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Palladium-Catalyzed Intramolecular Direct Arylation of Benzoic Acids by Tandem Decarboxylation/C−H Activation

Congyang Wang, Isabel Piel, and Frank Glorius*

Organisch-Chemisches Institut der Westfälischen Wilhelms-Universität Münster, Corrensstrasse 40, 48149 Münster, Germany

Received December 25, 2008; E-mail: glorius@uni-muenster.de

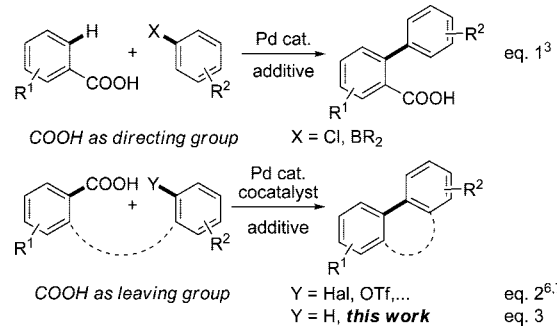
The biaryl moiety is a ubiquitous motif of polymeric materials, ligands, and biologically active compounds. Consequently, many methods have been developed for the formation of unsymmetrical biaryls,[1] the most versatile and powerful ones being transition-metal catalyzed cross-coupling reactions, such as the Suzuki−Miyaura coupling. As an alternative approach, direct arylation reactions of nonactivated arenes attract more and more attention,[2] because such C−H functionalizations often significantly streamline organic synthesis and decrease byproduct waste.

Carboxylic acids represent one of the most common and readily available functional groups in organic chemistry. Their use as directing groups in direct couplings has recently been reported by Yu et al. and Daugulis et al. in direct arylations of benzoic acids,[3] which provides an attractive alternative to more traditional ortho-metalation/cross-coupling sequences (Scheme 1, eq 1). Moreover, the use of carboxylates as *leaving groups* in cross-coupling reactions represents a major breakthrough.[4] Especially noteworthy are Heck-type couplings by Myers et al.[5] and the coupling of a variety of benzoic acids with aryl halides and triflates with carefully optimized catalyst systems by Goossen et al. (Scheme 1, eq 2).[6,7] Even though these decarboxylative cross-couplings still have some shortcomings like high reaction temperatures, the advantages in comparison to other cross-couplings that employ costly, sensitive, and toxic organometallic compounds are obvious. As part of our ongoing research on challenging cross-coupling reactions,[8] we aimed at the difficult but highly desirable direct cross-coupling of benzoic acids with simple arenes instead of aryl halides or triflates. Such a process makes use of readily available and cheap benzoic acids and simple arenes, avoiding the need for handling sensitive organometallic coupling partners. Herein, we report the first highly chemo- and regioselective, efficient palladium-catalyzed intramolecular direct arylation of benzoic acids by tandem decarboxylation/C−H activation (Scheme 1, eq 3).[9] In these direct arylation reactions the COOH group acts as a halide free leaving group that provides a handle for obtaining high levels of regioselectivity.

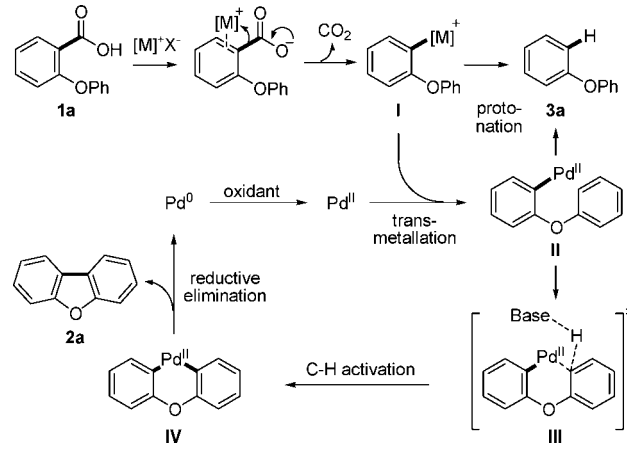
The following mechanism was envisaged (Scheme 2): transition-metal mediated decarboxylation of 2-phenoxybenzoic acid **1a** affords arylmetal species **I**.[4a] The following transmetalation with a Pd^{II} complex results in the formation of an arylpalladium intermediate **II**, which can undergo intramolecular C−H activation to palladacycle **IV**. Finally, reductive elimination provides dibenzofuran **2a** and Pd^0, the latter one of which can be oxidized to Pd^{II}, closing the catalytic cycle. In undesired side-reactions, **I** or **II** can undergo proto-demetalation to give the decarboxylated, albeit uncyclized diphenyl ether **3a**. Thus, suppression of the competitive protonation represents a major challenge for the efficiency of the desired intramolecular C−H activation.

We figured that Cu and Ag salts can not only assist the decarboxylation step, but also act as oxidants for the following C−H activation.[2−7] After screening a wide range of reaction parameters[10] for substrate **1a**, we obtained the optimal conditions using $Pd(TFA)_2$ as the catalyst together with stoichiometric amounts of Ag_2CO_3, providing **2a** in 85% isolated yield with the ratio 68:1 of **2a/3a** (Table 1, entry 1).

Scheme 1. Comparison of Different Cross-Coupling Reactions Employing Carboxylic Acids



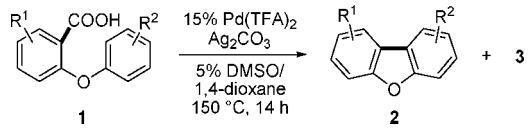
Scheme 2. