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Trimethylphosphate as a Methylating Agent for Cross Coupling: A Slow-Release Mechanism for the Methylation of Arylboronic Esters

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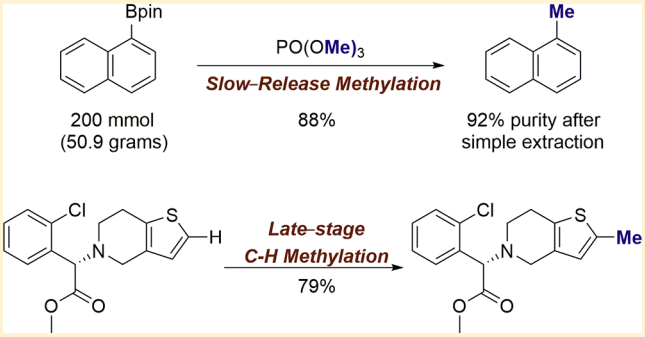
Supporting Information

ABSTRACT: A methyl group on an arene, despite its small size, can have a profound influence on biologically active molecules. Typical methods to form a methylarene involve strong nucleophiles or strong and often toxic electrophiles. We report a strategy for a new, highly efficient, copper and iodide co-catalyzed methylation of aryl- and heteroarylboronic esters with the mild, nontoxic reagent trimethylphosphate, which has not been used previously in coupling reactions. We show that it reacts in all cases tested in yields that are higher than those of analogous copper-catalyzed reactions of MeOTs or MeI. The combination of C−H borylation and this methylation with trimethylphosphate provides a new approach to the functionalization of inert C−H bonds and is illustrated by late-stage methylation of four medicinally active compounds. In addition, reaction on a 200 mmol scale demonstrates reliability of this method. Mechanistic studies show that the reaction occurs by a slow release of methyl iodide by reaction of $PO(OMe)_3$ with iodide catalyst, rather than the typical direct oxidative addition to a metal center. The low concentration of the reactive electrophile enables selective reaction with an arylcopper intermediate, rather than nucleophilic groups on the arylboronate, and binding of *tert*-butoxide to the boronate inhibits reaction of the electrophile with the *tert*-butoxide activator to form methyl ether.



INTRODUCTION

A methyl group is the smallest nonpolar substituent in organic chemistry and is inert toward most organic transformations. Many studies have shown that a methyl group modulates the solubility, hydrophilicity, and conformation of a drug, thus leading to the term "magic methyl effect".[1] In addition, isotopically labeled methyl groups are important for medicinal chemistry. For example, Austedo, an FDA-approved drug for the treatment of chorea, contains a deuterated methyl group to attenuate the drug metabolism and improve tolerability by reducing adverse events related to peak plasma concentrations.[2] Attesting to this profound effect of a methyl group, a survey by Njardarson showed that over 67% of the top 200 selling small-molecule drugs in 2011 contained at least one methyl group.[1c] Hence, efficient methods for selective installation of methyl groups, particularly installation at the position of a C−H bond, are highly desirable.[3]

Arylboronic acids are versatile reagents and can be accessed by numerous synthetic methodologies.[4] Direct methylation of arylboronic acids or derivatives of them would be a convenient method to introduce a methyl group into widely existing aromatic structures in biologically active molecules. However, reports of methods to couple arylboronic acids or esters with a methyl electrophile are scarce.[5] In 2004, Gooßen developed a Pd-catalyzed cross-coupling reaction of $ArB(OH)_2$ with MeI as the methyl electrophile.[5a] More recently, Liu reported the methylation of two arylboronic neopentanediolate esters (ArBneop) with MeOTs as the electrophile in the presence of a Cu catalyst.[5b] In both cases, the substrate scope is limited. Because MeI and MeOTs are highly reactive methyl electrophiles, it is possible that substrates containing basic functional groups or heteroaryl groups would undergo uncatalyzed methylation to form undesired side products.

A reliable method for the methylation of arylboronic esters with broad scope could be valuable for many applications, particularly the overall conversion of an aryl or heteroaryl C−H bond to the corresponding aryl- or heteroarylmethane (Scheme 1). However, to be applicable for such processes, the reaction must meet several requirements. First, the methylation process must occur with pinacol-substituted aryl- and heteroarylboronates, because this class of arylboronates is formed by the borylation of C−H bonds.[6] Second, a higher tolerance for basic and heteroaryl moieties must be realized than that of reactions of aryl- and heteroarylboronates with MeI or MeOTs. Presumably, this higher tolerance would require a milder source of methyl electrophile than has been used previously for the coupling with arylboronates. Finally, for the

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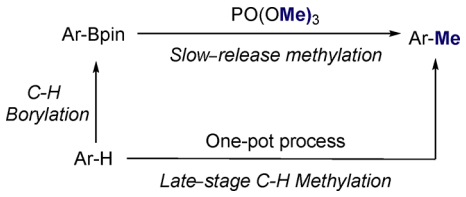
Scheme 1. Research Design



most practical applications, a methyl electrophile should be used that is inexpensive, available on large scale, and less mutagenic than the standard highly reactive methyl halides, sulfates, and sulfonates.[7]

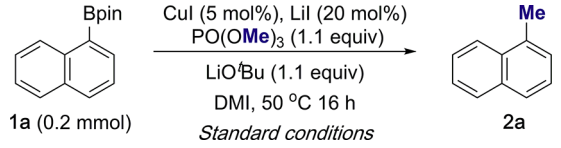
We report the copper and iodide co-catalyzed methylation of a wide range of aryl and heteroaryl pinacolboronates with trimethylphosphate as a new methylating agent in coupling reactions.[8] Detailed mechanistic analysis of the process shows that the phosphate does not react directly with the copper catalyst. Instead, the conditions developed lead to a slow release of MeI that reacts rapidly with an arylcopper species. By this slow-release mechanism, the reaction occurs with a wide range of both aryl- and heteroarylboronates in yields that are much higher than those obtained with the analogous copper-catalyzed reactions with MeI, MeOTs, or Me_2SO_4. Studies on the combined borylation and methylation of medicinally active compounds show that this process is suitable for the site-selective methylation of biologically active compounds, and reactions on 200 mmol of arylboronate show that this methylation process should be suitable for process scale.

RESULTS AND DISCUSSION

Reaction Development. To develop the methylation of aryl pinacolboronates, we studied the reactions of 1-naphthyl-Bpin (**1a**) as the model substrate, in part because of the high boiling point of the product and ability to detect the protodeboronation product. A series of experiments showed (see Supporting Information (SI) for details) that the methylated product **2a** was obtained in 93% yield with a copper catalyst, iodide co-catalyst, LiO^{t}Bu as the base, and $PO(OMe)_3$ as the source of methyl group in DMI solvent at 50 °C (Table 1, standard condition).

The series of experiments shown in Table 1 reveal the importance of each component. Conventional methylation reagents, like MeI, MeOTs, Me_2SO_4, and $CO(OMe)_2$ reacted in much lower yield (Table 1, entry 2–5, 0–54% vs 93%). Reactions in the absence of CuI formed no methylated product (entry 6). The presence of iodide in the system seemed crucial for obtaining high yields. Reactions with copper catalysts lacking iodide occurred in much lower yield than those catalyzed by CuI, and reactions catalyzed by CuI with added LiI occurred in a much higher yield (entry 1, 93%) than those in the absence of LiI (entry 7, 29%). Because the reactions with and without LiI also contain LiO^{t}Bu, the iodide in the LiI is important. To exclude the potential requirement that the reaction requires CuI, other types of copper sources were tested. In the absence of an added catalytic amount of LiI, CuBr·Me_2S was the only complex of five tested that gave product, and this catalyst gave the product in a low 36% yield; none of the reactions catalyzed by CuOAc, CuCl, CuTc, or $Cu(MeCN)_4PF_6$ gave methylated product **2a** (entry 8). However, product **2a** was observed in over 60% yield from reactions initiated with all of these catalyst precursors when the

