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Palladium-Catalyzed Methylation of Aryl, Heteroaryl, and Vinyl Boronate Esters

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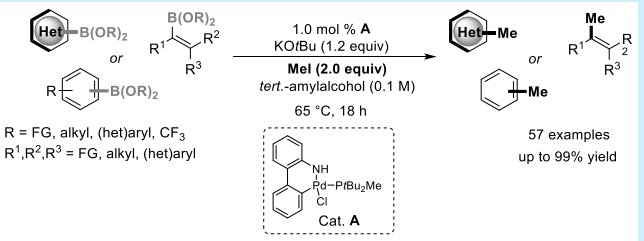
Supporting Information

ABSTRACT: A method for the direct methylation of aryl, heteroaryl, and vinyl boronate esters is reported, involving the reaction of iodomethane with aryl-, heteroaryl-, and vinylboronate esters catalyzed by palladium and $PtBu_2Me$. This transformation occurs with a remarkably broad scope and is suitable for late-stage derivatization of biologically active compounds via the boronate esters. The unique capabilities of this method are demonstrated by combining carbon−boron bond-forming reactions with palladium-catalyzed methylation in a tandem transformation.



Although a methyl group is the smallest alkyl group, the presence or absence of this group in a molecule can have a large effect on the medicinal activity of a compound.[1] The methyl group can affect the solubility (by influencing conformation),[2] selectivity for one protein over another[3] and metabolic half-life,[4] among other properties.[5] In an extreme example, a 208-fold increase in potency of an inhibitor of p38α MAP3 kinase (**5**) was observed upon simple methylation (Figure 1).[2a] This large effect of the small methyl group has recently been coined the "magic methyl effect."[1a,b]

Because pharmacaphores commonly contain aromatic or heteroaromatic units and because the simple reaction of aryl organometallic reagents with methyl electrophiles generally occurs in moderate yields,[6] mild, catalytic methods to attach methyl groups to arenes and heteroarenes are particularly important to develop. The classic strategies for methylation of aromatic and heteroaromatic compounds rely in many cases on either a lithium−halide exchange or an ortho-metalation of the corresponding aryl halide, followed by trapping with a methyl electrophile, such as methyl halides, triflates, or tosylates.[7] Of course, this sequence requires the absence of auxiliary electrophilic and protic functional groups. Alternatively, addition of methyl radicals to arenes or heteroarenes can lead to the corresponding methyl derivatives. A protocol developed by Minisci and co-workers for methylation of electron-deficient hetereoarenes with methyl radicals leads to reaction at the electron-poor positions.[8] Minisci-type C−H functionalizations conducted with photoredox catalysts and peroxo sources[9] or methanol[10] to form methylated heteroarenes have been reported recently[11] with similar regioselectivity.

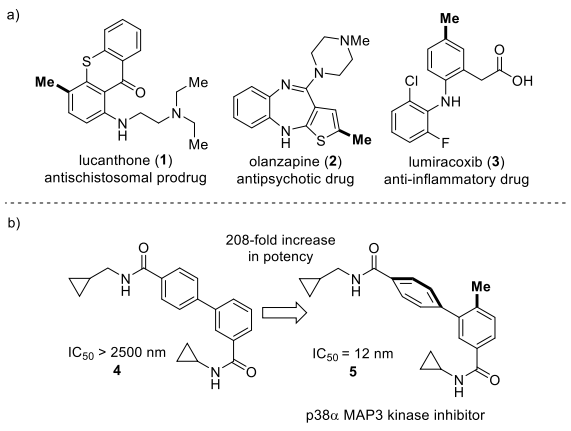


Figure 1. (a) Examples of drugs containing carbon-bound methyl groups being important for their bioactivity. (b) An example for the magic methyl effect.

Reactions catalyzed by transition-metal complexes that form carbon−carbon bonds also can be used to prepare methylarenes and -heteroarenes. Most common is the coupling of aryl halides with a methyl nucleophile. Those couplings (X = Hal, OTf) have typically been conducted with magnesium,[12] tin,[13] boron,[14] zinc,[15] or aluminum[16] reagents. Alternatively, methylation at a C−H bond catalyzed by a transition-metal complex directed by coordinating functionality has been reported.[17]

The coupling of an aryl nucleophile with a methyl electrophile is much less developed than the coupling of aryl electrophiles with methyl nucleophiles. The most valuable of such a reaction would occur with arylboronates, particularly arylboronate esters that are more stable than the corresponding boronic acids and can be formed by C−H bond functionalization. The coupling of arylboronic acids was first reported by Gooßen and co-workers,[18a] but these reactions

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occurred in modest yield with limited scope, and published reactions of arylboronic esters have been conducted with a large excess of the boron reagent, which would typically be the most valuable component.[18b] More recent methodologies reported by us[18c] and other groups[18d] rely on copper catalysts. However, applicable palladium-catalyzed solutions remain undeveloped.

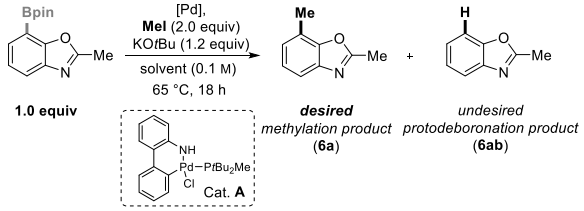
We report a straightforward palladium-catalyzed methylation of aryl and heteroaryl boronate esters with methyl iodide and abundant and easily accessible boron sources. The reactions occur with low catalyst loadings, under mild conditions, with excellent functional-group tolerance, and with a simple reaction procedure that would be easily scaled. This method was successfully applied to late-stage derivatization of active pharmaceutical ingredients and, when combined with C−B bond-forming reactions, provides access to methylated compounds directly from arenes, heteroarenes, or acetylenes.

Several aspects of the reactivity of alkyl halides makes the development of coupling reactions with methyl iodide more complex that one might expect. Palladium complexes undergo oxidative addition and reductive elimination of alkyl halides more slowly than they undergo addition of aryl halides,[19] and methyl electrophiles can react with phosphines to form phosphonium salts[20] that would poison the catalyst. However, sterically hindered phosphines should undergo alkylation more slowly than less hindered phosphines, and strongly electron-donating phosphines should cause oxidative addition to be fast.[21]

Initial studies to develop synthetically useful conditions for the methylation of arenes and heteroarenes were conducted by exposing CH_3I and the pinacolboronate of benzoxazole **6a**, which is accessible by Ir-catalyzed C−H borylation of 2-methylbenzoxazole,[22] to a series of reaction conditions (Table 1).[23] The methylation product was obtained in only 48% yield under the conditions initially reported by Suzuki and co-workers (entry 1). The methylation process under these conditions was accompanied by the formation of large amounts of arene side product (27%) by protodeboronation. Variation of the conditions to improve this yield showed that the identity of the solvent was crucial to suppress the protodeboronation to form **6ab**. Among various protic and aprotic polar solvents we tested (see the Supporting Information for details), reactions using the sterically hindered *tert*-amyl alcohol occurred in the highest yield (entry 2). Studies of the effect of the palladium precursor and studies that evaluated several classes of ligands showed that reactions catalyzed by combinations of bulky alkylphosphines and $[Pd(OAc)_2]$ as a catalytic precursor occurred in high yields, and the reaction catalyzed by $PtBu_2Me$ occurred in a high 92% yield (entry 3). Reactions conducted with palladacycle **A** containing this phosphine as the palladium source occurred in similar yields with a lower catalyst loading. Under the conditions of entry 5 with a catalyst loading of only 1.0 mol %, the methylated compound formed in 94% yield (entry 5).

The scope of the reactions with a range of benzo-fused five membered heteroarylboronates (**6a**−**z**), which are important for medicinal or agrochemistry, is shown in Scheme 1. The scope of the reactions with a range of heteroarylboronates (**6a**−**z**), which are important for medicinal or agrochemistry, is shown in Scheme 1. Reactions of such substrates derived from (di)benzofurans, (di)benzothiophenes, carbazoles, indoles, indazoles, furans and pyrazoles occurred in good to excellent yields.

