

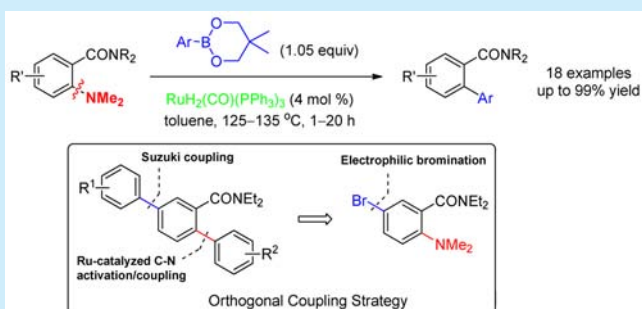
Beyond Directed *Ortho* Metalation: Ruthenium-Catalyzed Amide-Directed C_{Ar}–N Activation/C–C Coupling Reaction of Anthranilamides with Organoboronates

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S Supporting Information

ABSTRACT: A new, catalytic, and general methodology for the synthesis of biaryls and heterobiaryls by the cross coupling of anthranilamide derivatives (*o*-NMe₂ benzamides) with aryl boroneopentylates is described. The reaction proceeds under catalytic RuH₂(CO)(PPh₃)₃ conditions driven by the activation of the unreactive C–N bond by amide directing group (DG)-Ru catalyst chelation. High regioselectivity, orthogonality with the Suzuki–Miyaura reaction, operational simplicity, and convenient scale-up are features of these reactions which may lend themselves to industrial applications.



Although still in nascent development, the area of activation of unreactive C–H, C–O, and C–N bonds mediated by transition-metal catalysis promises to greatly enrich the toolbox of synthetic organic chemists.¹ Amines constitute one of the most prevalent and unreactive classes of organic compounds, among which the arylamines have particularly high C–N bond dissociation energy² whose cleavage usually invokes conversion to more reactive leaving groups³ such as diazonium salts,^{3a–c} ammonium salts,^{3d–h} triazenes,³ⁱ azoles,^{3j} and arylhydrazines.^{3k} Although scattered observations of aniline C–N bond cleavage had been reported,^{3d–h,k,4} it was the discovery of Kakiuchi in 2007 which provided the first, catalytic C–N coupling reaction of *o*-NMe₂ substituted pivalophenones with organoboronates under RuH₂(CO)(PPh₃)₃-catalyzed conditions^{1g} (Table 1), parallel to their equally important original findings of the aryl C–OMe bond activation–cleavage process in the corresponding *o*-OMe substituted aryl ketones.⁵ In the Kakiuchi C–NMe₂

activation reaction, consistent also with the requirements for C–H and C–OMe activation processes,^{5,6} chelation assistance from an anchoring ketone directing group (DG)⁷ was established as the significant initial event of the highly efficient C–NMe₂ activation/organoboronate cross coupling reactions (Table 1, DG = C(O)Me and C(O)-*t*-Bu).

Motivated by these findings, we proposed that the tertiary amide CONEt₂, a powerful directed metalation group (DMG), widely exploited in directed *ortho* metalation (DoM) synthetic strategies,⁸ may offer a chelating DG consequence for C–H, C–O, and C–N bond activation/cross-coupling reactions based on the following rationale: the CONEt₂ group should exhibit greater coordinating ability than esters and ketones,⁹ DGs whose activation of these bonds has been established; although two different reaction types are compared, the well-known steric bulk of CONEt₂ in DoM chemistry in resisting nucleophilic attack by organolithium reagents suggested that it would exhibit properties similar to those of the *tert*-butyl group in *o*-NMe₂/OMe-pivalophenones in preventing nonregioselective C–H, C–O, and C–N activation and, therefore, diarylation.^{1g,5}

In pursuit of demonstration of these objectives, we have recently achieved the Ru-catalyzed *N,N*-diethyl *o*-OMe benzamide (*o*-anisamide)/aryl boronate cross-coupling reaction.¹⁰ Coincident with these studies, we initiated work on the corresponding *o*-NMe₂ benzamide/aryl boronate coupling (Table 1, DG = CONEt₂) and herein report our preliminary results. We demonstrate that the DG = CONEt₂ serves effectively for C–NMe₂ activation in the Ru-catalyzed cross coupling with aryl boroneopentylates (ArBneop), thus

Table 1. Selectivity of Ketone- and Amide-Directed C–NMe₂ and C–H Activation/Coupling Reactions

DG	R	activation/coupling via C–H	activation/coupling via C–N	product	ref
C(O)Me	NMe ₂	✓	✓	3	1g
C(O) <i>t</i> -Bu	NMe ₂ , NHMe, NH ₂ , N(Me)Ac	X	✓	2	1g
CONEt ₂	NMe ₂	X	✓	2	this work

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providing a new general methodology which (a) displays all the advantageous attributes of the regioselective DoM strategy in pre- and postcoupling modes; (b) offers complementarity to the DoM reaction in a process that avoids cryogenic temperatures and strong base conditions; (c) is amenable to orthogonal cross coupling variation;¹¹ and (d) provides opportunity for ready amide to other functional group conversions.¹² Combined, these features offer new promising opportunities for synthetic aromatic chemistry.

In the prototype experiment, treatment of *N,N*-diethyl *o*-NMe₂ benzamide (anthranilamide) with PhBneop under conditions similar to those applied in the *o*-anisamide reaction¹⁰ afforded the diphenyl amide **2a** (Table 2) in quantitative yield

Table 2. Screening Amino Groups for the Cross-Coupling Reaction of *o*-Amino Benzamides with PhBneop

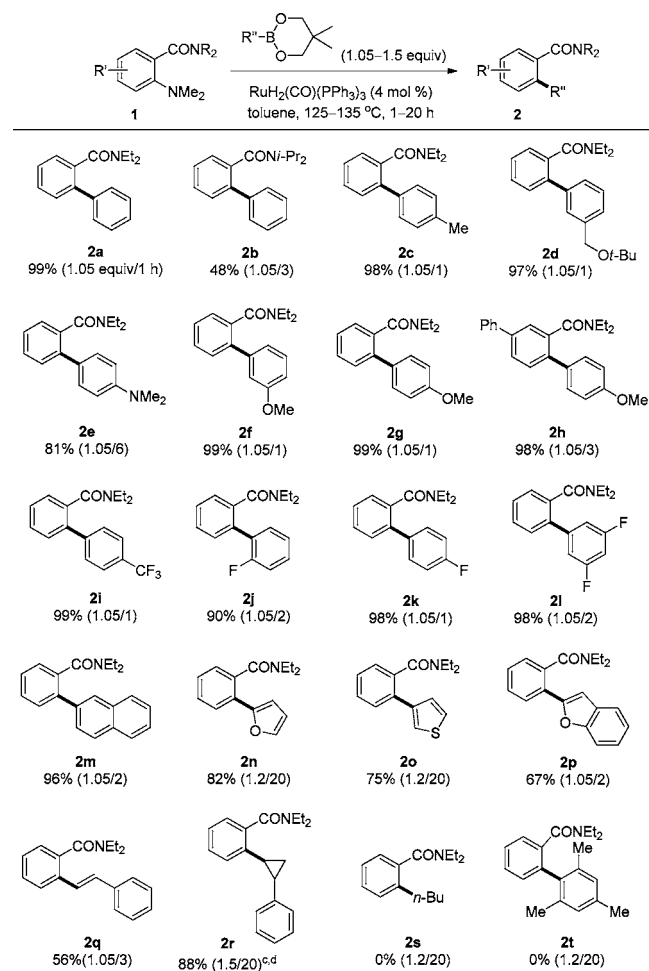
entry	amide	time (h)	product	yield (%)
1		1	2a	99 ^a
2		20	2a	(44) ^b
3		20	---	--- ^c

^aYields are of isolated and purified products. ^bYield determined by GC-MS analysis; PhNHMe was also formed in 11% yield (GC). ^cStarting material recovery (95%).

in a 1 h reaction time with no detectable product of alternative C-H activation/cross coupling. As established also in the *o*-anisamide coupling reaction,¹⁰ the significance of DG-chelation assistance was demonstrated by treatment of *N,N*-diethyl 3- and 4-NMe₂ benzamides with PhBneop for an extended time (20 h) which resulted in recovery of starting material with <4% detection of phenylated products (GC-MS analysis, see the SI). Similar to our observations for the C-OMe activation/coupling reactions¹³ and as reported by Kakiuchi,⁵ aryl boroneopentylates appear to be unique in reactivity as the corresponding boropinacولات and boronic acids failed to give C-N activation/cross coupling products (SI). To obtain appreciation of amide N-substitution steric effects, *N,N*-diisopropyl *o*-NMe₂ benzamide was tested and found, even under 3 h refluxing toluene conditions, to give the corresponding 2-phenyl derivative **2b** in much decreased (48%) yield (Scheme 1). *N,N*-Dimethyl benzamides were not considered in view of their ineffectiveness in DoM chemistry.¹⁴

Brief examination of *N*-2-amino substitution (Table 2) showed that the bulky 2-N(Me)Ph group inhibited the reaction leading to the corresponding 2-phenyl-coupled product **2a** in only 44% yield after a 20 h reaction time and also to the formation of byproduct PhNHMe (11% yield), as direct evidence of reductive deamination. When *N,N*-diethyl 2-NH₂ benzamide was subjected to the coupling reaction conditions, starting material was recovered in quantitative yield, in contrast

Scheme 1. Ru-Catalyzed Cross Coupling Reaction of *o*-NMe₂ Benzamides with Bneops^{a,b}



^aYields are of isolated and purified products. ^bEquivalents of boroneopentylates/reaction times in hours are shown in parentheses. ^c10 mol % catalyst loading. ^d*cis* or *trans* stereochemistry not established by ¹H NMR due to almost identical *J*_{*cis*} and *J*_{*trans*} coupling constants¹⁹ and unavailability of crystalline material for X-ray analysis.

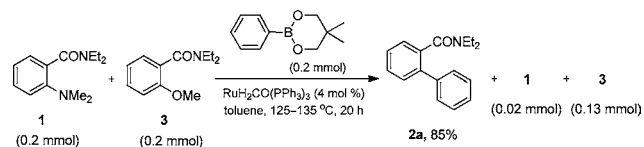
to the observations in ketone-directed C-N activation/coupling in which 2-NH₂ (and 2-NHMe) did not prevent efficient aryl coupling.¹⁸ Thus, it appears that minimal steric hindrance and unavailability of N-H bonds are important requirements to achieve a highly efficient amide-directed C-N activation/cross-coupling result.

To complete our screening experiments, optimum temperatures for short reaction time (130 °C/1 h) and boroneopentylate reactant (1.05 equiv) and RuH₂(CO)(PPh₃)₃ catalyst (4 mol %) stoichiometries were determined (SI). With these control and structural parameters in hand, we proceeded to test the generality of the reaction with a variety of aryl boroneopentylates. The results are shown in Scheme 1 and deserve comment. First, the coupling reaction proceeds mostly in excellent yields for EDGs (electron-donating groups) such as Me, CH₂O-*t*-Bu, NMe₂, and OMe (**2c–h**, Scheme 1). However, EWGs (electron-withdrawing groups) showed a range of effects. When F- and CF₃-bearing aryl Bneops were employed, the coupling reaction proceeded in high yields (**2i–l**). However, when CHO-, CN-, and NO₂-substituted ArBneops were used, the arylation was completely inhibited even after a

