Organic LETTERS

Letter

pubs.acs.org/OrgLett

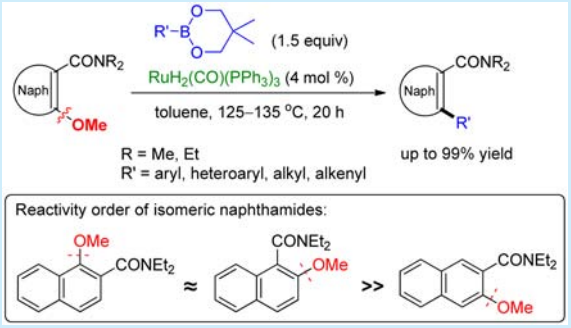
Beyond Directed *ortho* Metalation: Ruthenium-Catalyzed Amide-Directed C_{Ar}–OMe Activation/Cross-Coupling Reaction of Naphthamides with Aryl Boronates

Yigang Zhao and Victor Snieckus*

Department of Chemistry, Queen's University, 90 Bader Lane, Kingston, ON K7L 3N6, Canada

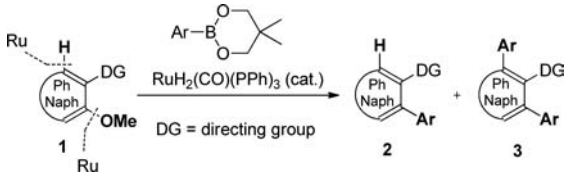
Supporting Information

ABSTRACT: A new and general synthetic methodology for the construction of biaryl, heterobiaryl, and polyaryl molecules by the ruthenium-catalyzed cross-coupling of *ortho*-methoxy naphthamides with aryl boroneopentylates is described. The isomeric 1-MeO-2-naphthamides and 2-MeO-1-naphthamides furnish an expansive series of arylated naphthamides in excellent yields. Competition experiments showed the higher reactivity of 1-MeO-2-naphthamide over 2-MeO-benzamide. Orthogonality between the C–O activation/cross-coupling and the Suzuki–Miyaura reactions was established. The method provides naphthalenes which are difficult to prepare by directed *ortho* metalation.



The C–OMe bond of the aryl ether class of organic molecules is ubiquitous in natural products, pharmaceuticals, and commodity chemicals. Until recently, the aryl C–OMe to C–C bond transformation has required prior conversion into C–OTf, C–OMs, C–OTs, and C–OAc derivatives followed by use of various cross-coupling protocols.[1] In early salient contributions, Wenkert first demonstrated the direct Corriu–Kumada aryl C–OMe activation/C–C cross-coupling reaction under Ni(0) catalysis.[2] The recent comprehensive studies[3] of Kakiuchi and Chatani have provided new types of Ru- and Ni-catalyzed C–OMe to C–C bond conversion of aryl ethers with[4] or without[5] directing group (DG) activation. In the Kakiuchi process, both C–H and C–OMe activation/coupling reactions occur simultaneously to give 2,6-disubstituted acetophenone products (Table 1, entry 1, **1** → **3**).[6] In order to avoid the undesired C–H activation, advantage was taken of steric shielding (entry 2, **1** → **2**) or blocking (using 6-methyl-2-methoxyacetophenone) effects to obtain satisfactory regioselective C–OMe activation/boroneopenylate (Bneop) coupling products.[4a] Recently, we have reported[7] the catalytic, high yielding, and decidedly regioselective cross-coupling reaction of *ortho*-anisamides with aryl Bneop derivatives (entry 3, **1** → **2**, DG = $CONEt_2$) driven by amide group–Ru catalyst chelation.[8] Herein we disclose a general Ru-catalyzed cross-coupling of *ortho*-OMe naphthamides with aryl Bneops (entry 4, **1** → **2**, DG = $CONEt_2$). The methodology (a) constitutes the first systematic Ru-catalyzed C–O activation/coupling reaction of the naphthalene ring system;[9] (b) provides an efficient protocol for the synthesis of a variety of arylated naphthalenes which are difficult or unachievable by the established directed *ortho* metalation (DoM)–cross-coupling protocol,[10] and (c) establishes an orthogonal link to the Suzuki–Miyaura cross-coupling reaction.

Table 1. Selectivity of Ketone- and Amide-Directed (DG) C–OMe and C–H Activation/Coupling Reactions



			activation/coupling			
entry	DG	substrate	via C–H	via C–O	product	ref
1	C(O)Me	phenyl	√	√	**3**	6
		naphthyl	√	√	**3**	this work
2	C(O)*t*-Bu	phenyl	×	√	**2**	4a
		naphthyl	–[a]	–[a]	–[a]	–[a]
3	$CONEt_2$	phenyl	×	√	**2**	7
4	$CONEt_2$	naphthyl	×	√	**2**	this work

[a]Not reported.

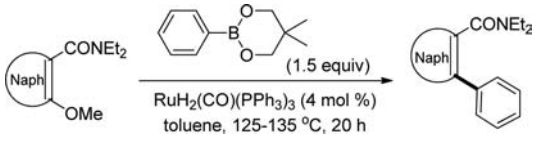
Interest for the use of this chemistry in the construction of complex polycyclic aromatics[11] may be therefore anticipated.

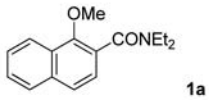
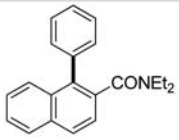
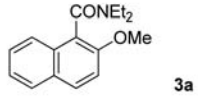
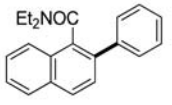
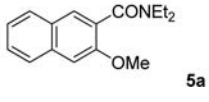
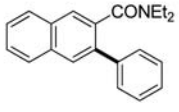
In the initial test studies, three isomeric *ortho*-methoxy naphthamides were examined under the previously established catalytic $RuH_2(CO)(PPh_3)_3$ conditions[7] which showed that the yields of cross-coupling products varied as a function of the methoxy naphthamide isomers (Table 2). Thus, 1-MeO-2-naphthamide **1a** and 2-MeO-1-naphthamide **3a** underwent the C–O activation/cross-coupling reaction to afford the biaryl

Received: July 9, 2015
Published: September 15, 2015

DOI: 10.1021/acs.orglett.5b01913
Org. Lett. 2015, 17, 4674–4677

Table 2. Ru-Catalyzed C−OMe Activation/Cross-Coupling Reaction of Isomeric Naphthamides



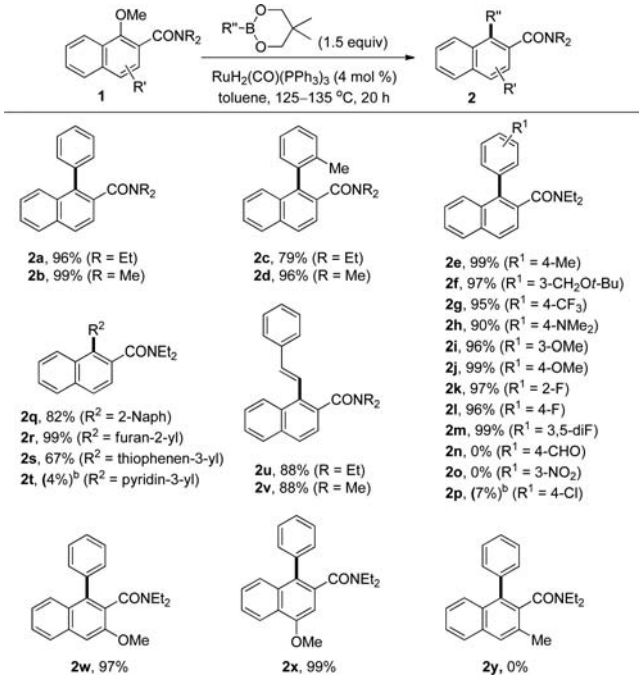
entry	amide	product	Yield (%)[a]
1	 1a	 2a	96
2	 3a	 4a	97
3	 5a	 6a	30

