JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

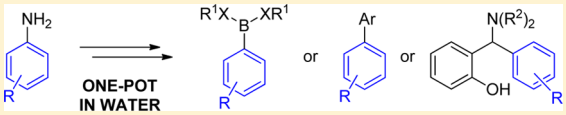
Sequential One-Pot Access to Molecular Diversity through Aniline Aqueous Borylation

William Erb, Mathieu Albini, Jacques Rouden, and Jérôme Blanchet*

Laboratoire de Chimie Moléculaire et Thio-organique, ENSICAEN, Université de Caen Basse-Normandie, CNRS, 6 boulevard du Maréchal Juin, 14050 Caen, France

Supporting Information

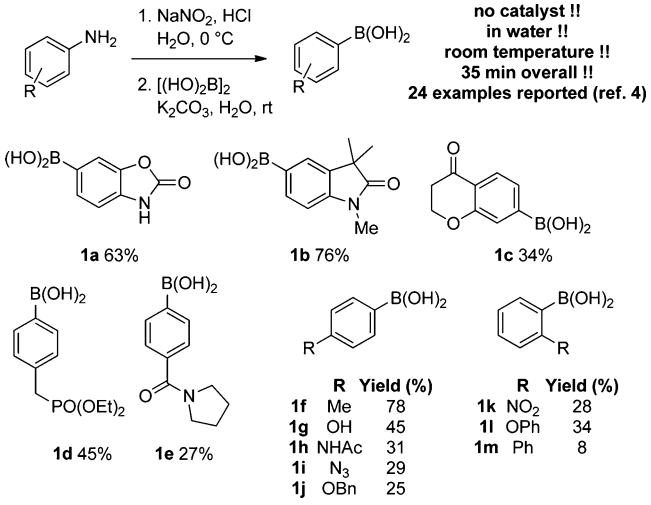
ABSTRACT: On the basis of our recently reported aniline aqueous borylation, molecular diversity was achieved in a one-pot process by combining other reactions such as esterification, Suzuki−Miyaura coupling, hydrogenolysis, or Petasis borono-Mannich.



Boronic acids and their derivatives are now ubiquitous and versatile compounds that find widespread applications in organic synthesis, medicinal and material chemistry. Over the past two decades their synthesis has triggered a tremendous regain of interest to complete the traditional anionic preparations involving aryl lithium or magnesium reagents. Indeed, transition metal-catalyzed borylation of aryl halides[1] or arenes through C−H bond activation[2] and Sandmeyer-type borylation involving anilines[3] have strongly diversified the methods for the synthesis of aryl boronic acids.

Anilines are attractive starting materials as many of them are commercially available or easily prepared from their nitroarene precursors. We have recently reported a highly practical aqueous borylation of anilines involving diboronic acid through the in situ generation of a diazonium ion.[4] Here are reported additional examples attesting the high functional group tolerance of our borylation (Scheme 1). Indeed, several heterocycles (benzoxazolone, indole, chromanone) or groups (phosphonate, amide or even azido) are compatible with our borylation procedure, and the corresponding boronic acids have been isolated for the first time. The key features of this reaction are the absence of catalyst, extremely fast kinetic and very mild reaction conditions (Scheme 1).

Scheme 1. Aqueous Borylation Additional Results



With this robust methodology in hand we decided to investigate the possibility to achieve molecular diversity through additional reactions using mild conditions.

Indeed, the rapid access to complex molecular architectures starting from simple substrates while avoiding intermediate purification steps is a relevant trend of contemporary organic chemistry.

We initially turned our attention toward the synthesis of various aryl boronates of increased stability that are commonly used in metal-catalyzed cross-couplings.[5]

Versatile direct access to boronates from anilines has been previously reported by Wang and others;[3] however, we were curious about the possibility to carry out a similar transformation in aqueous conditions. This may result in a cost-effective process avoiding the use of expensive alkoxydiboron reagents and hazardous alkyl nitrites.

Recently, Pucheault reported the useful transformation of potassium aryl trifluoroborates to boronic acids and esterification of the latter mediated by $FeCl_3$/imidazole.[6] The possibility to perform such a reaction in aqueous conditions led us to investigate the compatibility of the reported esterification method with the aqueous borylation of anilines.

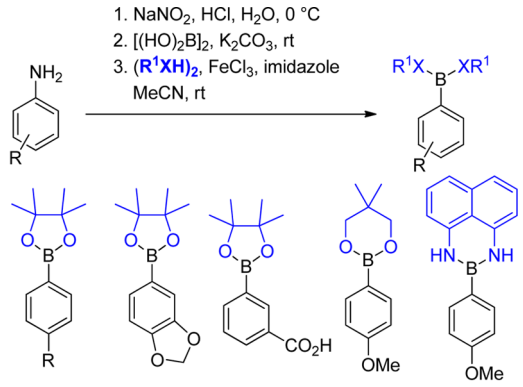
Pleasingly, this additional step was compatible with our conditions and various protected boronic acids were obtained. Electron-rich anilines always afforded the title compounds in higher yields compared to electron-poor ones,[7] whereas pinacol, neopentylglycol and 1,8-diaminonaphtalene all gave the products in similar yields (Scheme 2). While the observed global yields were moderate to low for the sequence, the access to boronates through the aqueous borylation of anilines has been established.

The emergence of mild Miyaura and Masuda Pd-catalyzed borylations paved the way for the development of one-pot methodologies toward biologically relevant biaryls whereby one

Received: July 23, 2014
Published: September 30, 2014

dx.doi.org/10.1021/jo501665e | J. Org. Chem. 2014, 79, 10568−10580

Scheme 2. Scope of Boronate Synthesis[a]



R	Yield (%)				
2a OMe	43 (77)	**2d**	**2e**	**2f**	**2g**
2b Me	37 (78)	32% (73)	22% (53)	31% (77)	42% (77)
2c F	21 (73)				

[a]Yield in brackets refers to isolated yield of borylation.

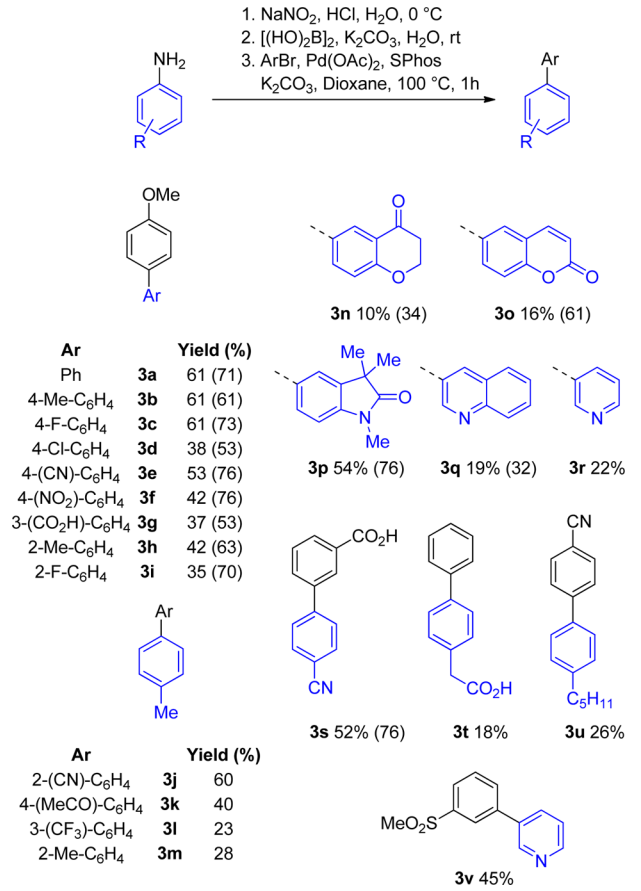
catalyst could promote both borylation and coupling processes.[8] Interestingly, to the best of our knowledge, only one report deals with the sequential borylation-Suzuki coupling starting from anilines.[3a,d] More generally, only limited direct synthesis of biaryls involving anilines is known and is generally restricted to the use of an excess of electron-rich (hetero)arenes as coupling partners.[9] Accordingly, a set of one-pot sequences involving an additional Suzuki−Miyaura coupling step was carried out. Initial investigations showed that the Leadbeater ligandless conditions[10] were not suitable for all substrates. After optimization, the use of Buchwald's SPhos ligand[11] afforded a three steps synthesis of biaryls from anilines with good to low yields (61−10%). Such sequence complements other known Gomberg−Bachmann arylations of diazonium salts[12] with the advantage of avoiding the isolation of those potentially hazardous intermediates.

A wide range of anilines has been efficiently coupled with 4-bromoanisole respect to the previously determined borylation yield (**3a**−**i**). Furthermore, the reaction conditions tolerate chlorine atoms, nitrile groups and carboxylic acids (**3d**,**e**) allowing further functionalization. Steric bulk at the ortho position resulted in moderate yields of the biaryl products (**3h**,**i**). Heteroanilines were also engaged in this process; except for **3p**, low yields were invariably observed (**3n**−**r**) due to decomposition of the intermediate boronic acid. Relevant biaryls such as **3t** (nonsteroidal anti-inflammatory), **3u** (liquid crystal) or **3v** (intermediate in OSU 6162 synthesis[13]) were isolated with moderate yields.

No deactivation of the palladium catalyst arising from the complex reaction mixture was observed, allowing us to add a fourth step to the process (hydrogenation of nitro group, Scheme 3). Indeed, we found that aniline **5** could be efficiently prepared from nitroaniline **4a** in 46% yield over 4 steps (Scheme 4), thus paving the way for further incrementing borylation/arylation steps.

However, if a nitro group reduction was successful, the remaining palladium was not able to promote the deprotection of Cbz amine and additional Pd/C was required. In these modified conditions, the precursor **6** of fexaramine **8** (nonsteroidal agonist of farnesoid X receptor[14]) was obtained from **4b** albeit in a moderate 14% yield. Similarly the 2-cyano biaryl amine **7**, which could serve as a starting material for the synthesis of sartan drugs **9**-**10** (Figure 1), was obtained in a

Scheme 3. Scope of Sequential Synthesis of Biaryls[a]

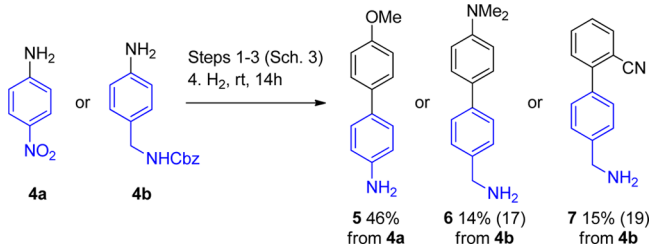


Ar		Yield (%)
Ph	**3a**	61 (71)
4-Me-C_6H_4	**3b**	61 (61)
4-F-C_6H_4	**3c**	61 (73)
4-Cl-C_6H_4	**3d**	38 (53)
4-(CN)-C_6H_4	**3e**	53 (76)
4-(NO_2)-C_6H_4	**3f**	42 (76)
3-(CO_2H)-C_6H_4	**3g**	37 (53)
2-Me-C_6H_4	**3h**	42 (63)
2-F-C_6H_4	**3i**	35 (70)

Ar		Yield (%)
2-(CN)-C_6H_4	**3j**	60
4-(MeCO)-C_6H_4	**3k**	40
3-(CF_3)-C_6H_4	**3l**	23
2-Me-C_6H_4	**3m**	28

[a]Yield in brackets refers to isolated yield of steps 1−2.

Scheme 4. One More Step toward Useful Biaryls[a]



[a]Yield in brackets refers to isolated yield of steps 1−3.

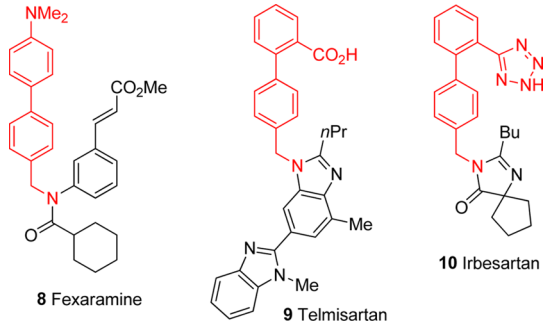


Figure 1. Relevant biaryls.

15% global yield. Initial investigations have shown that known selective diazotization of aniline in the presence of a primary amine[15] was not amenable with deprotected **4b**.

dx.doi.org/10.1021/jo501665e | J. Org. Chem. 2014, 79, 10568−10580

In order to access aminodiarylmethanes of biological interest, such as meclozine **11** or cetirizine **12** (Figure 2), we finally evaluated the compatibility of our aqueous borylation with the Petasis borono-Mannich reaction.[16]

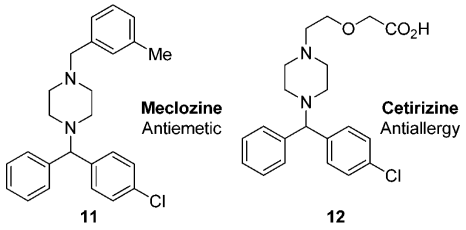
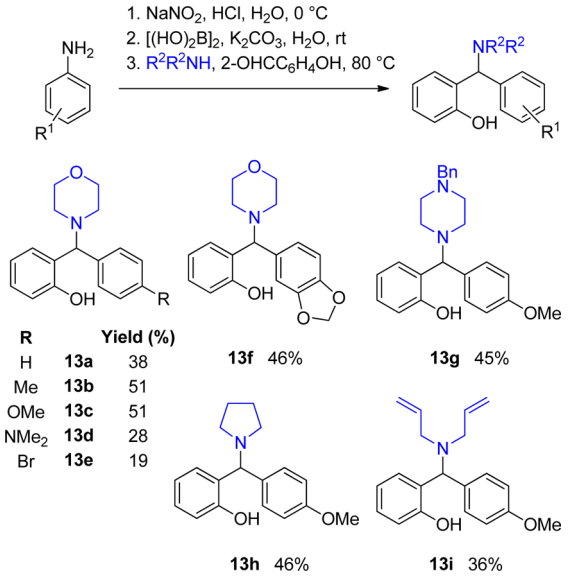


Figure 2. Relevant aminodiarylmethanes.

During the optimization process, the choice of base for the borylation was found to be crucial for a positive outcome of the Petasis step (see Supporting Information). Various amines were found to be compatible, including morpholine, monoprotected piperazine, pyrrolidine and bisallylamine (Scheme 5). However,

Scheme 5. Sequences Involving Petasis Reaction



only electron-rich anilines could be used, since a competitive side-reaction of reductive amination of salicylaldehyde was always observed with electron-deficient anilines.

In summary, our recently developed aqueous borylation was applied to the synthesis of various structures through selected additional steps. First, boronic esters and boronamide were obtained by in situ protection, albeit with moderate yields. Then, the three step synthesis of biaryl compounds under functional group tolerant conditions was successfully developed. The usefulness of this process was further demonstrated by a fourth step of hydrogenation or deprotection to access relevant biaryls. Finally the Petasis borono-Manich reaction toward aminodiarylmethanes was found to be compatible with our borylation conditions.

Overall the sequential one-pot procedures described above, featuring inexpensive starting materials and short reaction times without isolating potentially unstable intermediates, allowed for straightforward access to structurally diverse molecules. These characteristics fit the major requirements of modern compound discovery process and should be of interest in many areas of chemistry.

EXPERIMENTAL SECTION

General Procedure A for (Hetero)arene Boronic Acids Synthesis. To a suspension of aniline (1.0 mmol, 1.0 equiv) in water (1.0 mL) at room temperature was added HCl (37% in water, 208.0 μL, 2.5 mmol, 2.5 equiv), and the reaction mixture was stirred for 1 min before being cooled to 0 °C. A solution of $NaNO_2$ (2.4 M in water, 0.5 mL, 1.2 mmol, 1.2 equiv) was added dropwise with a syringe, and the reaction mixture was stirred for 15 min at 0 °C. Tetrahydroxydiboron (179.3 mg, 2.0 mmol, 2.0 equiv), NaOAc (164.0 mg, 2.0 mmol, 2.0 equiv) and water (6.0 mL) were added to the reaction mixture, which was warmed to room temperature and stirred for 20 min. EtOAc (20 mL) and saturated K_2CO_3 were added to the reaction mixture until pH ≈ 8. This was extracted with sorbitol/Na_2CO_3 (1 M solution in water, 2 × 10 mL, 5 min of stirring). The combined aqueous layers were washed with EtOAc (10 mL) and then acidified until pH = 1 with HCl (6M). The aqueous layer was extracted with EtOAc (4 × 10 mL), the combined organic layers were washed with water (2 × 5 mL), brine (5 mL), dried over $MgSO_4$, filtered and concentrated under vacuum to give the title product.