20 h reaction time (SI).¹⁵ While CHO-, CN-, and NO₂-substituted ArBneops were not studied in the *o*-NMe₂ pivalophenones by Kakiuchi, these workers also observed, as part of an insightful mechanistic study, a similar higher reactivity of the corresponding CF₃-arylBneop derivative which was attributed to an accelerating effect of the amido Ru species–arylboronate transmetalation step due to higher Lewis acidity at the boron atom.^{7b,16} Similar to our results for the *o*-OMe aryl amide C–O activation/arylation reaction,¹³ chloro- and bromo-ArBneop derivatives were found not to undergo this coupling reaction (SI) possibly due to hydrodehalogenation which was not studied in the C–O and C–N pivalophenone series.¹⁵ The naphthalen-2-ylboroneopentylate was found to afford the arylated product **2m** in high yield, and the thiophenyl, furanyl, and benzofuranyl Bneop derivatives gave good yields of products **2n–p** using a slight excess of boronates and prolonged reaction times (Scheme 1). When a sterically congested boroneopentylate was employed, the expected coupled product **2t** was not detected, and deboronation and reductive de-NMe₂ became the major reactions. The (*E*)-styrylBneop underwent arylation to give the stilbene product **2q** in modest yield. Two alkyl boroneopentylates were tested: while *n*-butyl Bneop failed to undergo the coupling reaction to form product **2s** (isolation of starting material), cyclopropyl Bneop afforded the interesting derivative **2r**. It appears that, in contrast to a single case reported for the 2-amino pivalophenone,¹⁵ a 2-amino benzamide/C_{sp³} boroneopentylate coupling reaction fails in both oxidative addition and transmetalation steps as evidenced by quantitative isolation of starting amide. The successful behavior of the cyclopropyl Bneop coupling reaction may be partially attributed to the established C_{sp²} character of the cyclopropyl C–H bonds¹⁷ but is perhaps surprising in view of the ring-opening reactivity of cyclopropyl derivatives with low-valent transition metals.¹⁸

In order to qualitatively obtain a direct reactivity comparison between the C–N and C–O bond activation/cross-coupling reactions, a competitive experiment was carried out using a 1:1:1 mixture of *N,N*-diethyl *o*-NMe₂ benzamide **1**, *N,N*-diethyl *o*-OMe benzamide **3**, and PhBneop (Scheme 2). The result,

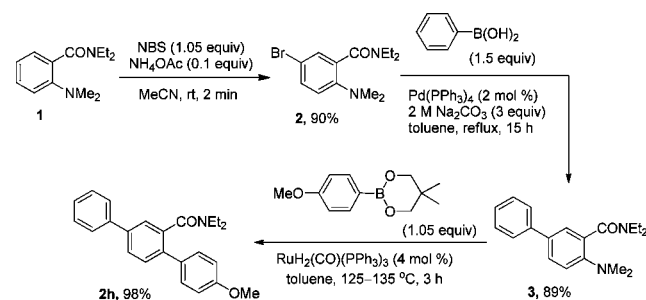
Scheme 2. Competition Experiment for the C–N and C–O Activation/Cross-Coupling Processes



indicating that C–N activation is faster than C–O activation, is consistent with the short reaction times required for the C–N coupling process compared to that of the corresponding C–O reaction.¹⁰

As demonstrated in the *N,N*-diethyl *o*-anisamide/ArBneop coupling studies,¹⁰ advantage may be taken of the expected high S_EAr reactivity of the *N,N*-diethyl 2-NMe₂-benzamide derivatives for devising orthogonal cross coupling chemistry^{11a} (Scheme 3). In this pursuit, treatment of *N,N*-diethyl *o*-NMe₂ benzamide with NBS gave the bromobenzamide **2** which, upon standard Suzuki–Miyaura cross-coupling conditions, afforded the biaryl **3**. Subjection of **3** to the Ru-catalyzed coupling procedure using *p*-anisyl Bneop provided the teraryl **2h** in 80%

Scheme 3. Synthesis of Teraryls via Sequential Bromination, Suzuki–Miyaura Cross-Coupling, and Ru-Catalyzed C–NMe₂ Activation/Coupling Reactions



overall yield in three steps. This may be considered as a prototype sequence for extension to tandem catalysis, tailor-made ligand design and construction,²⁰ and defined π -conjugated oligomer synthesis.²¹

In summary, the first catalytic amide-directed C–N activation/C–C bond-forming reaction for the synthesis of biaryls and heterobiaryls has been demonstrated. Similar to the Ru-catalyzed *o*-anisamide/aryl boroneopentylate cross-coupling process,¹⁰ the corresponding, readily derived²² *N,N*-diethyl *o*-NMe₂ benzamide/cross-coupling reaction is general, robust, and proceeds with high efficiency and regioselectivity uncompromised by the competitive C–H activation/cross-coupling reaction as observed for the corresponding *o*-NMe₂ acetophenone derivatives.¹⁸ Coupled with the standard Suzuki–Miyaura protocol, it has advantages of orthogonal reaction sequences and may be exploited in DoM and DreM (directed *remote* metalation)⁸ chemistry prior²³ or post to the C–N cross-coupling event for the construction of more highly substituted and polycondensed aromatic derivatives (Figure 1,

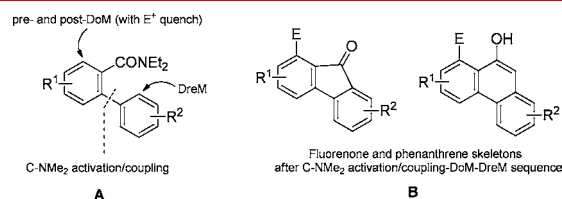


Figure 1. Synthetic potential of combined C–NMe₂ activation/cross coupling–DoM–DreM chemistry.

A and B). Of greatest significance, the *N,N*-diethyl *o*-NMe₂ benzamide/ArBneop cross-coupling reaction presents a new catalytic methodology for the synthesis of biaryl- and polyarylamides which complements the stoichiometric DoM–Suzuki–Miyaura cross-coupling two-step combination²⁴ but proceeds under noncryogenic temperatures and without use of strong organolithium bases. In view of these features, the application of the coupling reaction for convenient and effective new synthetic methodology may be anticipated.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for new compounds and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Selected recent publications: (a) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (b) Yu, J.-Q.; Shi, Z.; Eds. *Top. Curr. Chem.* **2010**, *292*, 1. (c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (d) Li, B. J.; Yu, D. G.; Sun, C. L.; Shi, Z. *J. Chem.—Eur. J.* **2011**, *17*, 1728. (e) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A. M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346. (f) Yu, D. G.; Li, B. J.; Shi, Z. *J. Acc. Chem. Res.* **2010**, *43*, 1486. (g) Ueno, S.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 6098.
- (2) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255. For comparison, bond enthalpies ΔH_{298} : Ph-NH₂ = 104 kcal/mol vs Ph-Br = 84 kcal/mol.
- (3) Catalytic methods: (a) Felpin, F. X.; Nassar-Hardy, L.; Le Callonnec, F.; Fouquet, E. *Tetrahedron* **2011**, *67*, 2815. (b) Taylor, J. G.; Moro, A. V.; Correia, C. R. D. *Eur. J. Org. Chem.* **2011**, 1403. (c) Roglans, A.; Pla-Quintana, A.; Moreno-Manas, M. *Chem. Rev.* **2006**, *106*, 4622. (d) Zhang, X. Q.; Wang, Z. X. *J. Org. Chem.* **2012**, *77*, 3658. (e) Xie, L. G.; Wang, Z. X. *Angew. Chem., Int. Ed.* **2011**, *50*, 4901. (f) Reeves, J. T.; Fandrick, D. R.; Tan, Z. L.; Song, J. J.; Lee, H.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 4388. (g) Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046. (h) Wenkert, E.; Han, A. L.; Jenny, C. J. *J. Chem. Soc., Chem. Commun.* **1988**, 975. (i) Saeki, T.; Son, E. C.; Tamao, K. *Org. Lett.* **2004**, *6*, 617. (j) Liu, J. Q.; Robins, M. J. *Org. Lett.* **2004**, *6*, 3421. (k) Zhu, M. K.; Zhao, J. F.; Loh, T. P. *Org. Lett.* **2011**, *13*, 6308.
- (4) Stoichiometric cleavages and insertions by transition metals: (a) Koreeda, T.; Kochi, T.; Kakiuchi, F. *J. Am. Chem. Soc.* **2009**, *131*, 7238. (b) Cameron, T. M.; Abboud, K. A.; Boncella, J. M. *Chem. Commun.* **2001**, 1224. (c) Bonanno, J. B.; Henry, T. P.; Neithamer, D. R.; Wolczanski, P. T.; Lobkovsky, E. B. *J. Am. Chem. Soc.* **1996**, *118*, 5132.
- (5) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706.
- (6) (a) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936. (b) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698.
- (7) Mechanistic studies: (a) Ueno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516. (b) Koreeda, T.; Kochi, T.; Kakiuchi, F. *Organometallics* **2013**, *32*, 682. Also see ref 4a.
