Olefin Functionalization

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Alternative Pathways for Heck Intermediates: Palladium-Catalyzed Oxyarylation of Homoallylic Alcohols**

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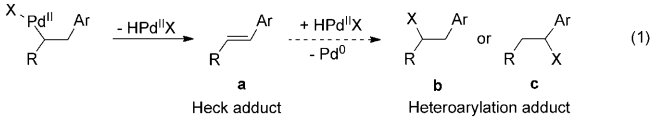
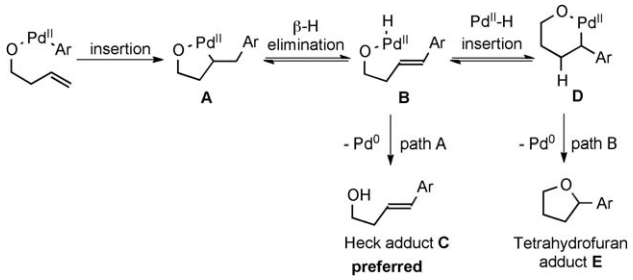
Direct functionalization of olefins provides a powerful tool for C–C bond formation.[1] As a prime example, Heck-type reactions have found broad utility in the synthesis of natural products and pharmaceuticals.[2] Typically, olefin insertion into the palladium–aryl bond is followed by a β-H elimination to give Heck product **a**, and also terminates the reaction [Eq. (1); X = O, N or halogen]. However, further reaction of



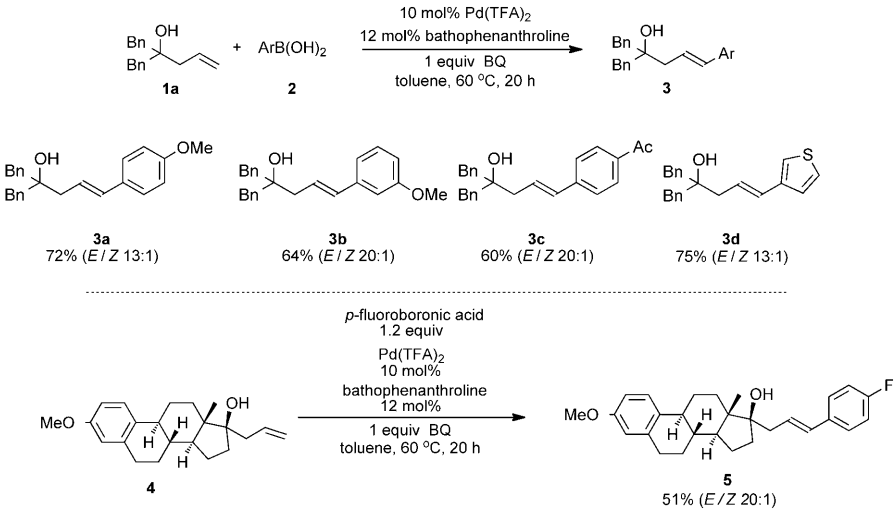
(1)

adduct **a** with the nascent HPd^{II}X species and a subsequent loss of palladium(0) would constitute a cascade process and result in the heteroarylation adduct **b** or **c** [Eq. (1)].[3] This cascade would be valuable in extending the scope of the Heck process to achieve greater molecular diversity. Indeed, related efforts have been demonstrated by Yoshida and co-workers,[3b,c] Sanford and co-workers,[3d,g,h] and Sigman and co-workers.[3e,f] In relation to our continuous interest in the functionalization of olefins,[4] herein we describe unprecedented alternative pathways for the Heck reaction: 1) homoallylic-alcohol-directed oxidative Heck reactions, and 2) interception of the Heck intermediate by a novel intramolecular palladium-catalyzed olefinic oxyannulation for the in situ construction of α aryltetrahydrofurans.[5]

In the specific case of homoallylic alcohols, we envision the olefin would regioselectively insert into a hydroxy-coordinated palladium(II) aryl complex to give the five-membered cyclic intermediate **A** (Scheme 1). A subsequent β-hydride elimination would create the Heck intermediate **B**. Reductive elimination



Scheme 1. Alternative pathways for the Heck intermediate.



Scheme 2. Oxidative Heck reaction of homoallylic alcohols. The reactions were conducted with homoallylic alcohol (0.1 mmol), boronic acid (0.12 mmol), Pd(TFA)$_2$ (10 mol%), bathophenanthroline (12 mol%) and BQ (0.1 mmol) in toluene at 60°C for 20 h. The yields are of the isolated products. Bn = benzyl, BQ = benzoquinone, TFA = trifluoroacetic acid.

(path A) would lead to the Heck adduct **C**,[6] however an alternate pathway is possible (path B). It is known that β-hydride elimination is reversible and can lead to the relatively stable σ-alkyl palladium intermediate by a π-benzyl interaction.[3d–h] Intramolecular addition of the intermediate HPd^{II}O species **B** to the olefin would form the six-membered cyclic intermediate **D**, and the reductive elimination would yield tetrahydrofuran adduct **E**. Thus, the challenge is to direct the reaction of intermediate **B** towards tetrahydrofuran adduct **E**.

As expected, in the presence of Pd(TFA)$_2$ and the reoxidant benzoquinone, the reaction readily yielded conven-

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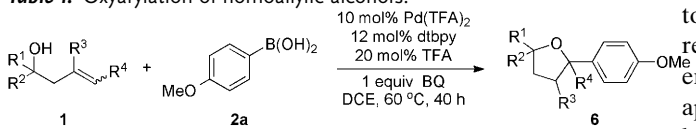
tional Heck adducts (Scheme 2). A wide variance in the electronic properties of the boronic acid partner was tolerated. Styrenyl olefins (**3a**–**3c**), as well as a heterocycle-substituted olefin (**3d**), were afforded in good yields and with a strong preference for the *E* stereoisomer. Notably, substantially bulky substrates (e.g. estrogen **4**) survived in this oxidative version of the Heck reaction without compromising the yield.

Encouraged by the above results, we investigated the intramolecular oxyannulation of homoallylic alcohol **1a**. After screening a variety of additives, to our delight, catalytic amounts of trifluoroacetic acid (TFA; 20 mol%) significantly accelerated the addition of the $HPd^{II}O$ species with the olefin to give tetrahydrofuran adducts.[7] Further optimization of the reaction conditions improved the yield to 75% (Table 1, entry 1).[8] With the optimized reaction conditions in hand, we applied them to a diverse range of molecules that contain homoallylic alcohols (Table 1). All the primary, secondary, and tertiary alcohols were smoothly converted into the corresponding tetrahydrofurans (entries 2–5). Interestingly, spiro tetrahydrofuran **6f** was formed in good yield from cyclic alcohol **1f** (entry 6). Significantly, not only terminal olefins but also internal olefins were compatible with these reaction conditions. For example, (*Z*)-**1g** and (*E*)-**1g** were transformed into the same product, **6g**, which contains a new quaternary carbon center (entries 7 and 8). Branched olefin **1h** stereospecifically gave **6h** despite the steric hindrance, which might impact the olefin insertion into the palladium–aryl bond during the transition state (entry 9).[9] Impressively, this method was also applicable to some more complex molecules. Despite of their crowded skeletons, tetrahydrofurans **6i** and **6j** were readily obtained from estrogen **4** and fatty acid **1j**, respectively (entries 10 and 11).

As well as boronic acid **2a**, other boronic acids were also surveyed and furnished the corresponding products **6k**–**6m** (Scheme 3). An electron-rich arene on the olefin was found to be critical for the insertion of the olefin into the $HPd^{II}O$ species. Importantly, potassium trifluoroborates were also competent reagents for the transmetallation, and gave comparable results to those given by the related boronic acid **2a** (Scheme 3, **6a** and Table 1, entry 1).

