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Aerobic Oxidative α-Arylation of Furans with Boronic Acids *via* Pd(II)-Catalyzed C–C Bond Cleavage of Primary Furfuryl Alcohols: Sustainable Access to Arylfurans

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Aerobic oxidative  $\alpha$ -arylation of furans with boronic acids *via* Pd(II)-catalyzed C–C bond cleavage of primary furfuryl alcohols provides sustainable access to arylfurans. The protocol opens a new avenue for the transformation of readily available furans into other useful compounds.

Transition-metal-catalyzed cleavage of C-C bonds allows reorganization of bond connections and thus can facilitate the synthesis of complex molecules of interest.<sup>1</sup> However, cleaving C-C bonds is usually difficult due to their inherent stability. Cleavage of C-C bonds in unstrained molecules is particularly difficult because of the lack of a driving force for the reaction. For unstrained molecules, a driving force can be provided by incorporating a good leaving group into the substrate<sup>3</sup> or by using a chelation auxiliary that stabilizes the reaction intermediate.<sup>4</sup> For example, tertiary alcohols can undergo catalytic selective C–C bond cleavage via  $\beta$ -carbon elimination to form an organometallic intermediate and a ketone. Such organometallic intermediates can be coupled with organic halides,<sup>5</sup> alkenes,<sup>6</sup> aldehydes,<sup>7</sup> or imines<sup>8</sup> to produce a variety of molecules (Scheme 1). In addition, Shi et al. recently reported Rh(III)-catalyzed C-C bond cleavage reactions of secondary alcohols by means of  $\beta$ -carbon elimination directed by a pyridinyl group to form a five-membered rhodacycle intermediate, which underwent further alkenylation with various olefins.<sup>6b</sup> However, transition-metal-catalyzed C-C bond cleavage reactions of primary alcohols have rarely been reported.4j

Substituted furfuryl alcohols are readily accessible from furfural, which is produced on a large scale by acid hydrolysis of polysaccharide-containing plant materials, and these alcohols are excellent five-carbon building blocks with unique reactivities that allow the construction of numerous molecules of interest.<sup>9</sup> For example, acid-catalyzed hydrolysis of furfuryl alcohols affords furan oxonium ion intermediates, which can be transformed into an array of structures.<sup>10</sup> In addition, oxidative cleavage of furfuryl alcohols produces synthetically useful hydroxyl-substituted *Z*-enediones.<sup>11</sup> Considering that the furan ring is a good leaving group, we hypothesized that Pd(II)-catalyzed C–C bond cleavage reactions of furfuryl alcohols **1** to form 2-furyl palladium compounds **2** would be an excellent method for the synthesis of furan derivatives. As part of our ongoing work on the synthetic applications of furans,<sup>12</sup> we herein report a method for sustainable access to arylfurans **3** via aerobic oxidative  $\alpha$ -arylation of furans with boronic acids (Scheme 1). Arylfurans, which have interesting bioactivities and physical properties,<sup>13</sup> are usually synthesized via Suzuki coupling of the corresponding halides and boronic acids.<sup>14</sup>



The success of this oxidative coupling relies on the use of suitable substrates **1** to guarantee formation of palladium compounds **2** and the development of reaction conditions to suppress side reactions such as oxidation of the electron-rich furan ring, oxidation of the primary hydroxyl group, oxidation of phenylboronic acid,  $\beta$ -arylation, and oligomerization of the furan rings. We began by exploring the reaction of (5-phenyl-furan-2-yl)-methanol (**1a**) with phenylboronic acid (Table 1). Gratifyingly, in the presence of Pd(OAc)<sub>2</sub> (10 mol %) as the catalyst, 1,10-phenanthroline (L<sup>1</sup>, 12 mol %) as the ligand, KF (200 mol %) as an additive, and DCE (1.5 mL) as the solvent, reaction of **1a** at 70 °C for 15 h afforded desired product **3a** in 63% yield (entry 1). Screening of various other palladium

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catalysts (entries 1-8) indicated the Pd(OAc)<sub>2</sub> was optimal. Examination of several bidentate nitrogen ligands (entries 9-14) revealed that the electronic and steric properties of the ligand apparently influenced the reaction outcome. 2,9-Dimethyl-1,10-phenanthroline  $(L^2)$ , which was sterically bulkier than L<sup>1</sup>, gave only a trace of **3a** (entry 9). The electrondeficient ligand 1,10-phen-5,6-dione  $(L^3)$  gave **3a** in a very low yield (27%, entry 10). The use of several 2,2'-bipyridine ligands led to good yields (entries 11-14), and 4,4'-dimethyl-2,2'bipyridyl (L<sup>7</sup>) provided the best yield (69%). Replacing KF with other additives (K<sub>2</sub>CO<sub>3</sub>, KOAc, K<sub>3</sub>PO<sub>4</sub>, or CsF) did not improve the yield (entries 15-18). We were pleased to find that when the Pd(OAc)<sub>2</sub> loading was reduced to 5 mol %, the yield improved slightly to 73% (entry 19). However, further decreasing the Pd(OAc)<sub>2</sub> loading to 2 mol % diminished the yield to 47% (entry 20). In the absence of either  $Pd(OAc)_2$  or the ligand, none of the desired product was obtained (entries 21 and 22); and in the absence of KF, the yield of 3a was only 21% (entry 23). Thus, we concluded that the optimal conditions for this reaction involved the use of Pd(OAc)<sub>2</sub> (5 mol %) as the catalyst, L' (12 mol %) as the ligand, KF (200 mol %) as the additive, DCE as the solvent, and 70 °C as the reaction temperature (entry 19).

Table 1 Optimization of reaction conditions<sup>a</sup>

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| Ρ               | h OH + Phi<br>1a                      | B(OH) <sub>2</sub> [Pd],<br>DCE, C | ligand, additive<br>D <sub>2</sub> (balloon), 70 °C | Ph OPh<br>3a           |  |
|-----------------|---------------------------------------|------------------------------------|---|------------------------|--|
| entry           | [Pd]                                  | ligand                             | additive  | yield (%) <sup>b</sup> |  |
| 1               | Pd(OAc)₂                              | L1                                 | KF  | 63                     |  |
| 2               | PdBr <sub>2</sub>                     | L1                                 | KF  | 62                     |  |
| 3               | PdCl <sub>2</sub>                     | L1                                 | KF  | 10                     |  |
| 4               | Pd(dppf) <sub>2</sub> Cl <sub>2</sub> | L1                                 | KF  | 15                     |  |
| 5               | $Pd(CH_3CN)_2Cl_2$                    | L1                                 | KF  | 58                     |  |
| 6               | Pd₂(dba)₃                             | L1                                 | KF  | 44                     |  |
| 7               | Pd(CF <sub>3</sub> COO) <sub>2</sub>  | L1                                 | KF  | 17                     |  |
| 8               | $Pd[O_2C(CH_3)_3]_2$                  | L1                                 | KF  | 56                     |  |
| 9               | Pd(OAc)₂                              | L <sup>2</sup>                     | KF  | trace                  |  |
| 10              | Pd(OAc)₂                              | L <sup>3</sup>                     | KF  | 27                     |  |
| 11              | Pd(OAc)₂                              | L <sup>4</sup>                     | KF  | 67                     |  |
| 12              | Pd(OAc)₂                              | L <sup>5</sup>                     | KF  | 65                     |  |
| 13              | Pd(OAc)₂                              | L <sup>6</sup>                     | KF  | 60                     |  |
| 14              | Pd(OAc)₂                              | L <sup>7</sup>                     | KF  | 69                     |  |
| 15              | Pd(OAc) <sub>2</sub>                  | L <sup>7</sup>                     | K <sub>2</sub> CO <sub>3</sub>                      | 52                     |  |
| 16              | Pd(OAc)₂                              | L <sup>7</sup>                     | KOAc  | 50                     |  |
| 17              | Pd(OAc) <sub>2</sub>                  | L <sup>7</sup>                     | K₃PO₄   | 35                     |  |
| 18              | Pd(OAc)₂                              | L <sup>7</sup>                     | CsF   | 21                     |  |
| 19 <sup>c</sup> | Pd(OAc)₂                              | L <sup>7</sup>                     | KF  | 73                     |  |
| 20 <sup>d</sup> | Pd(OAc)₂                              | L <sup>7</sup>                     | KF  | 47                     |  |
| 21 <sup>c</sup> | _                                     | L <sup>7</sup>                     | KF  | 0                      |  |
| 22 <sup>c</sup> | Pd(OAc)₂                              | _                                  | KF  | 0                      |  |
| 23 <sup>°</sup> | Pd(OAc) <sub>2</sub>                  | L7                                 | _   | 21                     |  |