*2-Oxo-2,3-dihydrobenzo[d]oxazol-6-ylboronic acid (**1a**).* Following the general procedure A, **1a** was obtained from 6-aminobenzo-[*d*]oxazol-2(3*H*)-one[17] (150.1 mg, 1.0 mmol) as a brown solid (113.3 mg, 63%) after trituration in hot acetone/CH_2Cl_2 (1:1) following the sorbitol-mediated extraction: ν_{max} (film)/cm^{-1} 3306, 1738, 1628, 1421, 1335, 1266, 1174, 1101, 943, 703, 673; ^{1}H NMR (400.0 MHz; Acetone-d_6 + D_2O) δ_H = 7.67 (d, J = 7.8 Hz, 1H, ArH), 7.61 (s, 1H, ArH), 7.11 (d, J = 7.8 Hz, 1H, ArH); ^{13}C NMR (100.6 MHz; Acetone-d_6 + D_2O) δ_C = 155.7 (C═O), 144.5 (ArC), 133.1 (ArC), 131.1 (ArCH), 115.1 (ArCH), 109.9 (ArCH); ^{11}B NMR (128.4 MHz; Acetone-d_6 + D_2O) δ_B = 28.2 (br s); HRMS (ESI) calcd for $C_7H_5{}^{11}BNO_4$ $[M - H]^-$ 178.0312, found 178.0314.

*1,3,3-Trimethyl-2-oxoindolin-5-ylboronic acid (**1b**). Preparation of 1,3,3-Trimethylindolin-2-one (**S1**).* A modified procedure of Shibata was used.[18] To a suspension of NaH (60% in mineral oil, 1.95 g, 45.0 mmol, 1.5 equiv) in xylene (50 mL) at 130 °C was added 2-oxindole (4.0 g, 30.0 mmol, 1.0 equiv) portionwise under argon. After addition, the reaction mixture was heated under reflux for 1 h, and dimethylsulfate (4.3 mL, 5.7 g, 45.0 mmol, 1.5 equiv) was then added dropwise. After addition, the reaction mixture was heated under reflux for 1 h before being cooled to rt. This was diluted with EtOAc (100 mL) and water (50 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated under a vacuum to give the crude product. This was purified by column chromatography on silica, eluting with pentane/EtOAc (80:20 to 50:50) to give 1-methylindolin-2-one (0.94 g, 21%), 1,3-dimethylindolin-2-one (0.83 g, 17%) and the title product **S1** as a light orange oil (1.3 g, 25%). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[19] ν_{max} (film)/cm^{-1} 1703, 1611, 1492, 1471, 1457, 1381, 1346, 1304, 1246, 1127, 1072, 937, 753, 741, 697; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.20 (dt, J = 7.7, 1.0 Hz, 1H, ArH), 7.15 (dd, J = 7.4, 1.0 Hz, 1H, ArH), 7.00 (dt, J = 7.4, 0.7 Hz, 1H, ArH), 6.79 (d, J = 7.7 Hz, 1H, ArH), 3.16 (s, 3H, CH_3), 1.32 (s, 6H, 2 × CH_3); ^{13}C NMR (400.0 MHz; $CDCl_3$) δ_C = 181.3 (C═O), 142.6 (ArC), 135.7 (ArC), 127.7 (ArCH), 122.5 (ArCH), 122.2 (ArCH), 108.0 (ArCH), 44.1 (Cq), 26.2 (CH_3), 24.4 (2 × CH_3); m/z (EI) 175 $[M]^+$, 160, 145, 132, 117.

*Preparation of 1,3,3-Trimethyl-5-nitroindolin-2-one (**S2**).* To a solution of **S1** (1.3 g, 7.4 mmol, 1.0 equiv) in H_2SO_4 (96%, 10 mL) at 0 °C was added HNO_3 (65%, 621.0 μL, 8.9 mmol, 1.2 equiv) dropwise, and the reaction mixture was stirred at 0 °C for 30 min after addition. The reaction mixture was poured onto an ice/water mixture, and the resulting solids were filtrated and washed with H_2O (3 × 30 mL). The solids were dissolved in EtOAc (50 mL), and the resulting solution was washed with water (15 mL), brine (15 mL), dried over $MgSO_4$, filtrated and concentrated under a vacuum to give the crude

dx.doi.org/10.1021/jo501665e | J. Org. Chem. 2014, 79, 10568−10580

product. This was purified by column chromatography on silica, eluting with pentane/EtOAc (70:30 to 60:40) to give 1,3,3-trimethyl-5,7-dinitroindolin-2-one (0.32 g, 16.5%) and the title product **S2** as a light yellow solid (0.88 g, 54%). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[20] mp 207−208 °C; ν_{max} (film)/cm^{-1} 1721, 1613, 1507, 1489, 1462, 1329, 1292, 1118, 1038, 941, 894, 834, 755, 736; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 8.21 (dd, J = 8.7, 2.3 Hz, 1H, ArH), 8.06 (d, J = 2.3 Hz, 1H, ArH), 6.90 (d, J = 8.7 Hz, 1H, ArH), 3.25 (s, 3H, CH_3), 1.39 (s, 6H, 2 × CH_3); ^{13}C NMR (400.0 MHz; $CDCl_3$) δ_C = 181.4 (C═O), 148.5 (ArC), 143.6 (ArC), 136.6 (ArC), 125.3 (ArCH), 118.4 (ArCH), 107.8 (ArCH), 44.4 (Cq), 26.8 (CH_3), 24.3 (2 × CH_3); m/z (EI) 220 $[M]^+$, 205, 190, 174, 159, 147, 130, 116, 103.

*Preparation of 5-Amino-1,3,3-trimethylindolin-2-one (**S3**).* To a mixture of **S2** (0.8 g, 3.6 mmol, 1.0 equiv) and Pd/C (10%, 50% wet, 20.0 mg) in EtOH (15/0 mL) and EtOAc (15.0 mL) was vigorously stirred under an atmosphere of hydrogen overnight at rt. The reaction mixture was flushed with argon and was filtered over Celite which was washed with EtOAc (100 mL). The combined filtrates were concentrated under a vacuum to give the crude product. This was purified by column chromatography on silica, eluting with pentane/EtOAc (60:40 to 70:30) to give the title product **S3** as a light brown solid (663.0 mg, 96%): mp 147−148 °C; ν_{max} (film)/cm^{-1} 3446, 3356, 3328, 2221, 1669, 1636, 1597, 1491, 1476, 1459, 1385, 1370, 1310, 1254, 1122, 1064, 815, 697, 617; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 6.63 (m, 3H, ArH), 3.61 (br s, 2H, NH_2), 3.14 (s, 3H, CH_3), 1.31 (s, 6H, 2 × CH_3); ^{13}C NMR (400.0 MHz; $CDCl_3$) δ_C = 181.0 (C═O), 141.8 (ArC), 137.4 (ArC), 135.2 (ArC), 114.0 (ArCH), 111.2 (ArCH), 108.7 (ArCH), 44.7 (Cq), 26.4 (CH_3), 24.6 (2 × CH_3); HRMS (ESI) calcd for $C_{11}H_{15}N_2O$ $[M + H]^+$ 191.1184, found 191.1175.

Following the general procedure A, **1b** was obtained from 5-amino-1,3,3-trimethylindolin-2-one (**S3**, 190.2 mg, 1.0 mmol) as a light yellow solid (166.6 mg, 76%): ν_{max} (film)/cm^{-1} 3334 (br), 1683, 1614, 1384, 1337, 1279, 1249, 1128, 1066, 1032, 761, 715, 675; ^{1}H NMR (400.0 MHz; Acetone-d_6 + D_2O) δ_H = 7.78 (d, J = 7.6 Hz, 1H, ArH), 7.74 (s, 1H, ArH), 6.91 (d, J = 7.6 Hz, 1H, ArH), 3.14 (s, 3H, CH_3), 1.25 (s, 6H, 2 × CH_3); ^{13}C NMR (100.6 MHz; Acetone-d_6 + D_2O) δ_C = 182.5 (C═O), 145.3 (ArC), 135.4 (ArC), 135.2 (ArCH), 128.5 (ArCH), 108.4 (ArCH), 44.4 (ArC), 26.4 (CH_3), 24.4 (2 × CH_3); ^{11}B NMR (128.4 MHz; Acetone-d_6 + D_2O) δ_B = 29.1 (br s); HRMS (ESI) calcd for $C_{11}H_{13}{}^{11}BNO_3$ $[M - H]^-$ 218.0988, found 218.0983.

*4-Oxochroman-7-ylboronic acid (**1c**). Preparation of 7-Nitrochroman-4-one (**S4**).* A modified procedure of Hay was used;[20] To a solution of 4-chromanone (7.30 g, 5.0 mmol, 1.0 equiv) in H_2SO_4 (96%, 125 mL) at 0 °C was added a solution of potassium nitrate (5.56 g, 5.5 mmol, 1.1 equiv) in H_2SO_4 (96%, 125 mL) dropwise. After addition, the reaction mixture was stirred for 10 min at 0 °C and was then poured into an ice/water mixture. The resulting solids were filtered and washed with H_2O (3 × 100 mL) before being dissolved in EtOAc. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and concentrated under a vacuum to give the crude product. This was purified by column chromatography on silica, eluting with pentane/EtOAc (60:40) to give 6-nitrochroman-4-one (2.16 g, 22%) and the title product **S4** as a light yellow solid (623.6 mg, 6.5%): mp 128−130 °C; ν_{max} (film)/cm^{-1} 1683, 1609, 1522, 1478, 1465, 1446, 1358, 1300, 1250, 1230, 1078, 102, 932, 813, 765, 747, 671; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 8.11 (dd, J = 7.8, 1.7 Hz, 1H, ArH), 8.05 (dd, J = 7.8, 1.7 Hz, 1H, ArH), 7.09 (t, J = 7.8 Hz, 1H, ArH), 4.68 (t, J = 6.4 Hz, 2H, CH_2), 2.89 (t, J = 6.4 Hz, 2H, CH_2); ^{13}C NMR (400.0 MHz; $CDCl_3$) δ_C = 189.5 (C═O), 155.1 (ArC), 139.6 (ArC), 132.6 (ArCH), 131.5 (ArCH), 123.6 (ArC), 120.6 (ArCH), 68.4 (CH_2), 37.3 (CH_2).

*Preparation of 7-Aminochroman-4-ol (**S5**).* Following an unoptimized procedure, a mixture of **S4** (550.0 mg, 2.85 mmol, 1.0 equiv) and Pd/C (10%, 50% wet, 30.0 mg) in MeOH (20.0 mL), EtOAc (20.0 mL) and AcOH (4.0 mL) was vigorously stirred under an atmosphere of hydrogen overnight at rt. The reaction mixture was flushed with argon and was filtered over Celite which was washed with EtOAc (200 mL). The combined filtrates were washed with K_2CO_3 sat. (2 × 40 mL), brine (20 mL), dried over $MgSO_4$ and concentrated under a vacuum to give the crude product. This was purified by column chromatography on silica, eluting with pentane/EtOAc (60:40 to 50:50) to give the title product **S5** as a light brown solid (376.0 mg, 80%): ^{1}H NMR (400.0 MHz; MeOD-d_4) δ_H = 6.74−6.65 (m, 3H, ArH), 4.68 (t, J = 4.2 Hz, 1H, CH), 4.31−4.24 (m, 2H, CH_2), 2.12−2.04 (m, 1H, C*H*H), 2.01−1.95 (m, 1H, CH*H*); ^{13}C NMR (400.0 MHz; MeOD-d_4) δ_C = 144.3 (ArC), 136.6 (ArC), 125.6 (ArC), 121.3 (ArCH), 120.8 (ArCH), 116.3 (ArCH), 63.9 (CH), 63.4 (CH_2), 32.7 (CH_2); HRMS (ESI) calcd for $C_9H_{12}NO_2$ $[M + H]^+$ 166.0868, found 166.0873.

*Preparation of 7-Aminochroman-4-one (**S6**).* Following an unoptimized procedure, to a solution of **S5** (376.0 mg, 2.3 mmol, 1.0 equiv) in dioxane (30 mL) at 90 °C was added MnO_2 (1.97 g, 2.27 mmol, 10.0 equiv) portionwise. After addition, the reaction mixture was stirred overnight at 90 °C under air. After being cooled to rt, the reaction mixture was filtered over Celite which was washed with EtOAc (100 mL). The combined filtrates were concentrated under a vacuum to give the crude product. This was purified by column chromatography on silica, eluting with pentane/EtOAc (60:40 to 0:100) to give the title product **S6** as a light yellow solid (38.0 mg, 10%): ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.27 (dd, J = 7.8, 1.3 Hz, 1H, ArH), 6.85 (dd, J = 7.8, 1.3 Hz, 1H, ArH), 6.79 (t, J = 7.8 Hz, 1H, ArH), 4.54 (t, J = 6.3 Hz, 2H, CH_2), 2.78 (t, J = 6.3 Hz, 2H, CH_2); ^{13}C NMR (400.0 MHz; $CDCl_3$) δ_C = 192.2 (C═O), 149.9 (ArC), 136.3 (ArC), 121.4 (ArCH), 120.2 (ArCH), 116.1 (1 × ArC, 1 × ArCH), 67.4 (CH_2), 38.1 (CH_2); HRMS (API) calcd for $C_{18}H_{15}N_2O_4$ dimer 323.1032, found 323.1027.

Following the general procedure A, **1c** was obtained from 7-aminochroman-4-one (**S6**, 38.7 mg, 0.24 mmol) as an orange solid (15.5 mg, 34%): ν_{max} (film)/cm^{-1} 3501 (br), 3335 (br), 1673, 1584, 1474, 1440, 1372, 1344, 1281, 1254, 1072, 1027, 753; ^{1}H NMR (400.0 MHz; Acetone-d_6 + D_2O) δ_H = 7.96 (dd, J = 7.1, 1.8 Hz, 1H, ArH), 7.87 (dd, J = 7.8, 1.8 Hz, 1H, ArH), 7.06 (m, 1H, ArH), 4.66 (t, J = 6.3 Hz, 2H, CH_2), 2.81 (t, J = 6.3 Hz, 2H, CH_2); ^{13}C NMR (100.6 MHz; Acetone-d_6 + D_2O) δ_C = 192.8 (C═O), 167.1 (ArC), 143.0 (ArCH), 130.2 (ArCH), 122.0 (ArCH), 121.7 (ArC), 68.2 (CH_2), 37.9 (CH_2); ^{11}B NMR (128.4 MHz; Acetone-d_6 + D_2O) δ_B = 28.5 (br s); m/z (ESI) 417.1, 365.1 $[2M - H_2O - H]^-$, 271.0, 253.0, 195.0, 176.9, 97.0; HRMS (ESI) calcd for $C_9H_8{}^{11}BO_4$ $[M - H]^-$ 191.0516, found 191.0521.

*4-((Diethoxyphosphoryl)methyl)phenylboronic acid (**1d**).* Following the general procedure A, **1d** was obtained from diethyl 4-aminobenzylphosphonate (243.2 mg, 1.0 mmol) as a light yellow solid (122.4 mg, 45%): ν_{max} (film)/cm^{-1} 3330 (br), 1608, 1417, 1350, 1318, 1223, 1018, 976, 826, 790, 645; ^{1}H NMR (500.0 MHz; Acetone-d_6 + D_2O) δ_H = 7.78 (d, J = 7.6 Hz, 2H, ArH), 7.28 (dd, J = 7.6, 1.9 Hz, 2H, ArH), 3.98 (m, 4H, 2 × CH_2), 3.20 (d, J = 22.0 Hz, 2H, CH_2), 1.17 (t, J = 7.1 Hz, 6H, 2 × CH_3); ^{13}C NMR (125.7 MHz; Acetone-d_6 + D_2O) δ_C = 135.0 (d, J = 3.1 Hz, 2 × ArCH), 134.9 (d, J = 9.3 Hz, ArC), 129.9 (d, J = 6.6 Hz, 2 × ArCH), 62.9 (d, J = 6.6 Hz, 2 × CH_2), 33.6 (d, J = 136.8 Hz, CH_2), 16.5 (d, J = 6.0 Hz, 2 × CH_3); ^{11}B NMR (160.4 MHz; Acetone-d_6 + D_2O) δ_B = 28.8 (br s); ^{31}P NMR (202.4 MHz; Acetone-d_6 + D_2O) δ_P = 26.7 (s); HRMS (ESI) calcd for $C_{11}H_{17}{}^{11}BO_5P$ $[M - H]^-$ 271.0907, found 271.0919.

*4-(Pyrrolidine-1-carbonyl)phenylboronic acid (**1e**).* Following the general procedure A, **1e** was obtained from (4-aminophenyl)-(pyrrolidin-1-yl)methanone[21] (190.2 mg, 1.0 mmol) as a light yellow solid (59.1 mg, 27%): ν_{max} (film)/cm^{-1} 3344 (br), 1597, 1549, 1512, 1442, 1401, 1374, 1340, 1112, 1017, 844, 727; ^{1}H NMR (400.0 MHz; DMSO-d_6 + D_2O) δ_H = 8.42 (d, J = 7.8 Hz, 2H, ArH), 8.04 (d, J = 7.8 Hz, 2H, ArH), 4.05 (t, J = 6.7 Hz, 2H, CH_2), 3.93 (t, J = 6.5 Hz, 2H, CH_2), 2.43 (m, 2H, CH_2), 2.37 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz; DMSO-d_6 + D_2O) δ_C = 168.3 (C═O), 138.6 (ArC), 133.9 (2 × ArCH), 125.9 (2 × ArCH), 48.9 (CH_2), 45.9 (CH_2), 25.9 (CH_2), 23.9 (CH_2); ^{11}B NMR (160.4 MHz; Acetone-d_6 + D_2O) δ_B = 28.4 (br s); m/z (ESI) 419.2 $[2M - H_2O - H]^-$, 298.1, 264.1, 218.1 $[M - H]^-$.

*p-Tolylboronic acid (**1f**).* Following the general procedure A, **1f** was obtained from *p*-aminotoluidine (115.0 mg, 1.0 mmol) as a white solid

dx.doi.org/10.1021/jo501665e | J. Org. Chem. 2014, 79, 10568−10580

(114.0 mg, 78%). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[22] ν_{max} (film)/cm^{-1} 2921 (br), 1612, 1402, 1366, 1343 (br), 1309, 1181, 1110, 1021, 819, 731, 681; ^{1}H NMR (400.0 MHz; DMSO-d_6 + D_2O) δ_H = 7.67 (d, J = 7.8 Hz, 2H, ArH), 7.13 (d, J = 7.8 Hz, 2H, ArH), 2.27 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; DMSO-d_6 + D_2O) δ_C = 140.0 (ArC), 134.6 (2 × ArCH), 130.8 (ArC), 128.6 (2 × ArCH), 21.5 (CH_3); ^{11}B NMR (128.4 MHz; DMSO-d_6 + D_2O) δ_B = 28.8 (br s).

*4-Hydroxyphenylboronic acid (**1g**).* Following the general procedure A, **1g** was obtained from 4-hydroxyaniline (109.1 mg, 1.0 mmol) as a brown solid (62.8 mg, 45.5%): ν_{max} (film)/cm^{-1} 3315 (br), 2461 (br), 1697, 1601, 1578, 1512, 1321, 137, 1174, 1103, 1081, 1014, 830, 783, 729; ^{1}H NMR (400.0 MHz; Acetone-d_6 + D_2O) δ_H = 7.67 (d, J = 8.4 Hz, 2H, ArH), 6.76 (d, J = 8.4 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz; Acetone-d_6 + D_2O) δ_C = 160.2 (ArC), 136.7 (2 × ArCH), 115.2 (2 × ArCH); ^{11}B NMR (128.4 MHz; Acetone-d_6 + D_2O) δ_B = 29.1 (br s); HRMS (ESI) calcd for $C_6H_6{}^{11}BO_3$ $[M - H]^-$ 137.0410, found 137.0406.

*4-Acetamidophenylboronic acid (**1h**).* Following the general procedure A, **1h** was obtained from *N*-(4-aminophenyl)acetamide[23] (150.2 mg, 1.0 mmol) as a white solid (55.4 mg, 31%): ν_{max} (film)/cm^{-1} 3304 (br), 1665, 1590, 1530, 1401, 1337, 1317, 1257, 1177, 1011, 835, 742, 643; ^{1}H NMR (500.0 MHz; Acetone-d_6 + D_2O) δ_H = 7.76 (d, J = 8.3 Hz, 2H, ArH), 7.58 (d, J = 8.3 Hz, 2H, ArH), 2.07 (s, 3H, CH_3); ^{13}C NMR (125.7 MHz; Acetone-d_6 + D_2O) δ_C = 170.0 (C═O), 141.9 (ArC), 135.7 (2 × ArCH), 188.8 (2 × ArCH), 24.1 (CH_3); ^{11}B NMR (160.4 MHz; Acetone-d_6 + D_2O) δ_B = 28.9 (br s); HRMS (ESI) calcd for $C_8H_9{}^{11}BNO_3$ $[M - H]^-$ 178.0675, found 178.0682.

*4-Azidophenylboronic acid (**1i**).* Following the general procedure A, **1i** was obtained from 4-azidoaniline[24] (134.1 mg, 1.0 mmol) as a brown solid (47.2 mg, 29%): ν_{max} (film)/cm^{-1} 3285 (br), 2536, 1450, 1091, 1597, 1564, 1338, 1285, 1268, 1131, 1109, 844, 822, 727, 643, 622; ^{1}H NMR (400.0 MHz; Acetone-d_6 + D_2O) δ_H = 7.86 (d, J = 8.5 Hz, 2H, ArH), 7.01 (d, J = 8.5 Hz, 2H, ArH); ^{13}C NMR (100.6 MHz; Acetone-d_6 + D_2O) δ_C = 142.4 (ArC), 136.7 (2 × ArCH), 118.8 (2 × ArCH); ^{11}B NMR (128.4 MHz; Acetone-d_6 + D_2O) δ_B = 28.2 (br s); HRMS (ESI) calcd for $C_6H_5{}^{11}BN_3O_2$ $[M - H]^-$ 162.0475, found 162.0482.

*4-(Benzyloxy)phenylboronic acid (**1j**).* Following the general procedure A, **1j** was obtained from 4-(benzyloxy)aniline[25] (199.2 mg, 1.0 mmol) as a white solid (57.3 mg, 25%). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[26] ν_{max} (film)/cm^{-1} 3363 (br), 2479, 1604, 1337 (br), 1245, 1176, 1110, 1009, 821, 749, 704; ^{1}H NMR (400.0 MHz; Acetone-d_6 + D_2O) δ_H = 7.80 (d, J = 8.6 Hz, 2H, ArH), 7.44 (d, J = 7.8 Hz, 2H, ArH), 7.36 (t, J = 7.8 Hz, 2H, ArH), 7.29 (t, J = 7.8 Hz, 1H, ArH), 6.96 (d, J = 8.6 Hz, 2H, ArH), 5.09 (s, 2H, CH_2); ^{13}C NMR (100.6 MHz; Acetone-d_6 + D_2O) δ_C = 161.4 (ArC), 138.1 (ArC), 136.7 (2 × ArCH), 129.2 (2 × ArCH), 128.6 (ArCH), 128.3 (2 × ArCH), 114.7 (2 × ArCH), 70.1 (CH_2); ^{11}B NMR (128.4 MHz; Acetone-d_6 + D_2O) δ_B = 28.6 (br s).

*2-Nitrophenylboronic acid (**1k**).* Following the general procedure A, **1k** was obtained from 2-nitroaniline (138.1 mg, 1.0 mmol) as a brown solid (46.2 mg, 28%). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[27] ν_{max} (film)/cm^{-1} 3253 (br), 152, 1475, 1337, 1277, 1250, 1135, 980, 855, 739, 696; ^{1}H NMR (400.0 MHz; DMSO-d_6 + D_2O) δ_H = 8.11 (d, J = 7.3 Hz, 1H, ArH), 7.72 (t, J = 7.3 Hz, 1H, ArH), 7.56 (t, J = 7.3 Hz, 1H, ArH), 7.51 (d, J = 7.3 Hz, 1H, ArH); ^{13}C NMR (100.6 MHz; DMSO-d_6 + D_2O) δ_C = 150.4 (ArC), 134.9 (ArCH), 132.8 (ArCH), 129.9 (ArCH), 123.3 (ArCH); ^{11}B NMR (128.4 MHz; Acetone-d_6 + D_2O) δ_B = 29.2 (br s).

*2-Phenoxyphenylboronic acid (**1l**).* Following the general procedure A, **1l** was obtained from 2-phenoxyaniline (185.2 mg, 1.0 mmol) as a light gray solid (72.7 mg, 34%): ν_{max} (film)/cm^{-1} 3333 (br), 1602, 1588, 1475, 1442, 1388, 1329, 1223, 1165, 1008, 871, 797, 745, 651; ^{1}H NMR (400.0 MHz; Acetone-d_6 + D_2O) δ_H = 7.87 (dd, J = 7.5, 1.5 Hz, 1H, ArH), 7.40−7.34 (m, 3H, ArH), 7.17−7.10 (m, 2H, ArH), 7.04 (d, J = 8.2 Hz, 2H, ArH), 6.73 (d, J = 8.2 Hz, 1H, ArH); ^{13}C NMR (100.6 MHz; Acetone-d_6 + D_2O) δ_C = 163.1 (ArC), 157.3 (ArC), 137.3 (ArCH), 132.9 (ArCH), 130.8 (2 × ArCH), 124.8 (ArCH), 123.9 (ArCH), 120.2 (2 × ArCH), 117.8 (ArCH); ^{11}B NMR (128.4 MHz; Acetone-d_6 + D_2O) δ_B = 28.8 (br s); HRMS (ESI) calcd for $C_{24}H_{19}{}^{11}B_2O_5$ $[2M - H_2O - H]^-$ 409.1419, found 409.1434.

*Biphenyl-2-ylboronic acid (**1m**).* Following the general procedure A, **1m** was obtained from 2-aminobiphenyl (169.2 mg, 1.0 mmol) as a white solid (16.2 mg, 8%). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[28] ν_{max} (film)/cm^{-1} 3304 (br), 1594, 1477, 1433, 1336, 1153, 1113, 1091, 1051, 1008, 822, 780, 740; ^{1}H NMR (500.0 MHz; DMSO-d_6 + D_2O) δ_H = 7.50 (d, J = 7.5 Hz, 1H, ArH), 7.47 (d, J = 7.5 Hz, 2H, ArH), 7.42 (m, 3H, ArH), 7.37−7.32 (m, 3H, ArH); ^{13}C NMR (125.7 MHz; DMSO-d_6 + D_2O) δ_C = 144.9 (ArC), 143.8 (ArC), 137.4 (ArC), 132.9 (ArCH), 129.2 (ArCH), 128.9 (3 × ArCH), 128.8 (2 × ArCH), 127.5 (ArCH), 126.8 (ArCH); ^{11}B NMR (160.4 MHz; DMSO-d_6 + D_2O) δ_B = 32.6 (br s).

General Procedure B for Boronates Synthesis. To a solution of aniline (1.0 mmol, 1.0 equiv) in HCl (2.1 M in water, 1.2 mL, 2.5 mmol, 2.5 equiv) at 0 °C was added a solution of $NaNO_2$ (2.4 M in water, 0.5 mL, 1.2 mmol, 1.2 equiv) dropwise, and the reaction mixture was stirred for 15 min at 0 °C. Tetrahydroxydiboron (179.3 mg, 2.0 mmol, 2.0 equiv) and water (2.0 mL) were added, followed by a solution of K_2CO_3 (138.2 mg, 1.0 mmol, 1.0 equiv) in water (1.0 mL) slowly introduced directly inside the reaction mixture using a syringe. After addition, the mixture was warmed to room temperature and stirred for 20 min. MeCN (1.0 mL), $FeCl_3$ (8.1 mg, 0.05 mmol, 5 mol %), imidazole (204.2 mg, 3.0 mmol, 3.0 equiv), and the corresponding diol or diamine (1.0 mmol, 1.0 equiv) were added to the reaction mixture which was stirred at room temperature for 30 min. Water (5 mL) were added to the reaction mixture which was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water (5 mL), brine (5 mL), dried over $MgSO_4$, filtered and concentrated under a vacuum to give the crude product. This was purified by column chromatography on silica to give the title compounds.

*2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2a**).* Following the general procedure B, **2a** was obtained from *p*-anisidine (151.9 mg, 1.0 mmol) and pinacol (118.2 mg, 1.0 mmol) as an orange oil (100.9 mg, 43%) after column chromatography on silica, eluting with pentane/EtOAc (100:10). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[29] ν_{max} (film)/cm^{-1} 2977, 1603, 1396, 1356, 1316, 1244, 1140, 1090, 1028, 961, 859, 829, 736, 670, 653; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.76 (d, J = 8.7 Hz, 2H, ArH), 6.89 (d, J = 8.7 Hz, 2H, ArH), 3.80 (s, 3H, CH_3), 1.32 (s, 12H, 4 × CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 162.3 (ArC), 136.7 (2 × ArCH), 113.4 (2 × ArCH), 83.7 (2 × Cq), 55.2 (CH_3), 25.0 (4 × CH_3); ^{11}B NMR (128.4 MHz; $CDCl_3$) δ_B = 30.9 (br s).

*4,4,5,5-Tetramethyl-2-p-tolyl-1,3,2-dioxaborolane (**2b**).* Following the general procedure B, **2b** was obtained from *p*-toluidine (107.2 mg, 1.0 mmol) and pinacol (118.2 mg, 1.0 mmol) as a light yellow oil (80.4 mg, 37%) after column chromatography on silica, eluting with pentane/EtOAc (250:1 to 250:5). The ^{1}H, ^{13}C and ^{11}B data were consistent with those reported in the literature:[30] ν_{max} (film)/cm^{-1} 2978, 1612, 1397, 1357, 1317, 1142, 1087, 1022, 962, 858, 815, 725, 654; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.70 (d, J = 7.9 Hz, 2H, ArH), 7.18 (d, J = 7.9 Hz, 2H, ArH), 2.36 (s, 3H, CH_3), 1.33 (s, 12H, 4 × CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 141.6 (ArC), 135.0 (2 × ArCH), 128.7 (2 × ArCH), 83.8 (2 × Cq), 25.1 (4 × CH_3), 21.9 (CH_3); ^{11}B NMR (128.4 MHz; $CDCl_3$) δ_B = 30.9 (br s).

*2-(4-Fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2c**).* Following the general procedure B, **2c** was obtained from 4-fluoroaniline (112.1 mg, 1.0 mmol) and pinacol (118.2 mg, 1.0 mmol) as an orange oil (45.8 mg, 20.5%) after column chromatography on silica, eluting with pentane/EtOAc (150:10). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[29] ν_{max} (film)/cm^{-1} 2979, 1602, 1398, 1357, 1317, 1220, 1141, 1086, 962, 836, 729, 650; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.78 (dd, J = 8.4, 6.4 Hz, 2H, ArH), 7.03 (t, J = 9.0 Hz, 2H, ArH), 1.32 (s, 12H, 4 × CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 165.3 (d, J = 250.0 Hz, ArC), 137.2 (d, J = 8.2 Hz, 2 × ArCH), 115.0 (d, J = 20.3 Hz, 2 × ArCH), 84.1 (s, 2 × Cq), 25.1 (s, 4 × CH_3); ^{11}B NMR (128.4

dx.doi.org/10.1021/jo501665e | J. Org. Chem. 2014, 79, 10568−10580

MHz; $CDCl_3$) δ_B = 30.7 (br s). ^{19}F NMR (376.4 MHz; $CDCl_3$) δ_F = −108.4 (s).

*2-(Benzo[d][1,3]dioxol-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2d**).* Following the general procedure B, **2d** was obtained from 3,4-(methylenedioxy)aniline (137.1 mg, 1.0 mmol) and pinacol (118.2 mg, 1.0 mmol) as a light yellow oil (79.4 mg, 32%) after column chromatography on silica, eluting with pentane/EtOAc (150:10). The ^1H and ^{13}C data were consistent with those reported in the literature:[31] ν_{max} (film)/cm^{-1} 2977, 1432, 1352, 1336, 1233, 1141, 1104, 1037, 854, 679; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.34 (dd, J = 8.0, 0.7 Hz, 1H, ArH), 7.23 (s, 1H, ArH), 6.82 (d, J = 8.0 Hz, 1H, ArH), 5.93 (s, 2H, CH_2), 1.31 (s, 12H, 4 × CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 150.3 (ArC), 147.4 (ArC), 129.9 (ArCH), 114.1 (ArCH), 108.4 (ArCH), 100.9 (CH_2), 83.8 (2 × Cq), 25.0 (4 × CH_3); ^{11}B NMR (128.4 MHz; $CDCl_3$) δ_B = 30.6 (br s).

*3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (**2e**).* Following the general procedure B, **2e** was obtained from 3-aminobenzoic acid (137.2 mg, 1.0 mmol) and pinacol (118.2 mg, 1.0 mmol) as a white solid (53.3 mg, 21.5%) after column chromatography on silica, eluting with pentane/EtOAc (100:10 to 70:30). The ^1H data were consistent with those reported in the literature:[32] mp 206−209 °C; ν_{max} (film)/cm^{-1} 2977 (br), 1678, 1606, 1355, 1288, 1269, 1143, 962, 946, 848, 697, 687; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 8.55 (s, 1H, ArH), 8.18 (d, J = 7.8 Hz, 1H, ArH), 8.02 (d, J = 7.8 Hz, 1H, ArH), 7.48 (t, J = 7.8 Hz, 1H, ArH), 1.36 (s, 12H, 4 × CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 172.2 (CO_2H), 140.2 (ArCH), 136.8 (ArCH), 133.0 (ArCH), 128.9 (ArC), 128.1 (ArCH), 84.4 (2 × Cq), 25.1 (4 × CH_3); ^{11}B NMR (128.4 MHz; $CDCl_3$) δ_B = 31.1 (br s).

