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Directing Group-Promoted Inert C–O Bond Activation Using Versatile Boronic Acid as Coupling Agent

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Dedication ((optional))

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Abstract: A simple $Ni(cod)_2$ and carbene mediated strategy facilitates the efficient catalytic cross-coupling of methoxyarenes with a variety of organoboron reagents. Directing groups facilitate the activation of inert C–O bonds in vastly under-utilized aryl methyl ethers enabling their adaptation for C–C cross-coupling reactions as less toxic surrogates to the ubiquitous haloarenes. The method reported enables C–C cross-coupling with readily available and economical arylboronic acid reagents, which is unprecedented, and additionally to other organoboron reagents with similarly high reactivity. Extension to directing group assisted chemo-selective C–O bond cleavage, and further application towards the synthesis of novel bifunctionalized biaryls is reported. Key to the success of this protocol is the use of directing groups proximal to the reaction center to facilitate the activation of the inert C–OMe bond.

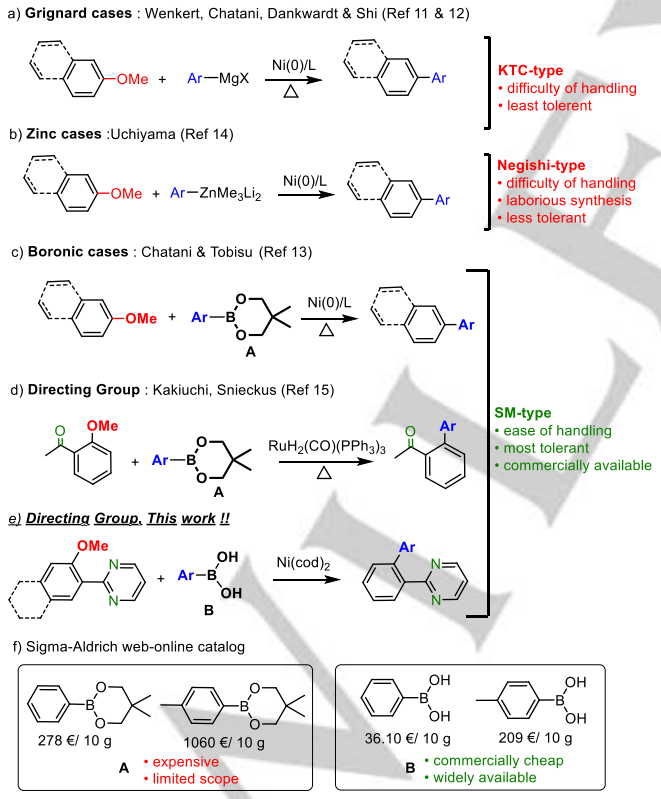
Over the past decade, C_{Ar}–O electrophiles have been regarded as potential surrogates to the ubiquitous aryl halides in the cross-coupling reaction, thus expanding the substrate scope and engendering enhanced synthetic flexibility for pivotal C–C bond formations.[1] Phenolic derivatives are naturally abundant, and in many cases significantly less toxic than their aryl halide counterparts.[2] This makes their increasing use in cross-coupling reactions all-the-more promising. There are notably a number of C_{Ar}–O electrophiles already in use as coupling partners, such as sulfonates,[3] carbamates,[4] triflates,[5] mesylates,[6] phosphonates,[7] tosylates,[8] sulfamates,[9] and esters.[10] However, the high energy required for breaking the C–OMe bond of aryl ethers has dramatically slowed the broad scope utilization of this otherwise highly promising chemical synthon.