Table 1. Standard Reaction Conditions and Control Experiments



entry	variation from the standard conditions	yield[a] (%)
1	none	93[b]
2	MeI instead of $PO(OMe)_3$	24
3	MeOTs instead of $PO(OMe)_3$	54
4	Me_2SO_4 instead of $PO(OMe)_3$	23
5	$CO(OMe)_2$ instead of $PO(OMe)_3$	n.d.
6	without CuI	n.d.
7	without LiI	29
8	other [Cu] sources instead of CuI, no LiI	0–36
9	other [Cu] sources instead of CuI, with LiI	61–85

	[Cu]				
	CuOAc	CuCl	CuBr·Me_2S	CuTc	$Cu(MeCN)_4PF_6$
no LiI	n.d.	trace	36%	n.d.	n.d.
with LiI	61%	70%	85%	75%	75%

[a]Determined by crude ^{1}H NMR spectroscopy with CH_2Br_2 as the internal standard. [b]Isolated yield. DMI = 1,3-dimethyl-2-imidazolidinone; n.d. = not detected.

reactions contained 20 mol% of LiI (entry 9). The precise role of each of the reaction components was elucidated by mechanistic studies described in the final section of this paper.

Scope of Arylboronic Esters That Undergo Methylation with $PO(OMe)_3$. The scope of the methylation of a group of arylboronic esters with $PO(OMe)_3$ was assessed, and the results are summarized in Scheme 2. Electron-withdrawing substituents, such as Cl, Br, and I, were well tolerated, affording the corresponding methylarene in 70–85% yield (**2b–2d**). These reactions occur without any interference from the halides or reaction between the boronate unit and a halide. Arylboronic esters containing electron-donating groups (**1e**, **1h**) also were suitable for the methylation with $PO(OMe)_3$, providing products **2e** and **2h** in 69% and 58% yield, respectively. Reaction of the electron-rich ferrocenylboronate **1i** afforded the methylated product **2i** in 79% yield. An *ortho*-substituent did not inhibit the process; rather product **2g** formed in a high 97% yield. Substrates containing ester, amide, or OTBS functionality also underwent methylation, in this case to form **2f**, **2j**, and **2k** in 68–76% yield. Finally, the methylation process was applied to complex molecules **1l** and **1m**; the methylation of these compounds occurred in 71% and 68% yield, respectively.

To assess whether $PO(OMe)_3$ was a more effective agent for methylation than more commonly used MeOTs or MeI, we tested these reactions with the copper catalyst and alkoxide activator with these two reagents. These data are included in Scheme 2. These data show that methylation of each substrate occurred in higher yield with $PO(OMe)_3$ than with MeI or MeOTs. For example, product **2b** was obtained in 85%, 33%, and 10% yield from the copper-catalyzed reactions with $PO(OMe)_3$, MeOTs, and MeI, respectively. Likewise, the simple 2-methylbiphenyl product **2g** formed in 97% yield with $PO(OMe)_3$ but only 33% yield with MeOTs and 27% yield with MeI. For all of the cases in Scheme 2, the advantage of using $PO(OMe)_3$ was obvious for increasing the reaction efficiency.

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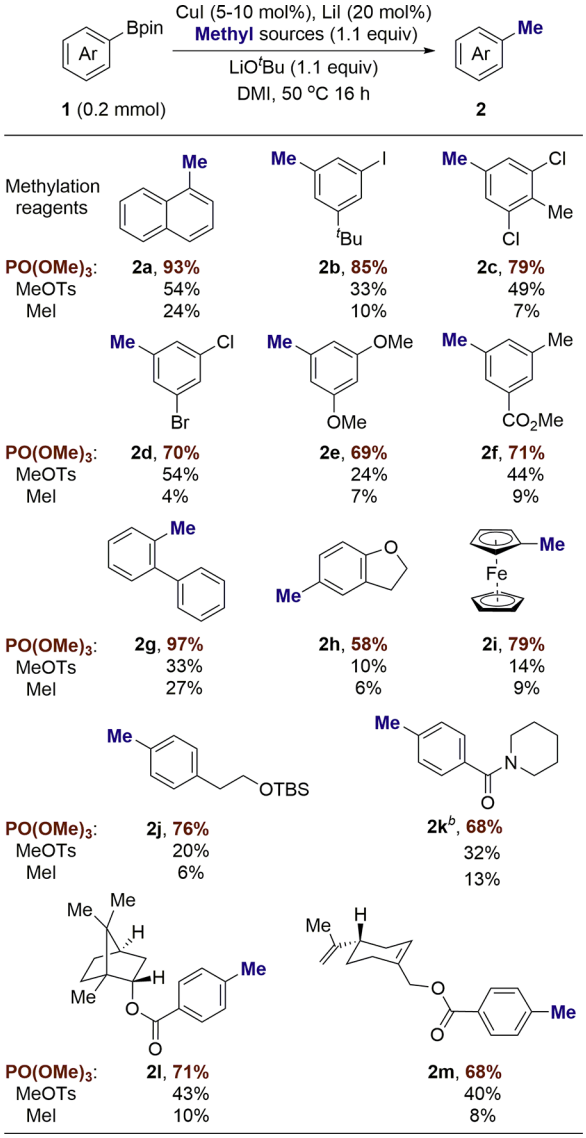
Scheme 2. Scope of Arylboronic Esters That Undergo Methylation with $PO(OMe)_3$[a]

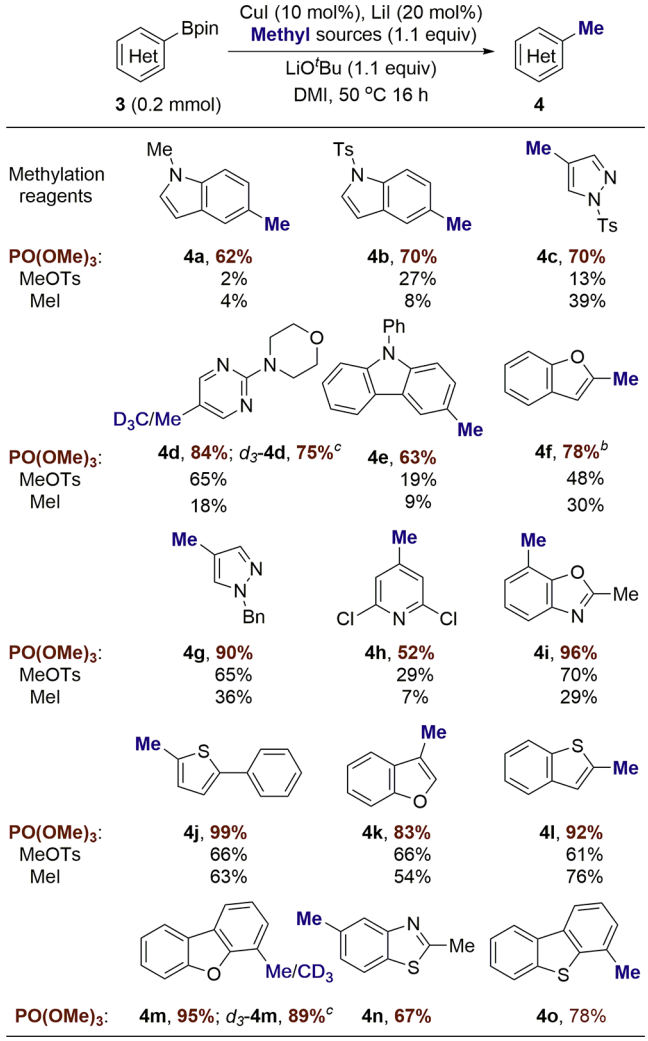


[a]Conditions: **1** (1.0 equiv), $PO(OMe)_3$ (1.1 equiv), CuI (5−10 mol %), LiI (20 mol%), LiO^{t}Bu (1.1 equiv), DMI (0.66M), 50 °C. Isolated yields are reported. For cases of MeOTs and MeI, yields were determined by crude ^{1}H NMR or ^{19}F NMR. [b]Determined by crude ^{1}H NMR.

Scope of Heteroarylboronic Esters That Undergo Methylation with $PO(OMe)_3$. Heteroaromatic moieties are ubiquitous in biologically active molecules, but cross-couplings of heteroarenes are usually more challenging to achieve than those with less polar and less basic arenes. Substrates containing a basic nitrogen could be a particular challenge for reactions with an electrophilic methyl group, due to the potential of uncatalyzed methylation of the basic nitrogen atom and the potential to sequester the unligated copper catalyst.

Nevertheless, the results in Scheme 3 showed that the methylation occurred with a broad range of heteroaryl pinacolboronic esters. Nitrogen-containing heterocycles like indole, pyrazole, pyrimidine, and carbazole were well tolerated and produced the corresponding methylated heteroarenes in

Scheme 3. Scope of Heteroarylboronic Esters That Undergo Methylation with $PO(OMe)_3$[a]



[a]Conditions: **3** (1.0 equiv), $PO(OMe)_3$ (1.1 equiv), CuI (10 mol%), LiI (20 mol %), LiO^{t}Bu (1.1 equiv), DMI (0.66M), 50 °C. Isolated yields are reported. [b]Reaction performed at 2 mmol scale. [c]CuI (20 mol%) was used.

62−90% yield (**4a**−**4e**, **4g**). A sterically hindered pyridine **3h** afforded **4h** in moderate yield. Reaction of the heteroarylboronates, which contain oxygen and sulfur heterocycles (**3f**, **3j**−**3l**, **3m**, **3o**), gave the corresponding methyl-heteroarenes in 78−99% yield. Likewise, reactions of benzoxazole and benzothiazole (**3i**, **3n**), as representative heteroarenes containing multiple heteroatoms, afforded the corresponding methyl-heteroarenes **4i** and **4n** in 96% and 67% yield, respectively. Due to the value of labeled methyl groups in the medicinal field, the reactions of **3d** and **3m** with commercially available $PO(OCD_3)_3$ were also tested, giving d_3-**4d** and d_3-**4m** in high isolated yields (75% and 89%, respectively).

As we did for the copper-catalyzed methylation of arenes, we tested the copper-catalyzed methylation of heteroarenes with MeOTs and MeI as methylating agents. Again, the yields were uniformly higher for reactions with trimethylphosphate than for those with MeOTs or MeI. For example, indole **3a** reacted with $PO(OMe)_3$ in 62% yield while it reacted with both MeOTs and MeI in less than 5% yield; For other substrates,

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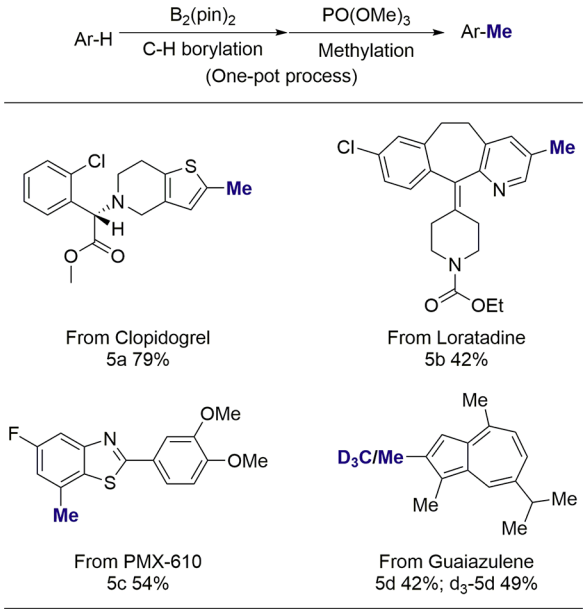
the yields of reactions of MeOTs and MeI were 16−57% lower than those of the reactions of $PO(OMe)_3$.

A robustness test[9] was also conducted to provide more general information on the tolerance of the process for a series of functional groups and potential limitation of $PO(OMe)_3$ as a methylating agent (see SI for detailed results). Reactions with added unprotected amine, alcohol, or amide occurred in low to moderate yield because methylation of the functional groups in these additives was more facile than methylation of the arylboronate, and competitive protodeboronation of the arylboronate occurred. In contrast, high yields were observed when reactions were run with analogous additives in which the free N−H or O−H groups were protected by Boc, TIPS, or TBS groups. Likewise, the methylation reactions conducted with an added secondary dialkylamine, tertiary amine, allylic ester, epoxide, pyridine, pyridine-1-oxide, nitrile, alkene, ketone, imine, or aldehyde all gave the methylarene product in high yield. The methylation reaction with a terminal alkyne as additive gave only 7% yield, but the reaction with an internal alkyne occurred in high yield.

