Communication

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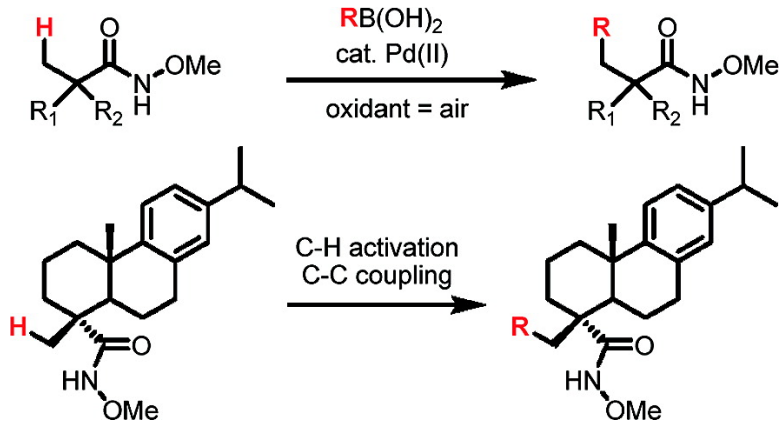

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Pd(II)-Catalyzed Cross-Coupling of sp^3 C−H Bonds with sp^2 and sp^3 Boronic Acids Using Air as the Oxidant

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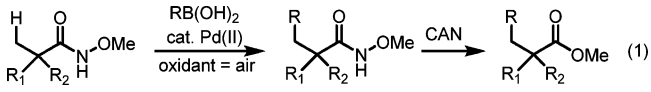
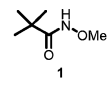
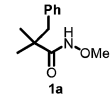
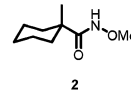
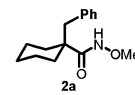
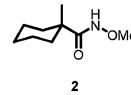
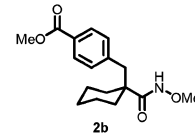
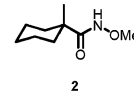
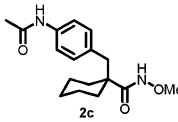
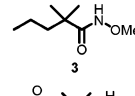
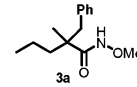
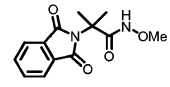
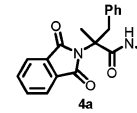
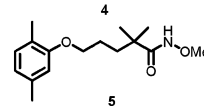
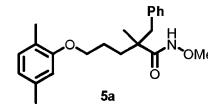
Palladium-catalyzed cross-coupling reactions using organohalides and other surrogates[1] are among the most powerful and versatile tools for forming carbon−carbon bonds.[2] Recently, feasibility of oxidative coupling of C−H bonds with organometallic reagents has also been demonstrated via Pd(II)/Pd(0) catalysis.[3,4] Upon further improvement of the substrate scope and catalytic system, these C−H activation/C−C coupling reactions[5] could serve as a complementary tool for cross-couplings when the regioselective introduction of halides in a particular synthetic intermediate is problematic or requires multistep operation. We have recently reported the coupling of β-C−H bonds in carboxylic acids with organoboron reagents.[3c] However, major limitations of the current protocol for C−H activation/C−C coupling reactions remain to be addressed. First, the C−H activation/C−C coupling reactions of carboxylic acid substrates only work with aryl boronic esters and methylboronic acids. Second, the coupling of sp^3 C−H bonds with sp^3 boron reagents has not been achieved to date despite the remarkable progress made in sp^3−sp^3 cross-coupling reactions.[6] Third, the use of Ag_2CO_3 or Ag_2O as the stoichiometric oxidant is not practical. To overcome these limitations, we here report a new protocol using readily accessible and synthetically useful methyl hydroxamic acids as substrates (eq 1).