Since the seminal report by Wenkert[11] in 1979, Ni-promoted cross-coupling of aryl methyl ethers has been actively and aggressively expanded in substrate scope, predominantly via the Kumada-Tamao-Corriu (KTC) with Grignard reagents,[12] Suzuki-Miyaura (SM) with boron reagents[13] and Negishi with Zn reagents[14] protocols (Scheme 1). For KTC, Grignard reagents are not only an effective coupling partner, but their high Lewis acidity plays a critical role in assisting the C–O bond activation. Notwithstanding the historical importance of the KTC reaction, the use of organomagnesium results in low functional group tolerance and can impose difficulty of handling, thus limiting substrate scope and broader utility. This motivates the development of Grignard-free routes to C-O bond activation.

Uchiyama and co-workers reported Negishi coupling utilizing Zn reagent for C–OMe bond functionalization. However, the preparation of Zn adduct was laborious, and the overall scope was limited. Chatani and co-workers developed an Ni-mediated SM-type coupling protocol with aryl methyl ether and sterically bulky organoboron **A** (Scheme 1c).[14] The latter demarcated the possibility of broad substrate scope and functional group tolerance for boron reagents as coupling partners for aryl methyl ethers. Other notable examples come from Kakiuchi and Snieckus who reported an Ru-catalyzed protocol which enables good activity with aryl ethers bearing carbonyl as a directing group at ortho position relative to OMe when using organoboron **A**,[15] and more recently, Zeng and coworkers who reported Cr-mediated cross-coupling between inert aryl methyl ether with aryl esters.[16]

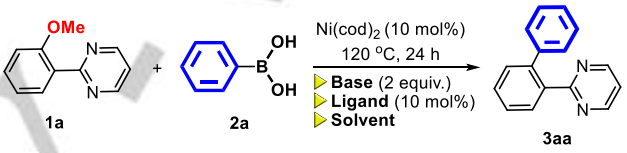
Owing to their low cost, widespread availability, air and moisture stability, and low toxicity, arylboronic acids **B** are distinctly more favorable organoboron reagents for traditional cross-coupling reactions (Scheme 1f).[17] It appears that steric bulk on the backbone of **A** is an essential requirement in previously reported nickel catalyzed cross-coupling of aryl ethers; arylboronic acids **B** were not effective under similar conditions (Scheme 1c, d). Martin reported that trace amounts of water generated from arylboronic acids upon heating led to the formation of catalytically inactive hydoxy-bridged nickel dimer

which impedes catalytic turnover.[18] Additionally, Garg and co-workers' experimental and computational studies revealed that H_2O serves to stabilize the Ni-carbamate catalyst in a resting state, which ultimately decreases the rate of coupling of carbamates. In the present study, we utilize directing groups as a possible strategy for the suppression/circumvention of these undesired pathways.[19] Consequently, there are currently no reported examples of C–O bond activation with arylboronic acids **B**. This presents a compelling opportunity given associated reagent cost and availability; *e.g.* **A** = USD $302 per 10 g, **B** = USD $39 per 10 g. Taking inspiration from the work of Kakiuchi and Snieckus, we hypothesized that a similar directing group strategy could be used to promote the Ni-mediated C–O bond activation using the preferred organoboron reagent **B**. The target substrate scope is focused on pyrimidine or pyridine, both ubiquitous functionalities present in many biologically active natural products,[20] pharmaceuticals,[21] and optoelectronic materials.[22] The use of pyridine and pyrimidine as directing groups for arylation by various transition metal catalysts is well documented for C–H functionalization.[23] Herein we report the nickel-promoted, pyrimidine/pyridine directing group assisted C–O activation with arylboronic acids **B** to furnish corresponding functionalized coupling products in good yields. By utilizing Earth-abundant Ni-based catalysts with lower toxicity aryl methyl ether substrates, and lower-cost, synthetically more accessible organoboron coupling partners, our findings contribute to a growing "tool-box" of sustainable C–C cross-coupling protocols.



Scheme 1. C–C cross-coupling via C–O activation.

