JOC The Journal of Organic Chemistry

Article

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Selective Formation of *ortho*-Aminobenzylamines by the Copper-Catalyzed Amination of Benzylamine Boronate Esters

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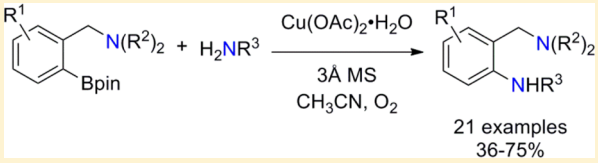
Supporting Information

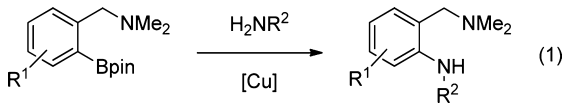
ABSTRACT: The copper-catalyzed coupling between benzylamino boronate esters and aryl amines has been investigated. Formation of *ortho*-aminobenzylamines was achieved under oxidative conditions in the presence of copper(II) acetate. The major side product of the transformation is the homocoupling of the aryl boronate ester. The formation of the desired diamines was found to be improved in the absence of base, increasing selectivity over the homocoupled product. Both electron-donating and electron-withdrawing substituents are tolerated on both the boronate ester substrate and the aniline coupling partner under the reaction conditions. The presence of the adjacent benzylamine moiety appears to enhance the reactivity of the boronate ester and influence the resulting product distribution, likely by affecting the competing rates of transmetalation in the catalytic cycles.



INTRODUCTION

Owing to the ubiquitous nature of C−N bonds in natural products and pharmaceuticals, a huge portion of synthetic research has been invested into new methods to install amines into organic substrates. The transformation of C−N bonds from C−B bonds under copper-mediated conditions, first discovered by Chan[1] and Lam[2] and later shown to proceed under catalytic conditions from boronic acids,[3−7] has proven invaluable in the synthesis of biologically relevant molecular structures, with many examples occurring in the past few years.[8−16] The majority of transformations that describe this reaction utilize boronic acid coupling partners, while limited examples employ trifluoroborates[17] and boronate esters.[18,19] With the development of iridium-catalyzed aryl C−H borylation reactions, resulting in the facile installation of a boronate ester functional group,[20−23] additional methods that allow the formation of C−N bonds from boronate esters would expand applications of this valuable process.

Substrate-directed C−H borylation has received a great deal of attention over the past decade as a powerful way to selectively form new C−B bonds from unreactive C−H bonds.[24−29] One such method has employed a pendant amine to achieve directed *ortho*-C−H borylation, yielding benzylamine boronate esters.[30−32] The conversion of these boronate esters into aminobenzylamines has not yet been reported but appeared to be feasible under copper-catalyzed conditions. While the coupling between an aryl halide and an amine in the presence of a pendant amine is known,[33] the use of a pendant coordinating group in the copper-catalyzed coupling of a boronate ester with an amine has not been reported. Furthermore, no examples could be found on the direct conversion of benzylamines into *ortho*-aminobenzylamines, compounds which have potential as effective ligands.[34] Having successfully synthesized benzylamine boronate esters through iridium-catalyzed C−H borylation,[30,31] we sought to develop copper-catalyzed conditions to *ortho*-aminobenzylamines from these boronate ester substrates (eq 1).

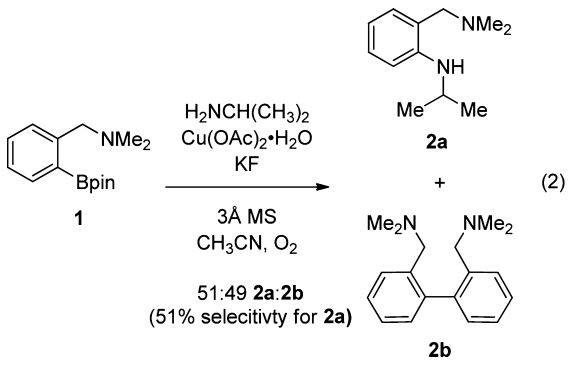


RESULTS AND DISCUSSION

Initial conditions were chosen which employed a boronate ester as the limiting reagent in an amine coupling reaction.[19] The investigation began with the coupling of aryl boronate ester **1** with alkyl amines since alkyl amines were shown to have better reactivity than anilines in the amination of aryl boronate esters. Upon coupling compound **1** with isopropylamine using 10 mol % of copper(II) acetate at 80 °C for 2 h, we were gratified to find that 2-((dimethylamino)methyl)-*N*-isoproylaniline (**2a**) was produced (eq 2). Analysis of the crude reaction mixture revealed complete consumption of the starting boronate ester and evidence of an additional product, identified as biaryl **2b**. Formation of this product was foreseeable as the homocoupling of arylboronic acids and boronate esters has been observed under oxidative palladium-catalyzed conditions[35−38] and under copper-catalyzed conditions.[39−42] The synthesis of compound **2b** has previously been achieved under stoichiometric copper-mediated conditions from an arylcuprate[43] or aryl halide,[44] although catalytic methods from benzylamine boronate ester substrates to the corresponding biphenyls have not been reported. The product distribution, however, was unanticipated, which was found to consist of 51% of **2b** with the remaining

Received: May 13, 2015
Published: June 12, 2015

DOI: 10.1021/acs.joc.5b01074
J. Org. Chem. 2015, 80, 7193−7204



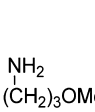
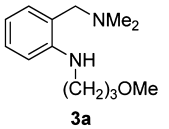
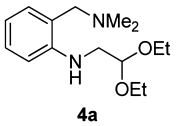
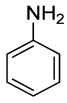
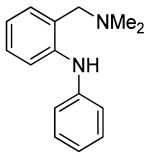
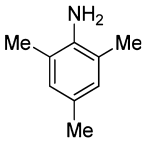
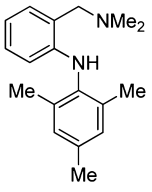
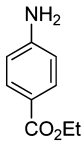
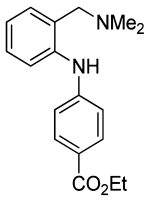
49% of **2a**.[45] Alternative conditions which were reported to successfully couple aliphatic amines with aryl boronic acids or trifluoroborates[17] were also investigated,[46] but the reaction only progressed to 55% conversion with 27% selectivity for **2a**. The initial reaction conditions chosen were used as a starting point to optimize for the formation of **a** and avoid the formation of the homcoupling product **b**.

Other alkyl amines were investigated, and in both cases, the formation of the diamine **a** was found to be the minor product (Table 1, entries 1−2). Anilines were then investigated to determine their effect on the selectivity of **a**, although simple boronate esters were previously found to not be reactive enough to couple with aryl amines.[19] Remarkably, the coupling of substrate **1** and aniline led to significant improvement in the formation of the *ortho*-aminobenzylamine **5a** with 98% selectivity over **2b** (Table 1, entry 3). This outcome was found to be consistent with that of other aryl amines (Table 1, entries 4−5), indicating that the nature of the amine coupling partner influences the rate of the coupling reaction and thus the product distribution. Previous studies on copper-mediated C−N bond forming reactions have revealed that the pK_a of the N−H bond plays a role in the rate of the coupling reaction, with more acidic substrates exhibiting faster reactivity.[47] Alternatively, alkyl amines may also undergo oxidative deamination under the copper-mediated conditions,[48,49] thus limiting the formation of the desired product **a**.[50] Since the inherent selectivity of the aryl amine coupling favors the desired diamine **a**, optimization of the reaction conditions focused on anilines.

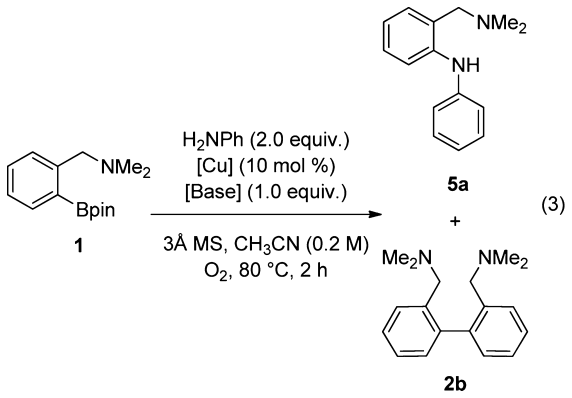
In the reaction between boronate ester **1** and aniline in the presence of KF (1.0 equiv), the initial concentration of 0.2 M provided the best selectivity of **5a** using the least amount of solvent. At room temperature, lower conversion and selectivity of **5a** was observed even with a longer reaction time (87% conversion and 66% selectivity for **5a**, 18 h) as compared to the reaction at 80 °C, indicating that heat is beneficial for both the conversion and selectivity of **a**. Using the optimized concentration and temperature, the effect of the copper precatalyst was then examined (eq 3). Replacing copper(II) acetate with copper(II) trifluoroacetate, copper(II) acetylacetonate, or copper(II) methoxide shifted the product distribution to favor compound **2b** over the *ortho*-aminobenzylamine **5a**, while the use of copper(II) trifluoromethanesulfonate improved the selectivity toward **5a** (Table 2, entries 2−5). Although copper(II) trifluoromethanesulfonate appeared to shift the product distribution toward **5a**, this trend was not extended to substituted systems;[51] consequently, copper(II) acetate was chosen as the optimal catalyst for the reaction.

A brief base screen was used to investigate the influence of carbonate and fluoride salts on the selectivity of **5a** formation (Table 2, entries 1, 6−12). Interestingly, a distinct trend

Table 1. Product Selectivity for Initial Analysis of the Amine Coupling Reaction[a]

Entry	H_2NR^2	Selectivity for **a**[b]	Product
1		22%	 **3a**
2		12%	 **4a**
3		98%	 **5a**
4		89%	 **6a**
5		82%	 **7a**

[a]Reaction conditions: **1**, H_2NR^2 (2.0 equiv), $Cu(OAc)_2·H_2O$ (10 mol %), KF (1.0 equiv), 3 Å MS, CH_3CN (0.2 M), O_2, 80 °C, 2 h. [b]Determined by integration of product peaks in a crude mixture by ^1H NMR spectroscopy.



emerged that related the counterion of the base to the product distribution. The smaller counterion of NaF improved the product ratio to favor the diamine product **5a** (>99:1) compared to that of KF (98:2), while the larger counterion

DOI: 10.1021/acs.joc.5b01074
J. Org. Chem. 2015, 80, 7193−7204

Table 2. Copper Catalyst and Base Screen for the Amine Coupling Reaction (Eq 3)

entry	[Cu]	[base]	selectivity[a] of **5a**
1	$Cu(OAc)_2 \cdot H_2O$	KF	98%
2[b]	$Cu(OCOCF_3)_2 \cdot XH_2O$	KF	44%
3	$Cu(acac)_2$	KF	26%
4[b]	$Cu(OCH_3)_2$	KF	21%
5	$Cu(OTf)_2$	KF	>99%
6	$Cu(OAc)_2 \cdot H_2O$	CsF	94%
7	$Cu(OAc)_2 \cdot H_2O$	NaF	>99%
8[b]	$Cu(OAc)_2 \cdot H_2O$	Cs_2CO_3	35%
9[b]	$Cu(OAc)_2 \cdot H_2O$	K_2CO_3	94%
10	$Cu(OAc)_2 \cdot H_2O$	Na_2CO_3	99%
11	$Cu(OAc)_2 \cdot H_2O$	Li_2CO_3	>99%
12	$Cu(OAc)_2 \cdot H_2O$	none	>99%

[a]Determined by integration of product peaks in a crude mixture by ^{1}H NMR spectroscopy; the remaining percentage corresponds to **2b**; [b]Reaction did not proceed to completion.

of CsF (94:6) showed a slight decrease in the selectivity of **5a** (Table 2, entries 6–7), demonstrating a dependence on counterion size. Changing to carbonate bases showed a more drastic influence on product distribution. Cesium carbonate significantly impacted the selectivity of **5a** (35:65), shifting the distribution in favor of compound **2b** (Table 2, entry 8). Incremental changes in the selectivity which favored diamine **5a** were observed by changing the counterion from potassium to sodium to lithium (Table 2, entries 9–11). A smaller counterion, which would bind more tightly to the base, appeared to favor the formation of product **5a** over compound **2b**. The counterion of the base may influence the rate of transmetalation of the boronate ester substrate,[52,53] thus influencing the product distribution. To examine whether the base was necessary for the reaction to occur, the reaction was performed without the addition of base and found to proceed fully to the desired diamine **5a** (Table 2, entry 12), implicating the benzylamine moiety in the transmetalation step.

With several effective sets of conditions for the coupling reaction in hand, a full investigation of the substrate scope was initiated to provide a practical method for the synthesis of complex diamines and to probe how electronic effects influence the distribution of the corresponding diamine (**a**) to homocoupled product (**b**). Although multiple bases proved advantageous in the coupling reaction between substrate **1** and aniline, the reported sensitivity of copper-catalyzed amination reactions to steric and electronic effects[54] led us to investigate the scope of the reaction using three sets of conditions ($Cu(OAc)_2$ with KF, Li_2CO_3, or no base) to determine the most general system for electronically diverse substrates. For most of the substrates investigated, the selectivity of **a** was maintained or improved as the base was changed from KF to Li_2CO_3 to the absence of base (Table 3). Using these conditions, some clear trends of selectivity emerged. In most cases, the diamine could be accessed as the only observed product when the reaction was performed in the absence of base. Interestingly, halogens had a significant impact on the distribution of diamine (**11a** and **13a**) to the homocoupled product (**11b** and **13b**, respectively), which is not observed with other electron withdrawing substituents, suggesting that the role of inductive and resonance effects on the relative rate of the key steps is not straightforward. The improved selectivity of diamines (**a**) observed with Li_2CO_3 or in the absence of base when coupling anilines led us to reexamine the coupling of substrate **1** and alkyl amines (see eq 2) under these conditions. Although improved selectivity of **a** was observed, these reactions did not reach the highly selective ratios seen in the aryl amine couplings.[55]

While the couplings of a range of boronate esters proceeded in good conversion and high chemoselectivity for the desired diamine **a**, isolation of the *ortho*-aminobenzylamines was challenging, resulting in moderate to good yields (Figure 1).

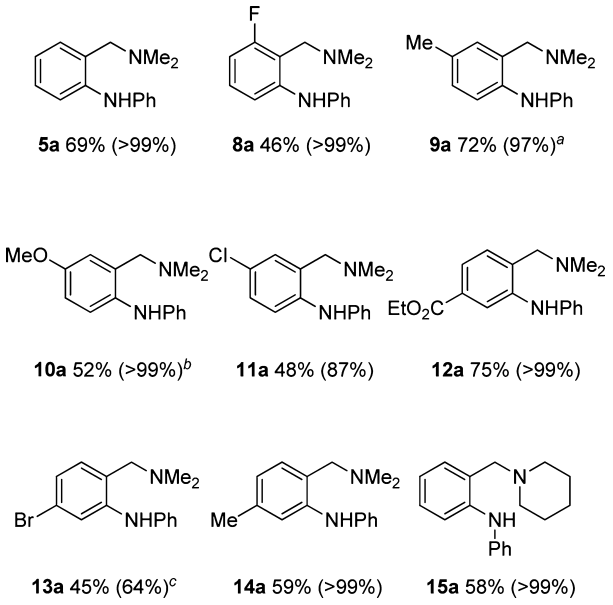
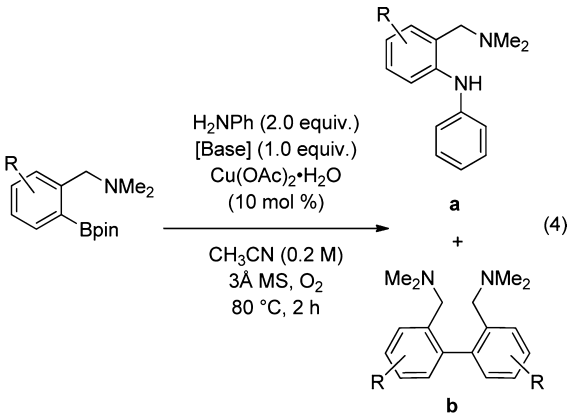


Figure 1. Yields of *ortho*-aminobenzylamine products from copper-catalyzed couplings without base. ^{1}H NMR spectroscopy of a crude reaction mixture used to determine the selectivity of **a** is shown in parentheses. *a*: Reaction performed with KF. *b*: Reaction performed with Li_2CO_3. *c*: ^{1}H NMR spectroscopy peaks of **13a**/**13b** were poorly resolved.

Although attempts to isolate **a** from the crude reaction mixture using extraction and Kugelrohr distillation were unsuccessful, column chromatography using either silica gel or basic alumina provided compounds **a** in high purity. The use of tetramethylethylenediamine to complex with the residual copper prior to silica gel column chromatography proved to enhance the yield of certain compounds, while for other compounds the use of triethylamine in the elution solvent worked well. In some cases, pinacol was observed along with product **a**, but removal of this impurity was achieved azeotropically with ethanol. The challenging isolation is likely due to the diamine moiety in the products being strongly absorbed to the silica during purification or by the formation of stable complexes with the residual copper in the crude reaction mixture. Regardless, a range of novel *ortho*-aminobenzylamines has been achieved in moderate to good yields and high purity. The reaction tolerates a variety of substituents on the benzylamine boronate ester substrate, including electron-donating groups ($-OCH_3$ and $-CH_3$) and electron-withdrawing ($-CO_2Et$, $-F$, $-Cl$, and $-Br$) groups at different positions on the aromatic ring, all of which selectively produce the diamine **a** over the homocoupled product **b**. The reaction also proceeded well when the dimethylamine moiety was changed to a piperidine group, proceeding without base in full conversion to *N*-phenyl-2-(piperidin-1-ylmethyl)aniline (**15a**).

DOI: 10.1021/acs.joc.5b01074
J. Org. Chem. 2015, 80, 7193–7204

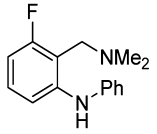
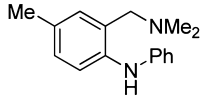
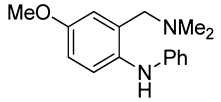
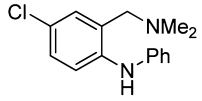
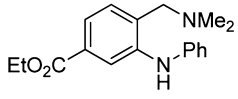
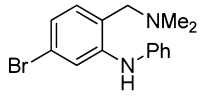
Crude benzylamine boronate ester **1** could also be used under the reaction conditions with aniline and KF to provide desired product **5a**, albeit in lower yield (47%).



Substitution on the aniline was also tolerated under the reaction conditions leading to predominant formation of **a** in all cases (Figure 2). As in the case of substituents on the aryl boronate ester, change, or removal of the base improved the selectivity of product **a**.[56] Increasing the steric bulk around the amine did not appear to impact the product distribution providing compound **6a** when **1** was coupled with 2,4,6-trimethylaniline; electron-withdrawing ($-CO_2Et$) and electron-donating ($-OCH_3$) groups also resulted in predominant formation of the desired aminobenzylamines **7a** and **16a**, respectively. While *para*−Cl and −Br aniline proceeded with high conversion to diamines **17a** and **20a**, a significant shift toward product **b** was observed with the proximity of Cl from *para* to *meta* to *ortho*, indicating the amination is strongly influenced by the electronics of the amine. While both resonance and induction of Cl on the aniline may play a role, it appears that the inductive effect has the strongest impact on the product distribution. The coupling of 2-aminopyridine proceeded in high conversion to compound **20a**, showing a tolerance of the reaction for heteroaromatic amines. The broad utility of this reaction was further demonstrated through the coupling of substituted boronate ester substrates with various aryl amines.[57] The product selectivity for compounds **21a**, **22a**, and **23a** are consistent with the previous results for each coupling partner, while in the case of product **24a** more **15b** was produced than expected. The successful coupling of varying anilines and benzylamine boronate esters conveys the robust nature of this reaction in synthesizing *ortho*-aminobenzylamines.

The biaryl coupling reaction to form product **b** was also investigated in the absence of the added aniline. While the identity of the counterion in the precatalyst proved important in the amination reaction, the use of copper(II) acetate monohydrate and copper(II) acetylacetonate in the presence of KF both led to the biaryl **2b** after 2 h.[58] The biaryl coupling transformation worked well with a variety of substituted benzylamine boronate esters (Scheme 1).[59] \Similar to the *ortho*-aminobenzylamines, purification of the homocoupling products **b** was rather challenging; the use of column chromatography on basic alumina proved successful in most cases. In the case of biaryl **2b**, the coupling was also performed without the base in the presence of copper(II) acetate monohydrate yielding the product in full conversion, suggesting

Table 3. Crude Product Ratios of Optimized Base Systems Substituted Aryl Boronate Esters and Aniline (Eq 4)

Product (**a**)	Selectivity[a] of **a** (KF)	(Li_2CO_3)	(No Base)
 **8a**	40%	52%	>99%
 **9a**	97%	>99%	>99%
 **10a**	80%	>99%	>99%
 **11a**	63%	48%	87%
 **12a**	76%	90%	>99%
 **13a**	48%	50%	64%

[a]Determined by integration of product peaks in a crude mixture by ^{1}H NMR spectroscopy; the remaining percentage corresponds to **8b**−**13b**, respectively.

that the benzylamine moiety may assist in both transmetalation steps of the catalytic cycle.

While detailed mechanistic studies on the copper-catalyzed amination reaction between an aryl amine and aryl boronic acid or boronate ester have yet to be disclosed, mechanisms based on preliminary studies exclude radical pathways and instead focus on Cu^{II} and Cu^{III} pathways.[48,60] To gain more insight into the catalytic cycle, experiments were performed in the absence of oxygen. Under the optimized conditions, the amine coupling reaction resulted in five percent conversion to diamine **a** (eq 5), while the homocoupling reaction gave 10% conversion to product **b** (eq 6).[61] Both of these reactions reveal a Cu^{II}/ product stoichiometry of 2:1, which is consistent with previous mechanistic reports on Chan, Evans,[62] and Lam reactions[63,64] and a previously proposed mechanism for the copper-catalyzed homocoupling reaction.[40] The results support disproportionation of Cu^{II} into Cu^{I} and Cu^{III} complexes in the catalytic cycle,

DOI: 10.1021/acs.joc.5b01074
J. Org. Chem. 2015, 80, 7193−7204

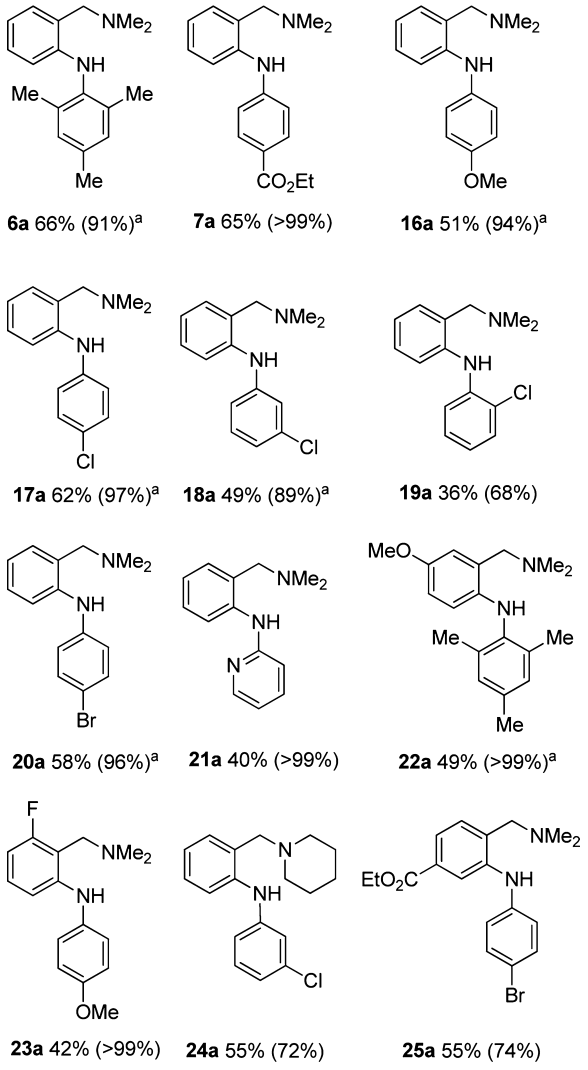
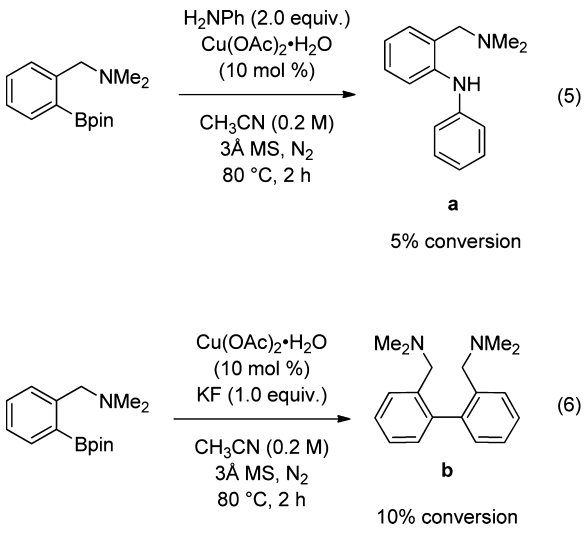
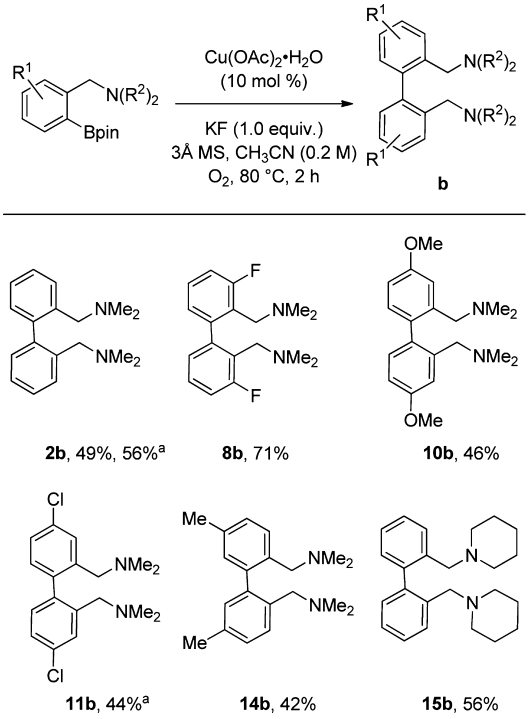


Figure 2. Yields of *ortho*-aminobenzylamines from copper-catalyzed couplings without base. ^{1}H NMR spectroscopy of a crude reaction mixture used to determine the selectivity of **a** is shown in parentheses. *a*: Reaction performed with KF.



while O_2 serves to turn over the catalyst through the oxidation of Cu^I to Cu^{II}.[63,64]

Scheme 1. Yields of Select Homocoupling Products Formed from Benzylamine Boronate Esters in the Presence of KF[a]



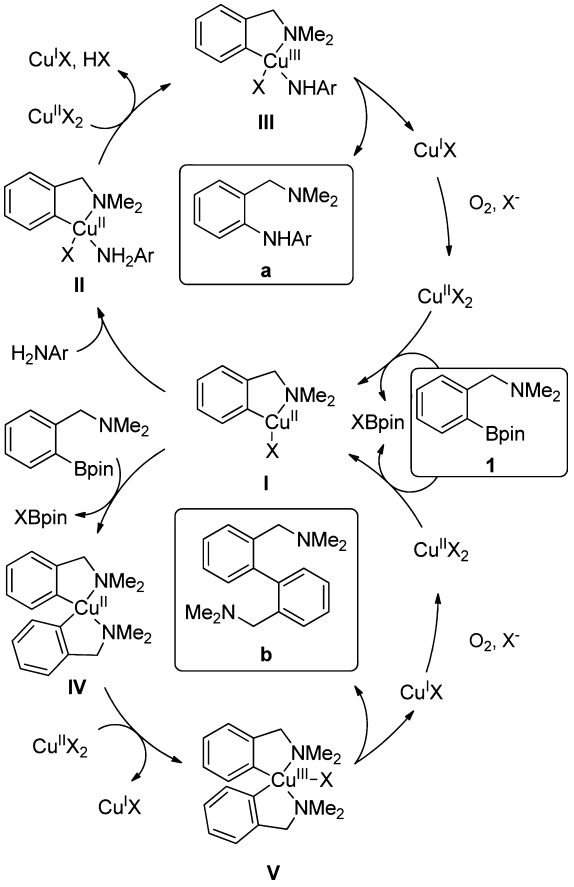
[a]The reaction was performed without a base.

Drawing from previously proposed mechanisms[4,63−65] and our experimental results, a two-pathway catalytic cycle has been proposed (Scheme 2) that accounts for the formation of the diamine (**a**) and the homocoupled product (**b**). The catalytic cycle is initiated with transmetalation of the boronate ester **1** with $Cu(OAc)_2$ to form complex **I**. The two mechanisms diverge from intermediate **I** depending on whether the amine coordinates (**I** to **II**) or a second transmetalation takes place (**I** to **IV**). Upon coordination of the aryl amine to copper to form **II**, the complex is oxidized from Cu^{II} to Cu^{III} via disproportionation with Cu^{II}, forming complex **III** which is poised to undergo reductive elimination to provide the diamine product **a** and Cu^IX. Oxidation of Cu^I to Cu^{II} by O_2 regenerates the active catalyst. If intermediate **I** undergoes a second transmetalation instead of being captured by an aniline, intermediate **IV** will form, followed by disproportionation to form the Cu^{III} complex **V**, which upon reductive elimination would then produce the homocoupling product **b**. The Cu^I intermediate is then oxidized to the active catalyst.[66] In the formation of diamine **a**, a pathway in which coordination of the amine occurs prior to transmetalation cannot be ruled out.[65]

The presented results reveal a complex dual catalytic process for the formation of diamine **a** and biaryl **b**. The observed dependence of product distributions on the boronate ester and aniline electronics likely arises from the competing rates of coordination (to form complex **II**)/oxidation to form complex **III** versus transmetalation to form complex **IV**. The different product distributions observed for alkyl amine versus aryl amine couplings indicates that the nucleophilicity and acidity of the amine coupling partner plays a significant role in the pathway toward diamine **a**.[47] In the aryl amine couplings done without base, the benzylamine moiety likely assists in transmetalation of the boronate ester, which is supported by

DOI: 10.1021/acs.joc.5b01074
J. Org. Chem. 2015, 80, 7193−7204

Scheme 2. Proposed Catalytic Cycles for the Formation of the *ortho*-Aminobenzylamine (a, Top) and the Homocoupling Product (b, Bottom)



previous reports of dative bonds between benzylamines and *ortho*-boronic acids and boronate esters.[26,67] Furthermore, the amination of PhBpin with aniline under base-free conditions proceeded in less than 10% conversion, supporting the assertion that the adjacent benzylic amine plays an important role in the catalytic cycle. The high selectivity of **a** observed in the absence of base likely results from the formation of a copper species with counterion X that is more reactive toward the coordination of the amine, leading to complexes **II** and **III**, rather than a second transmetalation, leading to complex **IV**. The identity of the counterion (X) has been shown to have a significant influence on the rate of the transmetalation step of the Suzuki–Miyaura coupling reaction.[68] Although further studies were beyond the scope of this investigation, experiments that elucidate the active catalytic species and kinetics of these reactions would provide great insight into the copper-catalyzed transformations between aryl boronate esters and amines.

CONCLUSIONS

The synthesis of novel *ortho*-aminobenzylamines **2a–24a** have been achieved through the copper-catalyzed coupling of benzylamine boronate esters and anilines. The coupling reaction was initially plagued by the competitive formation of homocoupled biaryl products. The formation of these biaryl products was largely suppressed when the conditions were modified to remove the base additive. The reaction tolerates both electron-donating and electron-withdrawing substituents on the benzylamine boronate ester substrates and aniline coupling partners, resulting in optimized conditions for a large array of *ortho*-aminobenzylamines. The selective formation of the homocoupled product could also be achieved in the absence of an added amine. Overall, the presence of the *ortho*-benzylic amine significantly alters the reactivity of aryl boronate esters, providing divergent reactivity profiles from typical systems. This work demonstrates how the reactivity of an aryl boronate ester can be modified through the use of a pendant amine to achieve coupling of aryl boronate esters.

EXPERIMENTAL SECTION

General Experimental Details. All procedures were performed in oven-dried glassware under purified nitrogen until O_2 gas was introduced. *N*,*N*-Dimethylbenzylamine boronate esters were synthesized following the published procedures.[30,31] All other materials, including solvents, were purchased and used as received. Concentration was performed by rotary evaporation. TLC analysis was performed on 60 Å silica layer fluorescence UV plates. Flash column chromatography was carried out on hand-packed columns of silica gel, 40–63 μm, 60 Å or aluminum oxide, basic, Brockman I, 50–200 μm, 60 Å. NMR spectra were collected at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C{^{1}H} NMR, or at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C{^{1}H} NMR. ^{1}H NMR spectra are referenced to $CDCl_3$ at 7.26 ppm or to an internal tetramethylsilane (TMS) standard at 0.00 ppm. The ^{1}H NMR spectral data are reported as follows: chemical shift ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, hex = hextet, sep = septet, oct = octet, m = multiplet), coupling constants (Hz), and integration. ^{13}C{^{1}H} NMR spectra are referenced to $CDCl_3$ at 77.0 ppm. In some of the spectra, interference from the NMR spectrometer is visible at 5.96 ppm for ^{1}H NMR spectra and 104.9 ppm for ^{13}C{^{1}H} NMR spectra, and this interference is likely the result of a problematic component of the probe that failed during this study and has not been repaired to date. Fourier transform infrared (FTIR) spectra were obtained from thin film in dichloromethane or chloroform-*d* and absorptions reported in cm^{-1}. High-resolution mass spectrometry was obtained by time-of-flight electrospray ionization.

Representative Procedure A. To a Schlenk flask was added 3 Å molecular sieves (0.300 g), substrate **1** (0.100 g, 0.383 mmol), potassium fluoride (0.0220 g, 0.394 mmol), aniline (0.070 mL, 0.766 mmol), and acetonitrile (1.9 mL). Oxygen was bubbled through the mixture for 5 min, then copper(II) acetate monohydrate (0.0077 g, 0.0385 mmol) was added. After 2 h at 80 °C under positive oxygen pressure, the mixture was allowed to cool to room temperature, then transferred and concentrated in vacuo to give a black oil (0.1532 g). The crude product (ratio[45] **5a**/**2b** 98:2) was purified by silica gel column chromatography using ethyl acetate, followed by treatment with ethanol and concentration to remove pinacol impurities azeotropically (3 × 2 mL) to afford product **5a** as a brown oil (0.0495 g, 0.219 mmol, 57%).

Representative Procedure B. To a Schlenk flask was added 3 Å molecular sieves (0.304 g), substrate **1** (0.100 g, 0.383 mmol), potassium fluoride (0.0220 g, 0.394 mmol), copper(II) acetate (0.0075 g, 0.0383 mmol), and acetonitrile (2.00 mL). Oxygen was bubbled through the mixture for 5 min. After 2 h at 80 °C under oxygen, the mixture was allowed to cool to room temperature, then transferred and concentrated in vacuo to give a light green solid (0.0942 g). The crude mixture was purified by Kugelrohr distillation (0.5 mmHg, up to 80 °C) to afford **2b** as a colorless solid (0.025 g, 0.0931 mmol, 49%).

*2-((Dimethylamino)methyl)-N-isopropylaniline (**2a**).* Following representative procedure A using substrate **1** (0.100 g, 0.343 mmol) and isopropyl amine (0.063 mL, 0.766 mmol), the crude mixture (ratio[45] **2a**:**2b** 28:72) was purified by column chromatography on basic alumina (25:75 ethyl acetate/hexanes) to afford **2a** as a tan oil (0.0042 g, 0.0218 mmol, 6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.13 (m, 1H), 6.95 (d, J = 7.3 Hz, 1H), 6.62 (d, J = 8.1 Hz, 1H), 6.57 (t, J = 7.3 Hz, 1H), 3.61 (sep, J = 6.2 Hz, 1H), 3.38 (s, 2H), 2.17 (s,

DOI: 10.1021/acs.joc.5b01074
J. Org. Chem. 2015, 80, 7193–7204

6H), 1.21(d, J = 6.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 147.9, 130.1, 128.3, 122.7, 115.3, 110.4, 63.8, 44.6, 43.4, 23.0; IR (thin film, $CDCl_3$) 3268 (br), 2967 (s), 2855 (m), 2818 (m), 2772 (m), 1606 (s), 1589 (s), 1523 (s), 1463 (s), 1382 (m), 1363 (s), 1325 (s) cm^{-1}. HRMS (ESI): m/z calcd for $C_{12}H_{21}N_2$ $[M + H]^+$ 193.1705, found 193.1707.

*2-((Dimethylamino)methyl)-N-(3-methoxypropyl)aniline (**3a**).* Following representative procedure A without base using substrate **1** (0.100 g, 0.343 mmol) and 3-methoxypropylamine (0.078 mL, 0.766 mmol), the crude mixture (ratio[45] **3a**:**2b** 52:48) was purified by column chromatography on basic alumina (4:1 to 1:1 hexanes/ethyl acetate) to afford **3a** as a tan oil (0.0118 g, 0.053 mmol, 14%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 (t, J = 8.0 Hz, 1H), 6.96 (d, J = 7.2 Hz, 1H), 6.63−6.58 (m, 2H), 6.16 (br s, 1H), 3.50 (t, J = 6.2 Hz, 2H), 3.38 (s, 2H), 3.36 (s, 3H), 3.22 (t, J = 6.7 Hz, 2H), 2.17 (s, 6H), 1.91 (q, J = 6.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 148.5, 129.9, 128.4, 122.7, 115.6, 109.7, 70.7, 63.8, 58.7, 44.8, 40.2, 29.4; IR (thin film, $CDCl_3$) 3281 (br), 3044 (m), 2975 (m), 2942 (s), 2854 (s), 2817 (s), 2771 (s), 1607 (s), 1589 (s), 1523 (s), 1468 (s), 1389 (m), 1362 (m), 1332 (m), 1313 (m) cm^{-1}. HRMS (ESI): m/z calcd for $C_{13}H_{22}N_2ONa$ $[M + Na]^+$ 245.1630, found 245.1637.

*N-(2,2-Diethoxyethyl)-2-((dimethylamino)methyl)aniline (**4a**).* Following representative procedure A using substrate **1** (0.100 g, 0.383 mmol), aminoacetaldehydediethyl acetate (0.111 mL, 0.766 mmol), and Li_2CO_3 (0.0291 g, 0.394 mmol), the crude mixture (ratio[45] **4a**/**2b** 40:60) was purified by silica gel column chromatography (99:1 to 85:15 dichloromethane/ethyl acetate, then 80:19.5:0.5 dichloromethane/ethyl acetate/triethylamine) to afford **4a** as a yellow oil (0.0083 g, 0.0312 mmol, 8%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.17 (td, J = 7.8, 1.6 Hz, 1H), 6.97 (d, J = 6.8 Hz, 1H), 6.63−6.60 (m, 2H), 4.76 (t, J = 5.9 Hz, 1H), 3.72 (ddd, J = 7.1, 9.4, 14.2 Hz, 2H), 3.59 (ddd, J = 7.1, 9.4, 14.2 Hz, 2H), 3.39 (s, 2H), 3.26 (d, J = 5.9 Hz, 2H), 2.17 (s, 6H), 1.24 (t, J = 7.1 Hz, 6H) (N−H resonance could not be identified); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.1, 129.9, 128.4, 123.3, 116.1, 109.9, 100.9, 63.6, 61.7, 45.7, 44.8, 15.3; IR (thin film, $CDCl_3$) 3270 (br), 3045 (s), 2975 (s), 2929 (s), 2854 (s), 2817 (s), 2770 (s), 1729 (s), 1684 (m), 1607 (s), 1588 (s), 1520 (s), 1456 (s), 1373 (m) cm^{-1}. HRMS (CI): m/z calcd for $C_{15}H_{27}N_2O_2$ $[M + H]^+$ 267.2072, found 267.2076.

*2-((Dimethylamino)methyl)-N-phenylaniline (**5a**).* Following representative procedure A, without base, using substrate **1** (0.1032 g, 0.395 mmol), the crude mixture (ratio[45] **5a**/**2b** 100:0) was purified by silica gel column chromatography (99:1 to 90:10 dichloromethane/EtOAc) to afford **5a** as a tan oil (0.0618 g, 0.273 mmol, 69%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.57 (br s, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.29 (t, J = 7.7 Hz, 2H), 7.23−7.19 (m, 1H), 7.14−7.12 (m, 3H), 6.92 (t, J = 7.4 Hz, 1H), 6.83 (t, J = 7.4 Hz, 1H), 3.49 (s, 2H), 2.27 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 143.7, 143.2, 130.5, 129.2, 128.0, 125.8, 120.2, 119.2, 117.8, 115.0, 63.6, 44.8; IR (thin film, $CDCl_3$) 3250 (br), 3045 (m), 2977 (m), 2945 (m), 2857 (m), 2820 (s), 2774 (s), 1594 (s), 1523 (s), 1497 (s), 1476 (s), 1462 (s), 1362 (m), 1326 (s), 1308 (s) cm^{-1}. HRMS (ESI): m/z calcd for $C_{15}H_{19}N_2$ $[M + H]^+$ 227.1548, found 227.1552.

*N-(2-((Dimethylamino)methyl)phenyl)-2,4,6-trimethylaniline (**6a**).* Following representative procedure A using substrate **1** (0.100 g, 0.383 mmol) and 2,4,6-trimethylaniline (0.108 mL, 0.766 mmol), the crude mixture (ratio[45] **6a**/**2b** 89:11) was purified by basic alumina column chromatography (100% dichloromethane), then silica gel column chromatography (100:0 to 95:5 dichloromethane/EtOAc) to afford **6a** as a tan oil (0.0679 g, 0.253 mmol, 66%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 7.08−7.03 (m, 2H), 6.96 (s, 2H), 6.66 (dd, J = 7.3, 1.1 Hz, 1H), 6.17 (d, J = 8.0 Hz, 1H), 3.56 (s, 2H), 2.33 (s, 3H), 2.28 (s, 6H), 2.16 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 146.4, 136.6, 134.6, 134.1, 129.8, 129.0, 128.1, 122.9, 116.5, 111.2, 63.7, 44.7, 20.9, 18.2; IR (thin film, $CDCl_3$) 3244 (br), 3007 (m), 2973 (s), 2943 (s), 2915 (s), 2854 (s), 2818 (s), 2772 (s), 1604 (s), 1505 (s), 1485 (s), 1467 (s), 1375 (m), 1362 (m), 1325 (s), 1309 (s) cm^{-1}. HRMS (ESI): m/z calcd for $C_{18}H_{25}N_2$ $[M + H]^+$ 269.2018, found 269.2019.