(1)

We previously found that the formation of sodium salts of carboxylic acids is crucial for the C−H activation and subsequent coupling with phenyl boronic ester and $MeB(OH)_2$.[3c] We hypothesize that the failure in using $PhB(OH)_2$ and other alkyl boronic acids as coupling partners is largely due to undesired homocoupling or β-hydride elimination from the alkyl fragments of the sp^3 boronic acids. We therefore decided to derivatize carboxylic acids to structurally analogous and stronger binding *O*-methyl hydroxamic acids.[7] Since CONHOMe groups can be readily converted to esters[8a] and amides[8b] or reduced to alkane fragments,[8b] C−H activation using this functionality will be synthetically useful. Thus, we began to screen various reaction conditions using our previous coupling protocol (see Supporting Information). We found stirring substrate **1** with 0.5 equiv of benzoquinone, 2 equiv of Ag_2O, 2 equiv of K_2CO_3, 1.5 equiv of $PhB(OH)_2$, and 10 mol % of $Pd(OAc)_2$ in *tert*-BuOH at 70 °C for 18 h afforded β-phenylated product **1a** in 85% isolated yield (Table 1, entry 1). The presence of K_2CO_3 is critical for the reaction to proceed. Other bases used for the coupling of carboxylic acid substrates are not effective in this case. We were pleased to find that substituted aryl boronic acids are also suitable coupling partners, albeit giving lower yields (entries 3 and 4). Notably, the coupling of amino acid derivative **4** provides a novel route to a wide range of amino acid analogues (entry 6). The coupling of amide **5** derivatized from the corresponding acid (Gemfibrozil, a lipid regulating agent) demonstrates the potential utility to access biologically active compounds in medicinal chemistry (entry 7).

Table 1. β-Arylation of *O*-Methyl Hydroxamic Acids[a]

entry	substrate	product	isolated yield (%)
1	 **1**	 **1a**	85[b]
2	 **2**	 **2a**	94
3	 **2**	 **2b**	62
4	 **2**	 **2c**	41
5	 **3**	 **3a**	78[b]
6	 **4**	 **4a**	75[b]
7	 **5**	 **5a**	59[b]

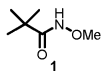
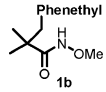
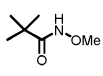
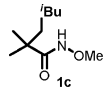
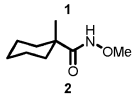
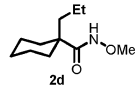
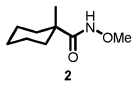
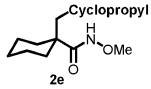
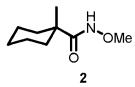
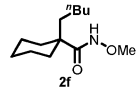
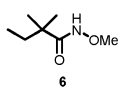
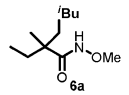
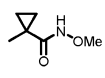
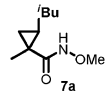
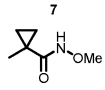
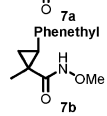
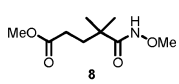
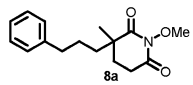
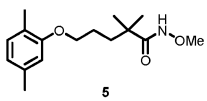
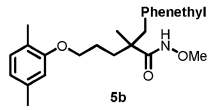
[a] Reaction conditions: *O*-methyl hydroxamic acid (0.5 mmol), arylboronic acid (0.8 mmol), $Pd(OAc)_2$ (0.05 mmol, 10 mol %), Ag_2O (1 mmol), benzoquinone (BQ, 0.25 mmol), K_2CO_3 (1 mmol), *t*-BuOH (3 mL), 70 °C, 18 h. Reactions were carried out in a Teflon cap-sealed tube. [b] *t*-BuOH:DMF = 4:1 as solvent.

However, the coupling of substrate **1** with phenylethyl- and butylboronic acids using this protocol did not give any desired product, presumably due to β-hydride elimination. Previous studies on sp^3−sp^3 cross-coupling reactions suggest that this undesired pathway could be suppressed by using a sterically hindered ligand and careful choice of solvents.[6] While the presence of sterically hindered ligands prevented C−H activation, the use of 2,2,5,5-tetramethyltetrahydrofuran as the solvent allows the coupling of sp^3 C−H bonds with alkylboronic acids (Table 2). We believe that this solvent serves as a sterically bulky ligand preventing homocoupling and β-hydride elimination. Substrates **1**, **2**, and **5**−**7** were coupled with phenylethyl-, *n*-butyl-, *i*-butyl-, ethyl-, and cyclopropylboronic acids to give the alkylated products in moderate yields (Table 2, entries 1−8 and 10). An ester group in substrate **8** was also tolerated, and the coupling product cyclized in situ to give the imide derivative **8a** (entry 9).