*2-(4-Methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (**2f**).* Following the general procedure B, **2f** was obtained from *p*-anisidine (151.9 mg, 1.0 mmol) and neopentyl glycol (104.2 mg, 1.0 mmol) as a light yellow solid (69.0 mg, 31%) after column chromatography on silica, eluting with pentane/EtOAc (150:10). The ^1H, ^{13}C and ^{11}B data were consistent with those reported in the literature:[33] mp 48−50 °C; ν_{max} (film)/cm^{-1} 2954, 1601, 1481, 1317, 1309, 1296, 1244, 1173, 1130, 1025, 836, 825, 646; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.73 (d, J = 7.8 Hz, 2H, ArH), 6.87 (d, J = 7.8 Hz, 2H, ArH), 3.80 (s, 3H, CH_3), 3.74 (s, 4H, 2 × CH_2), 1.00 (s, 6H, 2 × CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 161.9 (ArC), 135.7 (2 × ArCH), 113.3 (2 × ArCH), 75.4 (2 × CH_2), 55.2 (CH_3), 32.1 (Cq), 22.1 (2 × CH_3); ^{11}B NMR (128.4 MHz; $CDCl_3$) δ_B = 26.7 (br s).

*2-(4-Methoxyphenyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]-diazaborinine (**2g**).* Following the general procedure B, **2g** was obtained from *p*-anisidine (151.9 mg, 1.0 mmol) and 1,8-diaminonaphtalene (158.2 mg, 1.0 mmol) as a brown solid (113.9 mg, 41.5%) after preparative TLC on silica, eluting with pentane/EtOAc (85:15). The ^1H and ^{13}C data were consistent with those reported in the literature:[34] mp 128−131 °C; ν_{max} (film)/cm^{-1} 3408, 1723, 1595, 1492, 1406, 1224, 1179, 1085, 1028, 818, 760; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.57 (d, J = 8.1 Hz, 2H, ArH), 7.15 (t, J = 7.4 Hz, 2H, ArH), 7.06 (d, J = 8.1 Hz, 2H, ArH), 6.97 (d, J = 7.4 Hz, 2H, ArH), 6.40 (d, J = 7.4 Hz, 2H, ArH), 5.98 (br s, 2H, 2 × NH), 3.84 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 161.5 (ArC), 141.4 (ArC), 136.5 (ArC), 133.2 (2 × ArCH), 127.8 (2 × ArCH), 119.8 (2 × ArC), 117.8 (2 × ArCH), 114.0 (2 × ArCH), 106.1 (2 × ArCH), 55.3 (CH_3); ^{11}B NMR (128.4 MHz; $CDCl_3$) δ_B = 29.3 (br).

General Procedure C for Biaryl Compounds Synthesis. To a solution of aniline (93.1 mg, 1.0 mmol, 1.0 equiv) in HCl (2.1 M in water, 1.2 mL, 2.5 mmol, 2.5 equiv) at 0 °C was added a solution of $NaNO_2$ (2.4 M in water, 0.5 mL, 1.2 mmol, 1.2 equiv) dropwise, and the reaction mixture was stirred for 15 min at 0 °C. Tetrahydroxydiboron (179.3 mg, 2.0 mmol, 2.0 equiv) and water (2 mL) were added, followed by a solution of K_2CO_3 (138.2 mg, 1.0 mmol, 1.0 equiv) in water (1.0 mL) slowly introduced directly inside the reaction mixture using a syringe. After addition, the mixture was warmed to room temperature and stirred for 20 min. Aryl bromide (1.5 mmol, 1.5 equiv) and dioxane (2.5 mL) were added and argon was bubbled into the reaction mixture for 10 min. K_2CO_3 (345.5 mg, 2.5 mmol, 2.5 equiv), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol %) and SPhos (41.0 mg, 0.1 mmol, 10 mol %) were added to the reaction mixture which was sealed and vigorously stirred at 100 °C in a preheated oil bath for 1 h. The reaction mixture was cooled to room temperature and was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (5 mL), brine (5 mL), dried over $MgSO_4$, filtered and concentrated under a vacuum to give the crude product. This was purified by column chromatography on silica to give the biaryl compounds.

*4-Methoxybiphenyl (**3a**).* Following the general procedure C, **3a** was obtained from aniline (93.1 mg, 1.0 mmol) and *p*-bromoanisole (187.0 μL, 280.5 mg, 1.5 mmol) as a white solid (112.3 mg, 61%) after column chromatography on silica, eluting with pentane/CH_2Cl_2 (80:20). The ^1H and ^{13}C data were consistent with those reported in the literature:[35] mp 84−85 °C; ν_{max} (film)/cm^{-1} 2961, 2925, 1604, 1520, 1483, 1463, 1286, 1269, 1249, 1199, 1184, 1034, 833, 758, 686; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.62−7.56 (m, 4H, ArH), 7.46 (t, J = 7.4 Hz, 2H, ArH), 7.35 (t, J = 7.4 Hz, 1H, ArH), 7.03 (d, J = 8.7 Hz, 2H, ArH), 3.87 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 159.3 (ArC), 140.9 (ArC), 133.9 (ArC), 128.9 (2 × ArCH), 128.3 (2 × ArCH), 126.9 (2 × ArCH), 126.8 (ArCH), 114.4 (2 × ArCH), 55.4 (CH_3); m/z (EI) 184 $[M]^{+\cdot}$, 169, 152, 141, 126, 115.

*4-Methoxy-4′-methylbiphenyl (**3b**).* Following the general procedure C, **3b** was obtained from *p*-toluidine (107.2 mg, 1.0 mmol) and *p*-bromoanisole (187.0 μL, 280.5 mg, 1.5 mmol) as an orange solid (122.4 mg, 61%) after column chromatography on silica, eluting with pentane/CH_2Cl_2 (90:10 to 80:20). The ^1H and ^{13}C data were consistent with those reported in the literature:[36] mp 105−108 °C; ν_{max} (film)/cm^{-1} 2913, 1606, 1499, 1287, 1249, 1181, 1037, 1012, 806, 782, 658; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.57 (d, J = 8.7 Hz, 2H, ArH), 7.51 (d, J = 8.1 Hz, 2H, ArH), 7.28 (d, J = 8.1 Hz, 2H, ArH), 7.02 (d, J = 8.7 Hz, 2H, ArH), 3.88 (s, 3H, CH_3), 2.44 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 159.1 (ArC), 138.1 (ArC), 136.5 (ArC), 133.9 (ArC), 129.6 (2 × ArCH), 128.1 (2 × ArCH), 126.7 (2 × ArCH), 114.3 (2 × ArCH), 55.4 (CH_3), 21.2 (CH_3); m/z (EI) 198 $[M]^{+\cdot}$, 183, 155, 139, 128, 115.

*4-Fluoro-4′-methoxybiphenyl (**3c**).* Following the general procedure C, **3c** was obtained from 4-fluoroaniline (111.1 mg, 1.0 mmol) and *p*-bromoanisole (187.0 μL, 280.5 mg, 1.5 mmol) as a light orange solid (124.9 mg, 61.5%) after column chromatography on silica, eluting with pentane/CH_2Cl_2 (90:10 to 70:30). The ^1H, ^{13}C and ^{19}F data were consistent with those reported in the literature:[37] mp 87−89 °C; ν_{max} (film)/cm^{-1} 2923, 1606, 1598, 1493, 131, 1181, 1159, 1037, 824, 809, 790; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.52−7.47 (m, 4H, ArH), 7.11 (t, J = 8.6 Hz, 2H, ArH), 6.98 (d, J = 8.6 Hz, 2H, ArH), 3.85 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 162.3 (d, J = 245.3 Hz, ArC), 159.3 (s, ArC), 137.1 (d, J = 3.4 Hz, ArC), 132.9 (s, ArC), 128.4 (d, J = 7.9 Hz, 2 × ArCH), 128.2 (s, 2 × ArCH), 115.7 (d, J = 21.4 Hz, 2 × ArCH), 114.4 (s, 2 × ArCH), 55.5 (CH_3). ^{19}F NMR (376.4 MHz; $CDCl_3$) δ_F = −116.6 (s); m/z (EI) 202 $[M]^{+\cdot}$, 187, 159, 133.

*4-Chloro-4′-methoxybiphenyl (**3d**).* Following the general procedure C, **3d** was obtained from 4-chloroaniline (127.6 mg, 1.0 mmol) and *p*-bromoanisole (187.0 μL, 280.5 mg, 1.5 mmol) as a light orange solid (83.5 mg, 38%) after column chromatography on silica, eluting with pentane/CH_2Cl_2 (90:10). The ^1H and ^{13}C data were consistent with those reported in the literature:[38] mp 110−112 °C; ν_{max} (film)/cm^{-1} 1604, 1481, 1459, 1288, 1251, 1197, 1178, 1099, 1036, 1010, 819, 809, 735; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.50−7.45 (m, 4H, ArH), 7.37 (d, J = 8.6 Hz, 2H, ArH), 6.97 (d, J = 8.6 Hz, 2H, ArH), 3.84 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 159.5 (ArC), 139.4 (ArC), 132.8 (ArC), 132.6 (ArC), 129.0 (2 × ArCH), 128.2 (2 × ArCH), 128.1 (2 × ArCH), 114.5 (2 × ArCH), 55.5 (CH_3); m/z (EI) 218 $[M]^{+\cdot}$, 203, 175, 149, 139, 125, 113.

*4′-Methoxybiphenyl-4-carbonitrile (**3e**).* Following the general procedure C, **3e** was obtained from 4-aminobenzonitrile (118.2 mg, 1.0 mmol) and *p*-bromoanisole (187.0 μL, 280.5 mg, 1.5 mmol) as a white solid (110.7 mg, 53%) after column chromatography on silica, eluting with pentane/CH_2Cl_2 (70:30 to 50:50). The ^1H and ^{13}C data were consistent with those reported in the literature:[38] mp 103−105 °C; ν_{max} (film)/cm^{-1} 2223, 1604, 1493, 1294, 1240, 1176, 1036, 1020,

dx.doi.org/10.1021/jo501665e | J. Org. Chem. 2014, 79, 10568−10580

854, 822, 811; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.66 (d, J = 8.4 Hz, 2H, ArH), 7.61 (d, J = 8.4 Hz, 2H, ArH), 7.51 (d, J = 8.8 Hz, 2H, ArH), 6.98 (d, J = 8.8 Hz, 2H, ArH), 3.84 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 160.3 (ArC), 145.3 (ArC), 132.7 (2 × ArCH), 131.5 (ArC), 128.5 (2 × ArCH), 127.2 (2 × ArCH), 119.2 (CN), 114.7 (2 × ArCH), 110.2 (ArC), 55.5 (CH_3); m/z (EI) 209 $[M]^{+\cdot}$, 194, 166, 140.

*4-Methoxy-4′-nitrobiphenyl (**3f**).* Following the general procedure C, **3f** was obtained from 4-nitroaniline (138.1 mg, 1.0 mmol) and *p*-bromoanisole (187.0 μL, 280.5 mg, 1.5 mmol) as a yellow solid (46.2 mg, 28%) after column chromatography on silica, eluting with pentane/CH_2Cl_2 (80:20 to 70:30). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[39] mp 102−104 °C; ν_{max} (film)/cm^{-1} 2924, 1600, 1593, 1505, 1480, 1341, 1249, 1184, 1106, 1033, 1015, 838, 828, 815, 756, 722, 696; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 8.23 (d, J = 8.9 Hz, 2H, ArH), 7.66 (d, J = 8.9 Hz, 2H, ArH), 7.55 (d, J = 8.9 Hz, 2H, ArH), 7.00 (d, J = 8.9 Hz, 2H, ArH), 3.85 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 160.6 (ArC), 147.3 (ArC), 146.6 (ArC), 131.1 (ArC), 128.7 (2 × ArCH), 127.2 (2 × ArCH), 124.3 (2 × ArCH), 114.7 (2 × ArCH), 55.6 (CH_3); m/z (EI) 229 $[M]^{+\cdot}$, 199, 183, 168, 156, 139, 128.

*4′-Methoxybiphenyl-3-carboxylic acid (**3g**).* Following the general procedure C, **3g** was obtained from 3-aminobenzoic acid (137.2 mg, 1.0 mmol) and *p*-bromoanisole (187.0 μL, 280.5 mg, 1.5 mmol) as a light yellow solid (83.9 mg, 37%) after column chromatography on silica, eluting with pentane/EtOAc/AcOH (70:28:2). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[40] mp 204−205 °C; ν_{max} (film)/cm^{-1} 2955 (br), 1679, 1606, 1515, 1452, 1439, 1315, 1247, 1184, 1024, 836, 813, 792, 757, 722, 687, 663; ^{1}H NMR (400.0 MHz; MeOD-d_4) δ_H = 8.21 (s, 1H, ArH), 7.95 (d, J = 7.7 Hz, 1H, ArH), 7.80 (d, J = 7.7 Hz, 1H, ArH), 7.58 (dd, J = 8.6, 1.5 Hz, 2H, ArH), 7.51 (td, J = 7.7, 1.9 Hz, 1H, ArH), 7.02 (dd, J = 8.6, 1.5 Hz, 2H, ArH), 3.84 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; MeOD-d_4) δ_C = 170.0 (CO_2H), 161.3 (ArC), 142.6 (ArC), 133.9 (ArC), 132.6 (ArC), 132.1 (ArCH), 130.1 (ArCH), 129.1 (2 × ArCH), 128.9 (ArCH), 128.8 (ArCH), 115.6 (2 × ArCH), 55.0 (CH_3); m/z (ESI) 227 $[M - H]^-$, 195, 177, 97.

*4′-Methoxy-2-methylbiphenyl (**3h**).* Following the general procedure C, **3h** was obtained from *o*-toluidine (107.2 mg, 1.0 mmol) and *p*-bromoanisole (187.0 μL, 280.5 mg, 1.5 mmol) as an orange oil (82.9 mg, 42%) after column chromatography on silica, eluting with pentane/CH_2Cl_2 (90:10 to 80:20). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[41] ν_{max} (film)/cm^{-1} 2933, 2834, 1611, 1514, 1482, 1452, 1293, 1266, 1240, 1175, 1037, 1017, 831, 759, 730; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.31−7.26 (m, 6H, ArH), 6.99 (d, J = 8.8 Hz, 2H, ArH), 3.88 (s, 3H, CH_3), 2.32 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 158.7 (ArC), 142.7 (ArC), 135.6 (ArC), 134.5 (ArC), 130.5 (ArCH), 130.4 (2 × ArCH), 130.1 (ArCH), 127.1 (ArCH), 125.9 (ArCH), 113.1 (2 × ArCH), 55.4 (CH_3), 20.7 (CH_3); m/z (EI) 198 $[M]^{+\cdot}$, 183, 169, 155, 141, 128, 115.

*2-Fluoro-4′-methoxybiphenyl (**3i**).* Following the general procedure C, **3i** was obtained from 2-fluoroaniline (111.2 mg, 1.0 mmol) and *p*-bromoanisole (187.0 μL, 280.5 mg, 1.5 mmol) as a light orange solid (70.0 mg, 34.5%) after column chromatography on silica, eluting with pentane/CH_2Cl_2 (90:10 to 80:20). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[42] mp 45−47 °C; ν_{max} (film)/cm^{-1} 2840, 1607, 1518, 1482, 1448, 1296, 1247, 1208, 1175, 1101, 1028, 1016, 1002, 819, 794, 748; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.52 (dd, J = 8.8, 1.8 Hz, 2H, ArH), 7.43 (dt, J = 7.8, 1.7 Hz, 1H, ArH), 7.29 (m, 1H, ArH), 7.22−7.13 (m, 2H, ArH), 7.01 (dt, J = 8.8, 1.8 Hz, 2H, ArH), 3.86 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 159.9 (d, J = 247.5 Hz, ArC), 159.4 (s, ArC), 130.7 (d, J = 3.6 Hz, ArCH), 130.3 (d, J = 3.1 Hz, 2 × ArCH), 128.9 (d, J = 13.3 ArC), 128.6 (d, J = 8.1 Hz, ArCH), 128.5 (d, J = 3.8 Hz, ArCH), 128.3 (d, J = 0.8 Hz, ArC), 116.2 (d, J = 22.8 Hz, ArCH), 114.1 (s, 2 × ArCH), 55.4 (s, CH_3). ^{19}F NMR (376.4 MHz; $CDCl_3$) δ_F = −118.2 (s); m/z (EI) 202 $[M]^{+\cdot}$, 187, 159, 133.

*4′-Methylbiphenyl-2-carbonitrile (**3j**).* Following the general procedure C, **3j** was obtained from *p*-toluidine (107.2 mg, 1.0 mmol) and 2-bromobenzonitrile (273.0 mg, 1.5 mmol) as a light brown oil (116.6 mg, 60%) after column chromatography on silica, eluting with pentane/CH_2Cl_2 (90:10 to 70:30). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[43] ν_{max} (film)/cm^{-1} 3018, 2921, 2223, 1613, 1596, 1517, 1477, 1442, 1285, 1265, 1186, 1046, 1030, 820, 758, 745, 732; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.74 (dd, J = 7.7, 1.1 Hz, 1H, ArH), 7.61 (td, J = 7.7, 1.1 Hz, 1H, ArH), 7.49 (d, J = 7.7 Hz, 1H, ArH), 7.47 (d, J = 8.2 Hz, 2H, ArH), 7.40 (td, J = 7.7, 1.1 Hz, 1H, ArH), 7.30 (d, J = 8.2 Hz, 2H, ArH), 2.41 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 145.5 (ArC), 138.7 (ArC), 135.4 (ArC), 133.7 (ArCH), 132.8 (ArCH), 130.0 (ArCH), 129.5 (2 × ArCH), 128.7 (2 × ArCH), 127.4 (ArCH), 118.9 (CN), 111.2 (ArC), 21.4 (CH_3); m/z (EI) 193$[M]^{+\cdot}$, 177, 165, 151, 140, 127.

