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Allylic *Ethers* as Educts for Suzuki−Miyaura Couplings in Water at Room Temperature

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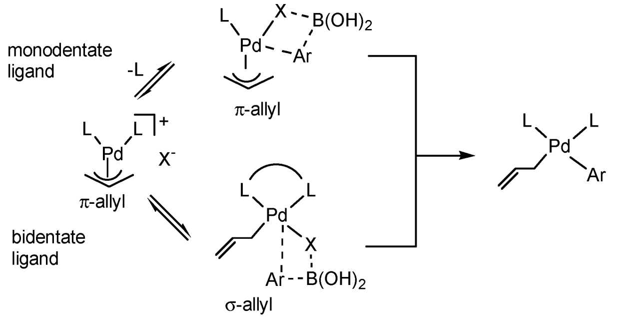
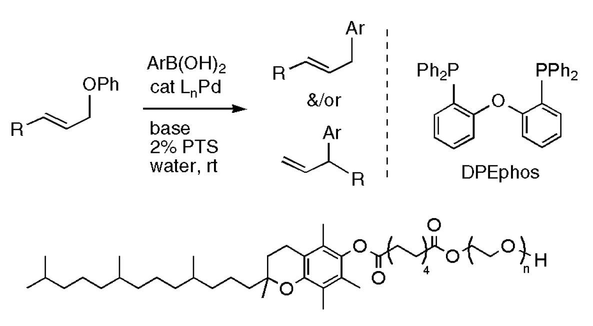
The Pd-catalyzed Suzuki−Miyaura coupling reaction, which employs air- and moisture-stable organoboronic acids,[1] is among the most valued of methods for C−C bond formation in organic synthesis. A broad range of electrophiles undergo cross-couplings with organoboronic acids, including alkyl, aryl, alkenyl, and alkynyl groups. However, reports on allylic partners, such as acetates, carbonates, halides and pseudohalides, are rare.[2,3] Generally, a monodentate phosphine is required to obtain a π-allylpalladium intermediate, which subsequently undergoes smooth transmetalation with arylboronic acids. Coordinatively saturated π-allylpalladium intermediates having bidentate phosphine ligands tend to slow transmetalation, since a π-allylpalladium species must rearrange to a σ-allylpalladium complex prior to transmetalation (Scheme 1). However, σ-allylpalladium species are stable only in the presence of bulky ligands (e.g., pincer ligands).[4] Thus, while phosphines typically promote oxidative addition, they may inhibit transmetalation.[5] This subtle phenomenon is still somewhat controversial but could be one explanation for the limited development of Suzuki−Miyaura couplings with allylic fragments. Recent related progress in this area includes the use of allylic trifluoroborates as nucleophiles; these have been applied to asymmetric cross-coupling reactions by Yamamoto and Miyaura.[6] Sawamura has described γ-selective couplings between allylic acetates and arylboronic acids in heated chlorinated media.[7] A number of issues remain to be addressed, including (1) development of reactions with functionalized allylic fragments, (2) couplings that involve allylic electrophiles other than carbonyl-containing esters and carbonates, (3) solutions to regiochemical issues, and (4) the discovery of "greener" processes that can be conducted under environmentally benign conditions.

Scheme 1. Transmetalation between π- or σ-Allylpalladium and Arylboronic Acid



Although oxidative addition of Pd(0) to electron-deficient bonds [e.g., C−X or C−OC(O)R] is facile, insertion into electron-rich functionality such as C−OH (or C-OR)[3,8] or into C−H bonds[9] is particularly challenging. There are no general methods that rely on allylic ethers,[2j,3b,10,11] in spite of their advantageous stability under acidic or basic aqueous conditions and toward nucleophilic attack. Only recently have Kakiuchi and Chatani found nickel or ruthenium to be an efficient catalyst for couplings of arylboronic acids with *aryl* ethers.[12] Herein we disclose the first Suzuki−Miyaura couplings with functionalized allylic ethers at ambient temperatures. This new methodology, which is conducted in water as the only medium, is made possible by micellar catalysis using the nonionic amphiphile PTS (Scheme 2).[13]

Scheme 2. Cross-Couplings with Allylic Ethers in Water at rt



PTS (n = *ca.* 13; MW = *ca.* 1200)