From the viewpoint of catalysis, the replacement of Ag(I) salt by an inexpensive and environmentally friendly oxidant such as

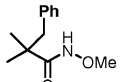
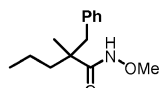
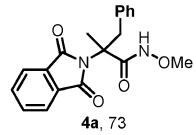
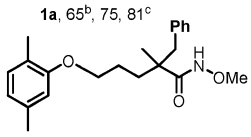
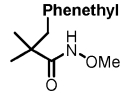
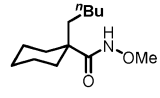
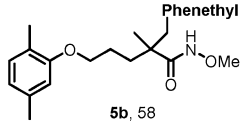
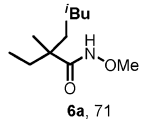
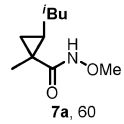
10.1021/ja801355s CCC: $40.75

Table 2. β-Alkylation of *O*-Methyl Hydroxamic Acids[a]

entry	substrate	product	isolated yield (%)
1	 **1**	 **1b**	65
2	 **1**	 **1c**	71
3	 **2**	 **2d**	60
4	 **2**	 **2e**	63
5	 **2**	 **2f**	64
6	 **6**	 **6a**	67
7	 **7**	 **7a**	58
8	 **7**	 **7b**	72
9	 **8**	 **8a**	54
10	 **5**	 **5b**	59

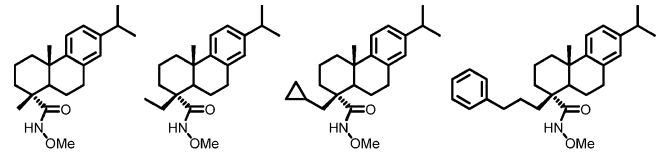
[a] Reaction conditions: *O*-methyl hydroxamic acid (0.5 mmol), alkylboronic acid (0.8 mmol), $Pd(OAc)_2$ (0.05 mmol, 10 mol%), Ag_2O (1 mmol), K_2CO_3 (1 mmol), benzoquinone (BQ, 0.25 mmol), 2,2,5,5-tetramethylTHF (3 mL, inhibitor free, anhydrous), 70 °C, 18 h. Reactions were carried out in a Teflon cap-sealed tube.

Table 3. C−H Activation/C−C Coupling Using Air as the Oxidant[a]

isolated yields of phenylation and alkylation (%)		
 **1a**, 65[b], 75, 81[c]	 **3a**, 86	 **4a**, 73
 **5a**, 57	 **1b**, 60	 **2f**, 67
 **5b**, 58	 **6a**, 71	 **7a**, 60

[a] Reaction conditions: *O*-methyl hydroxamic acid (0.5 mmol), boronic acid (0.8 mmol), $Pd(OAc)_2$ (0.05 mmol, 10 mol %), K_2CO_3 (1 mmol), benzoquinone (BQ, 0.25 mmol), 20 atm air and 20 atm N_2, 80 °C, 48 h. Solvent for arylation: *t*-BuOH (3 mL). Solvent for alkylation: 2,2,5,5-tetramethylTHF (3 mL). Reactions were carried out in a high pressure vessel. [b] 20 atm air. [c] 20 atm air and 60 atm N_2.

Scheme 1. Functionalization of Dehydroabietic Acid



9 **9a** 40% **9b** 52% **9c** 41%

air[9] will significantly improve the practicality of C−H coupling reactions. In the current study, we found that air could serve as an efficient stoichiometric oxidant for the newly developed C−H activation/C−C coupling reaction of substrates **1**−**7** (Table 3).

The potential utility of these types of C−H activation/C−C coupling reactions was further demonstrated by the alkylation of substrate **9** derived from dehydroabietic acid (Scheme 1), a natural product identified as an efficient BK channel opener.[10] Compounds exhibiting such activity could lead to useful treatments for diseases such as acute stroke, epilepsy, and asthma. Typically, diversification of such structures is difficult due to the general unreactivity of these molecules aside from the carboxylic acid moiety, which is essential for biological activity of the molecule. Masking the carboxylic acid as the hydroxamic acid allows for functionalization at the methyl C−H bond, affording a novel class of analogues that may display improved pharmacokinetic properties.

In summary, we have developed the first protocol for the coupling of sp^3 C−H bonds with both sp^2 and sp^3 boronic acids. The feasibility of using air as the oxidant is also demonstrated. Since the CONHOMe group can be readily converted to esters, amides, or hydrogens, this reaction is likely to find broad synthetic utility.

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Supporting Information Available: Experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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