Our optimization studies commenced with model substrates 2-(2-methoxyphenyl)pyrimidine **1a** and phenyl boronic acid **2a** (Fig. 1). After screening a series of bases (entries 1-5) with PCy_3 as a ligand we found that CsF was the optimal base (entry 3). Ligand screening revealed that bulky phosphine PBu_3 or bidentate phosphine dicyclohexylphosphinoethane (dcype) led to lower yields of 35-58% (entries 6-8). The highest yield of 93% was obtained with *N*-heterocyclic carbene IPr (entry 10). The stronger *σ*-donating electron-rich carbodicarbene[24] (**C_1-CDC**) was a close second with a good yield of 89% (entry 11). Solvents also play an important role in the reaction system, wherein toluene afforded the highest yields, followed by *p*-xylene and benzene, whereas cyclic ethers THF and dioxane resulted in markedly lower yields (entries 12-15). The control experiments conducted confirm that the combination of $Ni(cod)_2$ is necessary for the reaction to proceed in high yield (entries 17-18). However, a good yield (72%) under ligand-free conditions in presence of $Ni(cod)_2$ was observed (entry 16). There is a possibility that an added ligand serves to stabilize a resting state, prior to dissociate nickel from complexation for the C-O activation event.[25] Further details are provided in the Supporting Information (tables S1-S4).



Entry	Ligand	Base	Solvent	Yield [%]
1	PCy_3	NaO^tBu	toluene	37
2	PCy_3	LiO^tBu	toluene	42
3	PCy_3	CsF	toluene	79
4	PCy_3	CsCl	toluene	0
5	PCy_3	Cs_2CO_3	toluene	0
6	dcype	CsF	toluene	46
7	$P(^tBu)_3$	CsF	toluene	58
8	$P(^nBu)_3$	CsF	toluene	35
9	ICy	CsF	toluene	36
10	**IPr**	**CsF**	**toluene**	**93**
11	**C_1-CDC**	**CsF**	**toluene**	**89**
12	IPr	CsF	THF	57
13	IPr	CsF	dioxane	49
14	IPr	CsF	benzene	79
15	IPr	CsF	*p*-xylene	84
16[b]	--	CsF	toluene	72
17[c]	IPr	CsF	toluene	0
18[d]	--	CsF	toluene	0

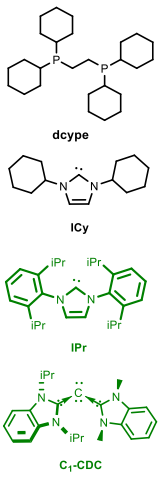


Figure 1. Selected optimization process for Ni-mediated, directing group assisted C–C cross-coupling via C–O bond activation. *Reaction conditions:* **1a** (0.25 mmol), **2a** (0.37 mmol), $Ni(cod)_2$ (10 mol%), ligand (10 mol%), and base (0.50 mmol) in 1 mL solvent at 120 °C for 24 h, yield = isolated yield. [a]No ligand used. [b]No $Ni(cod)_2$ used. [c]No $Ni(cod)_2$ and no ligand used.

With optimized conditions in hand, a variety of functionalized arylboronic acids were examined against pyrimidine **1a** (Fig. 2). The reaction worked well for *meta* and *para* substituted tolylboronic acids **2b**, **2c** and **2d**, delivering desired products **3ab**, **3ac** and **3ad** respectively in excellent yields. Reagents **2e** and **2f**, with a bulky *tert*-butyl group at the *para* position and a methyl group at the *meta* position respectively, demonstrated the feasibility of reaction at the boron over simple alkyl substitution. This synthetic methodology also exhibited a high level of tolerance toward substrates bearing electron-rich boronic coupling partners like 3-methoxy **2g**, 4-methoxy **2h**, 4-dimethylamine **2i**, and diphenylamine **2j** with good yields.

Electron withdrawing fluoride substituted boronic acids **2k**, **2l** and **2m**, were tolerated with this methodology leading to pharmaceutically-relevant molecules **3ak**, **3al** and **3am** in good yields. Other electron-withdrawing functionalities such as esters, ketone and phenyl groups (**2n**-**2r**) also furnished arylated products in moderate to good yields. This protocol could further be expanded to the heteroaromatic derivative **2s** to obtain arylated product **2as** in moderate yield. Finally, we provide examples of polyarene boronic acid derivatives **2t**, **2u** and **2v** to demonstrate the efficacy of the methodology. It should be noted that boronic reagents bearing Cl and Br substituents are not suitable for this reaction protocol owing to possible halide cleavage by the nickel catalyst.[26] Notably, 2-(2-methoxyphenyl)pyridine **4a** featuring the phenyl-pyridine directing group commonly used in C–H bond activation was also found suitable for our protocol, readily coupling with an array of arylboronic acids containing electron-neutral, -donating, -withdrawing and sterically bulky groups (Fig. 2).

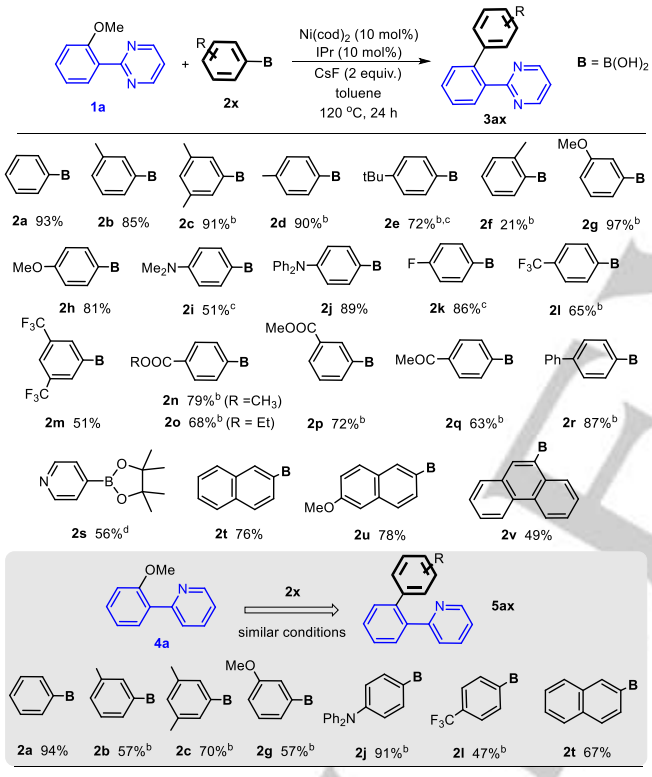


Figure 2. Scope of arylboronic acids for Ni-mediated, directing group assisted C–C cross-coupling via C–O bond activation. *Reaction conditions:* **1a** (0.25 mmol), arylboronic acid **2** (0.37 mmol), $Ni(cod)_2$ (10 mol%), IPr (10 mol %), CsF (0.50 mmol) in 1 mL toluene at 120 °C for 24 h, isolated yield. [a]C_1-CDC was used instead of IPr. [b]Reaction run for 48 h. [c]Pinacol boronic ester derivative was used instead of boronic acid.

An expanded scope of directing group bearing derivatives in C–O activation/C–C cross-coupling reaction was subsequently investigated (Fig. 3). Substrates derived from phenyl-pyridine **4b** and **4c** with methyl substitution at various positions furnished cross-coupling products in high yield. Notably, substrate **4d**, bearing an electron withdrawing CF_3 group resulted in 92% yield**.** Ester group substituted **4e** however resulted in only a moderate yield of 44%. Phenyl and *para*-tolyl substituted pyridine directed **4f** and **4g** substrates furnished the desired cross-coupling products in good yields of 71% and 72% respectively. Pyrimidine group directed **4h** with an isopropyl group installed on the benzene ring furnished coupling product in 88% yield, whereas its pyridine analog **4i** was limited to 44% yield of corresponding biaryls. The reaction of naphthalene containing substrate **4j** afforded the cross-coupling product in excellent yield at 93%. Importantly, this protocol was not restricted to only pyridine and pyrimidine as directing groups, other directing group substrates (**4k** and **4l**) were also tolerated.

Next, we sought to evaluate the effect of varying leaving groups for this directing group assisted C–O activation/C–C cross-coupling reaction system (Scheme 2a). Under similar reaction conditions, pyrimidine bearing ether moieties such as ethoxy (**7a**, 83%), isopropoxy (**7b**, 79%), phenoxy (**7c**, 95%) and benzyloxy (**7d**, 80%) proved suitable in this protocol. Similarly, with pyridine as the directing group, the additional leaving group molecules were similarly facile, except for 2-(2-ethoxyphenyl)pyridine (**8a**, 0%).

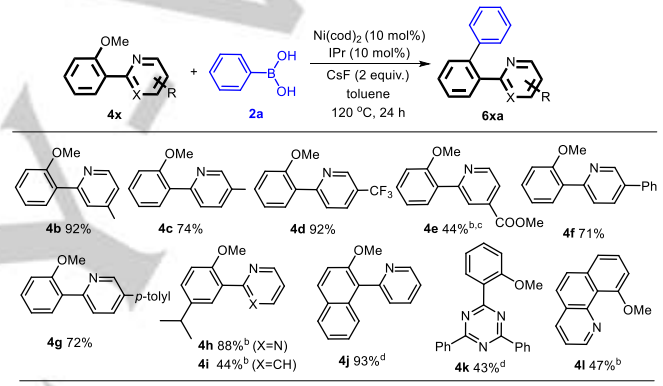
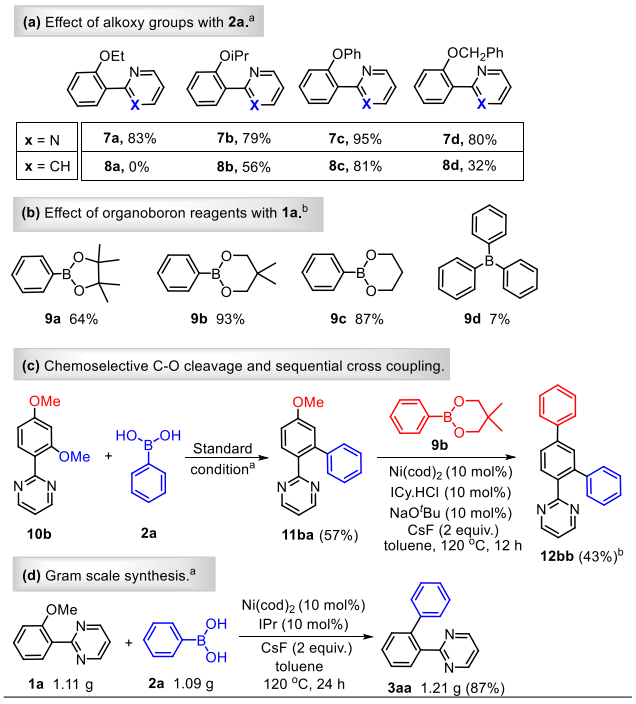


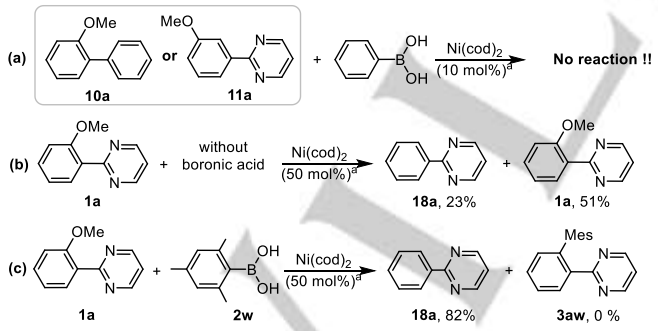
Figure 3. Scope of phenylpyrimidines and phenypyridine. *Reaction conditions:* **4** (0.25 mmol), **2a** (0.37 mmol), $Ni(cod)_2$ (10 mol%), IPr (10 mol%), CsF (0.50 mmol) in 1 mL toluene at 120 °C for 24 h, isolated yield. [a]C1-CDC was used instead of IPr. [b]Reaction run for 48 h. [c]No IPr used.



Scheme 2. Reactivity of different leaving groups and organoboron reagents. [a]*Reaction conditions:* **7**/**8** (0.25 mmol), **2a** (0.37 mmol), $Ni(cod)_2$ (10 mol%), IPr (10 mol%) and CsF (0.50 mmol) in 1 mL toluene at 120 °C for 24 h, isolated yield. [b]Reaction conditions: **1a** (0.25 mmol), **9** (0.37 mmol), $Ni(cod)_2$ (10 mol%), IPr (10 mol%) and CsF (0.50 mmol) in 1 mL toluene at 120 °C for 24 h, isolated yield.

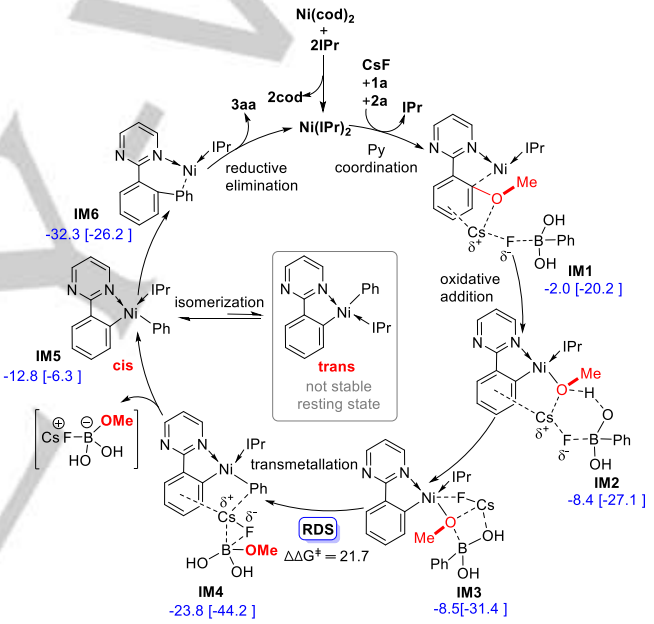
A significant advantage of this directing group strategy is the ability to use a broader scope of boronic ester derivatives such as **9a**, **9b** and **9c** and triphenylborane **9d** to afford **3aa** in good to excellent yields (Scheme 2b); thus demonstrating a high degree of synthetic flexibility.[27] Subsequently, we evaluated the chemo-selectivity for C–O activation with sequential orthogonality in cross-coupling and potential for gram scale synthesis (Scheme 2c,d). Dimethoxy compound **10b** could be cleaved selectively to give mono arylated coupling product **11ba** with simple **2a** which underwent further sequential selective functionalization using an established method[13b] to furnish cross-coupling product **12bb** in moderate yield with bulky boronic acid **9b** (Scheme 2b). Finally, we revisit the synthesis of **3aa** and demonstrate facile scale up to gram level in good yield (87%; Scheme 2d).

To delineate the mechanism of the directing group assisted C–O activation/C–C cross-coupling reaction, a series of experiments were performed (Scheme 3). C–O cleavage of biphenyl **10a** or pyrimidine **11a** bearing *meta* methoxy groups in the presence of 10 mol% Ni and boronic acid **1a** showed no activity, illustrating the role of the proximity effect for the directing group (Scheme 3a). Reaction of 50 mol% Ni catalyst in the absence of boronic acid furnished only 23% of 2-phenylpyridime **18a**[28] with recovered substrate **1a** at 50% (Scheme 3b). This points to a cooperative C–O bond activation supported by both proximal directing groups and the Lewis acidity of the boronic acid coupling partner. This effect was further confirmed by the experiment in Scheme 3c, where an equivalent of sterically encumbered mesitylboronic acid **2w** was added to afford mostly **18a** (82%). This outcome also suggests the possibility that the trans-metalation or reductive elimination is a rate determining step.



Scheme 3. Mechanistic investigations. [a]*Reaction conditions:* **Xa** (0.25 mmol), **2x** (0.37 mmol), $Ni(cod)_2$ (10/50 mol%), IPr (10/50 mol%), CsF (0.50 mmol) in 1 mL toluene at 120 °C for 24 h, isolated yield.

Based on the aforementioned experimental evidence and prior literature[29], as well as our DFT calculations, the mechanism of C–O activation/C–C cross-coupling reaction is proposed in Scheme 4. A stoichiometric amount of CsF with phenyl boronic acid activates the C–O cleavage of 2-(2-methoxyphenyl)pyrimidine **1a** and forms the intermediate **IM1**, followed by the oxidative addition step to give the more stable intermediate **IM2**, which can be easily isomerized to complex **IM3**. The proposal of species **IM1** is based on recent experimental and theoretical evidence reported by Chatani and Tobisu[18,30] where CsF and arylboronic ester interact with Ni complex to lower the energy barrier of C–O cleavage. Subsequent transmetallation onto **IM3** yields intermediate complex *cis*-**IM5** and elimination of salt as byproduct. It is worthy of mention that the *cis*-**IM5** is 8.3 kcal/mol more stable than the *trans*-**IM5**.[30] *cis*-**IM5** will undergo reductive elimination to give the desired arylated cross-coupling product **3aa** and regenerate the catalyst for the next cycle. As detailed by the results shown in Figure S2, each stage is kinetically and thermodynamically feasible. The energy profile analysis revealed that the transmetallation is the rate-determining step (RDS). As the reaction proceeds, the intermediate species become more and more thermodynamically favorable, which can provide the necessary driving force to reach the final product **3aa**.



Scheme 4. Proposed mechanism of nickel mediated C-O bond activation. The energy values of free energy [electronic energy] in kcal/mol were calculated based on the BP86+D3(BJ)/def2-TZVPP(SMD, solvent=Toluene)// BP86+D3(BJ)/def2-SVP (SMD, solvent=Toluene) level.

In summary, we have developed the directing group repertoire to activate rarely explored, inert C–OMe bond functionalized pyridines and pyrimidines followed by C–C cross-coupling to generate biaryl products. This protocol has eliminated the inclusion of highly reactive Grignard reagents to assist in breaking inert C–O bonds. Significantly, the synthetic protocol can utilize a diverse array of economical boronic acid derivatives to produce functionalized biaryl products. The reaction is mediated by an Earth-abundant Ni catalyst, thus providing an attractive alternative to the more common precious and semi-precious metal catalysts associated with cross-coupling methodology for the construction of bifunctionalized biaryls. Ongoing studies focus on expanding the derivatization of directing groups and seeking out additional catalytic systems suitable for this cross-coupling protocol.

Acknowledgements

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Keywords: C-O cleavage • DG assisted • cross-coupling • biaryls • phenylboronic acid

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[2] For example: Oral rat LD50: PhCl (1231 mg/kg); PhBr (2383 mg/kg); PhI (1749 mg/kg); PhOMe (5290 mg/kg). Source FisherSci/Sigma MSDS

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Table of Contents

DG assisted: Directing group assisted nickel catalyzed C−OMe bond activation for C–C cross-coupling is reported. C–O activation of rarely explored methyl ethers and C–C cross-coupling with a wide range of readily available boronic acid reagents is achieved. The strategy could be further extended to afford novel bifunctionalized biaryls.