[a]Yields are of isolated and purified products.

products **2a** and **4a** in excellent yields (entries 1 and 2) while the 3-MeO-2-naphthamide **5a** gave product **6a** in a much lower yield (entry 3). As also observed for the C−O cross-coupling reactions of benzamides,[7] the naphthamides undergo only *ortho* C−O activation/coupling reactions and are inert to *ortho* C−H bond activation (entries 1 and 3). In contrast, the DG = C(O)Me naphthalene derivatives give inconsistent results.[12] Thus, while the coupling of PhBneop with 2-MeO-1-acetylnaphthalene affords 2-phenyl-1-acetylnaphthalene in 84% yield,[4a] we find that the isomeric 1-MeO-2-acetylnaphthalene undergoes both C−H and C−OMe activation processes to give 1,3-diphenyl-2-acetylnaphthalene in quantitative yield.[12] Motivated by our comparative results, we investigated the generality of the reaction of naphthamides **1a** and **3a** with a variety of aryl Bneops (Schemes 1 and 2).[13]

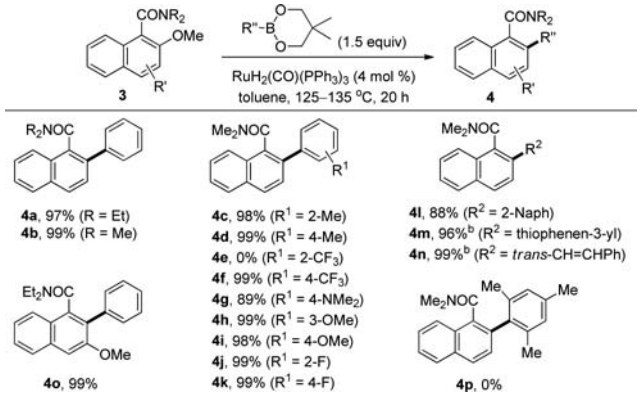
To optimize the conditions, the isomeric 1-MeO-2-naphthamide and 2-MeO-1-naphthamide were studied in both diethyl and dimethyl amide series. Thus, as observed for the conversion of the *N,N*-diethyl naphthamide **1a** → **2a** (Table 2), the corresponding *N,N*-dimethyl 1-MeO-2-naphthamide **1** (R = Me; R′ = H) underwent efficient C−OMe activation/coupling to afford the biaryl **2b** in quantitative yield (Scheme 1). Furthermore, coupling of 1-MeO-2-$CONEt_2$ and, in two cases, -2-$CONMe_2$ naphthyl derivatives with ArBneops bearing Me, CH_2Ot-Bu, NMe_2, and OMe EDGs (electron-donating groups) furnished biaryl products **2c−f, 2h−j** in good to excellent yields. Noteworthy is the comparison of couplings of the *N,N*-diethyl and *N,N*-dimethyl 1-MeO-2-naphthamides with the 2-methylphenyl Bneop derivative to give **2c** and **2d** respectively which shows the advantage of using the less sterically hindered naphthamide. ArBneops with F and CF_3 EWGs (electron-withdrawing groups) give the coupled products **2g, 2k−m** in high yields. However, reminiscent of the results and perhaps the associated rationalization of the *ortho*-anisamide studies,[7] coupling of naphthamides with ArBneops bearing CHO and NO_2 groups afforded no arylation products and starting materials were recovered in high yields (**2n** and **2o**).[12a] Analogously, a chloro derivative does not serve for this coupling reaction (**2p**) possibly due to dehalogenation.[12a] On the other hand, the reaction of the *N,N*-diethyl 1-MeO-2-naphthamide **1** (R = Et; R′ = H) with 2-naphthyl Bneop smoothly afforded the coupled product **2q** in good yield. Furanyl and thiophenenyl Bneops also furnished the expected heterobiaryls **2r** and **2s** in good yields while the pyridin-3-yl Bneop failed to give the coupled product **2t** echoing the studies with the corresponding *ortho*-anisamides.[7] The (*E*)-styryl Bnoep underwent the coupling reaction with both *N,N*-dimethyl and *N,N*-diethyl naphthamides to afford products **2u** and **2v** in high yields. These results establish a general and efficient method for the preparation of 1-arylated 2-naphthamides **2** from the readily available **1** which supersedes the ineffective method using directed *ortho* metalation (DoM) chemistry of the corresponding 2-naphthamide.[10f,14] The

Scheme 1. Ru-Catalyzed Cross-Coupling Reaction of 1-MeO-2-Naphthamides with Bneops[a]



[a]Yields are of isolated and purified products. [b]Conversion from GC-MS analysis.

Scheme 2. Ru-Catalyzed Cross-Coupling Reaction of 2-MeO-1-Naphthamides with Bneops[a]



[a]Yields are of isolated and purified products. [b]10 mol % catalyst loading.

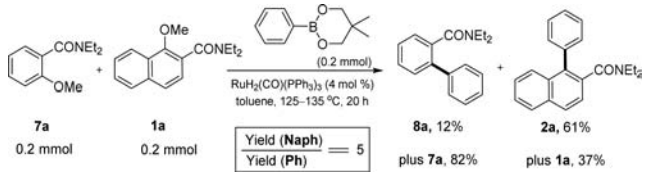
DOI: 10.1021/acs.orglett.5b01913
Org. Lett. 2015, 17, 4674−4677

selectivity and steric effects were briefly tested by examination of several disubstituted-2-naphthamides which were readily available from the corresponding commercial methoxy naphthalenes via DoM chemistry (see Supporting Information (SI)). Thus, the 1,3-dimethoxy-2-naphthamide showed highly selective 1-OMe coupling to give **2w** (structural assignment by NOESY; see SI), confirming the greater C-1 over C-3 C−OMe activation reactivity as perhaps already expected from the observed low yield of product **6a** (Table 2, entry 3) obtained for the coupling of 3-methoxy-2-naphthamide. In comparison, the failure to obtain 1-phenyl-3-methyl-2-naphthamide **2y** via the C−OMe activation/coupling reaction (98% recovery of starting material, 1-MeO-3-methyl-2-naphthamide) raises an as yet not understood interplay or juxtaposition of steric and electronic effects in these reactions which were also observed in the *ortho*-anisamide series.[7] The formation of 2-naphthamide **2x** reinforces the significance of amide chelation assistance in these syntheses of new naphthalene derivatives. The ready and general availability of coupled products **2** anticipates the potential of further useful DoM and DreM (Directed *remote* Metalation) chemistry.[10c,d,f] As indicated by the observed high yields in all reactions, a C−H *peri*-hindrance effect pertinent to naphthalenes does not inhibit the C−OMe activated/C-1 coupling.[15] More importantly, its synthetic value is underscored by the fact that the meager literature on *N,N*-diethyl 2-naphthamide metalation reactions shows that these derivatives undergo facile C-1 addition of RLi bases which prevents their use in the DoM−Suzuki cross-coupling protocol.[10f,14]