Late-Stage Site Selective C−H Methylation of Biologically Active Molecules. The current methods for the methylation of unactivated C−H bonds are limited to *N*-contained heteroaromatic compounds or arenes containing directing groups. Published methods include Minisci reactions with acetic acid as the methyl source,[10] the addition of methyl radicals to heteroarenes under both thermal and photoredox conditions,[11] and Pd- or Fe-catalyzed methylation of C−H bonds in arenes containing a directing group.[12]

Due to the limited methods to realize the methylation of inert C−H bonds,[10−12] particularly an undirected methylation of a C−H bond, we tested the combination of the methylation of arylboronates with the borylation of aryl- and heteroaryl C−H bonds.[6] Four medicinally active compounds were chosen to test this tandem process (Scheme 4). Clopidogrel,[13] a medication for heart disease and stroke known as Plavix, underwent the one-pot, Ir-catalyzed borylation and copper-catalyzed methylation with $PO(OMe)_3$ to install a methyl group selectively at the 2-position of the thiophene ring in high yield (**5a**, 79%). A similar one-pot process enabled the late-stage site-selective methylation of loratadine, sold as Claritin for the treatment of allergies,[14] in moderate yield (**5b**). The benzothiazole-based heterocycle, PMX-610,[15] which has exhibited high antitumor activity in breast-cancer cell lines, was modified by a stepwise borylation and methylation in 54% overall yield (**5c**). Finally, this methylation also was tested for the modification of the hydrocarbyl natural product guaiazulene which possesses anti-inflammatory and antioxidative activity,[16] providing methylated guaiazulene or CD_3-guaiazulene in 42% and 49% yield, respectively (**5d**, d_3-**5d**).

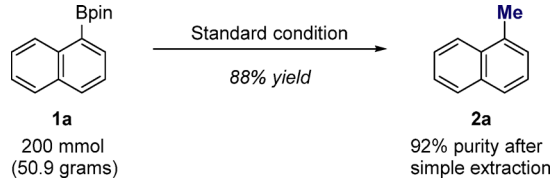
Scheme 4. Late-Stage Site-Selective C−H Methylation of Biologically Active Molecules[a]



[a]See SI for details.

Results with Reactions on 1000-Fold Larger Scale. The feasibility of this coupling reaction for process scale was assessed by conducting the reaction on a 200 mmol scale (Scheme 5). This reaction afforded **2a** in 88% isolated yield in 92% purity after simple extraction. This yield is nearly identical to that obtained with the same substrate on a smaller scale (0.2 mmol scale for 93% yield).

Scheme 5. Reaction with 200 mmol of Arylboronate



Mechanistic Studies. *Uncovering the Role of $PO(OMe)_3$ and Iodide.* Methyl electrophiles typically react with organometallic complexes by oxidative addition[5a] or S_N2 substitution.[5b] To determine whether trimethylphosphate reacted by one of these pathways, we conducted mechanistic studies.

The transmetalation of arylboronates to form arylcopper complexes is well precedented.[17] Thus, to understand how an arylcopper complex would undergo methylation in this system, we first studied reactions of Mes-Cu with $PO(OMe)_3$ and MeI (Scheme 6a). The reaction of Mes-Cu with $PO(OMe)_3$ gave no product after 20 h, but the reaction with MeI afforded Mes-Me in 20% yield after 5 h at 40 °C and 58% yield after 42 h. The analogous reactions also were conducted with the less hindered PhCu, which is not isolable but can be generated in situ.[18] The reaction of this species with $PO(OMe)_3$ gave no detectable product after 10 min; in contrast, the reaction with MeI occurred with a half-life of less than 2 min. These results fit our observation that the catalytic methylation reaction proceeds only in the presence of halide (Table 1, entries 8 and 9). These results suggest that the combination of LiI and trimethylphosphate generate MeI in the reaction system.