*1-(4′-Methylbiphenyl-4-yl)ethanone (**3k**).* Following the general procedure C, **3k** was obtained from *p*-toluidine (107.2 mg, 1.0 mmol) and *p*-bromoacetophenone (199.1 mg, 1.0 mmol) as a light brown solid (84.2 mg, 40%) after column chromatography on silica, eluting with pentane/CH_2Cl_2 (70:30). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[44] mp 118−120 °C; ν_{max} (film)/cm^{-1} 1675, 1599, 1422, 1397, 1360, 1263, 1199, 958, 805, 636; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 8.00 (d, J = 8.5 Hz, 2H, ArH), 7.65 (d, J = 8.5 Hz, 2H, ArH), 7.52 (d, J = 8.1 Hz, 2H, ArH), 7.26 (d, J = 8.1 Hz, 2H, ArH), 2.61 (s, 3H, CH_3), 2.39 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 197.8 (C═O), 145.8 (ArC), 138.3 (ArC), 137.1 (ArC), 135.7 (ArC), 129.8 (2 × ArCH), 129.0 (2 × ArCH), 127.2 (2 × ArCH), 127.0 (2 × ArCH), 26.7 (CH_3), 21.3 (CH_3); m/z (EI) 210 $[M]^{+\cdot}$, 195, 167, 115.

*4′-Methyl-3-(trifluoromethyl)biphenyl (**3l**).* Following the general procedure C, **3l** was obtained from *p*-toluidine (107.2 mg, 1.0 mmol) and 3-bromobenzotrifluoride (209.2 μL, 337.5 mg, 1.5 mmol) as a colorless oil (54.3 mg, 23%) after column chromatography on silica, eluting with pentane/CH_2Cl_2 (95:5 to 80:20). The ^{1}H, ^{13}C and ^{19}F data were consistent with those reported in the literature:[45] ν_{max} (film)/cm^{-1} 1486, 1438, 1331, 1260, 1162, 1120, 1096, 1073, 1036, 902, 795, 700; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.81 (s, 1H, ArH), 7.74 (d, J = 7.7 Hz, 1H, ArH), 7.57 (d, J = 7.7 Hz, 1H, ArH), 7.53 (t, J = 7.7 Hz, 1H, ArH), 7.49 (d, J = 7.9 Hz, 2H, ArH), 7.27 (d, J = 7.9 Hz, 2H, ArH), 2.40 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 142.1 (s, ArC), 138.2 (s, ArC), 137.1 (s, ArC), 131.4 (q, J = 32.2 Hz, ArC), 130.2 (d, J = 1.2 Hz, ArCH), 129.9 (s, 2 × ArCH), 129.4 (s, ArCH), 127.2 (s, 2 × ArCH), 124.4 (q, J = 272.0 Hz, Cq), 123.9 (q, J = 3.8 Hz, ArCH), 123.8 (q, J = 3.7 Hz, ArCH), 21.3 (s, CH_3). ^{19}F NMR (376.4 MHz; $CDCl_3$) δ_F = −62.6 (s); m/z (EI) 236 $[M]^{+\cdot}$, 217, 201, 183, 167, 153, 139, 126, 115.

*2,4′-Dimethylbiphenyl (**3m**).* Following the general procedure C, **3m** was obtained from *p*-toluidine (107.2 mg, 1.0 mmol) and 2-bromotoluene (180.4 μL, 256.5 mg, 1.5 mmol) as a colorless oil (51.0 mg, 28%) after column chromatography on silica, eluting with pentane/CH_2Cl_2 (90:10 to 80:20). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[46] ν_{max} (film)/cm^{-1} 3020, 1515, 1482, 1452, 1158, 1109, 1007, 821, 755, 727; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.26−7.20 (m, 8H, ArH), 2.40 (s, 3H, CH_3), 2.28 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 142.0 (ArC), 139.2 (ArC), 136.6 (ArC), 135.6 (ArC), 130.5 (ArCH), 130.0 (ArCH), 129.3 (2 × ArCH), 128.9 (2 × ArCH), 127.3 (ArCH), 125.9 (ArCH), 21.4 (CH_3), 20.7 (CH_3); m/z (EI) 182 $[M]^{+\cdot}$, 167, 152, 141, 128, 115.

*6-(4-Methoxyphenyl)chroman-4-one (**3n**).* Following the general procedure C, **3n** was obtained from 6-aminochroman-4-one[4] (146.9 mg, 0.9 mmol) and *p*-bromoanisole (171.0 μL, 252.7 mg, 1.35 mmol) as an orange solid (24.2 mg, 9.5%) after column chromatography on silica, eluting with pentane/EtOAc (70:30): mp 93−95 °C; ν_{max} (film)/cm^{-1} 2925, 1688, 1610, 1487, 1463, 1434, 1300, 1249, 1234, 1214, 1173, 1028, 815, 792; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 8.06 (d, J = 2.4 Hz, 1H, ArH), 7.66 (dd, J = 8.6, 2.4 Hz, 1H, ArH), 7.48 (d, J = 8.8 Hz, 2H, ArH), 7.01 (d, J = 8.6 Hz, 1H, ArH), 6.94 (d, J = 8.8 Hz, 2H, ArH), 4.55 (t, J = 6.5 Hz, 2H, CH_2), 3.82 (s, 3H, CH_3), 2.82 (t, J = 6.5 Hz, 2H, CH_2); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 192.1 (C═O), 161.0 (ArC), 159.3 (ArC), 134.6 (ArCH), 134.4 (ArC),

dx.doi.org/10.1021/jo501665e | J. Org. Chem. 2014, 79, 10568−10580

132.3 (ArC), 127.9 (2 × ArCH), 124.7 (ArCH), 121.5 (ArC), 118.5 (ArCH), 114.4 (2 × ArCH), 67.3 (CH_2), 55.5 (CH_3), 38.0 (CH_2); HRMS (ESI) calcd for $C_{16}H_{15}O_3$ $[M + H]^+$ 255.1021, found 255.1014.

*6-(4-Methoxyphenyl)-2H-chromen-2-one (**3o**).* Following the general procedure C, **3o** was obtained from 6-amino-2*H*-chromen-2-one[4] (161.2 mg, 1.0 mmol) and *p*-bromoanisole (187.0 μL, 280.5 mg, 1.5 mmol) as a light yellow solid (40.2 mg, 16%) after column chromatography on silica, eluting with pentane/EtOAc (70:30 to 50:50). The ^1H and ^{13}C data were consistent with those reported in the literature:[47] mp 154−156 °C; ν_{max} (film)/cm^{-1} 1737, 1604, 1567, 1513, 1480, 1435, 1302, 1244, 1179, 1101, 1023, 894, 813, 615; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.73 (d, *J* = 9.6 Hz, 1H, *H*C═CH), 7.68 (dd, *J* = 8.6, 2.0 Hz, 1H, ArH), 7.59 (d, *J* = 2.0 Hz, 1H, ArH), 7.48 (d, *J* = 8.6 Hz, 2H, ArH), 7.34 (d, *J* = 8.6 Hz, 1H, ArH), 6.97 (d, *J* = 8.6 Hz, 2H, ArH), 6.43 (d, *J* = 9.6 Hz, 1H, HC═C*H*), 3.84 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 160.9 (C═O), 159.7 (ArC), 153.2 (ArC), 143.7 (HC═CH), 137.6 (ArC), 130.5 (ArCH), 128.3 (2 × ArCH), 125.6 (ArCH), 124.6 (ArC), 119.2 (ArC), 117.3 (ArCH), 117.1 (HC═CH), 114.6 (2 × ArCH), 55.5 (CH_3); HRMS (ESI) calcd for $C_{16}H_{13}O_3$ $[M + H]^+$ 253.0865, found 253.0863.

*5-(4-Methoxyphenyl)-1,3,3-trimethylindolin-2-one (**3p**).* Following the general procedure C, **3p** was obtained from 5-amino-1,3,3-trimethylindolin-2-one (**S6**, 190.2 mg, 1.0 mmol) and *p*-bromoanisole (187.0 μL, 280.5 mg, 1.5 mmol) as a white solid (152.2 mg, 54%) after column chromatography on silica, eluting with pentane/EtOAc (80:20 to 75:25): mp 124−126 °C; ν_{max} (film)/cm^{-1} 2963, 1697, 1619, 1491, 1455, 1382, 1351, 1242, 1175, 1127, 1035, 818, 711; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.48 (d, *J* = 8.7 Hz, 2H, ArH), 7.42 (dd, *J* = 8.1, 1.7 Hz, 1H, ArH), 7.38 (d, *J* = 1.7 Hz, 1H, ArH), 6.96 (d, *J* = 8.7 Hz, 2H, ArH), 6.87 (d, *J* = 8.1 Hz, 1H, ArH), 3.82 (s, 3H, CH_3), 3.22 (s, 3H, CH_3), 1.40 (s, 6H, 2 × CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 181.4 (C═O), 159.0 (ArC), 141.6 (ArC), 136.4 (ArC), 135.8 (ArC), 133.8 (ArC), 127.9 (2 × ArCH), 126.1 (ArCH), 120.9 (ArCH), 114.3 (2 × ArCH), 108.3 (ArCH), 55.4 (CH_3), 44.4 (Cq), 26.4 (CH_3), 24.5 (2 × CH_3); HRMS (ESI) calcd for $C_{18}H_{20}NO_2$ $[M + H]^+$ 282.1494, found 282.1482.

*3-(4-Methoxyphenyl)quinoline (**3q**).* Following the general procedure C, **3q** was obtained from 3-aminoquinoline (144.2 mg, 1.0 mmol) and *p*-bromoanisole (187.0 μL, 280.5 mg, 1.5 mmol) as a light brown solid (44.7 mg, 19%) using a modified workup. After the reaction mixture has been cooled to rt, it was extracted with HCl (2 M in water, 3 × 10 mL). The combined aqueous layers were washed with EtOAc (2 × 10 mL), and the pH was adjusted to 8−9 with Na_2CO_3. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated under a vacuum to give the crude product. This was purified by column chromatography on silica, eluting with pentane/EtOAc (60:40 to 20:80). The ^1H and ^{13}C data were consistent with those reported in the literature:[48] mp 73−75 °C; ν_{max} (film)/cm^{-1} 2957, 1606, 1513, 1286, 147, 1177, 1027, 829, 807, 784, 751, 658; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 9.14 (s, 1H, ArH), 8.22 (d, *J* = 1.6 Hz, 1H, ArH), 8.11 (d, *J* = 8.3 Hz, 1H, ArH), 7.83 (d, *J* = 8.3 Hz, 1H, ArH), 7.67 (t, *J* = 8.3 Hz, 1H, ArH), 7.63 (d, *J* = 8.6 Hz, 2H, ArH), 7.53 (t, *J* = 8.3 Hz, 1H, ArH), 7.03 (d, *J* = 8.6 Hz, 2H, ArH), 3.85 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 159.9 (ArC), 149.8 (ArCH), 147.0 (ArC), 136.4 (ArC), 133.6 (ArC), 132.7 (ArCH), 130.4 (ArC), 129.3 (ArCH), 129.2 (ArCH), 128.7 (2 × ArCH), 128.0 (ArCH), 127.2 (ArCH), 114.9 (2 × ArCH), 55.6 (CH_3); *m*/*z* (EI) 235 $[M]^{+\cdot}$, 220, 192, 165.

*3-(4-Methoxyphenyl)pyridine (**3r**).* Following the general procedure C, **3r** was obtained from 3-aminopyridine (94.1 mg, 1.0 mmol) and *p*-bromoanisole (187.0 μL, 280.5 mg, 1.5 mmol) as a light orange solid (40.7 mg, 22%) using a modified workup. After the reaction mixture has been cooled to rt, it was extracted with HCl (2 M in water, 3 × 10 mL). The combined aqueous layers were washed with EtOAc (2 × 10 mL), and the pH was adjusted to 8−9 with Na_2CO_3. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated under a vacuum to give the crude product. This was purified by column chromatography on silica, eluting with pentane/EtOAc (60:40 to 20:80). The ^1H and ^{13}C data were consistent with those reported in the literature:[49] mp 54−57 °C; ν_{max} (film)/cm^{-1} 2934, 1607, 1516, 1471, 1431, 1282, 1247, 1178, 1028, 836, 800, 723, 704; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 8.79 (s, 1H, ArH), 8.52 (d, *J* = 4.7 Hz, 1H, ArH), 7.80 (dt, *J* = 7.8, 1.9 Hz, 1H, ArH), 7.49 (dt, *J* = 8.8, 1.9 Hz, 2H, ArH), 7.30 (dd, *J* = 7.8, 4.7 Hz, 1H, ArH), 6.98 (dd, *J* = 8.8, 1.9 Hz, 2H, ArH), 3.83 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 159.9 (ArC), 148.1 (ArCH), 147.9 (ArCH), 136.4 (ArC), 134.1 (ArCH), 130.3 (ArC), 128.4 (2 × ArCH), 123.7 (ArCH), 114.7 (2 × ArCH), 55.5 (CH_3); *m*/*z* (EI) 185 $[M]^{+\cdot}$, 170, 142, 115.

*4′-Cyanobiphenyl-3-carboxylic acid (**3s**).* Following the general procedure C, **3s** was obtained from 4-aminobenzonitrile (118.2 mg, 1.0 mmol) and 3-bromobenzoic acid (301.5 mg, 1.5 mmol) as a light yellow solid (116.4 mg, 52%) after column chromatography on silica, eluting with pentane/EtOAc/AcOH (70:28:2). The ^1H and ^{13}C data were consistent with those reported in the literature:[50] mp 200−202 °C; ν_{max} (film)/cm^{-1} 2954 (br), 2227, 1697, 1605, 1588, 1446, 1308, 1264, 839, 813, 755, 724, 686; ^1H NMR (400.0 MHz; MeOD-d_4) δ_H = 8.29 (s, 1H, ArH), 8.07 (d, *J* = 7.9 Hz, 1H, ArH), 7.90 (d, *J* = 7.9 Hz, 1H, ArH), 7.84−7.80 (m, 4H, ArH), 7.59 (t, *J* = 7.9 Hz, 1H, ArH), 4.91 (br s, 1H, CO_2H); ^{13}C NMR (100.6 MHz; MeOD-d_4) δ_C = 169.4 (CO_2H), 146.1 (ArC), 140.9 (ArC), 134.1 (2 × ArCH), 133.1 (ArC), 132.7 (ArCH), 130.9 (ArCH), 130.6 (ArCH), 129.5 (ArCH), 129.1 (2 × ArCH), 119.8 (CN), 112.6 (ArC); *m*/*z* (ESI) 222 $[M - H]^-$.

*2-(Biphenyl-4-yl)acetic acid (**3t**).* Following the general procedure C, **3t** was obtained from 4-aminophenylacetic acid (151.2, 1.0 mmol) and bromobenzene (158.0 μL, 235.5 mg, 1.5 mmol) as a white solid (38.3 mg, 18%) after column chromatography on silica, eluting with toluene/EtOAc/AcOH (70:28:2) and preparative TLC on silica, eluting with toluene/EtOAc/AcOH (70:28:2). The ^1H and ^{13}C data were consistent with those reported in the literature:[51] mp 160−162 °C; ν_{max} (film)/cm^{-1} 2927 (br), 1686, 1487, 1411, 1402, 1348, 1253, 1006, 927, 820, 763, 740, 696, 672; ^1H NMR (400.0 MHz; MeOD-d_4) δ_H = 7.62 (m, 4H, ArH), 7.42 (t, *J* = 7.4 Hz, 2H, ArH), 7.37 (d, *J* = 8.0 Hz, 2H, ArH), 7.32 (tt, *J* = 7.4, 7.1 Hz, 1H, ArH), 3.64 (s, 2H, CH_2); ^{13}C NMR (100.6 MHz; MeOD-d_4) δ_C = 176.1 (CO_2H), 142.3 (ArC), 141.2 (ArC), 135.6 (ArC), 131.0 (2 × ArCH), 129.9 (2 × ArCH), 128.4 (ArCH), 128.1 (2 × ArCH), 128.0 (2 × ArCH), 42.1 (CH_2); *m*/*z* (ESI) 423 $[2M - H]^-$, 211 $[M - H]^-$, 197, 167 $[M - CO_2H]^-$, 149, 127.

*4′-Pentylbiphenyl-4-carbonitrile (**3u**).* Following the general procedure C, **3u** was obtained from 4-pentylaniline (163.2 mg, 1.0 mmol) and *p*-bromobenzonitrile (273.0 mg, 1.5 mmol) as a colorless oil (65.8 mg, 26%) after column chromatography on silica, eluting with pentane/Et_2O (15:1) and preparative TLC on silica, eluting with pentane/Et_2O (10:1). The ^1H and ^{13}C data were consistent with those reported in the literature:[52] ν_{max} (film)/cm^{-1} 2955, 2927, 2856, 2225, 1605, 1493, 1005, 809; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.69 (dd, *J* = 6.5, 2.1 Hz, 2H, ArH), 7.65 (dd, *J* = 6.5, 2.1 Hz, 2H, ArH), 7.49 (d, *J* = 8.2 Hz, 2H, ArH), 7.28 (d, *J* = 8.2 Hz, 2H, ArH), 2.64 (t, *J* = 7.7 Hz, 2H, CH_2), 1.64 (quint., *J* = 7.7 Hz, 2H, CH_2), 1.37−1.30 (m, 4H, 2 × CH_2), 0.89 (t, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 145.8 (ArC), 143.9 (ArC), 136.6 (ArC), 132.7 (2 × ArCH), 129.4 (2 × ArCH), 127.6 (2 × ArCH), 127.2 (2 × ArCH), 119.2 (CN), 110.7 (ArC), 35.8 (CH_2), 31.7 (CH_2), 31.2 (CH_2), 22.7 (CH_2), 14.2 (CH_3); *m*/*z* (EI) 249 $[M]^{+\cdot}$, 192.

*3-(3-(Methylsulfonyl)phenyl)pyridine (**3v**). Preparation of 1-Bromo-3-(methylsulfonyl)benzene (**S7**).* A procedure of Rintaro was used.[53] To a solution of 3-bromothioanisole (2.5 g, 12.3 mmol, 1.0 equiv) in trifluoroacetic acid (7.2 mL, 10.7 g, 94.0 mmol, 7.6 equiv) at 0 °C was added H_2O_2 (30% in water, 4.8 mL). After addition, the reaction mixture was stirred at 0 °C for 15 min and then allowed to warm to room temperature and stirred for 2 h. Sodium hydroxide (5 M in water) was added to the reaction mixture until pH ≈ 12, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water (2 × 10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated under a vacuum to give the crude product. This was recrystallized from an acetone/cyclohexane mixture to give the title product **S7** as a colorless solid

dx.doi.org/10.1021/jo501665e | J. Org. Chem. 2014, 79, 10568−10580

(2.1 g, 73%). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[54] mp 102−104 °C; ν_{max} (film)/cm^{-1} 1570, 1468, 1414, 1403, 1307, 1293, 1147, 1097, 1086, 1067, 964, 953, 888, 801, 774, 736, 676, 650; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 8.04 (t, J = 1.7 Hz, 1H, ArH), 7.84 (ddd, J = 7.8, 1.7, 1.7 Hz, 1H, ArH), 7.74 (ddd, J = 7.8, 1.7, 1.7 Hz, 1H, ArH), 7.42 (t, J = 7.8 Hz, 1H, ArH), 3.03 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 142.4 (ArC), 136.9 (ArCH), 131.1 (ArCH), 130.5 (ArCH), 126.1 (ArCH), 123.4 (ArC), 44.6 (CH_3); m/z (EI) 236 [M]$^{+\cdot}$, 234 [M]$^{+\cdot}$, 221, 219, 174, 172, 157, 155, 145, 143.

Following the general procedure C, **3v** was obtained from 3-aminopyridine (94.1 mg, 1.0 mmol) and 1-bromo-3-(methylsulfonyl)-benzene (**S7**, 352.6 mg, 1.5 mmol) as a light brown oil (104.8 mg, 44.5%) after column chromatography on silica, eluting with CH_2Cl_2/MeOH/NEt_3 (95:4:1). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[55] ν_{max} (film)/cm^{-1} 3366 (br), 1466, 1429, 1394, 1298, 1143, 1096, 1017, 958, 791, 754, 709, 689; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 8.81 (s, 1H, ArH), 8.60 (d, J = 4.5 Hz, 1H, ArH), 8.09 (t, J = 1.7 Hz, 1H, ArH), 7.92 (dt, J = 7.8, 1.6 Hz, 1H, ArH), 7.87 (dt, J = 7.8, 1.6 Hz, 1H, ArH), 7.82 (dt, J = 7.8, 1.4, 1H, ArH), 7.64 (t, J = 7.8 Hz, 1H, ArH), 7.37 (dd, J = 7.8, 4.5 Hz, 1H, ArH), 3.06 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 149.6 (ArCH), 148.2 (ArCH), 141.7 (ArC), 139.4 (ArC), 134.7 (ArC), 134.6 (ArCH), 132.3 (ArCH), 130.4 (ArCH), 126.9 (ArCH), 125.9 (ArCH), 123.9 (ArCH), 44.6 (CH_3); m/z (EI) 233 [M]$^{+\cdot}$, 218, 171, 154, 142, 127.

*4′-Methoxybiphenyl-4-amine (**5**).* To a solution of *p*-nitroaniline (138.1 mg, 1.0 mmol, 1.0 equiv) in HCl (2.1 M in water, 1.2 mL, 2.5 mmol, 2.5 equiv) at 0 °C was added a solution of $NaNO_2$ (2.4 M in water, 0.5 mL, 1.2 mmol, 1.2 equiv) dropwise, and the reaction mixture was stirred for 15 min at 0 °C. Tetrahydroxydiboron (179.3 mg, 2.0 mmol, 2.0 equiv) and water (2.0 mL) were added, followed by a solution of K_2CO_3 (138.2 mg, 1.0 mmol, 1.0 equiv) in water (1.0 mL) slowly introduced directly inside the reaction mixture using a syringe. After addition, the mixture was warmed to room temperature and stirred for 20 min. *p*-Bromoanisole (187.0 μL, 280.5 mg, 1.5 mmol, 1.5 equiv) and dioxane (2.5 mL) were added and argon was bubbled into the reaction mixture for 10 min. K_2CO_3 (345.5 mg, 2.5 mmol, 2.5 equiv), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol %) and SPhos (41.0 mg, 0.1 mmol, 10 mol %) were added to the reaction mixture which was sealed and vigorously stirred at 100 °C in a preheated oil bath for 1 h. After being cooled to rt, the reaction mixture was flushed with hydrogen for 10 min before being vigorously stirred under an atmosphere of hydrogen overnight at rt. The reaction mixture was flushed with argon and was filtered over Celite which was washed with EtOAc (50 mL). The combined filtrates were washed with water (5 mL), brine (5 mL), dried over $MgSO_4$, filtered and concentrated under a vacuum to give the crude product. This was purified by column chromatography on silica, eluting with pentane/EtOAc (80:20 to 70:30) to give the title product **5** as a light brown solid (90.4 mg, 45.5%). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[56] mp 145−147 °C; ν_{max} (film)/cm^{-1} 3350, 1632, 1606, 1498, 1270, 1242, 1181, 1036, 815; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.46 (d, J = 8.7 Hz, 2H, ArH), 7.36 (d, J = 8.3 Hz, 2H, ArH), 6.95 (d, J = 8.7 Hz, 2H, ArH), 6.73 (d, J = 8.3 Hz, 2H, ArH), 3.83 (s, 3H, CH_3), 3.69 (br s, 2H, NH_2); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 158.5 (ArC), 145.5 (ArC), 134.0 (ArC), 131.5 (ArC), 127.8 (2 × ArCH), 127.5 (2 × ArCH), 115.6 (2 × ArCH), 114.3 (2 × ArCH), 55.5 (CH_3); m/z (EI) 199 [M]$^{+\cdot}$, 184, 171, 156, 139, 128.

*4′-(Aminomethyl)-N,N-dimethylbiphenyl-4-amine (**6**). Preparation of Benzyl 4-aminobenzylcarbamate (**S8**).* A modified procedure of Lee was used.[57] To a solution of 4-aminobenzylamine (2.1 g, 17.6 mmol, 1.0 equiv) in CH_2Cl_2 (30 mL) at room temperature was added benzyl chloroformate (2.2 mL, 2.7 g, 15.8 mmol, 0.9 equiv) followed by triethylamine (2.2 mL, 1.6 g, 15.8 mmol, 0.9 equiv), and the reaction mixture was stirred at room temperature for 15 min. Volatiles were removed under a vacuum, water (20 mL) and EtOAc (20 mL) were added to the mixture. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with $NaHCO_3$ sat. (10 mL), dried over $MgSO_4$, filtered and concentrated under a vacuum to give the crude product. This was purified by column chromatography on silica, eluting with $CHCl_3$/MeOH (25:1) to give the title product **S8** as a light yellow solid (1.6 g, 35.5%). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[58] mp 69−71 °C; ν_{max} (film)/cm^{-1} 3431, 3350 (br), 1681, 1625, 1612, 1531, 1516, 1454, 1270, 1252, 1210, 1124, 1039, 967, 841, 823, 750, 697; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.35−7.29 (m, 5H, ArH), 7.05 (d, J = 7.9 Hz, 2H, ArH), 6.60 (d, J = 7.9 Hz, 2H, ArH), 5.11 (br s, 3H, 1 × CH_2, 1 × NH), 4.23 (d, J = 5.7 Hz, 2H, CH_2), 3.63 (br s, 2H, NH_2); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 156.4 (C═O), 145.9 (ArC), 136.7 (ArC), 129.0 (2 × ArCH), 128.6 (2 × ArCH), 128.3 (ArC), 128.2 (3 × ArCH), 115.3 (2 × ArCH), 66.8 (CH_2), 44.9 (CH_2); m/z (EI) 279.2 [M + Na]$^+$, 257.2 [M + H]$^+$, 196.2, 184.3.

To a solution of benzyl 4-aminobenzylcarbamate (**S8**, 256.3 mg, 1.0 mmol, 1.0 equiv) in HCl (2.1 M in water, 1.2 mL, 2.5 mmol, 2.5 equiv) at 0 °C was added a solution of $NaNO_2$ (2.4 M in water, 0.5 mL, 1.2 mmol, 1.2 equiv) dropwise, and the reaction mixture was stirred for 15 min at 0 °C. Tetrahydroxydiboron (179.3 mg, 2.0 mmol, 2.0 equiv) and water (2.0 mL) were added, followed by a solution of K_2CO_3 (138.2 mg, 1.0 mmol, 1.0 equiv) in water (1.0 mL) slowly introduced directly inside the reaction mixture using a syringe. After addition, the mixture was warmed to room temperature and stirred for 20 min. 4-Bromo-*N*,*N*-dimethylaniline (300.1 mg, 1.5 mmol) and dioxane (2.5 mL) were added and argon was bubbled into the reaction mixture for 10 min. K_2CO_3 (345.5 mg, 2.5 mmol, 2.5 equiv), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol %) and SPhos (41.0 mg, 0.1 mmol, 10 mol %) were added to the reaction mixture which was sealed and vigorously stirred at 100 °C in a preheated oil bath for 1 h. After being cooled to rt, Pd/C (10%, 50% wet, 50.0 mg), MeOH (5.0 mL) and AcOH (0.2 mL) were added to the reaction mixture which was flushed with hydrogen for 10 min before being vigorously stirred under an atmosphere of hydrogen overnight at rt. The reaction mixture was flushed with argon, NEt_3 (1.0 mL) was added, and the mixture was filtered over Celite which was washed with MeOH (50 mL). The combined filtrates were concentrated under a vacuum to give the crude product. This was purified by column chromatography on silica (dry loading onto silica), eluting with CH_2Cl_2/MeOH (95:5 to 90:10) followed by preparative TLC on silica, eluting with CH_2Cl_2/MeOH (85:15) to give the product. This was finally purified by trituration in hot $CHCl_3$/MeOH (10:1) to give the title product **6** as a light brown solid (31.0 mg, 13.5%): mp 243−245 °C; ν_{max} (film)/cm^{-1} 3416 (br), 2893 (br), 1607, 1504, 1360, 1204, 806; ^{1}H NMR (400.0 MHz; MeOD-d_4) δ_H = 7.64 (d, J = 8.0 Hz, 2H, ArH), 7.52 (d, J = 8.5 Hz, 2H, ArH), 7.47 (d, J = 8.0 Hz, 2H, ArH), 6.84 (d, J = 8.5 Hz, 2H, ArH), 4.12 (s, 2H, CH_2), 2.97 (s, 6H, 2 × CH_3); ^{13}C NMR (100.6 MHz; MeOD-d_4) δ_C = 152.1 (ArC), 143.6 (ArC), 131.8 (ArC), 130.6 (2 × ArCH), 129.4 (ArC), 128.6 (2 × ArCH), 127.7 (2 × ArCH), 114.3 (2 × ArCH), 44.3 (CH_2), 40.9 (2 × CH_3); HRMS (ESI) calcd for $C_{15}H_{19}N_2$ [M + H]$^+$ 227.1548, found 227.1544.

The corresponding Cbz-protected benzyl amine benzyl (4′-(dimethylamino)biphenyl-4-yl)methylcarbamate (**S9**) was obtained following the general procedure C, from benzyl 4-aminobenzylcarbamate (**S8**, 256.3, 1.0 mmol) and 4-bromo-*N*,*N*-dimethylaniline (300.1 mg, 1.5 mmol) as a light yellow solid (59.5 mg, 17%) after column chromatography on silica, eluting with pentane/EtOAc (70:30): mp 102−104 °C; ν_{max} (film)/cm^{-1} 3320, 1691, 1607, 1538, 1504, 1357, 1253, 1229, 1143, 1048, 803, 732, 672; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.51 (d, J = 8.2 Hz, 2H, ArH), 7.48 (d, J = 8.9 Hz, 2H, ArH), 7.37−7.29 (m, 7H, ArH), 6.80 (d, J = 8.9 Hz, 2H, ArH), 5.14 (s, 2H, CH_2), 5.11 (br s, 1H, NH), 4.39 (d, J = 6.0 Hz, 2H, CH_2), 2.98 (s, 6H, 2 × CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 156.6 (C═O), 150.1 (ArC), 140.7 (ArC), 136.7 (ArC), 136.2 (ArC), 128.9 (ArC), 128.7 (2 × ArCH), 128.3 (2 × ArCH), 128.2 (2 × ArCH), 127.8 (3 × ArCH), 126.6 (2 × ArCH), 112.9 (2 × ArCH), 67.0 (CH_2), 45.1 (CH_2), 40.7 (2 × CH_3); HRMS (ESI) calcd for $C_{23}H_{25}N_2O_2$ [M + H]$^+$ 361.1916, found 361.1920.

*4′-(Aminomethyl)biphenyl-2-carbonitrile (**7**).* To a solution of benzyl 4-aminobenzylcarbamate (**S8**, 256.3 mg, 1.0 mmol, 1.0 equiv)

dx.doi.org/10.1021/jo501665e | J. Org. Chem. 2014, 79, 10568−10580

in HCl (2.1 M in water, 1.2 mL, 2.5 mmol, 2.5 equiv) at 0 °C was added a solution of $NaNO_2$ (2.4 M in water, 0.5 mL, 1.2 mmol, 1.2 equiv) dropwise, and the reaction mixture was stirred for 15 min at 0 °C. Tetrahydroxydiboron (179.3 mg, 2.0 mmol, 2.0 equiv) and water (2.0 mL) were added, followed by a solution of K_2CO_3 (138.2 mg, 1.0 mmol, 1.0 equiv) in water (1.0 mL) slowly introduced directly inside the reaction mixture using a syringe. After addition, the mixture was warmed to room temperature and stirred for 20 min. 2-Bromobenzonitrile (273.0 mg, 1.5 mmol, 1.5 equiv) and dioxane (2.5 mL) were added and argon was bubbled into the reaction mixture for 10 min. K_2CO_3 (345.5 mg, 2.5 mmol, 2.5 equiv), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol %) and SPhos (41.0 mg, 0.1 mmol, 10 mol %) were added to the reaction mixture which was sealed and vigorously stirred at 100 °C in a preheated oil bath for 1 h. After being cooled to rt, Pd/C (10%, 50% wet, 50.0 mg) and MeOH (5.0 mL) were added to the reaction mixture which was flushed with hydrogen for 10 min before being vigorously stirred under an atmosphere of hydrogen overnight at rt. The reaction mixture was flushed with argon and was filtered over Celite which was washed with EtOAc (50 mL). The combined filtrates were washed with water (5 mL), brine (5 mL), dried over $MgSO_4$, filtered and concentrated under a vacuum to give the crude product. This was purified by column chromatography on silica, eluting with CH_2Cl_2/MeOH (95:5) to give the title product **7** as a light yellow solid (31.1 mg, 15%). The ^1H data were consistent with those reported in the literature:[59] mp 104−106 °C; ν_{max} (film)/cm^{-1} 3323, 2918 (br), 2850 (br), 2220, 1639, 1586, 1477, 1463, 1370, 1327, 760; ^1H NMR (400.0 MHz; MeOD-d_4) δ_H = 7.81 (d, J = 7.7 Hz, 1H, ArH), 7.72 (dt, J = 7.7, 1.2 Hz, 1H, ArH), 7.58−7.52 (m, 3H, ArH), 7.52−7.47 (m, 3H, ArH), 3.90 (s, 2H, CH_2); ^{13}C NMR (100.6 MHz; MeOD-d_4) δ_C = 146.6 (ArC), 143.4 (ArC), 138.7 (ArC), 134.9 (ArCH), 134.5 (ArCH), 131.4 (ArCH), 130.2 (2 × ArCH), 129.2 (ArCH), 129.1 (2 × ArCH), 119.7 (CN), 112.2 (ArC), 46.2 (CH_2); m/z (EI) 208 $[M]^{+\cdot}$, 191, 180, 166, 152, 106.

The corresponding Cbz-protected benzyl amine benzyl (2′-cyanobiphenyl-4-yl)methylcarbamate (**S10**) was obtained following the general procedure C, from benzyl 4-aminobenzylcarbamate (**S8**, 256.3, 1.0 mmol) and 2-bromobenzonitrile (273.0 mg, 1.5 mmol) as a light orange solid (65.5 mg, 19%) after column chromatography on silica, eluting with pentane/EtOAc (70:30): mp 118−120 °C; ν_{max} (film)/cm^{-1} 3326 (br), 2226, 1688, 1542, 1291, 1258, 1138, 1049, 978, 765, 755, 689; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 7.74 (d, J = 7.8 Hz, 1H, ArH), 7.62 (td, J = 7.8, 0.9 Hz, 1H, ArH), 7.51−7.48 (m, 3H, ArH), 7.43 (dd, J = 7.8, 0.9 Hz, 1H, ArH), 7.40−7.30 (m, 7H, ArH), 5.26 (br s, 1H, NH), 5.14 (s, 2H, CH_2), 4.43 (d, J = 5.9 Hz, 2H, CH_2); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 156.6 (C═O), 145.2 (ArC), 139.3 (ArC), 137.4 (ArC), 136.6 (ArC), 133.9 (ArCH), 133.0 (ArCH), 130.1 (2 × ArCH), 129.2 (3 × ArCH), 128.7 (2 × ArCH), 128.3 (2 × ArCH), 127.9 (ArCH), 127.7 (ArCH), 118.7 (CN), 111.3 (ArC), 67.0 (CH_2), 44.8 (CH_2); HRMS (ESI) calcd for $C_{22}H_{18}N_2O_2Na$ $[M + Na]^+$ 365.1266, found 365.1269.

General Procedure D for Aminodiarylmethane Compounds Synthesis. To a solution of aniline (1.0 mmol, 1.0 equiv) in HCl (2.1 M in water, 1.2 mL, 2.5 mmol, 2.5 equiv) at 0 °C was added a solution of $NaNO_2$ (2.4 M in water, 0.5 mL, 1.2 mmol, 1.2 equiv) dropwise, and the reaction mixture was stirred for 15 min at 0 °C. Tetrahydroxydiboron (179.3 mg, 2.0 mmol, 2.0 equiv) and water (2.0 mL) were added, followed by a solution of K_2CO_3 (138.2 mg, 1.0 mmol, 1.0 equiv) in water (1.0 mL) slowly introduced directly inside the reaction mixture using a syringue. After addition, the mixture was warmed to room temperature and stirred for 20 min. An amine (2.0 mmol, 2.0 equiv) and salicylaldehyde (213.0 μL, 244.2 mg, 2.0 mmol, 2.0 equiv) were added to the reaction mixture which was stirred for 14 h at 80 °C in a preheated oil bath. The reaction mixture was cooled to room temperature and was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (5 mL), brine (5 mL), dried over $MgSO_4$, filtered and concentrated under a vacuum to give the crude product. This was purified by column chromatography on silica to give the title compounds.

*2-(Morpholino(phenyl)methyl)phenol (**13a**).* Following the general procedure D, **13a** was obtained from aniline (93.1 mg, 1.0 mmol), morpholine (175.0 μL, 174.2 mg, 2.0 mmol) and salicylaldehyde (213.0 μL, 244.2 mg, 2.0 mmol) as a light orange solid (102.0 mg, 38%) after column chromatography on silica, eluting with pentane/EtOAc (90:10 to 80:20). The ^1H and ^{13}C data were consistent with those reported in the literature:[60] mp 114−116 °C; ν_{max} (film)/cm^{-1} 2916 (br), 2852, 2826, 1582, 1486, 1474, 1451, 1398, 1275, 1248, 1114, 999, 936, 874, 804, 759, 747; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 11.72 (br s, 1H, OH), 7.41 (d, J = 6.7 Hz, 2H, ArH), 7.32−7.21 (m, 3H, ArH), 7.11 (t, J = 7.8 Hz, 1H, ArH), 6.93 (d, J = 7.8 Hz, 1H, ArH), 6.86 (d, J = 7.8 Hz, 1H, ArH), 6.71 (t, J = 7.8 Hz, 1H, ArH), 4.39 (s, 1H, CH), 3.80−3.65 (m, 4H, 2 × CH_2), 2.58 (br s, 2H, CH_2), 2.42 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 156.2 (ArC), 139.4 (ArC), 129.5 (ArCH), 129.1 (2 × ArCH), 128.8 (ArCH), 128.6 (2 × ArCH), 128.2 (ArCH), 124.9 (ArC), 119.7 (ArCH), 117.2 (ArCH), 76.9 (CH), 67.0 (2 × CH_2), 52.3 (2 × CH_2); m/z (ESI) 355, 270 $[M + H]^+$, 259, 183.

*2-(Morpholino(p-tolyl)methyl)phenol (**13b**).* Following the general procedure D, **13b** was obtained from *p*-toluidine (107.2 mg, 1.0 mmol), morpholine (175.0 μL, 174.2 mg, 2.0 mmol) and salicylaldehyde (213.0 μL, 244.2 mg, 2.0 mmol) as a light red solid (143.7 mg, 50.5%) after column chromatography on silica, eluting with pentane/EtOAc (90:10 to 80:20). The ^1H and ^{13}C data were consistent with those reported in the literature:[61] mp 110−111 °C; ν_{max} (film)/cm^{-1} 2837 (br), 1606, 1587, 1476, 1450, 1303, 1273, 1257, 1114, 995, 836, 751; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 11.77 (br s, 1H, OH), 7.31 (d, J = 7.5 Hz, 2H, ArH), 7.15−7.09 (m, 3H, ArH), 6.94 (d, J = 7.7 Hz, 1H, ArH), 6.87 (d, J = 7.7 Hz, 1H, ArH), 6.72 (t, J = 7.7 Hz, 1H, ArH), 4.38 (s, 1H, CH), 3.80−3.68 (m, 4H, 2 × CH_2), 2.58 (br s, 2H, CH_2), 2.44 (m, 2H, CH_2), 2.29 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 156.2 (ArC), 137.9 (ArC), 136.4 (ArC), 129.7 (2 × ArCH), 129.5 (ArCH), 128.7 (ArCH), 128.5 (2 × ArCH), 125.1 (ArC), 119.7 (ArCH), 117.1 (ArCH), 76.0 (CH), 67.0 (2 × CH_2), 52.3 (2 × CH_2), 21.2 (CH_3); m/z (ESI) 284 $[M + H]^+$, 197.

*2-((4-Methoxyphenyl)(morpholino)methyl)phenol (**13c**).* Following the general procedure D, **13c** was obtained from *p*-anisidine (151.9 mg, 1.0 mmol), morpholine (175.0 μL, 174.2 mg, 2.0 mmol) and salicylaldehyde (213.0 μL, 244.2 mg, 2.0 mmol) as a light orange solid (153.3 mg, 51%) after column chromatography on silica, eluting with pentane/EtOAc (80:20). The ^1H and ^{13}C data were consistent with those reported in the literature:[16c] mp 100−102 °C; ν_{max} (film)/cm^{-1} 2955 (br), 2842, 1584, 1475, 1253, 1114, 1027, 992, 872, 863, 840, 755; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 11.75 (br s, 1H, OH), 7.32 (d, J = 8.3 Hz, 2H, ArH), 7.10 (dt, J = 7.6, 1.5 Hz, 1H, ArH), 6.91 (dd, J = 7.6, 1.5 Hz, 1H, ArH), 6.87−6.79 (m, 3H, ArH), 6.71 (dt, J = 7.6, 1.5 Hz, 1H, ArH), 4.36 (s, 1H, CH), 3.77−3.67 (m, 7H, 2 × CH_2, 1 × CH_3), 2.55 (br s, 2H, CH_2), 2.43 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 159.4 (ArC), 156.2 (ArC), 131.4 (ArC), 129.9 (2 × ArCH), 129.5 (ArCH), 128.7 (ArCH), 125.2 (ArC), 119.7 (ArCH), 117.1 (2 × ArCH), 114.3 (ArCH), 76.2 (CH), 67.1 (2 × CH_2), 55.4 (CH_3), 53.1 (2 × CH_2); m/z (ESI) 300.1 $[M + H]^+$, 213.1.

*2-((4-(Dimethylamino)phenyl)(morpholino)methyl)phenol (**13d**).* Following the general procedure D, **13d** was obtained from *N*,*N*-dimethyl-*p*-phenylenediamine (136.2 mg, 1.0 mmol), morpholine (175.0 μL, 174.2 mg, 2.0 mmol) and salicylaldehyde (213.0 μL, 244.2 mg, 2.0 mmol) as a light yellow solid (87.6 mg, 28%) after column chromatography on silica, eluting with pentane/EtOAc (90:10 to 80:20) and preparative TLC on silica, eluting with pentane/EtOAc (70:30): mp 135−137 °C; ν_{max} (film)/cm^{-1} 2884, 2820 (br), 1613, 1524, 1477, 1360, 1252, 1115, 1093, 996, 934, 874, 806, 761; ^1H NMR (400.0 MHz; $CDCl_3$) δ_H = 11.90 (br s, 1H, OH), 7.24 (d, J = 7.7 Hz, 2H, ArH), 7.09 (td, J = 7.5, 1.3 Hz, 1H, ArH), 6.93 (d, J = 7.5 Hz, 1H, ArH), 6.84 (dd, J = 7.5, 1.3 Hz, 1H, ArH), 6.70 (td, J = 7.5, 1.3 Hz, 1H, ArH), 6.63 (d, J = 7.7 Hz, 2H, ArH), 4.34 (s, 1H, CH), 3.80−3.68 (m, 4H, 2 × CH_2), 2.89 (s, 6H, 2 × CH_3), 2.59 (br s, 2H, CH_2), 2.42 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 156.3 (ArC), 150.4 (ArC), 129.7 (2 × ArCH), 129.6 (ArCH), 128.5 (ArCH), 126.7 (ArC), 125.6 (ArC), 119.7 (ArCH), 117.0 (ArCH), 112.6 (2 × ArCH), 76.2 (CH), 67.1 (2 × CH_2), 52.2 (2 × CH_2), 40.6 (2 × CH_3);

dx.doi.org/10.1021/jo501665e | J. Org. Chem. 2014, 79, 10568−10580

HRMS (ESI) calcd for $C_{19}H_{23}N_2O_2$ $[M - H]^-$311.1760, found 311.1764.

*2-((4-Bromophenyl)(morpholino)methyl)phenol (**13e**).* Following the general procedure D, **13e** was obtained from 4-bromoaniline (172.0 mg, 1.0 mmol), morpholine (175.0 μL, 174.2 mg, 2.0 mmol) and salicylaldehyde (213.0 μL, 244.2 mg, 2.0 mmol) as an orange oil (84.1 mg, 19%) after column chromatography on silica, eluting with pentane/EtOAc (90:10 to 80:20). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[61] ν_{max} (film)/cm^{-1} 2961, 2850 (br), 1609, 1584, 1486, 1474, 1452, 1397, 1268, 1248, 1116, 875; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 11.53 (br s, 1H, OH), 7.41 (d, J = 8.5 Hz, 2H, ArH), 7.30 (d, J = 8.5 Hz, 2H, ArH), 7.12 (t, J = 7.7 Hz, 1H, ArH), 6.90 (d, J = 7.7 Hz, 1H, ArH), 6.85 (d, 7.7 Hz, 1H, ArH), 6.72 (t, J = 7.7 Hz, 1H, ArH), 4.35 (s, 1H, CH), 3.78−3.68 (m, 4H, 2 × CH_2), 2.57 (br s, 2H, CH_2), 2.42 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 156.0 (ArC), 138.5 (ArC), 132.3 (2 × ArCH), 130.3 (2 × ArCH), 129.4 (ArCH), 19.1 (ArCH), 124.4 (ArC), 122.3 (ArC), 119.9 (ArCH), 117.4 (ArCH), 76.3 (CH), 66.9 (2 × CH_2), 52.4 (2 × CH_2); m/z (ESI) 350 $[M + H]^+$, 348 $[M + H]^+$, 263, 261.

*2-(Benzo[d][1,3]dioxol-5-yl(morpholino)methyl)phenol (**13f**).* Following the general procedure D, **13f** was obtained from 3,4-(methylenedioxy)aniline (137.1 mg, 1.0 mmol), morpholine (175.0 μL, 174.2 mg, 2.0 mmol) and salicylaldehyde (213.0 μL, 244.2 mg, 2.0 mmol) as a light red solid (143.5 mg, 45.5%) after column chromatography on silica, eluting with pentane/EtOAc (90:10 to 80:20): mp 113−115 °C; ν_{max} (film)/cm^{-1} 2952 (br), 2879, 1606, 1584, 1485, 1440, 1252, 1237, 1118, 1035, 999, 930, 875, 816, 755; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 11.69 (br s, 1H, OH), 7.10 (t, J = 7.6 Hz, 1H, ArH), 6.97 (s, 1H, ArH), 6.92 (d, J = 7.6 Hz, 1H, ArH), 6.87−6.80 (m, 2H, ArH), 6.71 (m, 2H, ArH), 5.89 (dd, J = 10.4, 0.9 Hz, 2H, CH_2), 4.30 (s, 1H, CH), 3.80−3.67 (m, 4H, 2 × CH_2), 2.56 (br s, 2H, CH_2), 2.45−2.42 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 156.1 (ArC), 148.3 (ArC), 147.6 (ArC), 133.4 (ArC), 129.4 (ArC), 128.2 (ArCH), 125.0 (ArCH), 122.3 (ArCH), 119.8 (ArCH), 117.2 (ArCH), 108.4 (2 × ArCH), 101.3 (CH_2), 76.7 (CH), 67.0 (2 × CH_2), 52.3 (2 × CH_2); HRMS (ESI) calcd for $C_{18}H_{20}NO_4$ $[M + H]^+$ 314.1392, found 314.1399.

*2-((4-Benzylpiperazin-1-yl)(4-methoxyphenyl)methyl)phenol (**13g**).* Following the general procedure D, **13g** was obtained from *p*-anisidine (151.9 mg, 1.0 mmol), 1-benzylpiperazine (347.5 μL, 352.2 mg, 2.0 mmol) and salicylaldehyde (213.0 μL, 244.2 mg, 2.0 mmol) as an orange oil (165.6 mg, 44.5%) after column chromatography on silica, eluting with pentane/EtOAc (90:10 to 80:20) and preparative TLC on silica eluting with pentane/EtOAc (70:30): ν_{max} (film)/cm^{-1} 2813 (br), 1607, 1584, 1510, 1454, 1247, 1178, 1132, 1033, 996, 857, 826, 752, 734, 697; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 12.17 (br s, 1H, OH), 7.36−7.25 (m, 7H, ArH), 7.12 (t, J = 7.8 Hz, 1H, ArH), 6.92 (d, J = 7.8 Hz, 1H, ArH), 6.88 (d, J = 7.8 Hz, 1H, ArH), 6.83 (d, J = 8.9 Hz, 2H, ArH), 6.71 (t, J = 7.8 Hz, 1H, ArH), 4.42 (s, 1H, CH), 3.75 (s, 3H, CH_3), 3.51 (d, J = 2.1 Hz, 2H, CH_2), 2.49 (br s, 8H, 4 × CH_2); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 159.3 (ArC), 156.7 (ArC), 137.9 (ArC), 131.5 (ArC), 129.9 (2 × ArCH), 129.3 (ArCH), 129.2 (2 × ArCH), 128.5 (ArCH), 128.4 (2 × ArCH), 127.3 (ArCH), 125.6 (ArC), 119.4 (ArCH), 117.0 (ArCH), 114.2 (2 × ArCH), 75.4 (CH), 62.8 (CH_2), 55.3 (CH_3), 53.2 (4 × CH_2); HRMS (ESI) calcd for $C_{25}H_{29}N_2O_2$ $[M + H]^+$ 389.2229, found 389.2221.

*2-((4-Methoxyphenyl)(pyrrolidin-1-yl)methyl)phenol (**13h**).* Following the general procedure D, **13h** was obtained from *p*-anisidine (151.9 mg, 1.0 mmol), pyrrolidine (167.0 μL, 142.3 mg, 2.0 mmol) and salicylaldehyde (213.0 μL, 244.2 mg, 2.0 mmol) as a light orange solid (129.5 mg, 45.5%) after column chromatography on silica, eluting with pentane/EtOAc (90:10 to 80:20). The ^{1}H and ^{13}C data were consistent with those reported in the literature:[62] mp 99−100 °C; ν_{max} (film)/cm^{-1} 2930 (br), 2834, 1607, 1583, 1510, 1463, 1250, 1178, 1033, 835, 760; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 11.90 (br s, 1H, OH), 7.39 (d, J = 8.7 Hz, 2H, ArH), 7.11 (t, J = 7.5 Hz, 1H, ArH), 6.95 (d, J = 7.5 Hz, 1H, ArH), 6.87 (d, J = 7.5 Hz, 1H, ArH), 6.81 (d, J = 8.7 Hz, 2H, ArH), 6.71 (t, J = 7.5 Hz, 1H, ArH), 4.36 (s, 1H, CH), 3.74 (s, 3H, CH_3), 2.64 (br s, 2H, CH_2), 2.47 (br s, 2H, CH_2), 1.82 (m, 4H, 2 × CH_2); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 159.1 (ArC), 156.7 (ArC), 134.5 (ArC), 129.1 (2 × ArCH), 128.4 (ArCH), 128.3 (ArCH), 127.0 (ArC), 119.2 (ArCH), 116.9 (ArCH), 114.0 (2 × ArCH), 74.9 (CH), 55.3 (CH_3), 53.1 (2 × CH_2), 23.6 (2 × CH_2); HRMS (ESI) calcd for $C_{18}H_{22}NO_2$ $[M + H]^+$ 284.1651, found 284.1664.