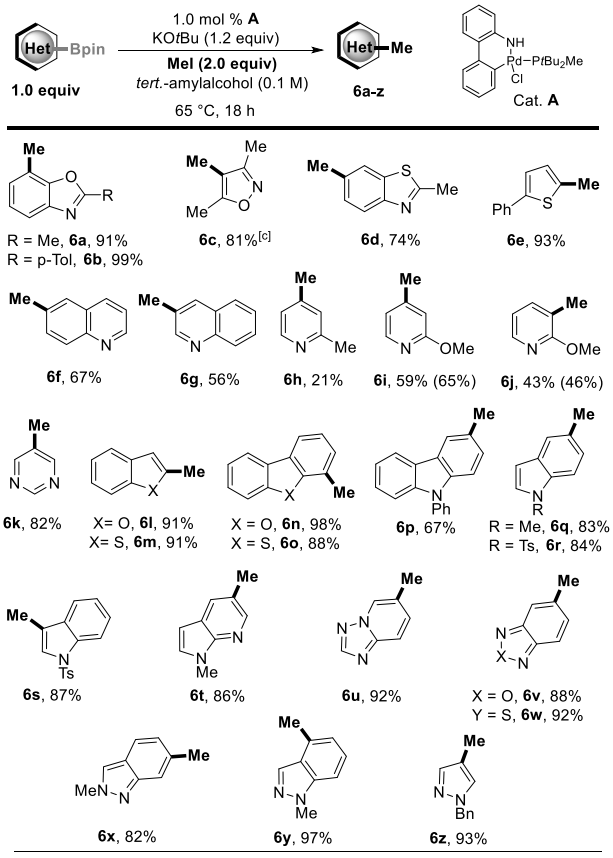
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (mol %)	solvent	yield (**6a**) (%)[b,c]	yield (**6ab**) (%)[b]
1	$[Pd_2(dba)_3]$ (2.5), $P(o\text{-tolyl})_3$ (10)	DMF/H_2O (9:1)	48	27
2	$[Pd(OAc)_2]$ (5), $P(o\text{-tolyl})_3$ (10)	TAA	75	1
3	$[Pd(OAc)_2]$ (5), $PtBu_2Me$ (10)	TAA	92	<1
4	**A** (5)	TAA	95	<1
5	**A** (1)	TAA	94(91)	<1

[a]Reaction conditions: Boronate ester (0.5 mmol), KO*t*Bu (0.6 mmol), MeI (1.0 mmol), cat. [Pd], solvent (0.1 M) at 65 °C, 18 h. [b]Yield was determined by GC using *n*-dodecane as the internal standard. [c]Value in parentheses is the yield of the isolated product. [d]Reaction performed with K_2CO_3 (2.0 equiv). Bpin = pinacolboronate, dba = dibenzylideneacetone, TAA = *tert*-amylalcohol.

Scheme 1. Methylation of Heteroaryl Boronate Esters[a,b]



[a]Yield of isolated product. [b]Value in parentheses is the yield determined by ^1H NMR spectroscopy (using 1,3,5-trimethoxybenzene as internal standard). [c]Reaction at 100 °C with 5.0 mol % of **A**.

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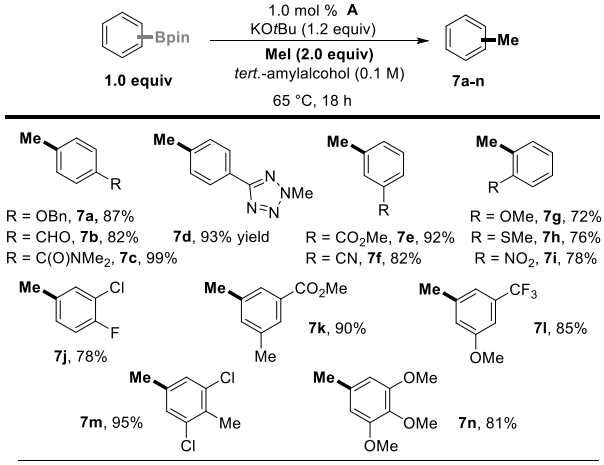
The methylation of a series of aryl boronates containing a variety of substituents under the developed conditions are shown in Scheme 2. A wide range of functional groups in the