<sup>a</sup>Reaction conditions, unless otherwise noted: 1a (0.2 mmol), PhB(OH)<sub>2</sub> (0.5 mmol), Pd catalyst (10 mol %), ligand (12 mol %), additive (200 mol %), O2 (in a balloon), DCE (1.5 mL), 70 °C, 15 h. <sup>b</sup>lsolated yield. <sup>c</sup>5 mol % Pd catalyst was used. <sup>d</sup>2 mol % Pd catalyst was used.

$$\begin{array}{c} & & & \\ & & & & \\ & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & &$$

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scope of the reaction by coupling 1a with various arylboronic acids (Table 2). Reaction of 1a with an arylboronic acid bearing an electron-donating group at the meta- or para-position afforded the corresponding products (3b-3f) in good yields (60-70%, entries 2-6). However, the reaction of 1a with 2methyl phenylboronic acid gave 3g in a very low yield (31%, entry 7), which indicated that the reaction was sensitive to the steric bulk of the arylboronic acid. 3,5-Dimethyl and 3,5dimethoxyl phenylboronic acids afforded 3h and 3i in 71% and 66% yields, respectively (entries 8 and 9). Arylboronic acids that were para-substituted with an electron-withdrawing group, such as a halogen atom, COOEt, CF<sub>3</sub>, CHO, CN, or NO<sub>2</sub>, reacted with 1a to give the corresponding coupling products in moderate to trace yields (entries 10-17). Reaction of 1a with 1-naphthylboronic acid gave **3r** in a low yield (29%, entry 18), whereas reaction with 2-naphthylboronic, which was less sterically bulky, afforded 3s in a higher yield (52%, entry 19); this result confirmed again that steric hindrance had a marked impact on the reaction outcome.

Table 3 Coupling of 1a with anylhoropic acide

| Table 2 Coupling of 1a with arylboronic acids |  |                                    |  |  |  |  |
|---|--|------------------------------------|--|--|--|--|
| Ph OH +                                       | ArB(OH) <sub>2</sub> Pd(OAc) <sub>2</sub> (5 mol %), L <sup>7</sup> (12<br>(2.5 equiv) KF (200 mol %), DCE, O <sub>2</sub> (ba | 2 mol %)<br>alloon), 70 °C Ph 3    |  |  |  |  |
| entry   | Ar   | <b>3</b> (yield [%] <sup>b</sup> ) |  |  |  |  |
| 1   | Ph   | <b>3a</b> (69)                     |  |  |  |  |
| 2   | $3-MeC_6H_4$   | <b>3b</b> (68)                     |  |  |  |  |
| 3   | 4-MeC <sub>6</sub> H <sub>4</sub>  | <b>3c</b> (64)                     |  |  |  |  |
| 4   | 3-MeOC <sub>6</sub> H <sub>4</sub>   | <b>3d</b> (70)                     |  |  |  |  |
| 5   | $4-MeOC_6H_4$  | <b>3e</b> (66)                     |  |  |  |  |
| 6 <sup>c</sup>                                | 4-t-BuC <sub>6</sub> H <sub>4</sub>  | <b>3f</b> (60)                     |  |  |  |  |
| 7   | 2-MeC <sub>6</sub> H <sub>4</sub>  | <b>3g</b> (31)                     |  |  |  |  |
| 8   | 3,5-diMeC₅H₄   | <b>3h</b> (71)                     |  |  |  |  |
| 9   | 3,5-diMeOC₅H₄  | <b>3i</b> (66)                     |  |  |  |  |
| 10  | $4-FC_6H_4$  | <b>3j</b> (55)                     |  |  |  |  |
| 11  | $4-BrC_6H_4$   | <b>3k</b> (58)                     |  |  |  |  |
| 12  | $4-CIC_6H_4$   | <b>3I</b> (33)                     |  |  |  |  |
| 13  | 4-COOEtC <sub>6</sub> H <sub>4</sub>   | <b>3m</b> (44)                     |  |  |  |  |
| 14  | $4-CF_3C_6H_4$   | <b>3n</b> (21)                     |  |  |  |  |
| 15  | $4-CHOC_6H_4$  | <b>3o</b> (18)                     |  |  |  |  |
| 16  | 4-CNC <sub>6</sub> H <sub>4</sub>  | <b>3p</b> (9)                      |  |  |  |  |
| 17  | $4-NO_2C_6H_4$   | <b>3q</b> (trace)                  |  |  |  |  |
| 18  | 1-Naphthyl   | <b>3r</b> (29)                     |  |  |  |  |
| 19  | 2-Naphthyl   | <b>3s</b> (52)                     |  |  |  |  |

<sup>a</sup>Reaction conditions, unless otherwise noted: 1a (0.5 mmol), ArB(OH)<sub>2</sub> (1.25 mmol), Pd(OAc)<sub>2</sub> (5 mol %), L<sup>7</sup> (12 mol %), KF (200 mol %), O<sub>2</sub> (in a balloon), DCE (1.5 mL), 70 °C, 15 h. <sup>b</sup>Isolated yield. <sup>c</sup>2.5 mL of DCE.

We explored the substrate scope of the reaction further by coupling 3,5-dimethylphenylboronic acid with furfuryl alcohols **1** bearing various substituents ( $R^1 - R^3$ , Table 3). The nature of the substituents played an important role in the reaction outcome. When  $R^2$  and  $R^3$  were H and  $R_1$  was a phenyl group with an electron-donating para-methyl or para-methoxyl group, the corresponding products (3t and 3u) were obtained Published on 19 October 2017. Downloaded by Freie Universitaet Berlin on 19/10/2017 13:19:29.

in good yields (76% and 82%, respectively; entries 1 and 2). In contrast, when  $R^1$  had an electron-withdrawing *para*-nitro group or *para*-fluorine atom, the yields of the corresponding products were lower (entries 3 and 4), presumably as a result of the lower electron density of the furan rings. A substrate with a thienyl group at  $R^1$  afforded **3x** in 47% yield, and when  $R^1$  was methyl or ethyl, **3y** or **3z**, respectively, was produced in a relatively low yield (entries 6 and 7). Notably, when furfuryl alcohol itself ( $R^1-R^3 = H$ ) was employed as the substrate, a complicated mixture of products formed, and only a trace amount of **3a'** was isolated (entry 8). Compound **1j**, with an electron-withdrawing methoxycarbonyl substituent at  $R^1$  failed to give the corresponding product (**3b'**, entry 9), perhaps because of the low electron density of the furan ring.

With  $R^1 = Ph$ , substrates with various  $R^2$  and  $R^3$  groups (**1**k-**10**) were also examined (entries 10–14). In the reactions of secondary alcohols, increasing the steric bulk around the hydroxyl group decreased the yield (**1**k > **1**l > **1**m > **1**n). Tertiary alcohol **10** gave only a very low yield of **3h** (8%).



