

## Unexpected Intermolecular Pd-Catalyzed Cross-Coupling Reaction Employing Heteroaromatic Carboxylic Acids as Coupling Partners

Pat Forgione,\* Marie-Christine Brochu, Miguel St-Onge, Kris H. Thesen, Murray D. Bailey, and François Bilodeau\*

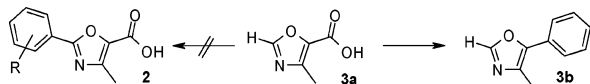
Boehringer Ingelheim (Canada), Limited, Research and Development, 2100 rue Cunard, Laval, Quebec, Canada, H7S 2G5

Received May 19, 2006; E-mail: pforgione@lav.boehringer-ingelheim.com; fbilodeau@lav.boehringer-ingelheim.com

Metal-catalyzed cross-coupling reactions continue to draw much attention and they remain one of the most efficient methods to access biaryl motifs.<sup>1</sup> Over the past years, a number of palladium mediated cross-coupling methods, such as the Suzuki–Miyaura<sup>2</sup> and Stille<sup>3</sup> couplings, have been developed. Although employed in a broad range of applications,<sup>4</sup> a potential limitation of these is the availability of appropriate cross-coupling partners.<sup>5</sup>

During our drug discovery efforts, compounds of general structure **2** were required. The C–H functionalization method was considered an appealing option to access these scaffolds,<sup>6</sup> although it can suffer from poor selectivity. In an attempt to circumvent this liability, we envisioned employing a carboxylic acid moiety as a blocking group that could later be functionalized or removed. Surprisingly, when a Pd-catalyzed cross-coupling reaction between **3a** and phenyl bromide was attempted, we did not obtain the C–H functionalization product **2**, but the unexpected formation of **3b** was observed (Scheme 1).<sup>7</sup>

### Scheme 1<sup>a</sup>



<sup>a</sup> Conditions: PhBr, DMF, *n*-Bu<sub>4</sub>N<sup>+</sup>Br<sup>−</sup>, Pd(P(*t*-Bu)<sub>3</sub>)<sub>2</sub>, μW, 170 °C, 8 min.

A thorough search of the literature revealed a single report of such a transformation by Steglich and co-workers,<sup>8</sup> although in this intramolecular case, no reactive C–H group was present. Thus, with a lack of information concerning substrate scope, reactivity in an intermolecular manifold, chemoselectivity, and mechanism, we embarked on an investigation of this reaction.

A preliminary study was performed to determine the influence of ammonium bases<sup>9</sup> as additives because they are known to have an effect on related transformations (Table 1). The heterocycle **4a** was selected as the model substrate because it contains both a C2-carboxylic acid and a C5-H, which allowed us to evaluate the selectivity of the reaction. During our investigations, it became clear that the primary byproduct in this reaction was **5** and the observed amounts varied with the additive. The absence of the additive (entry 1) did not have a considerable impact on the yield, although some 2,3-diphenylpyrrole **5** was produced. We also observed that tetrabutylammonium acetate (entry 2) gave lower yields and a significant amount of **5**, whereas tetrabutylammonium chloride hydrate (entry 6) afforded a clean reaction (i.e., trace amounts of **5** produced) with the best yield. In all cases, no product resulting from C–H functionalization was observed under these conditions.

In addition to oxazoles (Table 2, entry 1) and pyrroles (entry 2), we were pleased to observe that other heterocycles can also be employed, including furans (entries 3 and 4), thiazoles (entries 5 and 6), thiophenes (entry 7), and benzofurans (entry 8). Furthermore, in the case of both **6a** (entry 3) and **8a** (entry 5), coupling occurred