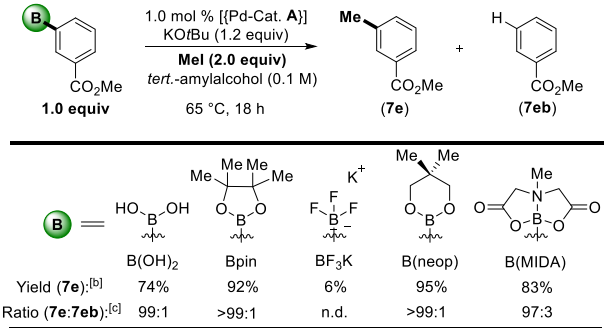
Scheme 2. Methylation of Heteroaryl Boronate Esters[a]



[a]Yield of isolated product.

starting material, including an alkoxy, thioalkoxy, formyl, carbamoyl, alkoxycarbonyl, cyano, nitro, trifluoromethyl, fluoro, or chloro group near the reaction site, as well as a heteroaryl substituent, were tolerated. In each case, the methylated product was obtained in excellent yield (**7a**–**n**). Furthermore, the conditions we developed for the methylation of pinacolate esters also induced the methylation of boronic acids and other commonly available boronic acid derivatives (Scheme 3).

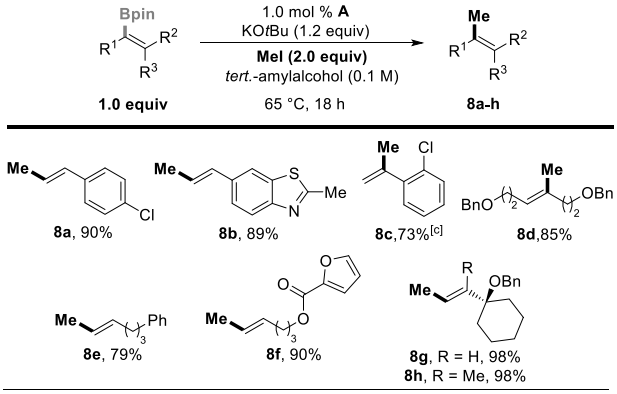
Scheme 3. Methylation of Various Boronic Acid Derivatives[a]



[a]Reaction conditions: Boronate ester (0.5 mmol), KO*t*Bu (0.6 mmol), MeI (1.0 mmol), **A** (1.0 mol %), *tert*-amylalcohol (0.1 M) at 65 °C, 18 h. [b]Yield of isolated product. [c]Ratio was determined by GC.

In addition to the methylation of aryl and heteroarylboronates, the methylation of vinyl boronate esters occurred in high yield with substrates bearing aromatic, heteroaromatic, or aliphatic moieties connected to the double bond (**8a**–**h**; Scheme 4). These reactions enabled the stereoselective synthesis of trisubstituted double bonds (**8g** and **8h**) in high yield, while retaining the *E* or *Z* configuration of the alkene unit. Classical approaches to prepare trisubstituted alkenes in which one of the groups is a methyl group typically involve

Scheme 4. Methylation of Vinyl Boronate Esters[a]

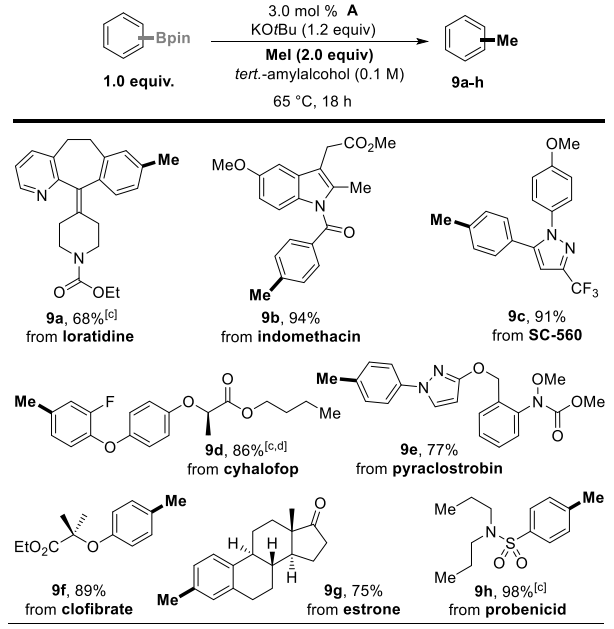


[a]Yield of isolated product. [b]Reaction with 5.0 mol % of **A**.

multiple synthetic operations and occur with moderate stereoselectivity.[24]

Having established the exceptional functional-group tolerance and broad scope of arenes and heteroarenes, we assessed the methylation process for the late-stage derivatization of active pharmaceutical ingredients and pharmaceutical candidates (**9a**–**h**; Scheme 5). Indeed, methylation of the eight pinacolboronates in Scheme 5 derived from active pharmaceutical ingredients occurred in good to excellent yields.