To assess this hypothesis, we studied the reaction of LiI with $PO(OMe)_3$ under conditions related to those of the catalytic process (Scheme 6b). This reaction was too slow to be a step of the catalytic process; only a trace of MeI was observed after 24 h at 40 °C. We considered that the Li^+ of LiO^tBu in the catalytic system could act as a Lewis acid to increase the electrophilicity of the methyl group of $PO(OMe)_3$. Indeed, the reaction of LiI with $PO(OMe)_3$ in the presence of an additional equimolar amount of $LiBF_4$ released MeI much faster than the reaction without $LiBF_4$; 66% of MeI formed

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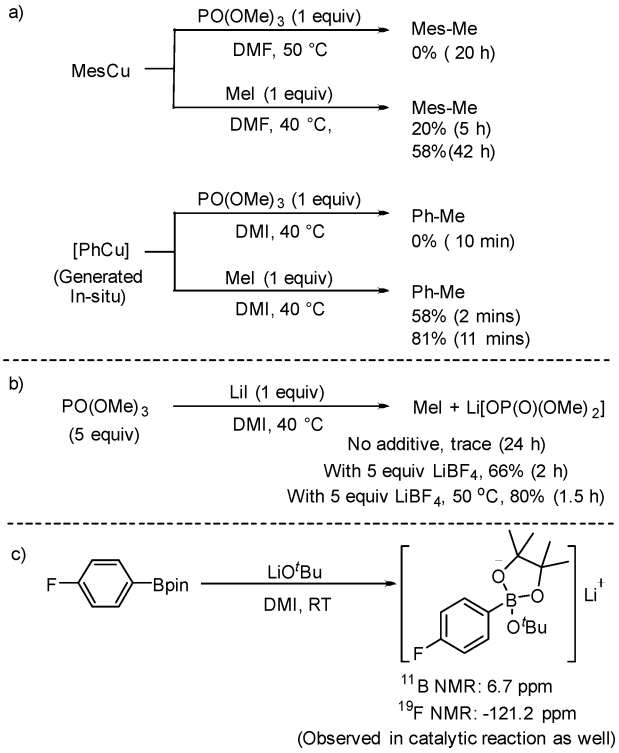
Scheme 6. Stoichiometric Reactions Potentially Occurring in the Catalytic System



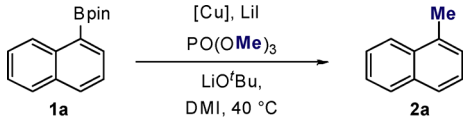
[a]Reactivity comparison of MeI and $PO(OMe)_3$ with ArCu. [b]MeI generation from $PO(OMe)_3$ and LiI. [c]Reaction of 4-FPhBpin with LiO^tBu.

after 2 h. The same reaction at 50 °C reached equilibrium after 1.5 h to generate MeI in 80% yield, based on the iodide added.

Although this experiment showed that Li^+ accelerates the reaction, the lithium cations are associated with iodide and alkoxide in the true reaction system. The Li^+ added to the system is not associated with a non-coordinating anion, such as BF_4^-, and if methyl iodide is formed, one might expect it to react with the *tert*-butoxide in the system. Indeed, the reaction of MeI with LiO^tBu to give methyl *tert*-butyl ether occurs in quantitative yield after 10 min at room temperature. To solve this paradox about how Li^+ could accelerate the formation of MeI and why MeO^tBu did not form from reaction of LiO^tBu and MeI in the catalytic reactions, we considered the role of the arylboronic ester. LiO^tBu reacted with the ArBpin reagent to form $Li[ArB(pin)O^tBu]$, as determined by ^{11}B NMR ^{19}F NMR spectroscopy of the reaction of these two components alone. This borate was also the major form of the boron reagent in the catalytic system, as determined by the similarity of the ^{11}B NMR and ^{19}F NMR resonances of the catalytic reaction to those of the borate generated separately (Scheme 6c).[19] The lithium cation in this boronate complex is more loosely bound than that in LiO^tBu and can act as the Lewis acid to catalyze formation of MeI. Moreover, the alkoxide unit in this borate complex is much less nucleophilic than that in LiO^tBu and does not react with MeI.[20]