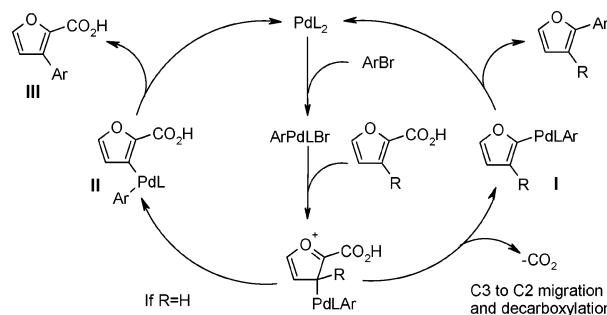
Table 1. Effect of the Additive

| entry | additive   | yield <b>4b</b> <sup>b</sup> (%) | % of <b>5</b> <sup>c</sup> |
|-------|--|----------------------------------|----------------------------|
| 1     | none   | 77                               | 9                          |
| 2     | <i>n</i> -Bu <sub>4</sub> N <sup>+</sup> AcO <sup>−</sup>                  | 64                               | 18                         |
| 3     | <i>n</i> -Bu <sub>4</sub> N <sup>+</sup> I <sup>−</sup>                    | 76                               | 8                          |
| 4     | <i>n</i> -Bu <sub>4</sub> N <sup>+</sup> Br <sup>−</sup>                   | 86                               | 5                          |
| 5     | <i>n</i> -Bu <sub>4</sub> N <sup>+</sup> Cl <sup>−</sup>                   | 74                               | trace                      |
| 6     | <i>n</i> -Bu <sub>4</sub> N <sup>+</sup> Cl <sup>−</sup> ·H <sub>2</sub> O | 88                               | trace                      |
| 7     | <i>n</i> -Bu <sub>4</sub> N <sup>+</sup> F <sup>−</sup> <sup>d</sup>       | 77                               | 11                         |

<sup>a</sup> Reaction conditions: additive (0.40 mmol, 1.0 equiv), heterocycle (2.0 equiv), phenyl bromide (1.0 equiv), Pd[P(*t*-Bu)<sub>3</sub>]<sub>2</sub> (5 mol %), Cs<sub>2</sub>CO<sub>3</sub> (1.5 equiv), DMF (4 mL), μW, 170 °C, 8 min. <sup>b</sup> Isolated yields. <sup>c</sup> Crude HPLC @ 220 nm. <sup>d</sup> 1 M in THF.

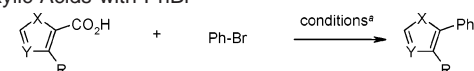


















exclusively at the more sterically hindered C2-position despite the possibility of coupling via C–H functionalization. Removal of the methyl substituent resulted in a decrease in yield (entries 3 and 5 versus 4 and 6, respectively). The position of the acid that undergoes coupling is also crucial to this reaction, as exposure of 3-furan-carboxylic acid to the reaction conditions did not lead to any of the desired product (entry 9).

### Scheme 2. Postulated Mechanism



Preliminary empirical evidence seems to support the mechanism shown above (Scheme 2). One of the main byproducts that was observed with 2-furancarboxylic acid (Table 2, entry 4) as the substrate was 2,3-diphenylfuran (similar to the pyrrole case, see Table 1). Thus, we postulate that the electrophilic Pd(II) intermediate generated from the oxidative addition is first coordinated by the carboxylate moiety<sup>10</sup> prior to an electrophilic palladation at the C3 position of furan.<sup>11</sup> This complex would explain the complete regioselectivity observed for this transformation. At this stage, two pathways are possible: first, a C3–C2 palladium migration<sup>11a,b</sup> and extrusion of CO<sub>2</sub> can occur to produce **I**, which then undergoes reductive elimination to yield the 2-substituted furan. Alternatively, in the case where R = H, the deprotonation to regenerate the aromatic furan **II** can compete, after which reductive elimination

**Table 2.** Pd-Catalyzed Arylation of Various Heteroaromatic Carboxylic Acids with PhBr

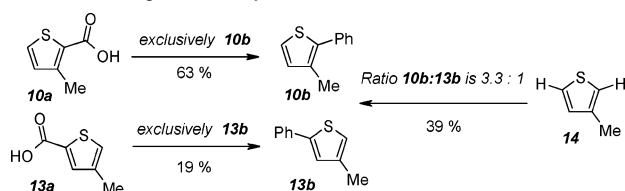
|  |   |                 |   |                           |
|---|---|-----------------|---|---------------------------|
| entry   | substrate   |                 | product   | yield <sup>b</sup><br>(%) |
| 1   |    | <b>3a</b>       |    | <b>3b</b> 53 <sup>c</sup> |
| 2   |    | <b>4a</b>       |    | <b>4b</b> 88              |
| 3   |    | R=Me, <b>6a</b> |    | R=Me, <b>6b</b> 86        |
| 4   |    | R=H, <b>7a</b>  |    | R=H, <b>7b</b> 41         |
| 5   |    | R=Me, <b>8a</b> |    | R=Me, <b>8b</b> 74        |
| 6   |    | R=H, <b>9a</b>  |    | R=H, <b>9b</b> 23         |
| 7   |    | <b>10a</b>      |    | <b>10b</b> 63             |
| 8   |   | <b>11a</b>      |   | <b>11b</b> 86             |
| 9   |  | <b>12a</b>      |  | <b>12b</b> 0              |