*Ethyl 4-((2-((dimethylamino)methyl)phenyl)amino)benzoate (**7a**).* Following representative procedure A using substrate **1** (0.100 g, 0.383 mmol) and ethyl 4-aminobenzoate (0.127 g, 0.766 mmol), the crude mixture (ratio[45] **7a**/**2b** 100:0) was treated with trimethylethylenediamine (0.15 mL), then purified by silica gel column chromatography (99:1 to 90:10 dichloromethane/EtOAc), and the resulting product residue was azeotroped with ethanol (3 × 2 mL) to afford product **7a** as a red/brown oil (0.0744 g, 0.249 mmol, 65%). ^1H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.92 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.1 Hz, 1H), 7.26−7.22 (m, 1H), 7.13 (d, J = 7.4 Hz, 1H), 7.04 (d, J = 8.8 Hz, 2H), 6.90 (td, J = 7.4, 0.9 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.45 (s, 2H), 2.24 (s, 6H), 1.38 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.6, 147.7, 141.8, 131.3, 130.6, 128.1, 127.3, 121.1, 120.7, 117.3, 114.8, 63.4, 60.3, 44.8, 14.4; IR (thin film, $CDCl_3$) 3237 (br), 3183 (m), 3057 (m), 2980 (m), 2948 (m), 2903 (m) 2859 (m), 2822 (m), 2776 (m), 1706 (s), 1591 (s), 1525 (s), 1457 (s), 1275 (s) cm^{-1}. HRMS (CI): m/z calcd for $C_{18}H_{23}N_2O_2$ $[M + H]^+$ 299.1760, found 299.1768.

*2-((Dimethylamino)methyl)-3-fluoro-N-phenylaniline (**8a**).* Following representative procedure A, without base, using substrate **27**[69] (0.0943 g, 0.338 mmol), the crude mixture (ratio[45] **8a**/**8b** 100:0) was purified by silica gel column chromatography (99:1 to 95:5 dichloromethane/EtOAc) to afford product **8a** as a light violet solid (0.0471 g, 0.155 mmol, 46%): mp 83.5−89.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.27 (t, J = 7.6 Hz, 2H), 7.10−7.05 (m, 4H), 6.93 (t, J = 7.3 Hz, 1H), 6.55−6.51 (m, 1H), 3.53 (d, J_{H-F} = 1.3 Hz, 2H), 2.26 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 161.9 (d, J_{C-F} = 241.8 Hz), 146.0 (d, J_{C-F} = 6.0 Hz), 142.7, 129.3, 128.5 (d, J_{C-F} = 10.5 Hz), 120.9, 118.7, 112.3 (d, J_{C-F} = 15.6 Hz), 110.1 (d, J_{C-F} = 2.8 Hz), 105.9 (d, J_{C-F} = 23.4 Hz), 53.4−53.3 (m), 44.7; IR (thin film, $CDCl_3$) 3237 (br), 3051 (m), 2981 (m), 2949 (m), 2864 (m), 2826 (m), 2779 (m), 1620 (s), 1596 (s), 1524 (m), 1498 (s), 1472 (s), 1365 (m), 1325 (m), 1265 (s), 1236 (s) cm^{-1}. HRMS (CI): m/z calcd for $C_{15}H_{18}FN_2$ $[M + H]^+$ 245.1454, found 245.1447.

*2-((Dimethylamino)methyl)-4-methyl-N-phenylaniline (**9a**).* Following representative procedure A using substrate **28**[69] (0.100 g, 0.363 mmol), the crude mixture (ratio[45] **9a**/**9b** 97:3) was purified by silica gel column chromatography (100:0 to 50:50 dichloromethane/EtOAc), and the resulting product residue was azeotroped with ethanol (3 × 2 mL) to afford product **9a** as a brown oil (0.0631 g, 0.263 mmol, 72%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.31 (br s, 1H), 7.27−7.21 (m, 3H), 7.05 (d, J = 7.8 Hz, 2H), 6.99 (d, J = 8.2 Hz, 1H), 6.90 (s, 1H), 6.83 (t, J = 7.3 Hz, 1H), 3.40 (s, 2H), 2.27 (s, 3H), 2.22 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 143.9, 140.9, 131.2, 129.2, 128.9, 128.4, 126.4, 119.6, 117.1, 116.0, 63.5, 44.8, 20.6; IR (thin film, $CDCl_3$) 3255 (br), 3105 (m), 3026 (m), 2975 (m), 2944 (m), 2915 (m), 2855 (m), 2819 (m), 2772 (m), 1598 (s), 1520 (s), 1497 (s), 1467 (m), 1455 (m), 1413 (m), 1358 (m), 1320 (s) cm^{-1}. HRMS (CI): m/z calcd for $C_{16}H_{21}N_2$ $[M + H]^+$ 241.1705, found 241.1702.

*2-((Dimethylamino)methyl)-4-methoxy-N-phenylaniline (**10a**).* Following representative procedure A using substrate **29**[69] (0.075 g, 0.258 mmol) and Li_2CO_3 (0.0197 g, 0.266 mmol), the crude mixture (ratio[45] **10a**/**10b** 100:0) was purified by silica gel column chromatography (99:1 to 50:50 dichloromethane/EtOAc), and the resulting product residue was azeotroped with ethanol (3 × 2 mL) to afford product **10a** as a brown oil (0.0328 g, 0.133 mmol, 52%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.30 (d, J = 8.7 Hz, 1H), 7.22 (t, J = 7.5 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 6.82−6.76 (m, 2H), 6.72 (s, 1H), 3.78 (s, 3H), 3.38 (s, 2H), 2.22 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.5, 144.6, 136.6, 129.2, 129.0, 119.0, 118.7, 116.6, 116.0, 112.6, 63.4, 55.5, 44.9; IR (thin film, $CDCl_3$) 3263 (br), 3033 (m), 2976 (m), 2945 (m), 2907 (m), 2854 (m), 2820 (m), 2773 (m), 1599 (s), 1515 (s), 1498 (s), 1267 (s) cm^{-1}. HRMS (CI): m/z calcd for $C_{16}H_{20}N_2O$ $[M]^+$ 256.1576, found 256.1575.

*4-Chloro-2-((dimethylamino)methyl)-N-phenylaniline (**11a**).* Following representative procedure A, without base, using substrate **30**[69] (0.1051 g, 0.356 mmol), the crude mixture (ratio[45] **11a**/**11b** 87:13) was purified by silica gel column chromatography (95:5 dichloromethane/EtOAc), then again by silica gel column chromatography

DOI: 10.1021/acs.joc.5b01074
J. Org. Chem. 2015, 80, 7193−7204

(99.5:0.5 to 95:5 dichloromethane/EtOAc) to afford product **11a** as a tan oil (0.0441 g, 0.169 mmol, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 7.28−7.24 (m, 3H), 7.11 (dd, J = 8.7, 2.5 Hz, 1H), 7.06−7.05 (m, 3H), 6.91 (t, J = 7.4 Hz, 1H), 3.41 (s, 2H), 2.24 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 142.8, 142.5, 130.1, 129.3, 127.8, 127.2, 123.5, 120.7, 118.1, 115.9, 63.1, 44.8; IR (thin film, $CDCl_3$) 3244 (br), 3029 (m), 2978 (m), 2947 (m), 2855 (m), 2822 (m), 2775 (m), 1592 (s), 1514 (s), 1474 (s), 1408 (s), 1321 (s) cm^{-1}. HRMS (CI): m/z calcd for $C_{15}H_{18}ClN_2$ $[M + H]^+$ 261.1158, found 261.1149.

*Ethyl 4-((dimethylamino)methyl)-3-(phenylamino)benzoate (**12a**).* Following representative procedure A, without base, using substrate **31**[69] (0.100 g, 0.300 mmol), the crude mixture (ratio[45] **12a**/**12b** 100:0) was purified by silica gel column chromatography (99:1 to 90:10 dichloromethane/EtOAc) to afford product **12a** as a yellow oil (0.0675 g, 0.226 mmol, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (br s, 1H), 8.01 (d, J = 1.6 Hz, 1H), 7.46 (dd, J = 7.8, 1.6 Hz, 1H), 7.29 (t, J = 8.4 Hz, 2H), 7.14−7.10 (m, 3H), 6.93 (t, J = 7.4 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 3.49 (s, 2H), 2.24 (s, 6H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.8, 143.9, 142.6, 130.4, 130.3, 130.2, 129.3, 120.8, 120.2, 118.1, 115.3, 63.3, 60.8, 44.8, 14.3; IR (thin film, $CDCl_3$) 3238 (br), 3109 (m), 3020 (m), 2979 (m), 2947 (m), 2904 (m), 2856 (m), 2822 (m), 2777 (m), 1715 (s), 1595 (s), 1577 (s), 1530 (s), 1497 (s), 1445 (s), 1423 (s) cm^{-1}. HRMS (CI): m/z calcd for $C_{18}H_{23}N_2O_2$ $[M + H]^+$ 299.1760, found 299.1753.

*5-Bromo-2-((dimethylamino)methyl)-N-phenylaniline (**13a**).* Following representative procedure A, without base, using substrate **32**[69] (0.100 g, 0.294 mmol), the crude mixture (ratio[45] **13a**/**13b** 64:36) was purified by silica gel column chromatography (99:1 to 95:5 dichloromethane/EtOAc) to afford product **13a** as a yellow oil (0.0405 g, 0.133 mmol, 45%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (br s, 1H), 7.42 (d, J = 1.7 Hz, 1H), 7.29 (t, J = 8.2 Hz, 2H), 7.09 (d, J = 7.7 Hz, 2H), 6.95 (t, J = 7.4 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.87 (dd, J = 7.9, 1.8 Hz, 1H), 3.40 (s, 2H), 2.22 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.5, 142.2, 131.6, 129.4, 123.9, 122.1, 121.5, 121.4, 119.0, 116.7, 63.1, 44.7; IR (thin film, $CDCl_3$) 3233 (br), 3092 (m), 3030 (m), 2977 (s), 2945 (s), 2857 (m), 2821 (s), 2774 (s), 1591 (s), 1576 (s), 1516 (s), 1497 (s), 1470 (s), 1411 (s), 1361 (m), 1324 (m) cm^{-1}. HRMS (CI): m/z calcd for $C_{15}H_{18}BrN_2$ $[M + H]^+$ 305.0653, found 305.0640.

*2-((Dimethylamino)methyl)-5-methyl-N-phenylaniline (**14a**).* Following representative procedure A, without base, using substrate **33**[69] (0.100 g, 0.343 mmol), the crude mixture (ratio[45] **14a**/**14b** 100:0) was treated with trimethylethylenediamine (0.15 mL), then purified by column chromatography (99:1 to 90:10 dichloromethane/EtOAc) to afford product **14a** as an orange oil (0.0517 g, 0.215 mmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (br s, 1H), 7.25 (t, J = 7.5 Hz, 2H), 7.18 (s, 1H), 7.09 (d, J = 7.6 Hz, 2H), 6.96 (d, J = 7.5 Hz, 1H), 6.87 (t, J = 7.3 Hz, 1H), 6.60 (d, J = 7.5 Hz, 1H), 3.40 (s, 2H), 2.27 (s, 3H), 2.21 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.5, 143.3, 137.8, 130.4, 129.2, 122.9, 120.1, 120.0, 117.9, 115.6, 63.2, 44.7, 21.4; IR (thin film, $CDCl_3$) 3250 (br), 3044 (m), 2976 (m), 2945 (m), 2855 (m), 2819 (m), 2773 (m), 1616 (m), 1593 (s), 1529 (s), 1497 (s), 1454 (s), 1417 (s), 1360 (m), 1325 (m), 1307 (m) cm^{-1}. HRMS (ESI): m/z calcd for $C_{16}H_{21}N_2$ $[M + H]^+$ 241.1705, found 241.1708.

*N-Phenyl-2-(piperidin-1-ylmethyl)aniline (**15a**).* Following representative procedure A, without base, using substrate **26**[69] (0.104 g, 0.345 mmol), the crude mixture (ratio[45] **15a**/**15b** 100:0) was purified by silica gel column chromatography (99:1 to 90:10 dichloromethane/EtOAc) to afford product **15a** as a tan oil (0.0537 g, 0.202 mmol, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.02 (br s, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.28−7.24 (m, 2H), 7.16 (t, J = 7.6 Hz, 1H), 7.09 (d, J = 8.3 Hz, 2H), 7.07 (d, J = 7.4 Hz, 1H), 6.89 (t, J = 7.4 Hz, 1H), 6.77 (t, J = 7.4 Hz, 1H), 3.51 (s, 2H), 2.51−2.27 (m, 4H), 1.61 (qn, J = 5.6 Hz, 4H), 1.57−1.44 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 143.8, 143.2, 130.5, 129.2, 127.9, 124.9, 120.2, 117.9, 114.1, 62.9, 53.8, 26.3, 24.4; IR (thin film, $CDCl_3$) 3236 (br), 3106 (m), 3045 (m), 2934 (s), 2851 (m), 2802 (m), 2758 (m), 1727 (m), 1593 (s), 1523 (s), 1497 (s), 1476 (s), 1462 (s), 1442 (s), 1390 (s), 1367 (s), 1342 (s), 1325 (s), 1308 (s) cm^{-1}. HRMS (ESI): m/z calcd for $C_{18}H_{23}N_2$ $[M + H]^+$ 267.1861, found 267.1860.

*2-((Dimethylamino)methyl)-N-(4-methoxyphenyl)aniline (**16a**).* Following representative procedure A using substrate **1** (0.0996 g, 0.381 mmol) and *p*-anisidine (0.0943 g, 0.766 mmol), the crude mixture (ratio[45] **16a**/**2b** 94:6) was purified by silica gel column chromatography (98:2 dichloromethane/EtOAc then switching to 89:10:1 dichloromethane/EtOAc/triethylamine) to afford product **16a** as a tan solid (0.0496 g, 0.193 mmol, 51%): mp 65.5−67.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (br s, 1H), 7.17−7.07 (m, 5H), 6.88 (d, J = 8.8 Hz, 2H), 6.74 (ddd, J = 7.0, 7.0, 2.0 Hz, 1H), 3.82 (s, 3H), 3.49 (s, 2H), 2.26 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 154.5, 145.5, 136.3, 130.4, 128.1, 124.3, 121.6, 118.1, 114.5, 113.2, 63.6, 55.5, 44.7; IR (thin film, $CDCl_3$) 3249 (br), 3105 (m), 3040 (m), 2976 (m), 2946 (s), 2904 (m), 2855 (m), 2820 (s), 2773 (s), 1601 (s), 1510 (s), 1458 (s), 1405 (m), 1362 (m), 1328 (s) cm^{-1}. HRMS (ESI): m/z calcd for $C_{16}H_{21}N_2O$ $[M + H]^+$ 257.1654, found 257.1647.

*N-(4-Chlorophenyl)-2-((dimethylamino)methyl)aniline (**17a**).* Following representative procedure A using substrate **1** (0.075 g, 0.287 mmol) and 4-chloroaniline (0.0732 g, 0.574 mmol), the crude mixture (ratio[45] **17a**/**2b** 97:3) was purified by silica gel column chromatography (9:1 dichloromethane/EtOAc) to afford product **17a** as a brown oil (0.0467 g, 0.179 mmol, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (br s, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.20−7.16 (m, 3H), 7.08 (dd, J = 7.4, 1.3 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 6.81 (ddd, J = 7.4, 7.4, 0.8 Hz, 1H), 3.44 (s, 2H), 2.23 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 143.3, 141.9, 130.6, 129.1, 128.1, 125.9, 124.5, 119.7, 118.8, 115.1, 63.5, 44.8; IR (thin film, $CDCl_3$) 3238 (br), 3178 (m), 3097 (m), 3025 (m), 2978 (m), 2946 (m), 2856 (m), 2821 (m), 2775 (m), 1591 (s), 1520 (s), 1492 (s), 1327 (s), 1310 (s) cm^{-1}. HRMS (CI): m/z calcd for $C_{15}H_{18}ClN_2$ $[M + H]^+$ 261.1158, found 261.1166.

*N-(3-Chlorophenyl)-2-((dimethylamino)methyl)aniline (**18a**).* Following representative procedure A using substrate **1** (0.100 g, 0.383 mmol) and 3-chloroaniline (0.081 mL, 0.766 mmol), the crude mixture (ratio[45] **18a**/**2b** 89:11) was purified by silica gel column chromatography (95:5 dichloromethane/EtOAc) to afford product **18a** as a tan oil (0.0486 g, 0.186 mmol, 49%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (br s, 1H), 7.35 (dd, J = 8.1, 0.6 Hz, 1H), 7.20 (td, J = 7.7, 1.6 Hz, 1H), 7.13 (t, J = 8.1 Hz, 1H), 7.09 (dd, J = 7.4, 1.3 Hz, 1H), 7.06 (t, J = 2.1 Hz, 1H), 6.95−6.93 (m, 1H), 6.85−6.80 (m, 2H), 3.43 (s, 2H), 2.22 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 144.7, 142.7, 134.8, 130.5, 130.2, 128.1, 126.4, 120.2, 119.7, 116.8, 115.9, 115.2, 63.5, 44.8; IR (thin film, $CDCl_3$) 3237 (br), 3178 (m), 3099 (m), 3057 (m), 3025 (m), 2946 (m), 2858 (m), 2822 (m), 2776 (m), 1589 (s), 1523 (s), 1480 (s), 1329 (s), 1309 (s) cm^{-1}. HRMS (CI): m/z calcd for $C_{15}H_{18}ClN_2$ $[M + H]^+$ 261.1158, found 261.1151.

*2-Chloro-N-(2-((dimethylamino)methyl)phenyl)aniline (**19a**).* Following representative procedure A, without base, using substrate **1** (0.100 g, 0.383 mmol) and 2-chloroaniline (0.081 mL, 0.766 mmol), the crude mixture (ratio[45] **19a**/**2b** 66:33) was purified by silica gel column chromatography (99:1 to 98:2 dichloromethane/EtOAc) to afford product **19a** as a tan oil (0.0355 g, 0.136 mmol, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (br s, 1H), 7.39 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 7.9 Hz, 1H), 7.20 (t, J = 8.2 Hz, 1H), 7.13−7.09 (m, 2H), 6.86 (t, J = 7.4 Hz, 1H), 6.76 (t, J = 7.8 Hz, 1H), 3.44 (s, 2H), 2.25 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 142.3, 140.3, 130.5, 129.9, 127.9, 127.4, 127.1, 122.1, 120.3, 119.7, 116.4, 115.7, 63.1, 44.5; IR (thin film, $CDCl_3$) 3218 (br), 3038 (m), 2976 (m), 2945 (m), 2857 (m), 2820 (m), 2774 (m), 1590 (s), 1525 (s), 1482 (m), 1466 (s), 1361 (m), 1329 (m), 1309 (m) cm^{-1}. HRMS (ESI): m/z calcd for $C_{15}H_{18}ClN_2$ $[M + H]^+$ 261.1158, found 261.1166.

*N-(4-Bromophenyl)-2-((dimethylamino)methyl)aniline (**20a**).* Following representative procedure A using substrate **1** (0.075 g, 0.287 mmol) and 4-bromoaniline (0.0987 mg, 0.574 mmol), the crude mixture (ratio[45] **20a**/**2b** 96:4) was purified by silica gel column chromatography (9:1 dichloromethane/EtOAc then 99:1 EtOAc/triethylamine) to afford product **20a** as a brown solid (0.0510 g, 0.167 mmol, 58%): mp 95.4−96.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (br s, 1H), 7.34−7.28 (m, 3H), 7.18 (app t, J = 8.3 Hz, 1H), 7.09 (d, J

DOI: 10.1021/acs.joc.5b01074
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= 7.4 Hz, 1H), 6.97−6.94 (m, 2H), 6.82 (t, J = 7.4 Hz, 1H), 3.44 (s, 2H), 2.23 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 143.2, 142.5, 132.0, 130.6, 128.1, 126.1, 119.9, 119.1, 115.3, 111.7, 63.5, 44.8; IR (thin film, $CDCl_3$) 3241 (br), 3045 (m), 2977 (m), 2945 (m), 2856 (m), 2821 (m), 2774 (m), 1587 (s), 1521 (s), 1488 (s), 1473 (s), 1455 (s) cm^{-1}. HRMS (CI): m/z calcd for $C_{15}H_{18}BrN_2$ $[M + H]^+$ 305.0653, found 305.0646.

*N-(2-((dimethylamino)methyl)phenyl)pyridin-2-amine (**21a**).* Following representative procedure A, without base, using substrate **1** (0.100 g, 0.383 mmol) and 2-aminopyridine (0.0721 mL, 0.766 mmol), the crude mixture (ratio[45] **21a**/**2b** 100:0) was purified by silica gel column chromatography (1:1 hexanes/EtOAc), and the resulting product residue was azeotroped with ethanol (3 × 2 mL) to afford product **21a** as a yellow oil (0.0350 g, 0.154 mmol, 40%). ^1H NMR (500 MHz, $CDCl_3$) δ 9.40 (br s, 1H), 8.23 (d, J = 4.2 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.49−7.45 (m, 1H), 7.28−7.25 (m, 1H), 7.11 (d, J = 7.3 Hz, 1H), 6.89 (t, J = 7.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.71−6.68 (m, 1H), 3.48 (s, 2H), 2.26 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.8, 148.3, 141.2, 137.3, 130.2, 128.1, 126.6, 120.8, 118.0, 114.5, 109.6, 63.5, 44.8; IR (thin film, $CDCl_3$) 3252 (br), 3015 (m), 2978 (m), 2946 (m), 2858 (m), 2822 (m), 2776 (m), 1595 (s), 1571 (s), 1525 (s), 1481 (s), 1455 (s), 1418 (s), 1348 (s), 1308 (s) cm^{-1}. HRMS (ESI): m/z calcd for $C_{14}H_{17}N_3Na$ $[M + Na]^+$ 250.1320, found 250.1328.