Next, we investigated the generality of the reaction of 2-MeO-1-naphthamides by systematic variation of the ArBneop coupling partner (Scheme 2). Based on the favorable effect of using DG = $CONMe_2$ rather than DG = $CONEt_2$ in the isomeric series **4a** and **4b** and the potential greater steric conflict between the *peri*-C−H and a 1-amide group, 2-MeO-*N,N*-dimethyl-1-naphthamide was employed in the initial study. As gleaned from Scheme 2, the tolerance of functional groups present in the Bneop systems is quite similar to that observed in the 1-MeO-2-naphthamide series. Thus, Me, NMe_2, and OMe EDGs and F and CF_3 EWGs gave high yields of biaryl products **4c−d**, **4f−k**. Furthermore, 2-naphthyl-, thiophenen-3-yl-, and styryl-Bneops also afforded biaryls **4l−n** in excellent yields. Also similarly, steric hindrance decreased the coupling efficiency although inconsistently since sterically congested Bneops failed to afford any C−O activation/coupling products **4e** and **4p** while an excellent yield of **4c** was obtained in the coupling reaction with 2-methylphenyl Bneop. Since we found that the prototype coupling reactions of $CONEt_2$ and $CONMe_2$ systems are equally efficient, the general use of the former amides to allow further DoM has validity. The now expected *ortho*-selective coupling of 2,3-dimethoxy-1-naphthamide, readily available from the corresponding commercial 2,3-dimethoxynaphthalene via DoM chemistry, was observed to give a quantitative yield of **4o** (structure confirmed by NOESY; see SI), a molecule poised for further DoM and DreM reactions.[10c,d,f] The comparative evaluation of this synthesis of 2-arylated-1-naphthamides to the DoM−Suzuki protocol remains to be established due to lack of data on the latter route.

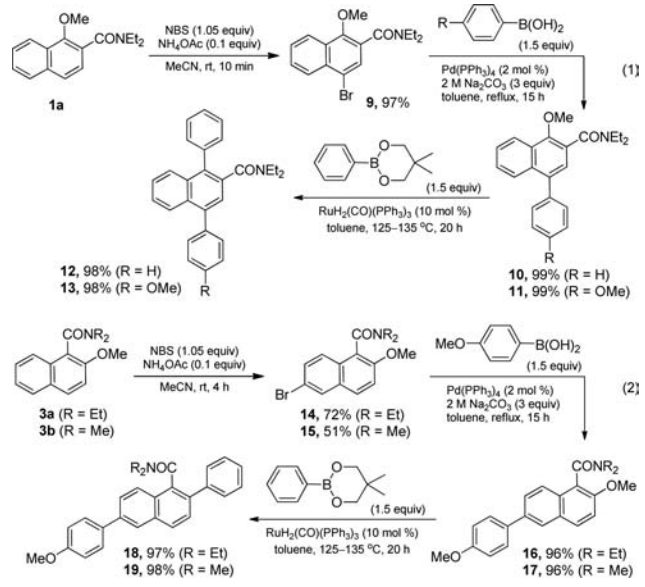
As a qualitative evaluation of relative reactivity, a competition experiment between 2-MeO-*N,N*-diethylbenzamide **7a** and 1-MeO-*N,N*-diethyl-2-naphthamide **1a** in the cross-coupling with PhBneop was carried out and showed that naphthalene ring activation is significantly greater than that of the benzene ring (Scheme 3), possibly a reflection of the well-known unequal distribution of resonance energy stabilization per ring of naphthalene (benzene = 36 kcal/mol; naphthalene = 61 kcal/mol).[16]

Scheme 3. Competition Experiment between 2-MeO Benzamide and 1-MeO-2-Naphthamide in Ru-Catalyzed Cross-Coupling with PhBneop



We then turned our attention to application of the *ortho*-methoxy naphthamide C−OMe activation/coupling chemistry. Considering that the presence of the electron-donating OMe group in these substrates provides the opportunity to establish orthogonal cross-coupling strategies,[5,7,17] we explored a sequential bromination, Suzuki−Miyaura cross-coupling, and Ru-catalyzed C−OMe activation/coupling process for construction of teraryls in two typical isomeric naphthamide series (Scheme 4). Thus, the selective electrophilic bromination of **1a**

