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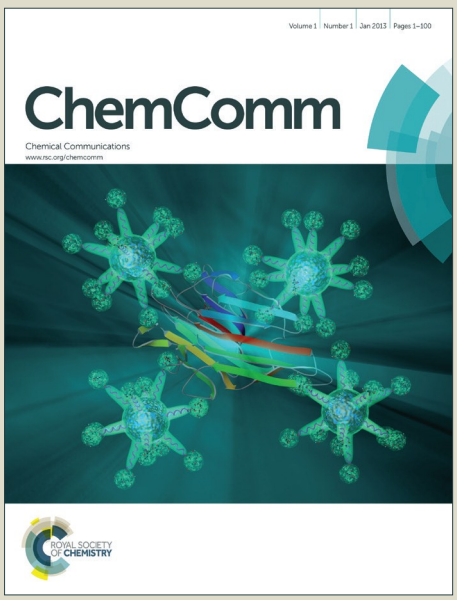

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Ester-Directed Ru-Catalyzed C-O Activation/C-C Coupling Reaction of *ortho*-Methoxy Naphthoates with Organoboroneopentylates†

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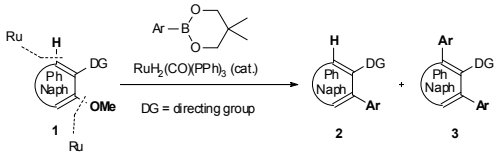
Yigang Zhao and Victor Snieckus*

A new, catalytic and general synthetic methodology for the construction of biaryls and heterobiaryls by the cross-coupling of *ortho*-methoxy naphthoates with organoboroneopentylates is disclosed. The reaction proceeds under $RuH_2(CO)(PPh_3)_3$-catalyzed conditions driven by unreactive C-O bond activation of a proximate ester directing group (DG)-catalyst chelation. This one-step synthesis of 2-aryl and -heteroaryl-1-naphthoates has the features of operational simplicity, minimum waste and convenient scale-up. The hierarchy of C(O)Me > $CONEt_2$ > CO_2Me coordination-assisted reactivity, of potential value in chemoselective synthesis, is also established.

The area of transition metal catalyzed C-H activation reactions, although of some vintage,[1] first definitely commanded our attention by the research of Murai and coworkers,[2] and particularly by the publication of the monograph,[3] which is heralding a revolution in the way we think about the construction of many classes of organic molecules.[4] Recently, transition metal catalyzed C-H activation processes have been augmented by the discovery of activation of normally inert C-O and C-N bonds thus providing new and evolving methodology for appendage of carbon substituents to aromatics and heteroaromatics.[5] Inspired by the seminal Kakiuchi reports of the acetyl and pivaloyl DG (directing group) C-O bond activation reactions[5g,6] (Table 1, entries 1 and 2) and consideration of the greater chelation property of amides over ketones,[7] we recently devised and successfully developed new and general Ru-catalyzed tertiary amide DG directed C-O activation/aryl boroneopentylate (Bneop) cross-coupling construction modes[8] (Table 1, entry 3). These complement and may potentially supercede directed ortho metalation (DoM)–cross-coupling strategies[9] in the construction of aromatic compounds.[10]

In continuation of this theme, we now report on a parallel study on the Ru-catalyzed 2-methoxy-1-naphthoate ester DG C-O activation/arylation reaction (Table 1, entry 4) which has the following notable features: a) it constitutes the first case of catalytic aryl C-O functionalization driven by ester chelation assistance not only for boronate coupling but for transition metal cross coupling processes in general; b) it complements the corresponding naphthamide C-O activation methodology[8b-d] for the synthesis of 2-aryl-1-naphthoate derivatives;[11] c) it proceeds from easily prepared and commercially available starting materials, shows broad scope for biaryl synthesis and is amenable to conventional ester functional group intercon versions;[12] d) it may be linked to the synthesis of fluorenone derivatives[13] and the classical and reliable Friedel-Crafts reaction,[14] and may complement the corresponding anionic equivalent amide directed *remote* metalation (DreM) reactions.[9c,9d,9f,15] As results of additional synthetic utility value, we also report on the relative reactivity and selectivity of naphthyl amide, ester, and ketone DGs in promoting the Ru-catalyzed C-O activation/cross-coupling reactions.

Table 1 Selectivity of ketone-, amide- and ester-directed Ru-catalyzed C-OMe and C-H activation/coupling reactions



Entry	DG	Substrate	Activation/Coupling via C-H	Activation/Coupling via C-O	Product	Ref
1	C(O)Me	phenyl	✓	✓	3	5i
		naphthyl	✓	✓	3	8b
2	C(O)*t*-Bu	phenyl	X	✓	2	5g
		naphthyl	--[a]	--[a]	--[a]	--[a]
3	$CONEt_2$	phenyl	X	✓	2	8a
		naphthyl	X	✓	2	8b
4	CO_2Me	phenyl	X	trace	2	this work
		naphthyl	X	✓	2	this work

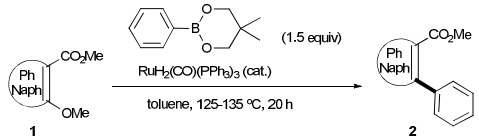
Department of Chemistry, Queen's University, 90 Bader Lane, Kingston, Ontario K7L 3N6, Canada. E-mail: snieckus@chem.queensu.ca

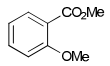
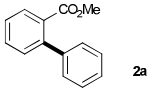
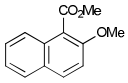
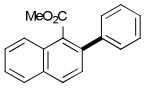
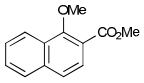
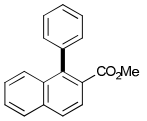
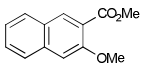
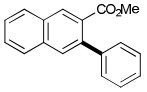
†Electronic Supplementary Information (ESI) available: Experimental procedures and analytical data for new compounds and products. See DOI: 10.1039/x0xx00000x

[a] Not reported.

To initiate the study, we probed the *ortho*-methoxy benzoate and naphthoate ester reactivity with the prototype PhBneop compound (Table 2). The commercially available *ortho*-anisic methyl ester led to only trace amounts of C-O activation/cross-coupling product **2a** (entry 1), suggesting that benzoates are not useful substrates for the C-O activation/coupling reaction. Of the three theoretically possible, regioisomeric naphthoates, the 2-MeO-1-naphthoate showed excellent reactivity affording the 2-phenyl derivative **2b** in quantitative yield (entry 2) while the isomeric 1-methoxy ester was modestly reactive to give **2c** (entry 3) and the 3-methoxy ester was unreactive (entry 4). Notably, unlike the DG = ketone case where both C-O and C-H activation occurs and leads to the formation of diphenylated product **4b** (Scheme 2, box **B**), the analogous ester DG directed C-H activation product was not observed in this case and only the mono C-O activation/phenylation product was obtained in 39% yield with incomplete conversion (recovery of starting material, 47 % yield) (Table 2, entry 3).

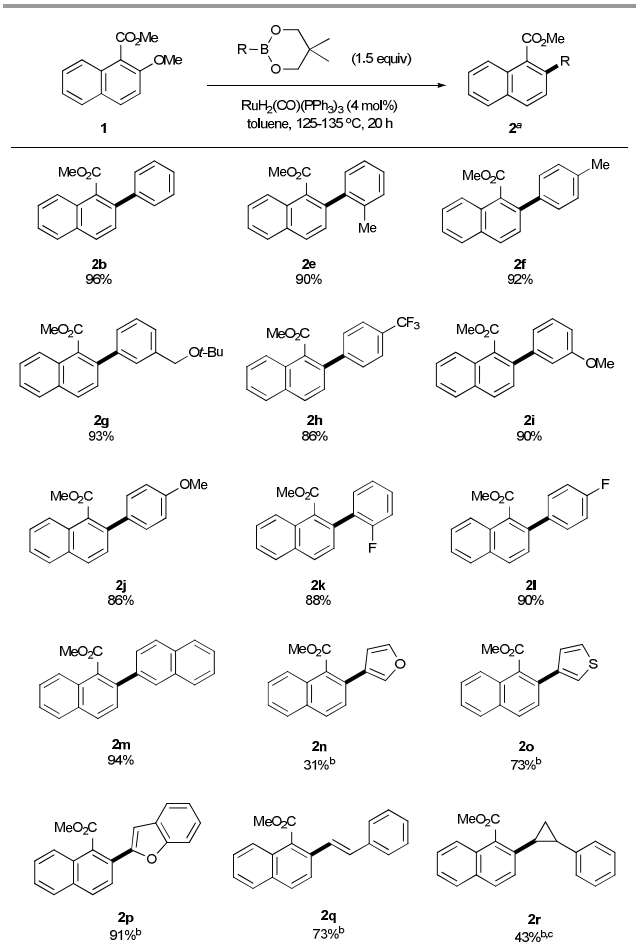
Table 2 Ru-catalyzed C-OMe activation/C-C coupling reactions of ester DG aromatic substrates



Entry	Substrate	Catalyst Loading (mol%)	Product	Yield (%)[a]
1		10	 **2a**	(4)[b]
2		4	 **2b**	96
3		10	 **2c**	39[c]
4		10	 **2d**	n.d.[d]

[a] Yields are of isolated and purified products. [b] 4% conversion (based on GC-MS analysis). [c] With recovery of starting material (47%); the C-H activation/cross-coupling product was not detected. [d] Loss of ester group was observed in 23% conversion (based on GC-MS analysis).

The recognition of the excellent reactivity of the 2-MeO-1-naphthoate motivated a study concerning the generalization of the reaction for a variety of aryl Bneops (Scheme 1). As expected from previous studies on C-O coupling reactions of amides,[8] aryl Bneops with Me, CH_2Ot-Bu and OMe EDGs (electron-donating groups) afforded arylation products **2e-g**, **2i-j** in good yields. Similarly, aryl Bneops with the F and CF_3 EWGs (electron-withdrawing groups) led to coupled products **2h**, **2k-l** in high yields. In addition, the modestly hindered 2-methylphenyl and 2-naphthyl Bneops underwent efficient coupling reactions (**2e** and **2m**). In the heterocyclic series, good yields were obtained for the thiophenenyl and benzofuranyl Bneop cases (**2o** and **2p**) but the 3-furanyl Bneop case afforded a low yield of product **2n** perhaps owing to its high propensity for protodeboronation.[16] The (*E*)-styryl and cyclopropyl Bneop coupling partners furnished 73% and 43% yields of products **2q** and **2r** respectively, in which **2q** retained *E*-stereochemical fidelity. These results constitute the first cases of an ester chelation-assisted C-O activation/cross-coupling reaction.

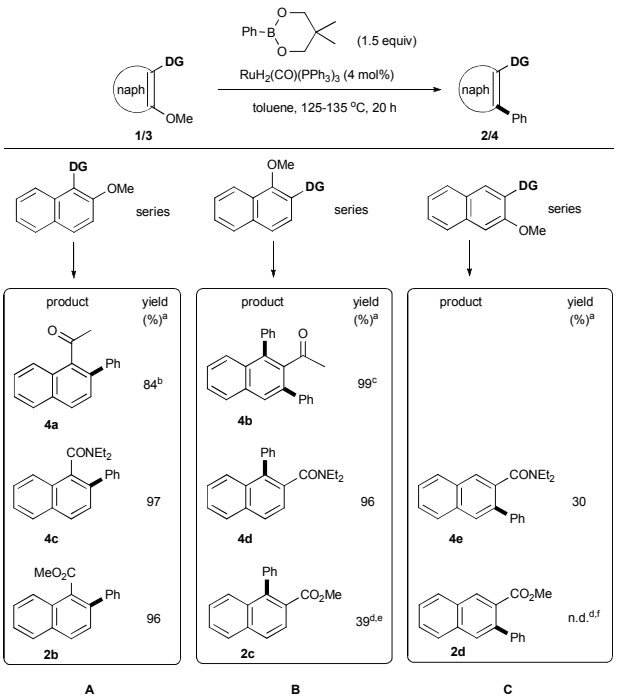


[a] Yields are of isolated and purified products. [b] 10 mol% catalyst loading. [c] *Cis* or *trans* stereochemistry was not established by ^{1}H NMR due to almost identical J_{cis} and J_{trans} coupling constants[17] and unavailability of crystalline material for X-ray analysis.

Scheme 1 Ru-catalyzed C-O activation/C-C coupling reactions of methyl 2-MeO-1-naphthoates with Organoboroneops

To provide additional reactivity data of potential value for synthetic application, we undertook a study of comparative

relative reactivity of ketone, amide, and ester in the naphthalene derivative series (Scheme 2).[18] Previously, Kakiuchi and co-workers established that 2-methoxy-1-acetylnaphthalene undergoes cross-coupling to give the 2-phenyl product **4a** in good yield (box **A**).[5g] We found that under our standard, somewhat different, conditions, the isomeric 1-methoxy-2-acetyl naphthalene participates in both ketone-directed C-H and C-O activation/cross-coupling reactions to afford the diphenylated product **4b** in almost quantitative yield.[8b,8d,19] In comparison to 2-methoxy-1-acetylnaphthalene, the same substituent-positional amide and ester naphthalenes behaved similarly and afforded the corresponding 2-phenyl products **4c**[8b,8d,19] and **2b** (box **A**) respectively in quantitative yields. On the other hand, comparison of 1-methoxy-2-acetyl naphthalene with the same substituent-positional amide and ester shows a difference in that the latter two undergo only the C-O activation/coupling reactions to give phenylated products **4d**[8b,8d,19] and **2c** respectively (box **B**) without detectable formation of the C-H activation/coupling products. Although data for 2-acetyl-3-methoxynaphthalene is not available,[5g] the same positional amide and ester furnish low yields of **4e**[8b,8d,19] and de-esterification product (box **C**) respectively. These studies establish the following order of relative reactivity of DGs: ketone > amide > ester and suggest that *the amide DG induces the highest selectivity and reactivity*.[8d] Notably, they also indicate the unique position of the 2-methoxy-1-naphthoate ester (Scheme 2, **2b**) within the isomeric series (**2b-d**) as an excellent DG for the C-O activation/aryl boronate cross-coupling reaction.



[a] Yields of isolated and purified products. [b] See ref 5g (1.2 equiv PhBneop and 1 h reflux conditions). [c] Yield is based on calculation of 50% ketone starting substrate since it acts as the hydride scavenger under the conditions of the reaction.[20] [d] 10 mol% catalyst loading. [e] With recovery of ester starting material (47%); the C-H activation/cross-coupling product was not detected. [f] Loss of ester group was detected in 23% conversion (based on GC-MS analysis).

Scheme 2 Comparison of relative cross-coupling reactivity of ketone-, amide- and ester-DG naphthalenes

In summary, a highly efficient and regioselective Ru-catalyzed ester-directed C-O activation/aryl boroneopentylate cross-coupling methodology has been discovered and generalized for the synthesis of 2-aryl and -heteroaryl substituted 1-naphthoates. It constitutes the first highly efficient catalytic ester-directed C-O activation/C-C bond forming reaction which uses commercially available compounds and provides a substantial body of results complementary to the C-H activation observation of the isopropyl benzoate from the Kakiuchi laboratories.[11,21] The 2-aryl 1-naphthoate products may be further useful in transformations of ester to other functional groups,[12] serve for classical Friedel-Crafts and other protocols for the construction of more highly condensed aromatics and heteroaromatics,[13-14,22] and may be viewed as a complement and possible future replacement of the DoM–Suzuki cross-coupling strategy, showing advantages of not requiring cryogenic temperatures and strong base conditions.[9a,9b,9g] Taken together with tertiary amide DG assisted C-O activation/cross-coupling reactions,[8] the results provide new general synthetic methodology of broad interest and potential to overtake traditional processes for the construction of aromatic and heteroaromatic molecules.

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Graphical Abstract: