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Oxygen and Base-Free Oxidative Heck Reactions of Arylboronic Acids with Olefins

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The palladium-catalyzed Mizoroki−Heck reaction is now one of the most important tools for constructing C−C bonds.[1] After the first report of Heck[2] and further development by Uemura[3] and Mori,[4] the transition metal-catalyzed coupling of organoboronic acids and olefins, known as the oxidative Heck reaction, had been extensively investigated,[5] particularly by the groups of Jung,[5c,d,m] Larhed,[5b,e,h,i] Lautens,[5j] and Brown,[5f] mainly because boronic acids are comparatively stable, nontoxic, and easily available. The methods developed thus far require the presence of an oxidant to reoxidize Pd(0), for example, $Cu(OAc)_2$, quinone, or O_2, producing stoichiometric amounts of metal waste or being associated with potentially hazardous handling and not suitable for air-sensitive conditions. Herein we disclose a new method that allows efficient oxidative Heck coupling of arylboronic acids with both electron-rich and -deficient olefins, *with no need for external oxidants*.

Previous studies suggest that the regeneration of Pd(II) after each catalytic cycle is the key step for the Pd-catalyzed oxidative Heck reaction.[5,6] We thought that following the release of the coupling product from Pd(II), the X−Pd−H intermediate might be intercepted by a hydrogen acceptor, such as acetone, thus regenerating the Pd(II) without forming Pd(0) and so circumventing the need for traditional oxidants or base (Scheme 1).[7]

With this hypothesis in mind we set out to examine the reaction of arylboronic acids with olefins in acetone under nitrogen. Delightfully, our initial study of 4-methoxy-phenylboronic acid (**1j**) coupling with the benchmark electron-rich olefin *n*-butyl vinyl ether (**2a**) catalyzed by Pd-dppp was met with very encouraging results under base-free conditions and with no extra oxidant (Table S1, Supporting Information). We then tested a range of different conditions in the hope to optimize the reaction. The results show that the use of acetone as solvent and dppp as ligand affords the best yield of ketone **3j**, obtained from the olefin product after in situ hydrolysis. The reaction was highly regioselective, with no linear olefin detected. Very low yields were obtained with PPh_3, 2,2′-bipyridine, or no ligand. When the reaction was run under an O_2 atmosphere, the yield decreased from 89% to 71%. We note that nitrogen ligands have been most successful when the reaction is run under oxygen.[5b−e,g−i]

Using the optimized conditions, we then examined the reaction of various arylboronic acids **1a**−**t** with olefins **2a**−**c**. The results are summarized in Table 1. As can be seen, the reactions afforded good to excellent yields of ketones **3**. Ortho substitution appears to lower the yield, so do electron-withdrawing groups (e.g., entries 3 vs 10; 10 vs 14 and 15). The observation is reminiscent of that found in the Heck reaction of aryl halides with **2a**.[8] Gratifyingly but unsurprisingly, the reaction works excellently for oxygen-sensitive substrates (entries 16−18).[9] To gain understanding of the reaction pathway, we studied an intramolecular competition reaction by coupling 4-bromophenylboronic acid (**1m**) with **2a**. As may be expected in the absence of a base, the oxidative Heck reaction product was exclusively produced in 89% yield; no other coupling products were detected (entry 13). Very good results were also obtained when the substituted vinyl ethers **2b**,**c** were used (entries 21−26), providing an alternative for preparing different aryl alkyl ketones.

Scheme 1

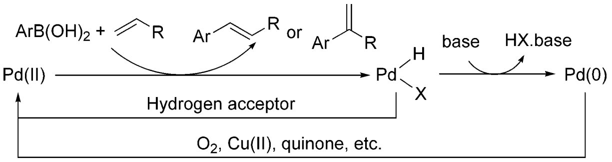
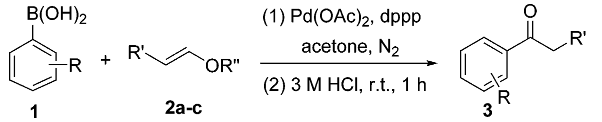
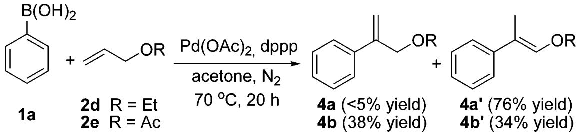


Table 1. Oxidative Coupling with Electron-Rich Olefins[a]



entry	R	R′, R″	product	yield (%)[b]
1	H **1a**	H, ^{n}Bu **2a**	**3a**	89
2	*o*-CH_3 **1b**	H, ^{n}Bu **2a**	**3b**	85
3	*o*-OCH_3 **1c**	H, ^{n}Bu **2a**	**3c**	74
4	*o*-Cl **1d**	H, ^{n}Bu **2a**	**3d**	70
5	*o*-F **1e**	H, ^{n}Bu **2a**	**3e**	61
6	*m*-CH_3 **1f**	H, ^{n}Bu **2a**	**3f**	90
7	*m*-Cl **1g**	H, ^{n}Bu **2a**	**3g**	93
8	*m*-NO_2 **1h**	H, ^{n}Bu **2a**	**3h**	92
9	*p*-CH_3 **1i**	H, ^{n}Bu **2a**	**3i**	92
10	*p*-OCH_3 **1j**	H, ^{n}Bu **2a**	**3j**	91
11	*p*-F **1k**	H, ^{n}Bu **2a**	**3k**	84
12	*p*-Cl **1l**	H, ^{n}Bu **2a**	**3l**	94
13	*p*-Br **1m**	H, ^{n}Bu **2a**	**3m**	89
14	*p*-NO_2 **1n**	H, ^{n}Bu **2a**	**3n**	81
15	*p*-$COCH_3$ **1o**	H, ^{n}Bu **2a**	**3o**	75
16	*p*-OH **1p**	H, ^{n}Bu **2a**	**3p**	92
17	*p*-SCH_3 **1q**	H, ^{n}Bu **2a**	**3q**	87
18	*p*-CH_2OH **1r**	H, ^{n}Bu **2a**	**3r**	85
19	1-naph **1s**[c]	H, ^{n}Bu **2a**	**3s**	90
20	2-naph **1t**[d]	H, ^{n}Bu **2a**	**3t**	91
21	H **1a**	CH_3, Et **2b**	**3u**	85
22	*p*-OCH_3 **1j**	CH_3, Et **2b**	**3v**	84
23	*p*-Br **1m**	CH_3, Et **2b**	**3w**	82
24	H **1a**	Et, Et **2c**	**3x**	81
25	*p*-OCH_3 **1j**	Et, Et **2c**	**3y**	84
26	*p*-Br **1m**	Et, Et **2c**	**3z**	80

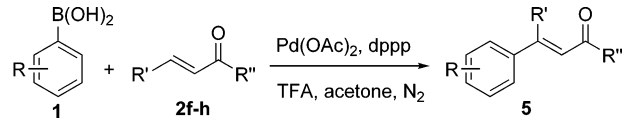
[a] All reactions were carried out with **1** (1.0 mmol), **2a**−**c** (2.0 equiv), $Pd(OAc)_2$ (2 mol %), and dppp (3 mol %) in 3 mL acetone at 70 °C for 15 h. [b] Isolated yields. [c] 1-Naphthylboronic acid. [d] 2-Naphthylboronic acid.



(1)

10.1021/ja0782955 CCC: $40.75

Table 2. Oxidative Coupling with Electron-Deficient Olefins[a]

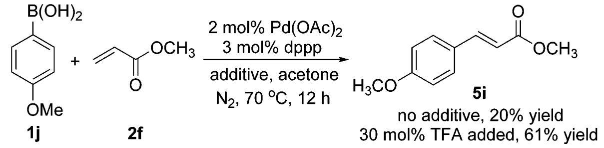


entry	R	R′, R″	product	yield (%)[b]
1	H **1a**	H, OCH_3 **2f**	**5a**	82
2	*o*-CH_3 **1b**	H, OCH_3 **2f**	**5b**	94
3	*o*-Cl **1d**	H, OCH_3 **2f**	**5c**	81
4	*o*-F **1e**	H, OCH_3 **2f**	**5d**	80
5	*m*-CH_3 **1f**	H, OCH_3 **2f**	**5e**	85
6	*m*-Cl **1g**	H, OCH_3 **2f**	**5f**	94
7	*m*-NO_2 **1h**	H, OCH_3 **2f**	**5g**	93
8	*p*-CH_3 **1i**	H, OCH_3 **2f**	**5h**	95
9	*p*-OCH_3 **1j**	H, OCH_3 **2f**	**5i**	86
10	*p*-Cl **1l**	H, OCH_3 **2f**	**5j**	96
11	*p*-Br **1m**	H, OCH_3 **2f**	**5k**	94
12	1-naph **1s**[c]	H, OCH_3 **2f**	**5l**	80
13	H **1a**	CH_3, OCH_3 **2g**	**5m**	78
14	*p*-OCH_3 **1j**	CH_3, OCH_3 **2g**	**5n**	83
15	*p*-Br **1m**	CH_3, OCH_3 **2g**	**5o**	82
16	H **1a**	H, $N(CH_3)_2$ **2h**	**5p**	75
17	*p*-OCH_3 **1j**	H, $N(CH_3)_2$ **2h**	**5q**	79
18	*p*-Br **1m**	H, $N(CH_3)_2$ **2h**	**5r**	80