Scheme 4. Synthesis of Biaryls and Teraryls via Sequential Bromination, Suzuki−Miyaura Cross-Coupling, and Ru-Catalyzed C−OMe Activation/Coupling Reactions



quantitatively furnished a single product **9** which, when subjected to Suzuki−Miyaura coupling with two commercially available aryl boronic acids, afforded **10** and **11** respectively also in quantitative yields. Their Ru-catalyzed C−OMe activation/PhBneop cross-coupling reactions proceeded efficiently to give 1,4-diaryl naphthamides **12** and **13** respectively. This efficient and operationally simple synthetic route to teraryl derivatives proceeds in three steps and >94% overall yield. The same sequence on the isomeric *N,N*-diethyl and *N,N*-dimethyl naphthamides **3a** and **3b** proceeded via the expected 6-bromo **14** and **15** and the corresponding 6-*para*-anisyl **16** and **17** derivatives to afford the 2,6-diaryl naphthamides **18** and **19** respectively in high yields. These orthogonal coupling routes to

DOI: 10.1021/acs.orglett.5b01913
Org. Lett. 2015, 17, 4674−4677

teraryls with a functionalized central naphthalene core are of potential interest in materials science research.[18]

In summary, we have demonstrated the first catalytic tertiary amide-directed C−OMe activation/C−C cross-coupling reaction in the *ortho*-methoxy naphthamide series for the synthesis of biaryl and heterobiaryl molecules. The new Ru-catalyzed methodology is general, efficient, and operationally simple; requires no additional ligands or base; and encompasses the following features: (a) the starting *ortho*-methoxy naphthamides are readily available from simple and inexpensive commodity chemicals (see SI); (b) compared to the salient Kakiuchi ketone-directed coupling reaction,[4a,6] the amide DG activation is highly C−OMe regioselective without competitive C−H activation process interference and provides products with amide functionality which is more amenable to synthetic operations compared to the acetyl or pivaloyl groups; (c) it has the advantages of the powerful DMG (directed metalation group), $CONEt_2$, which sets the stage for regioselective DoM, DreM, and combined DoM−Suzuki coupling chemistries[10,19] to be effected either pre- or post- the C-OMe activation/coupling reactions; (d) it allows further useful manipulation by the efficient method for amide to aldehyde conversion using an *in situ* Schwartz reduction recently developed in our laboratories;[20] (e) it provides aryl naphthamides (e.g., **2a−m**, **2q−s**, **2u−v**, **2x**, Scheme 1) which are difficult or impossible to prepare by the combined DoM−Suzuki coupling protocol;[10a,b,e] (f) it allows links to DreM syntheses of fused fluorenone and phenanthrol molecules;[10c,d] and (g) it lends to new synthetic concepts for orthogonal C−O activation and Suzuki cross-coupling sequences as exemplified by the preparation of teraryls (Scheme 4).

These efforts on the Ru-catalyzed C−O activation/coupling reactions are aimed to complement and arguably eventually to supersede our DoM−cross-coupling methodology.[10a,b] The present method and related work[7,20] has the distinct advantages over the widely practiced DoM strategy of nonrequirement of cryogenic temperatures and strong bases which augurs well for its broader application to provide unusually substituted and unavailable biaryl and polyaryl derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01913.

Experimental procedures and analytical data for new compounds and products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: snieckus@chem.queensu.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to NSERC Canada (Discovery Grant) for continuing support of our synthetic programs, Dr. Francoise Sauriol (Queen's University) for assistance with NMR spectroscopy, and Dr. Jiaxi Wang (Queen's University) for discussion of the MS.

■ REFERENCES

(1) Reviews: (a) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A. M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346. (b) Yu, D. G.; Li, B. J.; Shi, Z. J. *Acc. Chem. Res.* **2010**, *43*, 1486.

(2) (a) Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246. (b) Wenkert, E.; Michelotti, E. L.; Swindell, C. S.; Tingoli, M. *J. Org. Chem.* **1984**, *49*, 4894.

(3) For a review, see: Kakiuchi, F.; Kochi, T.; Murai, S. *Synlett* **2014**, 2390.

(4) (a) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706. (b) Ueno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516.