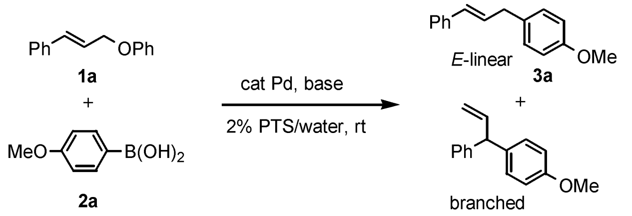
Optimization studies employed the combination of cinnamyl phenyl ether (**1a**, 0.25 mmol) and 4-methoxyphenylboronic acid (**2a**, 0.38 mmol) in the presence of a Pd catalyst in 2 wt % PTS/water at room temperature (Table 1). The effect of the base was examined initially. Although K_2CO_3 is effective in many Suzuki−Miyaura coupling protocols, only a trace amount of product **3a** was obtained (run 1). Use of a strong base, which could assist in transmetalation, is detrimental not only to the goal of mild reaction conditions but also to PTS diester stability. Therefore, several amines were screened (run 2), with triethylamine emerging as the best choice (runs 3−7). The preformed catalyst complex $PdCl_2$(D*t*-BPF) gave good conversions; its generation in situ from $Pd(OAc)_2$ and D*t*-BPF was notably less effective (run 5). Ultimately, preformed catalyst $PdCl_2$(DPEphos) was identified as the most effective at mediating the coupling in excellent yield (run 7).[14]

As illustrated in Table 2, several boronic acids can be coupled with allylic ether **1a** to give linearly coupled products akin to **3a**. Generally, ortho-substituted boronic acids, such as **2b**, **2c**, and **2d**, are more reluctant to participate in transmetalation, although on the other hand, once the aryl residue is metal-bound, reductive elimination is expected to occur readily. Under micellar catalysis conditions, the overall sequence led to excellent yields at room temperature within 5 h (runs 1−3). Although $PdCl_2$(DPEphos) was generally useful in this reaction, 4-chlorophenylboronic acid (**2e**) and 2-thiopheneboronic acid (**2f**) coupled more readily with **1a** in the presence of $PdCl_2$(D*t*-BPF) (runs 4 and 5). Arylboronic acid **2g** required 6 mol % catalyst to obtain a high yield of the corresponding *E*-linear allylic arene, although the catalyst loading could be reduced to only 0.5 mol % when the reaction was carried

10.1021/ja905082c CCC: $40.75

out at 40 °C (run 6). Nanomicelle reactor generation from surfactant PTS is also very important. The corresponding reaction with educt **2c** “on water” was very sluggish (run 2).[13b,d]

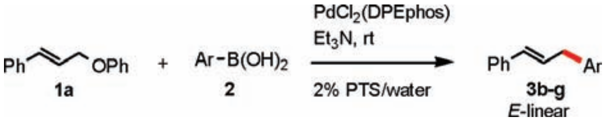
Table 1. Optimization of Suzuki−Miyaura Couplings with Ethers[a]

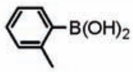
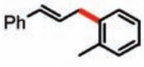
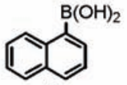
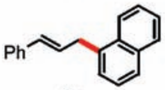
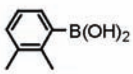
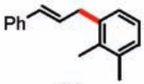
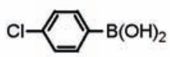
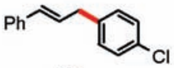
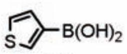
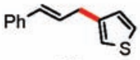
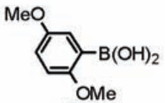


run	catalyst (3 mol %)	base (equiv)	% yield (lin:br)
1	$PdCl_2$(D*t*-BPF)	K_2CO_3(3)	trace
2	$PdCl_2$(D*t*-BPF)	amine[b] (3)	trace
3	$PdCl_2$(D*t*-BPF)	Et_3N (1.5)	20 (>25:1)
4	$PdCl_2$(D*t*-BPF)	Et_3N (3)	72 (88)[c] (>25:1)
5	$Pd(OAc)_2$/D*t*-BPF	Et_3N (3)	33 (>25:1)
6	$PdCl_2$(D*t*-BPF)	Et_3N (6)	78 (99)[c] (>25:1)
7[d]	$PdCl_2$(DPEphos)	Et_3N (3)	99 (>25:1)

[a] Conducted at rt for 6 h in 2% PTS/water with catalyst (3 mol %), base (3 equiv), **2a** (1.5 equiv), and **1a**. [b] Bu_3N, *i*-Pr_2EtN, $N(CH_2CH_2OCH_2CH_2OMe)_3$, $(Me_2NCH_2)_2CH_2$, or *N,N′*-dimethylpiperazine. [c] Run for 18 h. [d] Run for 5 h using 2 mol % Pd.

Table 2. Reactions of **1a** with Arylboronic Acids (**2**)[a]

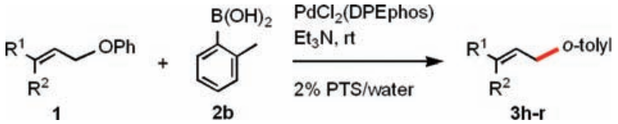


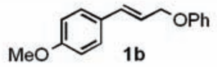
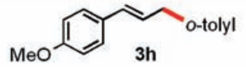
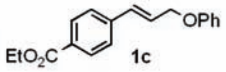
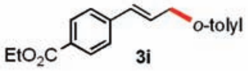
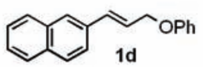
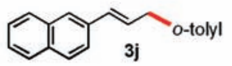
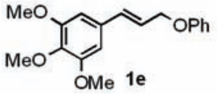
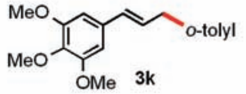
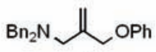
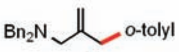
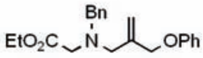
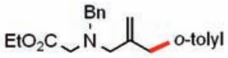
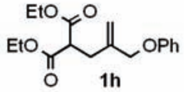
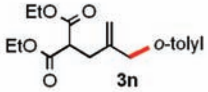
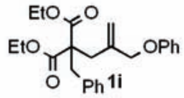
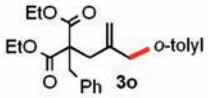
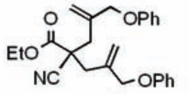
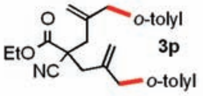
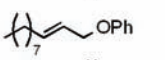
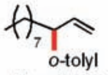
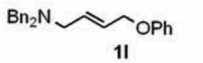
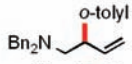
run	ArB(OH)$_2$	product	yield(%)
1	 **2b**	 **3b**	99
2	 **2c**	 **3c**	87 21 (on water)
3	 **2d**	 **3d**	99
4[b]	 **2e**	 **3e**	74
5[b]	 **2f**	 **3f**	96
6	 **2g**	 **3g**	70 (40 °C)[c] 90 (40 °C)[d] 99 (40 °C)[e] 90 (rt)

[a] Conducted at rt for 5 h in 2% PTS/water with 2 mol % $PdCl_2$(DPEphos), Et_3N (3 equiv), arylboronic acid (1.5 equiv), and **1a**. The linear:branched ratios of the products were >25:1. [b] Run for 20 h using 6 mol % $PdCl_2$(D*t*-BPF) as the catalyst. [c] Run for 22 h using 0.15 mol % catalyst. [d] Using 0.5 mol % catalyst. [e] Using 1 mol % catalyst.

Functionalized allylic fragments in Suzuki−Miyaura couplings have previously been shown to be especially challenging reaction partners. Nonetheless, under our conditions, allylic ethers having various functional groups can be coupled with ortho-substituted arylboronic acids (e.g., **2b**; Table 3). Cinnamic ethers bearing electron-withdrawing or -donating groups react uneventfully to afford the corresponding *E*-linear allylic arenes in excellent yields at room temperature in water in the presence of 2 mol % catalyst (runs 1−4). Representative examples of dibenzylamine-, amino acid-, and malonate ester-substituted allylic ethers underwent efficient cross-couplings to produce highly functionalized allylic arenes in excellent yields (runs 5−8). That bulky allylic ether **1i**

Table 3. Reactions of *o*-Tolylboronic Acid (**2b**) with Functionalized Allylic Phenyl Ethers[a]



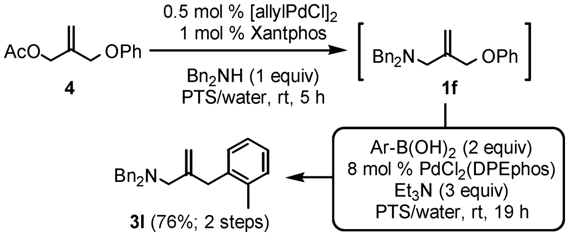
run	ether	product	yield(%)
1	 **1b**	 **3h**	82
2	 **1c**	 **3i**	85[b]
3	 **1d**	 **3j**	86[b]
4	 **1e**	 **3k**	90[b]
5	 **1f**	 **3l**	82[c,d]
6	 **1g**	 **3m**	90[c,d]
7	 **1h**	 **3n**	82[d] 80[d,e]
8	 **1i**	 **3o**	98[c,d]
9	 **1j**	 **3p**	72[c,d]
10	 **1k**	 **3q** l:b = 17:83	99[f]
11	 **1l**	 **3r** l:b = 14:86	71[d,f]