<sup>a</sup> Reaction conditions: heterocycle (0.80 mmol, 2.0 equiv), phenyl bromide (1.0 equiv), Pd[P(*t*-Bu)<sub>3</sub>]<sub>2</sub> (5 mol %), *n*-Bu<sub>4</sub>N<sup>+</sup>Cl<sup>-</sup>·H<sub>2</sub>O (1.0 equiv), Cs<sub>2</sub>CO<sub>3</sub> (1.5 equiv), DMF (4 mL),  $\mu$ W, 170 °C, 8 min. <sup>b</sup> Isolated yields. <sup>c</sup> Yield without additive (yield with *n*-Bu<sub>4</sub>N<sup>+</sup>Cl<sup>-</sup>·H<sub>2</sub>O = 74% (contains 10% of 1-methyl-2-pyrrole-*n*-butylester by <sup>1</sup>H NMR)).

will generate 3-phenyl-2-furan carboxylic acid **III**. This product can in turn re-enter the catalytic cycle and via **I** (where R = Ph) yield 2,3-diphenylfuran, accounting for the lower yields observed in the unsubstituted cases. Additionally, when 2-phenylfuran was subjected to the reaction conditions, only 2,5-diphenylfuran was observed, ruling out 2-phenylfuran as an intermediate for the formation of 2,3-diphenylfuran under these conditions.

A comparison of this decarboxylative cross-coupling with the C–H functionalization method was performed to further highlight its utility (Scheme 3). In contrast to the C–H functionalization, where a mixture of the two possible products was obtained (**10b** and **13b**), appropriate selection of either of the heterocyclic acids (**10a** and **13a**) afforded the corresponding regioisomer.

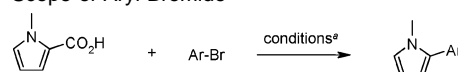
### Scheme 3. Regioselectivity<sup>a</sup>



<sup>a</sup> Conditions: PhBr, DMF, *n*-Bu<sub>4</sub>N<sup>+</sup>X<sup>-</sup>, Pd[P(*t*-Bu)<sub>3</sub>]<sub>2</sub>,  $\mu$ W, 170 °C, 8 min.

To further evaluate the scope of this reaction, a variety of aryl bromides were employed and produced the desired products in good

**Table 3.** Scope of Aryl Bromide

|  |                         |                    |
|--|-------------------------|--------------------|
| entry  | Ar–Br                   | isolated yield (%) |
| 1  | 4-MeO–PhBr              | 77                 |
| 2  | 4-NO <sub>2</sub> –PhBr | 66                 |
| 3  | 2-Br-5-Me-thiophene     | 78                 |
| 4  | 3-Br-pyridine           | 85                 |
| 5  | PhBr <sup>b</sup>       | 57                 |

<sup>a</sup> See Table 2. <sup>b</sup> Performed under thermal conditions (140 °C, 1 h).

yield (Table 3). Preliminary results show that thermal conditions can also be employed (entry 5).

Miura<sup>7</sup> reported the use of carboxamides as a sacrificial group in the arylation of thiazoles, however, multiple arylations were obtained. An important distinction between our work and that previously reported<sup>7,8</sup> is that it highlights the ability to selectively perform this reaction in the presence of a reactive C–H group in an intermolecular fashion and sheds light on the mechanism of this type of reactivity. Furthermore, it allows for the control of the arylation such that the monoarylated product is always the major product observed.

In summary, a decarboxylative cross-coupling reaction for preparing aryl-substituted heteroaromatics has been disclosed. Starting from stable and commercially available substrates, this method allows access to structural motifs that are difficult to obtain by other methods. The complete control of regiochemistry is an attractive complement to the existing C–H functionalization method. Efforts are underway to evaluate the scope and limitation of this reaction and details will be reported in due course.

**Acknowledgment.** We wish to thank A. B. Charette for valuable discussions concerning this work and our colleagues at Boehringer Ingelheim (Canada), Ltd., R&D for their support and useful suggestions during the preparation of this manuscript.

**Supporting Information Available:** Experimental procedures and spectroscopic characterization of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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