(5) Report of direct aryl ether/aryl Bneop coupling reaction under Ni-catalyzed conditions that is compromised by the low reactivity of the substrate anisoles and the requirement of a large excess of base (CsF): Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4866.

(6) Ueno, S.; Kochi, T.; Chatani, N.; Kakiuchi, F. *Org. Lett.* **2009**, *11*, 855.

(7) Zhao, Y.; Snieckus, V. *J. Am. Chem. Soc.* **2014**, *136*, 11224.

(8) The amide group exhibits greater coordinating ability than the ketone group; see: Kaye, G. W. C.; Laby, T. H. *Tables of Physical and Chemical Constants*, 16th ed.; Longman: New York, 1995.

(9) All previous coupling studies focus on phenyl ring systems; see refs 4 and 7. A single example of a naphthalene derivative, 2-MeO-1-acetylnaphthalene, has been reported; see ref 4a.

(10) (a) Snieckus, V.; Anctil, E. J. G. In *Metal-Catalyzed Cross-Coupling Reactions and More*; de Meijere, A., Brase, S., Oestreich, M., Eds.; Wiley: Weinheim, 2014; Vol. 3, p 1067. (b) Board, J.; Cosman, J. L.; Rantanen, T.; Singh, S. P.; Snieckus, V. *Platinum Met. Rev.* **2013**, *57*, 234. (c) Snieckus, V.; Macklin, T. In *Handbook of C-H Transformations*; Dyker, G., Ed.; Wiley: Weinheim, 2005; Vol. *1*, p 106. (d) Hartung, C. G.; Snieckus, V. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley: Weinheim, 2002; p 330. (e) Anctil, E. J. G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150. (f) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(11) (a) Harvey, R. G. *Polycyclic Aromatic Hydrocarbons*; Wiley: New York, 1997. (b) For large PAHs, see: Feng, X. L.; Pisula, W.; Mullen, K. *Pure Appl. Chem.* **2009**, *81*, 2203.

(12) (a) Zhao, Y. Ph.D. Thesis, Queen's University, Kingston, Ontario, Canada, 2010. (b) See Supporting Information.

(13) Arylboronic acid and its pinacol ester were tested in our Ru-catalyzed amide-directed C−N activation/coupling chemistry (see ref 12a and Zhao, Y.; Snieckus, V. *Org. Lett.* **2014**, *16*, 3200.) and found to be unsuccessful. Based on these observations, we did not attempt analogous C−O activation/coupling reactions, since the boroneopentylate (Bneop) reactions were found to proceed in high yields. (b) In amide-directed C−OMe activation/coupling reactions, use of pinacolone as a solvent afforded low yields of products.

(14) Bindal, R. D.; Katzenellenbogen, J. A. *J. Org. Chem.* **1987**, *52*, 3181.

(15) (a) Kumar, D.; Kumar, R.; Chakraborti, A. K. *Synthesis* **2008**, 1249. (b) Lakshmi, A.; Walker, S.; Weir, N. A.; Calderwood, J. H. *J. Phys. Chem.* **1978**, *82*, 1091.

(16) Wheland, G. W. *Resonance in Organic Chemistry*; Wiley: New York, 1955; p 830.

(17) (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.

(18) For very recent work, see: Filo, J.; Misicak, R.; Cigan, M.; Weis, M.; Jakabovic, J.; Gmucova, K.; Pavuk, M.; Dobrocka, E.; Putala, M. *Synth. Met.* **2015**, *202*, 73.

(19) (a) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206. (b) Tilly, D.; Magolan, J.; Mortier, J. *Chem. - Eur. J.* **2012**, *18*, 3804.

(20) (a) Zhao, Y.; Snieckus, V. *Org. Lett.* **2014**, *16*, 390. (b) Zhao, Y.; Snieckus, V. A. U.S. Patent 8,168,833, 2012.

DOI: 10.1021/acs.orglett.5b01913
Org. Lett. 2015, 17, 4674−4677