[a] Conducted at rt for 6 h in 2% PTS/water with 6 mol % $PdCl_2$(DPEphos), Et_3N (3 equiv), allylic ether, and **2b** (1.5 equiv). [b] Run for 10 h using 2 mol % catalyst. [c] Using 8 mol % catalyst. [d] Using 2 equiv of **2b**. [e] Run at 40 °C using 1 mol % catalyst. [f] Using 6 mol % $PdCl_2$(D*t*-BPF); *E*:*Z* of linear minor product was >25:1.

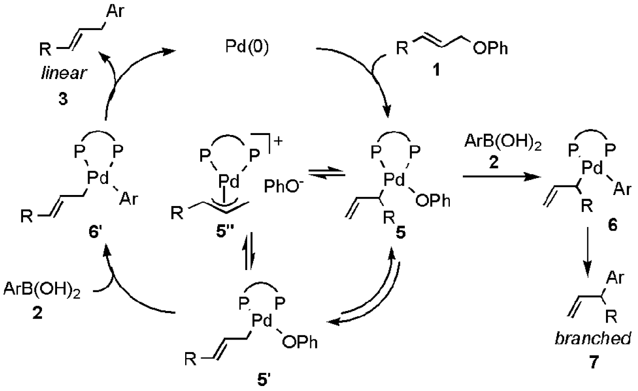
led to an almost quantitative yield of the desired product is especially noteworthy (run 8). Doubly allylated ether **1j** underwent successive couplings in one pot in the presence of 2 equiv of **2b** in good overall isolated yield (run 9). While most reactions of functionalized allylic ethers occurred at room temperature in the presence of ~2 mol % catalyst, catalyst loadings down to 1 mol % were effective with gentle heating to 40 °C (run 7). Although conjugated networks such as **1a** predominantly gave the linear coupling product, aliphatic ethers (e.g., **1k**, **1l**) selectively afforded branched products, reflecting the favored rate of reductive elimination from a more hindered Pd(II) intermediate (runs 10 and 11).[6]

For an allylic substrate containing both acetate and ether moieties (e.g., **4** in Scheme 3), reaction occurs first at the acetate and subsequently at the less reactive ether residue. Xantphos[15] was found to be the preferred ligand, leading to an initial chemoselective coupling product **1f**. Second-stage allylic alkylation completes a one-pot amination/Suzuki−Miyaura sequence to give the corresponding aminated methallylbenzene derivative **3l** in 76% isolated yield (Scheme 3).

Scheme 3. One-Pot Amination/Suzuki−Miyaura Coupling



Scheme 4. Proposed Mechanism



Although the mechanism of this reaction is still under investigation, one plausible pathway is shown in Scheme 4. The reaction starts with oxidative addition of palladium(0) to allylic ether **1** to produce an allylpalladium intermediate (**5**, **5′**, or **5″**) with the bidentate ligand. After generation of a σ-allylpalladium species (**5** or **5′**), transmetalation with arylboronic acid **2** takes place to give the σ-allylarylpalladium intermediate (**6** or **6′**). Linear product **3** or branched product **7** is then produced by reductive elimination from **6′** or **6**, respectively.

In conclusion, the first general Suzuki−Miyaura coupling of boronic acids with allylic ethers has been described. Conditions have been developed that are especially mild and do not rely on an organic solvent as the reaction medium. Further applications of transition-metal-catalyzed cross-coupling chemistry using such typically inert allylic ethers as reaction partners are currently under investigation.

Acknowledgment. We thank Zymes, LLC for financial support and Johnson Matthey for providing the catalysts PdCl$_2$(DPEphos) (Pd-117) and PdCl$_2$(D*t*-BPF) (Pd-118) used in this study.

Supporting Information Available: Experimental procedures 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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(14) Switching to cinnamic methyl ether, however, gave less than 40% yield of the corresponding coupling product under identical conditions after 48 h.

(15) Xantphos is 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

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