[a] All reactions were carried out with **1** (1.0 mmol), **2f-h** (2.0 equiv), $Pd(OAc)_2$ (2 mol %), dppp (3 mol %), and TFA (30 mol %) in 3 mL acetone at 70 °C for 20 h. [b] Isolated yields. [c] 1-Naphthylboronic acid.

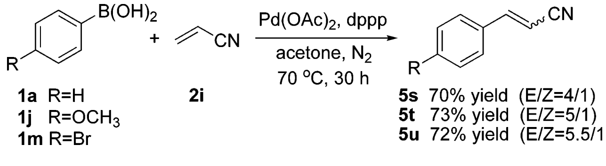
The catalysis also worked for the electron-rich olefins **2d**,**e** (eq 1). The products are again branched olefins. However, isomerization of the C=C bond occurred, affording a mixture of olefins, probably due to palladium or acid catalysis.[10]

With the success in electron-rich olefins, we then turned attention to a benchmark electron-deficient olefin methyl acrylate (**2f**). Unfortunately, using the same conditions, the coupling of **1j** with **2f** afforded only ca. 20% yield of **5i**. We then searched conditions to promote the reaction and to our delight, acids were found to significantly accelerate the reaction. In particular, **5i** could be obtained in over 60% isolated yield in the presence of 30 mol % trifluoroacetic acid (TFA) under otherwise similar reaction conditions (eq 2). The amount of the TFA had no significant effect on the yield when more than 30 mol % was used. Other acids were proven to be less effective, for example, acetic acid, benzoic acid, triflic acid, and *p*-toluenesulfonic acid. The effects of other variables echoed those found for **2a**.



(2)

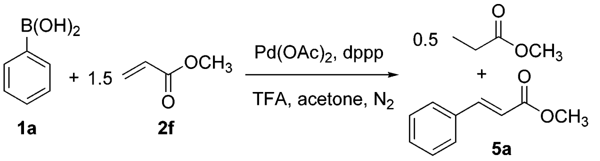
Using the conditions established (eq 2), we then coupled a variety of arylboronic acids with olefins **2f**−**h**. As can be seen from Table 2, excellent yields were obtained for most of the substrates under the catalysis with no addition of external oxidant, and in no cases were cis or branched products detected. We again examined a competition reaction by coupling 4-bromophenylboronic acid (**1m**) with the olefins **2f**−**h**, and found that only the oxidative products were produced (entries 11, 15, and 18).



(3)

The catalysis also worked for other electron-deficient olefins. An example is seen in the coupling of acrylonitrile **2i**, affording exclusively the linear olefins in good isolated yields (eq 3).

The reaction mechanism is yet to be fully studied. However, it is clear that the solvent acetone is not a hydrogen acceptor in the coupling of either electron-rich or deficient olefins on the basis of ^{1}H NMR investigations.[11] In the case of electron-deficient olefins, it is the substrate that acts as the hydrogen acceptor. Thus, ^{1}H NMR monitoring of the coupling of **1a** and **2f** in acetone-d_6 showed that **5a** and methyl propionate were formed concomitantly in a molar ratio of 2:1 during the entire reaction, and no hydrogen from the $-B(OH)_2$ group was incorporated into the propionate (eq 4). However, in the case of the electron-rich olefins, for example, **2a**, reduction of the substrates was not detected with either NMR or GC. The mechanism is under investigation in our lab.



(4)

In conclusion, we have developed an efficient protocol for the oxidative Heck coupling of arylboronic acids with both electron-rich and -deficient olefins. The method requires neither oxygen nor base to operate, broadening the scope of palladium-catalyzed coupling reactions.

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Supporting Information Available: Experimental details and spectroscopy data (^{1}H and ^{13}C NMR). This material is available free of charge via the Internet at http://pubs.acs.org.

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