<sup>*a*</sup>Reaction conditions, unless otherwise noted: **1** (0.5 mmol), 3,5-diMeC<sub>6</sub>H<sub>4</sub>B(OH)<sub>2</sub> (1.25 mmol), Pd(OAc)<sub>2</sub> (5 mol %), L<sup>7</sup> (12 mol %), KF (200 mol %), O<sub>2</sub> (in a balloon), DCE (1.5 mL), 70 °C, 15 h. <sup>*b*</sup>Isolated yield. <sup>c</sup>Yield determined by <sup>1</sup>H NMR spectroscopy of the crude products with dibromomethane as an internal standard. <sup>*d*</sup>ND = not detected.

To gain insight into the mechanism of the oxidative coupling, three control experiments was conducted (Scheme 2). Specifically, under the standard conditions, coupling of the aldehyde **4** or acid **5** with 3,5-dimethylphenylboronic acid did not afford product **3h** in considerable yields (reaction a and b), which indicated that **4** and **5** were not the main intermediate. Substrate **1p**, which lacked a hydroxyl group, afforded only a low yield (9%) of the C–C bond cleavage product **3h** (reaction

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c), indicating that the hydroxyl group facilitated the C-C bond cleavage.



Standard conditions: 4 or 5, or 1p (0.2 mmol), PhB(OH)<sub>2</sub> (0.5 mmol), Pd(OAc)<sub>2</sub> (5 mol %), L<sup>7</sup> (12 mol %), KF (200 mol %), O<sub>2</sub> (in a balloon), DCE (1.5 mL), 70 °C, 15 h. Isolated yield based on 4 or 5, or 1p. Scheme 2 Control experiments.

On the basis of the results reported above, as well as previously reported results on C–C bond cleavage reactions of alcohols via  $\beta$ -carbon elimination,<sup>5–8</sup> we propose the mechanism shown in Scheme 3. The palladation of furfuryl alcohols **1** with Pd(OAc)<sub>2</sub> produces Pd complexes **6**, which react with the boronic acid via release of HOAc to give **7**. Transmetallation of **7** followed by electrophilic palladation of the furan ring leads to **9**, which then undergoes aromatization-driven C–C bond cleavage to afford **10**. A reductive elimination reaction of **10** leads to products **3** and Pd(0). Oxidation of Pd(0) to Pd(II) by O<sub>2</sub> completes the catalytic cycle.<sup>15</sup>



In summary, we have developed a simple, practical protocol for the synthesis of arylfurans from sustainably produced substituted furfuryl alcohols. This protocol involves a novel palladium-catalyzed oxidative coupling reaction between commercially available boronic acids and  $\alpha$ -hydroxyalkylfurans with O<sub>2</sub> as the terminal oxidant, as well as a C–C bond cleavage reaction, which may be induced by aromatization. The protocol opens a new avenue for the transformation of readily available furans into other useful compounds and may facilitate the design of new reactions of furans. Further exploration of the reaction scope, coupling partners, and mechanism are underway in our laboratory.

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## **Conflicts of interest**

There are no conflicts to declare.

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 $\mathcal{H}^{R^2}_{R^3}$ Pd(OAc)<sub>2</sub> (5 mol %), L (12 mol %) ArB(OH)<sub>2</sub> Pd(OAc)<sub>2</sub> (5 mol %), L (12 mol %) (2.5 equiv) KF (2.0 equiv), DCE, O<sub>2</sub> (balloon), 70 °C + R<sup>1</sup> `O´ A 33 examples yields up to 82%

Aerobic oxidative  $\alpha$ -arylation of furans with boronic acids *via* Pd(II)-catalyzed C–C bond cleavage of primary furfuryl alcohol provides sustainable access to arylfurans.