.9 Hz, 4 H, CH_2CH_2), 2.31 (t, $^3J_{H,H}$ = 4.9 Hz, 4 H, CH_2CH_2).

^{13}C NMR (100 MHz, C_6D_6): δ = 157.6, 122.4, 122.3, 65.7, 51.8.

MS (70 eV, EI): *m*/*z* (%) = 250 (99), 249 (12), 248 (100), 192 (43), 190 (42), 169 (39), 111 (31).

HRMS (EI): *m*/*z* calcd for $C_7H_9BrN_2OS$: 247.9619; found: 247.9616.

2-Bromo-*N*,*N*-diisopropyl-1,3-thiazol-5-amine (5h, Table 1, entry 5)
Prepared according to Procedure 1 from 2-bromothiazole (1.64 g, 10.0 mmol) [reaction conditions: deprotonation with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ at 25 °C for 60 min] and LDA (20 mmol, 20 mL, 0.5 M in THF). Purification by flash chromatography (pentane–Et_2O; 100:1; Al_2O_3 III) yielded **5h** (1.71 g, 65%) as a colorless oil.

IR (ATR): 2968, 2930, 2871, 1538, 1518, 1446, 1416, 1382, 1365, 1328, 1271, 1240, 1204, 1178, 1149, 1122, 1101, 1089, 999, 907, 857, 840, 756, 719, 697, 635 cm^{-1}.

^1H NMR (300 MHz, C_6D_6): δ = 6.83 (s, 1 H, ArH), 3.08 [sept, $^3J_{H,H}$ = 6.8 Hz, 2 H, 2 × C*H*$(CH_3)_2$], 0.84 [d, $^3J_{H,H}$ = 6.8 Hz, 12 H, 2 × CH$(CH_3)_2$].

^{13}C NMR (75 MHz, C_6D_6): δ = 150.6, 133.0, 126.1, 51.1, 20.6.

MS (70 eV, EI): *m*/*z* (%) = 264 (24), 262 (13), 249 (37), 247 (54), 127 (38), 112 (38), 97 (46), 83 (40), 71 (37), 70 (36), 69 (62), 57 (100), 55 (51), 43 (75).

HRMS (EI): *m*/*z* calcd for $C_9H_{15}BrN_2S$: 262.0139; found: 262.0136.

5-(1,1,1,3,3,3-Hexamethyldisilazan-2-yl)-2-phenylsulfanylthiazole (5i, Table 1, entry 6)
Prepared according to Procedure 1 from 2-(phenylthio)thiazole (1.64 g, 10.0 mmol) [reaction conditions: deprotonation with $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ at 25 °C for 2 h] and $LiN(SiMe_3)_2$ (20.0 mmol, 20.0 mL, 1 M in THF). Purification by flash chromatography (pentane–Et_2O; 19:1; Al_2O_3 III) yielded **5i** (2.22 g, 63%) as a yellow oil.

IR (ATR): 2955, 1514, 1500, 1477, 1440, 1403, 1377, 1273, 1251, 1150, 1141, 1016, 922, 874, 840, 819, 739, 701, 686, 624 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 7.48–7.46 (m, 2 H, ArH), 7.06 (s, 1 H, ArH), 6.97–6.90 (m, 3 H, ArH), 0.00 [s, 18 H, 2 × $Si(CH_3)_3$].

^{13}C NMR (75 MHz, C_6D_6): δ = 156.6, 150.9, 138.1, 137.3, 133.5, 132.2, 129.9, 129.2, 128.1, 1.2.

MS (70 eV, EI): *m*/*z* (%) = 354 (18), 353 (28), 352 (100), 337 (23), 243 (32), 206 (11), 116 (22), 73 (84), 45 (10).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{24}N_2S_2Si_2$: 352.0919; found: 352.0912.

Diphenyl(1,3,5-trimethyl-1*H*-pyrazol-4-yl)amine (5j, Table 1, entry 7)
Prepared according to Procedure 2 from 4-bromo-1,3,5-trimethyl-1*H*-pyrazole (1.89 g, 10.0 mmol, stirring for 25 min) and $LiNPh_2$ [20.0 mmol, prepared by adding *n*-BuLi to a 0.5 M solution of Ph_2NH (3.38 g, 20.0 mmol) in THF at –20 °C and stirring for 30 min at 0 °C]. Purification by flash chromatography (pentane–Et_2O, 1:1) yielded **5j** (1.80 g, 65%) as a yellow solid; mp 78.8–80.3 °C.