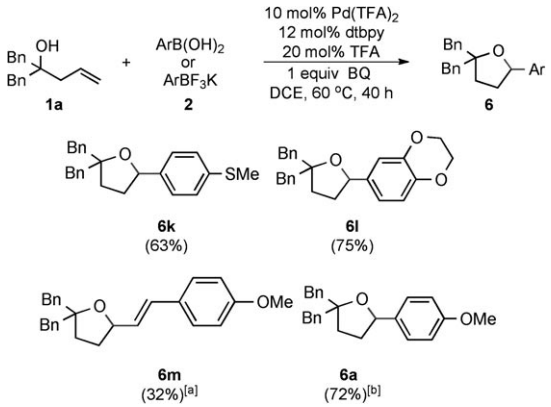
We next investigated the mechanism of these cascade transformations. First, experiments to understand the stereochemistry were carried out using both *trans* and *cis* olefins that were deuterium labeled at the terminal position of the

Table 1: Oxyarylation of homoallylic alcohols.[a]



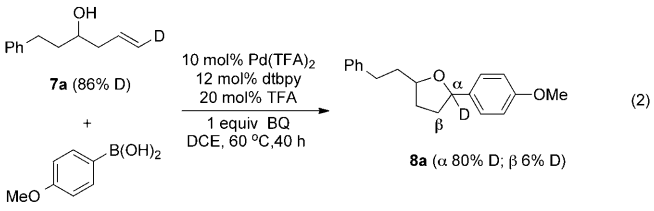
	Homoallylic alcohol	Tetrahydrofuran	Yield [%][b]
1	**1a**	**6a**	75
2	**1b**	**6b**	65
3	**1c**	**6c**	74[c]
4	**1d**	**6d**	80[d]
5	**1e**	**6e**	72
6	**1f**	**6f**	70
7	(*Z*)-**1g**	**6g**	52
8	(*E*)-**1g**	**6g**	61
9	**1h**	**6h**	31[e]
10	**4**	**6i**	63[f]
11	**1j**	**6j**	40[g]

[a] Entries 2, 7, 8, and 9 were conducted with 0.2 mmol homoallylic alcohol **1**; other entries were conducted with 0.1 mmol homoallylic alcohol **1**. [b] Yield of the isolated product. [c] d.r. 1.2:1. [d] d.r. 1.4:1. [e] *trans*/*cis* = 16:1. [f] d.r. 1.3:1. [g] d.r. 1.3:1. DCE = dichloroethane, dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridyl.

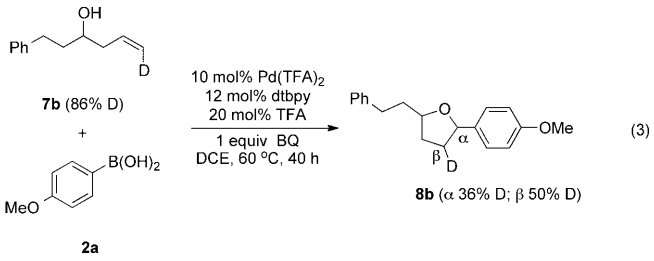


Scheme 3. Other applications. The reactions were conducted with 0.1 mmol of homoallylic alcohol **1a**. The yields are of the isolated products. [a] The reaction was performed at 90 °C for 40 h. [b] 1.2 equiv of $ArBF_3K$ was used instead of boronic acid **2a**.

alkene. When the deuterium-labeled *trans* olefin **7a** was utilized, the retention of deuterium in the product **8a** was observed on the same carbon atom (α carbon) [Eq. (2)]. In contrast, most of the deuterium in **8b** had migrated to the adjacent carbon atom (β carbon) when using the deuterium-labeled *cis* olefin **7b** [Eq. (3)].[10] These results suggested that



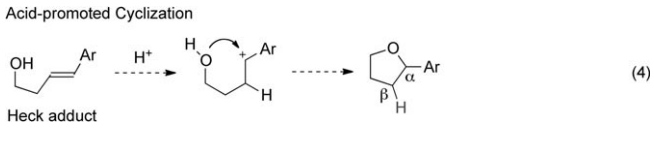
(2)



(3)

the *cis* hydrogen atom was preferred in the β-hydride elimination and then migration to the adjacent carbon atom occurred by a subsequent Pd–H insertion.

Two other pathways to the tetrahydrofuran adducts: acid-promoted cyclization [Eq. (4)] and Wacker-type cyclization [Eq. (5)], might be possible starting from the Heck adducts. In



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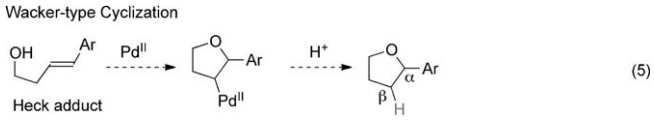
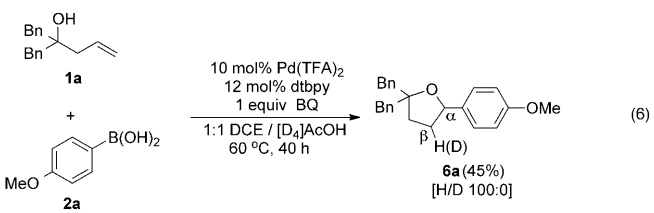


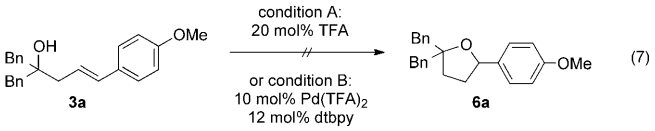
(5)

both cases, the proton on the β carbon atom comes from the acidic medium. To rule out these possibilities, a control experiment was conducted by performing the reaction using [D_4]acetic acid as a cosolvent [Eq. (6)]. Introduction of a



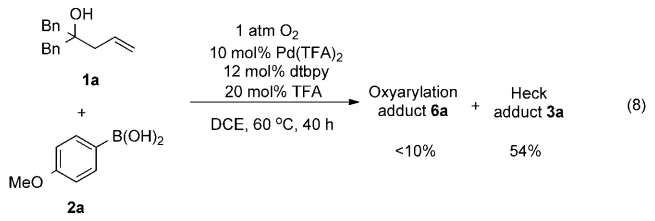
(6)

deuterium atom on the β-carbon atom was not observed in the reaction. Furthermore, on exposure of the Heck adduct **3a** to 20 mol% TFA or 10 mol% $Pd(TFA)_2$, decomposition occurred rather than the formation of the annulated product **6a** [Eq. (7)].



(7)

Another significant issue in the reaction was that BQ was the uniquely effective oxidant for the synthesis of desired oxyarylated product. Replacement of BQ with O_2 resulted in **3a**, not **6a**, as major product [Eq. (8)]. It was reasoned that: 1)



(8)

exposure to O_2 would quench intermediate **B** (Scheme 1), thus resulting in palladium(II) hydroperoxide and stopping path B,[11] 2) BQ could promote the formation of C–O bond by reductive elimination from palladium(II) in intermediate **D** (Scheme 1).[12] The role of TFA is ambiguous, however, at this preliminary stage, we believe it suppresses the reductive elimination of intermediate **B** and the regeneration of Pd^{II}–H from palladium(0).[13]

In summary, we have described two variants of the oxidative Heck reaction, in which the hydroxy group of an homoallylic alcohol coordinates with palladium and gives the products in good yields and regioselectivities. Moreover, the addition of a catalytic amount of TFA mediates the oxyarylation of the penultimate Heck intermediate giving rise to a wide range of tetrahydrofurans including highly functionalized scaffolds. Further studies into the mechanism and other applications are ongoing in our lab.

Experimental Section

General procedure for the oxidative Heck reaction: Homoallylic alcohol **1a** (25.2 mg, 0.1 mmol), boronic acid **2a** (18.2 mg, 0.12 mmol), benzoquinone (11 mg, 0.1 mmol), $Pd(TFA)_2$ (3.3 mg, 0.01 mmol) and bathophenanthroline (4.0 mg, 0.012 mmol) were loaded into a dry vial, which was subjected to evacuation/flushing with dry argon three times. Anhydrous toluene (0.8 mL) was syringed into the mixture, which was then stirred at 60 °C for 20 h or until the starting material had been consumed, as determined by TLC. Upon cooling to room temperature, all volatiles were evaporated and the residue was purified by preparative TLC (eluent: ethyl acetate/hexane 1:5) to give **3a** as yellow oil in 72% yield. $E/Z = 13:1$. *E* isomer: ^{1}H NMR (500 MHz): $\delta = 2.30$ (d, $J = 7.0$ Hz, 2H), 2.87 (s, 4H), 3.83 (s, 3H), 6.15

(ddd, $J = 7.5, 7.5, 15.5$ Hz, 1H), 6.37 (d, $J = 16.0$ Hz, 1H), 6.88 (d, $J = 9.0$ Hz, 2H), 7.19–7.35 ppm (m, 12H); ^{13}C NMR (125 MHz): $\delta = 42.6$, 46.1, 55.56, 55.59, 74.5, 114.2, 123.4, 126.8, 127.5, 128.5, 130.4, 131.1, 133.6, 137.5, 159.2 ppm. FT-IR (CH_2Cl_2): 3559, 3028, 2919, 2836, 2361, 2343, 1607, 1511, 1495, 1454, 1298, 1248, 1175, 1113, 1086, 1033, 970, 888, 834, 753, 725, 702 cm^{-1}. HRMS calcd for $C_{25}H_{27}O_2$ $[M+H]^+$ 359.2006, found 359.2000.

General procedure for the oxyarylation of olefins: Homoallylic alcohol **1a** (25.2 mg, 0.1 mmol), boronic acid **2a** (18.2 mg, 0.12 mmol), benzoquinone (11 mg, 0.1 mmol), $Pd(TFA)_2$ (3.3 mg, 0.01 mmol) and 4,4′-di-*tert*-butyl-2,2′-bipyridyl (3.2 mg, 0.012 mmol) were loaded into a dry vial, which was subjected to evacuation/flushing with dry argon three times. Anhydrous dichloroethane (0.8 mL) followed by trifluoroacetic acid (1.5 μL, 0.02 mmol) were syringed into the mixture, which was then stirred at 60 °C for 40 h or until the starting material had been consumed, as determined by TLC. Upon cooling to room temperature, all volatiles were evaporated and the residue was purified by preparative TLC (eluent: ethyl acetate/hexane 1:6) to give **6a** as pale yellow oil in 75% yield. ^{1}H NMR (400 MHz): $\delta = 1.37$–1.43 (m, 1H), 1.85–1.90 (m, 1H), 1.90–2.01 (m, 2H), 2.86 (d, 2.93, $J = 13.6$ Hz, 1H), 2.92 (d, $J = 13.6$ Hz, 1H), 2.99 (d, $J = 13.2$ Hz, 1H), 3.01 (d, $J = 13.6$ Hz, 1H), 3.80 (s, 3H), 4.47 (dd, $J = 5.2$, 9.6 Hz, 1H), 6.84 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 8.8$ Hz, 2H), 7.23–7.34 ppm (m, 10H); ^{13}C NMR (100 MHz): $\delta = 33.5$, 34.6, 46.1, 47.1, 55.5, 81.1, 85.7, 113.8, 126.4, 126.5, 128.0, 128.1, 128.2, 131.2, 131.3, 134.6, 138.3, 138.4, 159.2 ppm. FT-IR (CH_2Cl_2) 3060, 3027, 2936, 2835, 1613, 1513, 1494, 1454, 1302, 1246, 1173, 1082, 1035, 942, 827, 754, 736, 701 cm^{-1}. HRMS calcd for $C_{25}H_{27}O_2$ $[M+H]^+$ 359.2006, found 359.2016.

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[7] Excess TFA dehydrated the starting material resulting in diminished yields.

[8] For details, see the Supporting Information.

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