Kinetic Studies. To reveal the step that controls the overall rate of the reaction, we conducted kinetic studies (Scheme 7). The reaction was first order in both $[I^-]$ and $[PO(OMe)_3]$. In contrast to most catalytic processes, the reaction was zero-order in copper at the concentrations of the preparative

Scheme 7. Kinetic Order of the Methylation Reaction



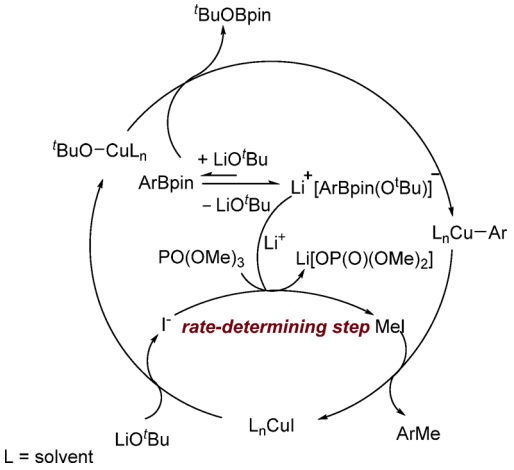
[Cu] = CuI or CuO^tBu

- 1st order in $[I^-]$
- 1st order in $[PO(OMe)_3]$
- Zero order in [Cu]
- 1st order in $[Li^+]$
- 1st order in **[1a]**
- 1st order in $[LiO^tBu]$

reactions. These data indicate that the generation of active methyl electrophile is the rate-determining step. The importance of the lithium cation generated from LiO^tBu and the ArBpin was supported by observing a first-order dependence of the rate on the concentration of both of these two components. The importance of Li^+ was also supported by the separate observation of a first-order dependence of the reaction rate on $LiBF_4$. These data imply that the reaction of the methyl electrophile with copper and formation of the methylarene are faster than generation of MeI. As described previously in this section, the reaction of $[I^-]$ with $[PO(OMe)_3]$ occurs on the time scale of hours at 40 °C, whereas the reaction of MeI with PhCu occurs within minutes.

Proposed Mechanism. Based on these results, a mechanism for the methylation of arylboronates with Cu(I) as catalyst and iodide as co-catalyst is depicted in Scheme 8. In a rate-

Scheme 8. Proposed Reaction Mechanism



determining step external to the catalytic cycle, iodide reacts with $PO(OMe)_3$ to release MeI. The slowly released MeI rapidly reacts with the arylcopper intermediate generated from the combination of CuI, LiO^tBu, and ArBpin, either from reaction of CuO^tBu with ArBpin or reaction of CuI with $[ArBpin(O^tBu)]^-$. The $^-O^tBu$ does not react with MeI because it is sequestered by the arylboronate, and the low concentration of MeI ensures that the MeI in the system reacts with the arylcopper species over many basic groups on the arylboronate reagent.

CONCLUSION

In summary, we reveal an approach based on slow-release of MeI for the methylation of arylboronates with trimethylphosphate. This reagent is inexpensive and nontoxic, but it has not been used previously as a source of a methyl group in

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coupling chemistry. By this unusual mechanism, the yields for methylation with $PO(OMe)_3$ are higher than those of the more reactive methyl electrophiles MeOTs and MeI. Although the mechanism involves a web of on-cycle and off-cycle steps that make the reaction occur in high yield, it is amenable to large scale and to the late-stage functionalization of pharmaceutical intermediates. The reaction with 200 mmol of arylboronate occurred the same yield as reactions with 0.2 mmol, and four medicinally active compounds were converted selectively into the methyl analogues. The formation of MeI from trimethylphosphate and LiI was rate limiting, and steps on the catalytic cycle, including the reaction of MeI with the arylcopper species, were fast. Overall, this process shows an approach to using a methylating agent that does not react directly with the metal center and is reminiscent of the use of MeOH with HI for rhodium- and iridium-catalyzed synthesis of acetic acid and acetic anhydride via the generation of MeI.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b10076.

Experimental details and procedures; spectra for all unknown compounds (PDF)

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Notes

The authors declare no competing financial interest.

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