*N-(2-((Dimethylamino)methyl)-4-methoxyphenyl)-2,4,6-trimethylaniline (**22a**).* Following representative procedure A using substrate **29**[69] (0.0871 g, 0.299 mmol) and 2,4,6-trimethylaniline (0.084 mL, 0.598 mmol), the crude mixture (ratio[45] **22a**/**10b** 100:0) was purified by silica gel column chromatography (100% dichloromethane then switching to 100% EtOAc) to afford product **22a** as a brown oil (0.0442 g, 0.148 mmol, 49%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (br s, 1H), 6.93 (s, 2H), 6.70 (d, J = 2.9 Hz, 1H), 6.60 (dd, J = 8.7, 3.0 Hz, 1H), 6.09 (d, J = 8.7 Hz, 1H), 3.74 (s, 3H), 3.51 (s, 2H), 2.31 (s, 3H), 2.26 (s, 6H), 2.13 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.3, 140.4, 137.3, 134.2, 133.6, 129.0, 124.5, 116.7, 112.4, 112.1, 63.6, 55.7, 44.8, 20.8, 18.2; IR (thin film, $CDCl_3$) 3250 (br), 2973 (s), 2943 (s), 2914 (s), 2853 (s), 2819 (s), 2772 (s), 1505 (s), 1486 (s), 1465 (s), 1425 (m), 1376 (m), 1358 (m), 1309 (m), 1292 (m), 1264 (m), 1231 (s), 1292 (s) cm^{-1}. HRMS (CI): m/z calcd for $C_{19}H_{26}N_2O$ $[M]^+$ 298.2045, found 298.2036.

*2-((Dimethylamino)methyl)-3-fluoro-N-(4-methoxyphenyl)-aniline (**23a**).* Following representative procedure A, without base, using substrate **27**[69] (0.0811 g, 0.291 mmol) and 4-anisidine (0.0717 g, 0.582 mmol), the crude mixture (ratio[45] **23a**:**8b** 100:0) was treated with tetramethylethylenediamine (0.15 mL), concentrated onto Celite, and purified by silica gel column chromatography (99:1 to 80:20 dichloromethane/EtOAc) to afford product **23a** as an orange oil (0.0332 g, 0.121 mmol, 42%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (br s, 1H), 7.08−7.01 (m, 3H), 6.88 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.2 Hz, 1H), 6.47 (t, J = 8.9 Hz, 1H), 3.82 (s, 3H), 3.57 (s, 2H), 2.28 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.9 (d, J_{C-F} = 241.1 Hz), 155.0, 147.9 (d, J_{C-F} = 5.9 Hz), 135.7, 128.5 (d, J_{C-F} = 11.0 Hz), 122.5, 114.6, 110.8 (d, J_{C-F} = 15.4 Hz), 108.5, 104.8 (d, J_{C-F} = 23.4 Hz), 55.6, 53.3 (d, J_{C-F} = 4.4 Hz), 44.6; IR (thin film, $CDCl_3$) 3238 (br), 3033 (m), 2947 (m), 2859 (m), 2826 (m), 2776 (m), 1620 (s), 1597 (s), 1583 (s), 1510 (s), 1471 (s), 1442 (m), 1365 (m), 1331 (m), 1288 (m), 1236 (s) cm^{-1}. HRMS (CI): m/z calcd for $C_{16}H_{19}FN_2O$ $[M]^+$ 274.1481, found 274.1487.

*N-(3-Chlorophenyl)-2-(piperidin-1-ylmethyl)aniline (**24a**).* Following representative procedure A, without base, using substrate **26**[69] (0.100 g, 0.332 mmol) and 3-chloroaniline (0.070 mL, 0.664 mmol), the crude mixture (ratio[45] **24a**/**15b** 72:28) was purified by silica gel column chromatography (99:1 to 90:10 dichloromethane/EtOAc) to afford product **24a** as an orange oil (0.0545 g, 0.181 mmol, 55%). ^1H NMR (500 MHz, $CDCl_3$) δ 9.16 (br s, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.20 (t, J = 7.7 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H), 7.09 (d, J = 7.4 Hz, 1H), 7.07 (br s, 1H), 6.94 (d, J = 8.2 Hz, 1H), 6.84−6.82 (m, 2H), 3.51 (s, 2H), 2.51−2.29 (m, 4H), 1.62 (qn, J = 5.4 Hz, 4H), 1.55−1.45 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.7, 142.8, 134.8, 130.6, 130.2, 128.0, 125.6, 119.9, 119.7, 116.7, 115.3, 115.2, 62.8, 53.8, 26.3, 24.3; IR (thin film, $CDCl_3$) 3228 (br), 3174 (m), 3055 (m), 2935 (s), 2851 (m), 2805 (m), 2759 (m), 1726 (m), 1589 (s), 1523 (s), 1479 (s), 1442 (m), 1417 (m), 1367 (m), 1341 (s) cm^{-1}. HRMS (ESI): m/z calcd for $C_{18}H_{22}ClN_2$ $[M + H]^+$ 301.1472, found 301.1469.

*Ethyl 3-((4-bromophenyl)amino)-4-((dimethylamino)methyl)-benzoate (**25a**).* Following representative procedure A, without base, using substrate **31**[69] (0.100 g, 0.300 mmol) and 4-bromoaniline (0.1032 mL, 0.600 mmol), the crude mixture (ratio[45] **25a**/**12b** 74:26) was treated with trimethylethylenediamine (0.1 mL), concentrated onto Celite, and purified by silica gel column chromatography (99:1 to 90:10 dichloromethane/EtOAc) to afford product **25a** as a brown oil (0.0623 g, 0.165 mmol, 55%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (br s, 1H), 7.95 (s, 1H), 7.49 (dd, J = 7.6, 1.0 Hz, 1H), 7.37 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 7.7 Hz, 1H), 6.99 (d, J = 8.7 Hz, 2H), 4.35 (d, J = 7.1 Hz, 2H), 3.49 (s, 2H), 2.24 (s, 6H), 1.37 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.6, 143.3, 141.8, 132.1, 130.5, 130.5, 130.4, 120.7, 119.4, 115.4, 112.4, 63.3, 60.9, 44.8, 14.3; IR (thin film, $CDCl_3$) 3231 (br), 2979 (m), 2904 (m), 2859 (m), 2823 (m), 2778 (m), 1716 (s), 1586 (s), 1526 (s), 1489 (s), 1439 (s), 1392 (m), 1363 (m), 1333 (s), 1301 (s) cm^{-1}. HRMS (ESI): m/z calcd for $C_{18}H_{21}BrN_2O_2Na$ $[M + Na]^+$ 399.0684, found 399.0677.

*2,2′-(N,N-Dimethylaminomethyl)-1,1′-biphenyl (**2b**).* See representative procedure B: mp 35.0−37.1 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, J = 7.8, 0.7 Hz, 2H), 7.35 (td, J = 5.1, 1.4 Hz, 2H), 7.25 (td, J = 4.6, 1.4 Hz, 2H), 7.08 (dd, J = 7.6, 1.4 Hz, 2H), 3.17 (d, J = 13.7 Hz, 2H), 3.06 (d, J = 13.8 Hz, 2H), 2.10 (s, 12 H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 140.7, 137.2, 129.6, 128.7, 127.3, 126.1, 60.9, 45.5; IR (thin film, CH_2Cl_2) 3056 (m), 3021 (m), 2972 (m), 2940 (m), 2853 (m), 2815 (m), 2767 (br), 1455 (s), 1442 (s), 1403 (s), 1362 (s), 1303 (m), 1264 (m), 1174 (s), 1147 (s), 1097 (s), 1029 (m), 1007 (s) cm^{-1}. HRMS (CI): m/z calcd for $C_{18}H_{24}N_2$ $[M + H]^+$ 269.2018, found 269.2014. This data corresponds to previously reported data.[70]

*1,1′-(3,3′-Difluoro-[1,1′-biphenyl]-2,2′-diyl)bis(N,N-dimethylmethanamine) (**8b**).* Following representative procedure B using substrate **27**[69] (0.100 g, 0.358 mmol), the crude mixture was purified by Kugelrohr distillation (0.5 mmHg, 60 °C, 45 min; 0.5 mmHg, 80 °C, 80 min) to yield product **8b** as a colorless oil (0.043 g, 0.128 mmol, 71%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.28−7.24 (m, 2H), 7.07 (td, J = 8.2, 1.2 Hz, 2H), 7.02 (dd, J = 7.5, 1.2 Hz, 2H), 3.38 (dd, J = 12.4, 1.9 Hz, 2H), 2.90 (dd, J = 12.4, 1.5 Hz, 2H), 2.01 (s, 12 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.6 (d, J_{C-F} = 245.5 Hz), 142.8, 127.8 (d, J_{C-F} = 9.5 Hz), 126.0, 124.9 (d, J_{C-F} = 14.7 Hz), 114.6 (d, J_{C-F} = 22.7 Hz), 54.1, 45.2; IR (thin film, CH_2Cl_2) 2971 (m), 2942 (m), 2858 (s), 2817 (m), 2769 (m), 1610 (s), 1577 (s), 1486 (m), 1364 (s), 1310 (s), 1258 (s), 1237 (s), 1184 (s), 1117 (s), 1096 (s), 1043 (s), 1023 (s) cm^{-1}. HRMS (CI): m/z calcd for $C_{18}H_{22}F_2N_2$ $[M + H]^+$ 305.1829, found 305.1830.

*1,1′-(4,4′-Dimethyl-[1,1′-biphenyl]-2,2′-diyl)bis(N,N-dimethylmethanamine) (**9b**).* Following representative procedure B using substrate **28**[69] (0.100 g, 0.363 mmol), the crude mixture was purified by basic alumina column chromatography (90:10 dichloromethane/ethyl acetate to 99:1 ethyl acetate/triethylamine) to afford product **9b** as a colorless solid (0.0214 g, 0.0722 mmol, 40%): mp 99.3−101.0 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 2H), 7.05 (d, J = 7.6 Hz, 2H), 6.95 (d, J = 7.7 Hz, 2H), 3.15 (d, J = 13.7 Hz, 2H), 3.05 (d, J = 13.6 Hz, 2H) 2.40 (s, 6 H), 2.10 (s, 12H); $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$) δ 137.7, 137.0, 136.8, 129.8, 129.1, 126.9, 60.8, 45.6, 21.2; IR (thin film, CH_2Cl_2) 3019 (br), 2972 (m), 2940 (m), 2854 (s), 2814 (s), 2765 (m), 1611 (s), 1485 (s), 1455 (m), 1361 (s), 1299 (m), 1262 (m), 1175 (s), 1148 (s), 1096 (s), 1031 (m), 1008 (s) cm^{-1}. HRMS (CI): m/z calcd for $C_{20}H_{28}N_2$ $[M + H]^+$ 297.2331, found 297.2331.

*1,1′-(4,4′-Dimethoxy-[1,1′-biphenyl]-2,2′-diyl)bis(N,N-dimethylmethanamine) (**10b**).* Following representative procedure B using substrate **29**[69] (0.100 g, 0.343 mmol), the crude mixture was purified by column chromatography on basic alumina (90:10 dichloromethane/ethyl acetate to 99:1 ethyl acetate/triethylamine) to afford product **10b** as a colorless solid (0.0257 g, 0.0783 mmol, 46%): mp

DOI: 10.1021/acs.joc.5b01074
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84.6−85.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 2.2 Hz, 2H), 6.96 (d, J = 6.7, 2H), 6.79 (dd, J = 6.6, 2.2 Hz, 2H), 3.86 (s, 6H), 3.11 (d, J = 11.1 Hz, 2H), 3.05 (d, J = 11.1 Hz, 2H), 2.11 (s, 12H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 158.8, 139.0, 132.8, 131.1, 113.5, 112.1, 61.0, 55.3, 45.6; IR (thin film, CH_2Cl_2) 2971 (br), 2941 (m), 2906 (br), 2854 (s), 2816 (m), 2767 (m), 1605 (s), 1570 (s), 1482 (s), 1466 (br), 1362 (s), 1276 (br), 1228 (s), 1174 (s), 1159 (s), 1146 (s), 1118 (s), 1097 (s), 1053 (m), 1030 (m), 1002 (s) cm^{-1}. HRMS (CI): m/z calcd for $C_{20}H_{28}N_2O_2$ [M + H]$^+$ 329.2229, found 329.2243.