- (8) (a) Snieckus, V.; Macklin, T. *Handb. C-H Transform.* **2005**, *1*, 106. (b) Hartung, C. G.; Snieckus, V. *Mod. Arene Chem.* **2002**, 330. (c) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (d) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.
- (9) Kaye, G. W. C.; Laby, T. H. *Tables of Physical and Chemical Constants*, 16th ed.; Longman: New York, 1995.
- (10) Zhao, Y.; Snieckus, V. Submitted for publication.
- (11) (a) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 3565. (b) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* **2009**, *131*, 17750. (c) Quasdorf, K. W.; Antoft-Finch, A.; Liu, P.; Silberstein, A. L.; Komaromi, A.; Blackburn, T.; Ramgren, S. D.; Houk, K. N.; Snieckus, V.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 6352.
- (12) For amide to aldehyde conversion using the Schwartz reagent, see: (a) Zhao, Y.; Snieckus, V. *Org. Lett.* **2014**, *16*, 390. (b) Zhao, Y.; Snieckus, V. US 8,168,833, 2012. For other transformations of amides, see: (c) Larock, R. C. *Comprehensive Organic Transformations. A Guide to Functional Group Preparations*, 2nd ed.; Wiley: New York, 2010.
- (13) Zhao, Y. Ph.D. Thesis, Queen's University, Kingston, ON, Canada, 2010.
- (14) (a) Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34. (b) Ludt, R. E.; Griffiths, J. S.; McGrath, K. N.; Hauser, C. R. *J. Org. Chem.* **1973**, *38*, 1668.
- (15) These substituent effect trends are quite similar as those found in the amide-directed C-OMe activation/arylation reaction of *N,N*-diethyl *o*-OMe benzamides and naphthamides; see refs 10 and 13.
- (16) Sivaev, I. B.; Bregadze, V. I. *Coord. Chem. Rev.* **2014**, *270–271*, 75.
- (17) Wiberg, K. B. *Acc. Chem. Res.* **1996**, *29*, 229.
- (18) Ruhland, K. *Eur. J. Org. Chem.* **2012**, 2683.
- (19) Wang, Q. W.; Mayer, M. F.; Brennan, C.; Yang, F. K.; Hossain, M. M.; Grubisha, D. S.; Bennett, D. *Tetrahedron* **2000**, *56*, 4881.
- (20) Nakao, Y.; Chen, J. S.; Tanaka, M.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 11694.
- (21) Grimsdale, A. C.; Mullen, K. *Macromol. Rapid Commun.* **2007**, *28*, 1676.
- (22) From commercial anthranilic acid, see: (a) Clayden, J.; Stimson, C. C.; Keenan, M. *Chem. Commun.* **2006**, 1393. (b) Kim, Y. K.; Lee, S. J.; Ahn, K. H. *J. Org. Chem.* **2000**, *65*, 7807.
- (23) For DoM reactions on *N,N*-diethyl *o*-NR₂ anthranilamides to derive useful 1,2,3-trisubstituted aromatics, see: (a) MacNeil, S. L.; Wilson, B. J.; Snieckus, V. *Org. Lett.* **2006**, *8*, 1133. (b) Rios, R.; Jimeno, C.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10272. (c) Hjelmencrantz, A.; Berg, U. *J. Org. Chem.* **2002**, *67*, 3585. Also see ref 22a. For combined DoM–DreM reactions on compound 2a, see: (d) Tilly, D.; Fu, J. M.; Zhao, B. P.; Alessi, M.; Castanet, A. S.; Snieckus, V.; Mortier, J. *Org. Lett.* **2010**, *12*, 68. With few exceptions, all compounds in Scheme 1 are potentially primed for this as well as yet unknown metalation chemistry.
- (24) (a) Snieckus, V.; Anctil, E. J. G. *Metal-Catalyzed Cross-Coupling Reactions and More*; Wiley: New York, 2014; Vol. 3, p 1067. (b) Board, J.; Cosman, J. L.; Rantanen, T.; Singh, S. P.; Snieckus, V. *Platinum Metals Rev.* **2013**, *57*, 234. (c) Anctil, E. J. G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150.