*2-((Diallylamino)(4-methoxyphenyl)methyl)phenol (**13i**).* Following the general procedure D, **13i** was obtained from *p*-anisidine (151.9 mg, 1.0 mmol), diallylamine (246.2 μL, 194.3 mg, 2.0 mmol) and salicylaldehyde (213.0 μL, 244.2 mg, 2.0 mmol) as a yellow oil (113.9 mg, 36%) after column chromatography on silica, eluting with pentane/EtOAc (100:10 to 90:10): ν_{max} (film)/cm^{-1} 2932 (br), 2836, 1608, 1583, 1511, 1465, 1248, 1179, 1033, 923, 830, 751; ^{1}H NMR (400.0 MHz; $CDCl_3$) δ_H = 12.24 (br s, 1H, OH), 7.33 (d, J = 8.6 Hz, 2H, ArH), 7.12 (t, J = 7.6 Hz, 1H, ArH), 6.90−6.85 (m, 3H, ArH), 6.82 (d, J = 7.6 Hz, 1H, ArH), 6.68 (t, J = 7.6 Hz, 1H, ArH), 5.90 (m, 2H, 2 × C*H*═CHH), 5.23 (d, J = 10.1 Hz, 2H, 2 × CH═C*H*H), 5.15 (d, J = 17.2 Hz, 2H, 2 × CH═CH*H*), 5.04 (s, 1H, CH), 3.79 (s, 3H, CH_3), 3.37 (dd, J = 14.0, 5.8 Hz, 2H, 2 × C*H*H), 3.01 (dd, J = 14.0, 7.5 Hz, 2H, 2 × CH*H*); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ_C = 159.4 (ArC), 157.7 (ArC), 133.7 (2 × CH═CH_2), 130.9 (ArC), 129.5 (2 × ArCH), 129.4 (ArCH), 128.6 (ArCH), 125.2 (ArC), 119.6 (2 × CH═CH_2), 119.0 (ArCH), 116.9 (ArCH), 114.0 (2 × ArCH), 69.1 (CH), 55.3 (CH_3), 52.4 (2 × CH_2); HRMS (ESI) calcd for $C_{20}H_{24}NO_2$ $[M + H]^+$ 310.1807, found 310.1800.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Optimization studies and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jerome.blanchet@ensicaen.fr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge Région Basse-Normandie for a fellowship to WE, MENRT for MA, ANR "NeoACAT" (JC 2012 program) and the European Union (FEDER funding) for financial support.

■ REFERENCES

(1) For a review, see: (a) Chow, W. K.; Yuen, O. Y.; Choy, P. Y.; So, C. M.; Lau, C. P.; Wong, W. T.; Kwong, F. Y. *RSC Adv.* **2013**, *3*, 12518−12539. For Miyaura Pd-borylation of ArX with alkoxydiboron, see: (b) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508−7510. For Ir-borylation, see: (c) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390−391. For Pd-borylation of ArX with dialkoxyborane, see: (d) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458−6459. For Pd-borylation of ArCl using diboronic acid, see: (e) Molander, G. A.; Trice, S. L. J.; Dreher, S. D. *J. Am. Chem. Soc.* **2010**, *132*, 17701−17703. For similar Ni-borylation, see: (f) Molander, G. A.; Cavalcanti, L. N.; García-García, C. *J. Org. Chem.* **2013**, *78*, 6427−6439. For Ni-borylation of ArX with dialkoxyborane, see: (g) Moldoveanu, C.; Wilson, D. A.; Wilson, C. J.; Corcoran, P.; Rosen, B. M.; Percec, V. *Org. Lett.* **2009**, *11*, 4974−4977.

(2) For a review, see: Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890−931.

(3) For a review, see: (a) Mo, F.; Dong, G.; Zhang, Y.; Wang, J. *Org. Biomol. Chem.* **2013**, *11*, 1582−1593. See also: (b) Qiu, D.; Jin, L.; Zheng, Z.; Meng, H.; Mo, F.; Wang, X.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2013**, *78*, 1923−1933. (c) Ma, Y.; Song, C.; Jiang, W.; Xue, G.; Cannon, J. F.; Wang, X.; Andrus, M. B. *Org. Lett.* **2003**, *5*, 4635−4638.

(d) Mo, F.; Jiang, Y.; Qiu, D.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1846−1849. (e) Zhang, J.; Wang, X.; Yu, H.; Ye, J. *Synlett* **2012**, *23*, 1394−1396. (f) Yu, J.; Zhang, L.; Yan, G. *Adv. Synth. Catal.* **2012**, *354*, 2625−2628.
(4) Erb, W.; Hellal, A.; Albini, M.; Rouden, J.; Blanchet, J. *Chem.—Eur. J.* **2014**, *20*, 6608−6612. See Supporting Information for optimization details.
(5) (a) Amatore, C.; Jutand, A.; Le Duc, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 1379−1382. (b) Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G. C.; Murray, P. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5156−5160. (c) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2013**, *43*, 412−443.
(6) Wood, J.; Marciasini, L.; Vaultier, M.; Pucheault, M. *Synlett* **2014**, *25*, 551−555.
(7) Considering electron-poor anilines, more classical conditions (toluene at reflux using a Dean−Stark trap) were also tested but without improvement on the yield, although full conversion of the intermediate boronic acid was achieved.
(8) For a review, see: (a) Müller, T. J. J. *Top. Organomet. Chem.* **2006**, *19*, 149−205. For selected reports, see: (b) Merkul, E.; Schäfer, E.; Müller, T. J. J. *Org. Biomol. Chem.* **2011**, *9*, 3139−3141. (c) Broutin, P.-E.; Cerna, I.; Campaniello, M.; Leroux, F.; Colobert, F. *Org. Lett.* **2004**, *6*, 4419−4422. (d) Molander, G. A.; Trice, S. L. J.; Kennedy, S. M. *J. Org. Chem.* **2012**, *77*, 8678−8688. (e) Baudoin, O.; Cesario, M.; Guenard, D.; Gueritte, F. *J. Org. Chem.* **2002**, *67*, 1199−1207. (f) Wang, L.; Cui, X.; Li, J.; Wu, Y.; Zhu, Z.; Wu, Y. *Eur. J. Org. Chem.* **2012**, *2012*, 595−603.
(9) Crisóstomo, F. P.; Martín, T.; Carrillo, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 2181−2185.
(10) (a) Arvela, R. K.; Leadbeater, N. E. *Org. Lett.* **2005**, *7*, 2101−2104. See Supporting Information for optimization details. For a key review on Suzuki−Miyaura coupling, see: (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.
(11) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696.
(12) For a copper-catalyzed coupling of arenediazonium salts with polyfluoroarenes, see: (a) Zhu, X.; Li, F.; Su, W. *Tetrahedron Lett.* **2013**, *54*, 1285−1289. For other arylation involving arenediazonium salts, see: (b) Bachmann, W. E.; Hoffman, R. A. In *Organic Reactions*; John Wiley & Sons, Inc.: New York, 2004. For a review dealing with the use of arenediazonium salts in Pd-catalysis, see: (c) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622−4643.
(13) Lipton, M. F.; Mauragis, M. A.; Maloney, M. T.; Veley, M. F.; VanderBor, D. W.; Newby, J. J.; Appell, R. B.; Daugs, E. D. *Org. Process Res. Dev.* **2003**, *7*, 385−392.
(14) Nicolaou, K. C.; Evans, R. M.; Roecker, A. J.; Hughes, R.; Downes, M.; Pfefferkorn, J. A. *Org. Biomol. Chem.* **2003**, *1*, 908−920.
(15) Zollinger, H. *The Chemistry of Amino, Nitroso, Nitro and Related Groups*; Patai, S., Ed.; John Wiley & Sons, Ltd.: New York, 1996.
(16) (a) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583−586. (b) Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169−6193. For previously reported example of the Petasis borono-Mannich reaction in water, see: (c) Candeias, N. R.; Veiros, L. V.; Afonso, C. A. M.; Gois, P.M. P. *Eur. J. Org. Chem.* **2009**, 1859−1863. (d) Candeias, N. R.; Cal, P. M. S. D.; André, V.; Duarte, M. T.; Veiros, L. F.; Gois, P. M. P. *Tetrahedron* **2010**, *66*, 2736−2745.
(17) Molteni, V.; Li, X.; Chianelli, D.; Loren, J.; Liu, Y.; Karanewsky, D. S.; Furet, P.; Guagnano, V.; You, S.; Nabakka, J.; Liu, X.; Pan, S. WO 2007/038669 A2, IRM LCC: Novartis, AS, 2007.
(18) Xu, X.-H.; Wang, X.; Liu, G.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2012**, *14*, 2544−2547.
(19) Liu, C.; Liu, D.; Zhang, W.; Zhou, L.; Lei, A. *Org. Lett.* **2013**, *15*, 6166−6169.
(20) Hay, M. P.; Blaser, A.; Denny, W. A.; Hicks, K. O.; Lee, H. H.; Pchalek, K.; Pruijn, F. B.; Siim, B. G.; Wilson, W. R.; Yang S. WO 2006/104406 A1, Auckland Uniservices Limited, 2006.
(21) (a) Otani, Y.; Nagae, O.; Naruse, Y.; Inagaki, S.; Ohno, M.; Yamaguchi, K.; Yamamoto, G.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2003**, *125*, 15191−15199. (b) Liang, C.; Li, Z. WO 2009/154769 A1, Xcovery Inc., 2009.
(22) Mothana, S.; Grassot, J.-M.; Hall, D. G. *Angew. Chem., Int. Ed.* **2010**, *49*, 2883−2887.
(23) Yadav, V.; Babu, K. G. *J. Org. Chem.* **2004**, *69*, 577−580.
(24) Zhu, W.; Ma, D. *Chem. Commun.* **2004**, 888−889.
(25) Malik, Q. M.; Jaz, S. I.; Craig, D. C.; Try, A. C. *Tetrahedron* **2011**, *67*, 5798−5805.
(26) Hu, W.-J.; Zhao, X.-L.; Ma, M.-L.; Guo, F.; Mi, X.-Q.; Jiang, B.; Wen, K. *Eur. J. Org. Chem.* **2012**, *7*, 1448−1454.
(27) Ozawa, T.; Kanematsu, M.; Yokoe, H.; Yoshida, M.; Shishido, K. *J. Org. Chem.* **2012**, *77*, 9240−9249.
(28) Leermann, T.; Leroux, F. R.; Colobert, F. *Org. Lett.* **2011**, *13*, 4479−4481.
(29) Mo, F.; Jiang, Y.; Qiu, D.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1846−1849.
(30) Pucheault, M. J. D.; Marciasini, L. D. A.; Vaultier, M. WO 2014/009169 A1, 2014.
(31) Steinke, N.; Frey, W.; Baro, A.; Laschat, S.; Drees, C.; Nimtz, M.; Hägele, C.; Giesselmann, F. *Chem.—Eur. J.* **2006**, *12*, 1026−1035.
(32) Almansa Rosales, C.; Virdili Bernadó, M. WO 2007/000339 A1, 2007.
(33) Haddenham, D.; Bailey, C. L.; Vu, C.; Nepomuceno, G.; Eagon, S.; Pasumansky, L.; Singaram, B. *Tetrahedron* **2011**, *67*, 576−583.
(34) Slabber, C. A.; Grimmer, C. D.; Robinson, R. S. *J. Organomet. Chem.* **2013**, *723*, 122−128.
(35) Qiuan, Q.; Zang, Z.; Wang, S.; Chen, Y.; Lin, K.; Gong, H. *Synlett* **2013**, *24*, 619−624.
(36) Albaneze-Walker, J.; Raju, R.; Vance, J. A.; Goodman, A. J.; Reeder, M. R.; Liao, J.; Maust, M. T.; Irish, P. A.; Espino, P.; Andrews, P. R. *Org. Lett.* **2009**, *11*, 1463−1466.
(37) Gurung, S. K.; Thapa, S.; Kafle, A.; Dickie, D. A.; Giri, R. *Org. Lett.* **2014**, *16*, 1264−1267.
(38) Leowanawat, P.; Zhang, N.; Resmerita, A.-M.; Rosen, B. M.; Percec, V. *J. Org. Chem.* **2011**, *76*, 9946−9955.
(39) Gu, Z.-S.; Shao, L.-X.; Lu, J.-M. *J. Organomet. Chem.* **2012**, *700*, 132−134.
(40) Bang, J. S.; Kim, Y. J.; Song, J.; Yoo, J.-S.; Lee, S.; Lee, M. J.; Min, H.; Hwang, K. W.; Min, K. H. *Bioorg. Med. Chem.* **2012**, *20*, 5262−5268.
(41) Nakamura, Y.; Yoshikai, N.; Ilies, L.; Nakamura, E. *Org. Lett.* **2012**, *14*, 3316−3319.
(42) Simeone, J. P.; Sowa, J. R. *Tetrahedron* **2007**, *63*, 12646−12654.
(43) Zhou, C.; Liu, Q.; Li, Y.; Zhang, R.; Fu, X.; Duan, C. *J. Org. Chem.* **2012**, *77*, 10468−10472.
(44) Papoian, V.; Minehan, T. *J. Org. Chem.* **2008**, *73*, 7376−7379.
(45) Ackermann, L.; Althammer, A. *Org. Lett.* **2006**, *8*, 3457−3460.
(46) Zhang, X.-Q.; Wang, Z.-X. *J. Org. Chem.* **2012**, *77*, 3658−3663.
(47) Starčević, S.; Brožič, P.; Turk, S.; Cesar, J.; Rižner, T. L.; Gobec, S. *J. Med. Chem.* **2011**, *54*, 248−261.
(48) Hartmann, R.; Frotscher, M.; Oberwinkler, S.; Ziegler, E.; Messinger, J.; Thole, H.-H. US 2010/0204234 A1, 2010.
(49) Kuriyama, M.; Matsuo, S.; Shinozawa, M.; Onomura, O. *Org. Lett.* **2013**, *15*, 2716−2719.
(50) Bolliger, J. L.; Frech, C. M. *Adv. Synth. Catal.* **2010**, *352*, 1075−1080.
(51) Alacid, E.; Nájera, C. *Org. Lett.* **2008**, *10*, 5011−5014.
(52) Ishii, G.; Harigae, R.; Moriyama, K.; Togo, H. *Tetrahedron* **2013**, *69*, 1462−1469.
(53) Rintaro, Y.; Minoru S. US 2005/0020623 A1, 2005.
(54) Kar, A.; Sayyed, I. A.; Lo, W. F.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Org. Lett.* **2007**, *9*, 3405−3408.
(55) Sonesson, C.; Lindborg, J. *Tetrahedron Lett.* **1994**, *35*, 9063−9066.
(56) Hoshi, T.; Honma, T.; Mori, A.; Konishi, M.; Sato, T.; Hagiwara, H.; Suzuki, T. *J. Org. Chem.* **2013**, *78*, 11513−11524.

(57) Lee, J.; Kang, S.-U.; Kil, M.-J.; Shin, M.; Lim, J.-O.; Choi, H.-K.; Jin, M.-K.; Kim, S. Y.; Kim, S.-E.; Lee, Y.-S.; Min, K.-H.; Kim, Y.-H.; Ha, H.-J.; Tran, R.; Welter, J. D.; Szabo, Y. W. T.; Pearce, L. V.; Lundberg, D. J.; Toth, A.; Pavlyukovets, V. A.; Morgan, M. A.; Blumberg, P. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4143−4150.
(58) Menard-Moyon, C.; Fabbro, C.; Prato, M.; Bianco, A. *Chem.—Eur. J.* **2011**, *17*, 3222−3227.
(59) Ashton, W. T.; Cantone, C. L.; Chang, L. L.; Hutchins, S. M.; Strelitz, R. A.; MacCoss, M.; Chang, R. S. L.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Bunting, P.; Schorn, T. W.; Kivlighn, S. D.; Siegl, P. K. S. *J. Med. Chem.* **1993**, *36*, 591−609.
(60) Nun, P.; Martinez, J.; Lamaty, F. *Synthesis* **2010**, *12*, 2063−2068.
(61) Liu, Y.; Wang, L.; Sui, Y.; Yu, J. *Chin. J. Chem.* **2010**, *28*, 2039−2044.
(62) Han, W.-Y.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14*, 976−979.