IR (ATR): 2919, 1584, 1482, 1457, 1448, 1386, 1373, 1322, 1287, 1276, 1198, 1170, 1153, 1116, 1075, 1037, 1025, 998, 983, 959, 916, 890, 831, 755, 712, 693, 644, 638, 628, 620, 605 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.20 (m, 4 H, ArH), 7.07–7.03 (m, 4 H, ArH), 6.94–6.89 (m, 2 H, ArH), 3.76 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3), 1.98 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.9, 145.1, 136.1, 129.0, 123.8, 121.1, 120.2, 36.4, 11.5, 9.2.

MS (70 eV, EI): *m*/*z* (%) = 278 (18), 277 (100), 56 (14).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{19}N_3$: 277.1579; found: 277.1574.

5-Bromo-*N*,*N*-diphenylpyridin-3-amine (5k, Table 1, entry 8)
Prepared according to Procedure 3 from 3,5-dibromopyridine (2.36 g, 10.0 mmol) and $LiNPh_2$ [20.0 mmol, prepared by adding *n*-BuLi to a 0.5 M solution of Ph_2NH (3.38 g, 20.0 mmol) in THF at –20 °C and stirring for 30 min at 0 °C]. Purification by flash chromatography (pentane–CH_2Cl_2, 1:1 to 1:2) yielded **5k** (2.88 g, 88%) as a colorless solid; mp 118.4–119.9 °C.

IR (ATR): 1586, 1570, 1557, 1544, 1485, 1456, 1438, 1424, 1329, 1276, 1270, 1232, 1191, 1098, 1069, 1005, 948, 903, 854, 844, 780, 758, 746, 702, 694, 665, 628, 620 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 8.36 (dd, $^3J_{H,H}$ = 6.1 Hz, $^4J_{H,H}$ = 2.9 Hz, 2 H), 7.37 (t, $^4J_{H,H}$ = 2.2 Hz, 1 H), 6.97–6.91 (m, 4 H), 6.85–6.76 (m, 6 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 146.5, 145.6, 143.7, 142.9, 130.6, 129.9, 125.0, 124.5, 120.7.

MS (70 eV, EI): *m/z* (%) = 327 (19), 326 (87), 325 (48), 324 (100), 323 (30), 245 (14), 244 (38), 243 (18), 217 (12), 167 (14), 115 (13), 77 (23).

HRMS (EI): *m/z* calcd for $C_{17}H_{13}BrN_2$: 324.0262; found: 324.0257.

(5-Bromopyridin-3-yl)dihexylamine (5l, Table 1, entry 9)

Prepared according to Procedure 3 from 3,5-dibromopyridine (2.36 g, 10.0 mmol) and $LiN(C_6H_{13})_2$ [20.0 mmol, prepared by adding *n*-BuLi to a 0.5 M solution of $(C_6H_{13})_2NH$ (3.71 g, 20.0 mmol) in THF at –20 °C and stirring for 30 min at 0 °C]. Purification by flash chromatography (pentane–Et_2O; 20:1) yielded **5l** (1.85 g, 54%) as a yellow oil.

IR (ATR): 2954, 2926, 2870, 2856, 1572, 1533, 1465, 1428, 1368, 1255, 1242, 1228, 1213, 1176, 1164, 1135, 1106, 992, 837, 822, 797, 725, 697, 657 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 8.24 (d, $^4J_{H,H}$ = 1.96 Hz, 1 H, ArH), 8.11 (d, $^4J_{H,H}$ = 2.74 Hz, 1 H, ArH), 6.97 (t, $^4J_{H,H}$ = 1.96 Hz, 1 H, ArH), 2.81 (t, $^3J_{H,H}$ = 7.63 Hz, 4 H, CH_2CH_2), 1.30–1.16 [m, 8 H, $(CH_2)_4$], 1.13–0.98 [m, 8 H, $(CH_2)_4$], 0.86 (t, 6 H, $^3J_{H,H}$ = 7.23 Hz, 2 × CH_3).

^{13}C NMR (100 MHz, C_6D_6): δ = 144.8, 137.2, 133.1, 121.1, 119.4, 50.3, 31.5, 26.7, 26.5, 26.4, 22.6, 13.8.

MS (70 eV, EI): *m/z* (%) = 342 (15), 340 (16), 272 (12), 271 (88), 270 (13), 269 (100), 201 (46), 199 (47), 187 (15), 185 (16), 43 (23).

HRMS (EI): *m/z* calcd for $C_{17}H_{29}BrN_2$: 340.1514; found: 340.1509.

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