Scheme 5. Late-Stage Methylation of Complex and Bioactive Molecules[a]



[a]Yield of isolated product. [b]Reaction with the B(neop) precursor. [c]Reaction performed in 0.2 mmol scale.

The value of this process is further demonstrated by combining the methylation with C–B bond-forming reactions. These C–B bond-forming reactions include iridium-catalyzed C–H borylation of arenes and heteroarenes,[25] as well as stereoselective hydroboration,[26,27] and carbaboration of alkynes (Scheme 6).[28] A two-step processes involving generation of an aryl or heteroaryl boronate ester and methylation of the boronate intermediate in one pot without

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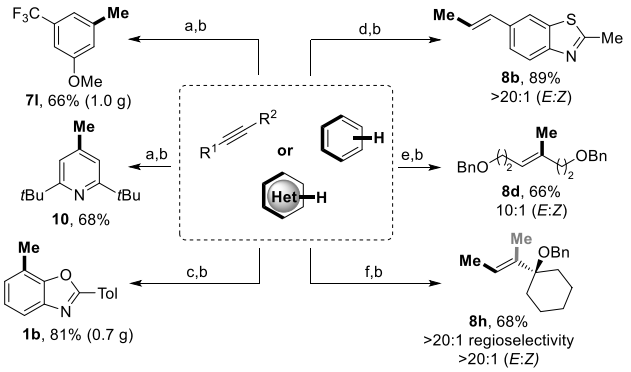
Scheme 6. Methylation of Arenes, Heteroarenes and Alkynes via One-Pot C−B Bond-Forming Reaction, Followed by Methylation



[a](a) [{Ir(cod)OMe}$_2$] (1.0 mol %), dtbpy (2.0 mol %), B_2pin_2, THF, 80 °C, 18 h then solvent removed; (b) **A** (1.0 mol %), KO*t*Bu, MeI, *tert*-amylalcohol, 65 °C, 18 h; (c) [{Ir(cod)OMe}$_2$] (0.5 mol %), Me_4phen (1.0 mol %), B_2pin_2, THF, room temperature, 18 h then solvent removed; (d) [$Ru(PPh_3)_3(CO)HCl$] (5.0 mol %), HBpin, toluene, 50 °C, 16 h then solvent removed; (e) [{$RuCp^*(MeCN)_3$}-PF_6] (5.0 mol %), HBpin, CH_2Cl_2, room temperature, 3 h then solvent removed; (f) CuCl (15 mol %), Xantphos (15 mol %), KO*t*Bu, B_2pin_2, MeI, THF, 50 °C then solvent removed. B_2pin_2 = bispinacolatodiboron, dtbpy = 4,4′-Di-*tert*-butyl-2,2′-bipyridine, Cp* = pentamethylcyclopentadiene, phen = phenanthroline.

purification of the boronate provided methylated arenes (**7l**) and heteroarenes (**1b** and **10**) in good yield, including two examples on the 700 mg to gram scale. Likewise, the stereoselective hydroboration of terminal or internal alkynes, followed by subsequent methylation, led to (*E*)-alkenes (**8b** and **8d**) selectively, and the regioselective carboboration of terminal alkynes, followed by palladium-catalyzed methylation of the resulting vinylboronate, generated a trisubstituted methylalkene (**8h**) with high stereoselectivity in good yield, directly from its corresponding alkyne.

In conclusion, an efficient method for the methylation of arylboronic acid esters has been developed with CH_3I as the source of the methyl group under mild conditions. The methylation proceeds with high functional-group compatibility and a broad scope of arenes, heteroarenes, and alkenes and is suitable for late-stage functionalization of complex structures. Sequential, one-pot processes allow the methylation of arenes, heteroarenes, and alkenes to occur through aryl or vinyl boronate ester intermediates generated in situ.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00025.

All synthetic procedures for new compounds as well as their analytical data, involving ^{1}H NMR, ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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