*1,1′-(4,4′-Dichloro-[1,1′-biphenyl]-2,2′-diyl)bis(N,N-dimethylmethanamine) (**11b**).* Following representative procedure B using substrate **30**[69] (0.050 g, 0.169 mmol) without base, the crude mixture was purified by column chromatography on basic alumina (90:10 dichloromethane/ethyl acetate to 99:1 ethyl acetate/triethylamine) to afford product **11b** as a colorless solid (0.0125 g, 0.0371 mmol, 44%): mp 107.6−109.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 2.3 Hz, 2H), 7.24 (dd, J = 8.1, 2.2 Hz, 2H), 6.98 (d, J = 8.1 Hz, 2H), 3.08 (d, J = 14.0 Hz, 2H), 3.00 (d, J = 14.0 Hz, 2H), 2.10 (s, 12H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 139.5, 137.9, 133.6, 130.8, 128.7, 126.5, 60.6, 45.5; IR (thin film, CH_2Cl_2) 2973 (m), 2942 (m), 2856 (s), 2817 (m), 2769 (m), 1589 (s), 1455 (m), 1395 (br), 1360 (s), 1295 (br), 1263 (br), 1244 (br), 1185 (br), 1148 (br), 1094 (m), 1033 (m), 1006 (s) cm^{-1}. HRMS (CI): m/z calcd for $C_{18}H_{22}Cl_2N_2$ [M + H]$^+$ 337.1238, found 337.1245.

*Diethyl 6,6′-bis((dimethylamino)methyl)-[1,1′-biphenyl]-3,3′-dicarboxylate (**12b**).* Following representative procedure B using substrate **31**[69] (0.100 g, 0.300 mmol), the crude mixture was purified by basica alumina column chromatography (90:10 dichloromethane/ethyl acetate to 99:1 ethyl acetate/triethylamine) to afford product **12b** as a colorless solid (0.0156 g, 0.0378 mmol, 25%): mp 97.0−99.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.4 Hz, 2H), 7.76 (s, 2H), 7.67 (d, J = 8.1 Hz, 2H), 4.37 (q, J = 7.08, 4H), 3.18 (d, J = 14.3 Hz, 2H), 3.09 (d, J = 14.3 Hz, 2H), 2.10 (s, 12H), 1.38 (t, J = 7.04, 6H); ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 166.5, 142.7, 139.8, 130.6, 128.8, 128.7, 128.6, 60.95, 60.90, 45.5, 14.3; IR (thin film, CH_2Cl_2) 2977 (m), 2941 (m), 2903 (br), 2856 (br), 2817 (m), 2769 (m), 1719 (m), 1606 (s), 1572 (br), 1456 (br), 1391 (m), 1365 (s), 1307 (s), 1278 (br), 1249 (br), 1227 (s), 1173 (s), 1148 (s), 1108 (m), 1028 (m) cm^{-1}. HRMS (ESI): m/z calcd for $C_{24}H_{32}N_2O_4Na$ [M + Na]$^+$ 435.2260, found 435.2259.

*1,1′-(5,5′-Dibromo-[1,1′-biphenyl]-2,2′-diyl)bis(N,N-dimethylmethanamine) (**13b**).* This byproduct of the amination reaction was not isolated in pure form. Diagnostic spectral data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, J = 8.4, 1.8 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 1.8 Hz, 2H), 3.11 (d, J = 13.9 Hz, 2H), 3.00 (d, J = 13.9 Hz, 2H), 2.11 (s, 12H).

*1,1′-(5,5′-Dimethyl-[1,1′-biphenyl]-2,2′-diyl)bis(N,N-dimethylmethanamine) (**14b**).* Following representative procedure B using substrate **33**[69] (0.100 g, 0.363 mmol), the crude mixture was purified by column chromatography on basic alumina (90:10 dichloromethane/ethyl acetate to 99:1 ethyl acetate/triethylamine) to afford product **14b** as a colorless solid (0.0224 g, 0.0756 mmol, 42%): mp 90.4−90.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 7.8 Hz, 2H), 7.16 (d, J = 8.8 Hz, 2H), 6.89 (s, 2H), 3.14 (d, J = 13.6 Hz, 2H), 3.03 (d, J = 13.6 Hz, 2H) 2.34 (s, 6H), 2.10 (s, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 140.7, 135.5, 134.1, 130.3, 128.5, 127.9, 60.6, 45.47, 21.03; IR (thin film, CH_2Cl_2) 3014 (br), 2972 (br), 2940 (br), 2853 (m), 2814 (m), 2764 (m), 1609 (m), 1454 (br), 1361 (s), 1298 (br), 1260 (br), 1174 (s), 1148 (s), 1130 (s), 1096 (s), 1030 (m) cm^{-1}. HRMS (ESI): m/z calcd for $C_{20}H_{28}N_2Na$ [M + Na]$^+$ 319.2150 found 319.2153.

*2,2′-Bis(piperidin-1-ylmethyl)-1,1′-biphenyl (**15b**).* Following representative procedure B using substrate **26**[69] (0.100 g, 0.332 mmol), the crude mixture was purified by column chromatography on basic alumina (90:10 dichloromethane/EtOAc then switching to 99:1 EtOAc/triethylamine) to afford product **15b** as a colorless oil (0.0322 g, 0.0924 mmol, 56%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 7.5 Hz, 2H), 7.32 (t, J = 7.0 Hz, 2H), 7.23 (t, J = 7.0 Hz, 2H), 7.08 (d, J = 7.5 Hz, 2H), 3.18 (d, J = 14.0 Hz, 2H), 3.09 (d, J = 14.5 Hz, 2H), 2.29−2.14 (m, 8H), 1.50−1.48 (m, 8H), 1.41−1.31 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 141.0, 137.1, 129.7, 128.7, 126.9, 125.8, 60.6, 54.6, 26.0, 24.4; IR (thin film, $CDCl_3$) 3057 (m), 3021 (m), 2932 (s), 2851 (s), 2794 (s), 2754 (s), 2721 (m), 2683 (m), 1467 (m), 1442 (m), 1390 (m), 1367 (m), 1344 (m), 1325 (m), 1301 (m) cm^{-1}. HRMS (ESI): m/z calcd for $C_{24}H_{32}N_2Na$ [M + Na]$^+$ 371.2463, found 371.2459.

*1-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-piperidine (**26**).* Following the published procedure, benzyl bromide and piperidine were used to synthesize 1-benzylpiperidine, which matched previously reported data.[71] To a solvent flask in a nitrogen-filled glovebox was added [Ir(OMe)COD]$_2$ (0.0597 g, 0.090 mmol), bis(pinacolato)diboron (1.27 g, 5.01 mmol), picolylamine (0.0186 g, 0.180 mmol), followed by 1-benzylpiperidine (1.05 g, 6.00 mmol), and methylcyclohexane (12 mL). The flask was sealed and heated at 90 °C for 33 h. Upon cooling to room temperature, the reaction was concentrated in vacuo and was found to have proceeded in 77% conversion and 87:13 mono-*ortho*/bis-*ortho* ratio of boronate esters by ^{1}H NMR spectroscopy. The crude brown oil (2.19 g) was purified by basic alumina column chromatography (98:1:1 dichloromethane/MeOH/triethylamine). The resulting product residue was further purified by Kugelrohr distillation (0.5 mmHg, 70 °C, 20 min, trap residue discarded; then 0.5 mmHg, 120 °C 1.5 h, trap residue discarded; then 0.5 mmHg, 120 °C, 1.5 h, trap residue was product) to afford **26** as a colorless oil (0.507 g, 1.68 mmol, 28%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 7.1 Hz, 1H), 7.26−7.23 (m, 1H), 7.20 (t, J = 6.7 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 3.79 (s, 2H), 2.60−2.58 (m, 4H), 1.60−1.56 (m, 4H), 1.52−1.49 (m, 2H), 1.34 (s, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.4, 133.1, 128.5, 126.6, 126.2, 81.7, 60.2, 52.8, 25.5, 23.8, 23.5; IR (thin film, $CDCl_3$) 2977 (s), 2934 (s), 2854 (m), 2800 (m), 1570 (m), 1601 (m), 1490 (m), 1443 (s), 1381 (s), 1371 (s), 1350 (s), 1310 (s) cm^{-1}. HRMS (ESI): m/z calcd for $C_{18}H_{28}BNO_2Na$ [M + Na]$^+$ 324.2114, found 324.2114.

■ ASSOCIATED CONTENT

Supporting Information

Molecular structures and the preparation of boronate ester substrates and ^{1}H and ^{13}C{^{1}H} NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01074.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the UCI Mass Spectrometry facility, National Science Foundation (CHE-1151092 and CHE-1339149), University of San Diego, and Research Corporation for Science Advancement Department Development Award.

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(46) Reaction conditions consisted of combining **1** with isopropylamine, 10 mol % $Cu(OAc)_2{\cdot}H_2O$, and 3Å MS in dichloromethane under O_2 and heating at 40 °C for 2 h.
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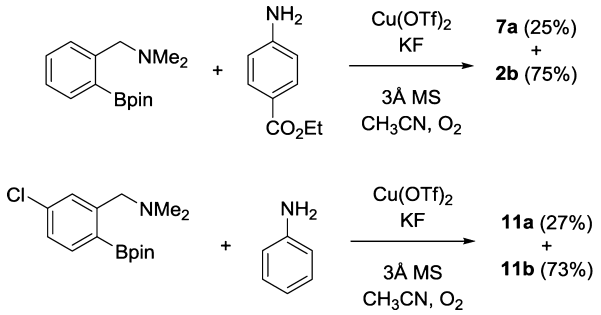
(50) Although evidence for aldehyde or imine formation was not observed in the crude reaction mixture, oxidative deamination cannot be ruled out.
(51) The following substituted substrates were investigated to determine the general use of $Cu(OTf)_2$. The percent selectivity of **a** and **b** is given in parenthases and was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.



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(55) See Supporting Information, Table S-1.
(56) See Supporting Information, Table S-2.
(57) The amination of **1** with *N*-methylaniline and phthalimide were examined in an effort to access tertiary amines. Both amines provided poor conversion to the desired diamine products.
(58) Minor formation of the protodeboration product was observed. See Supporting Information, Table S-3.
(59) The biaryl coupling of two different boronate esters with opposing electronic substituents ($-CO_2Et$ and $-OCH_3$) was found to form both homocoupling products (**10b** and **12b**) and the cross-coupled product, but no significant selectivity was observed.
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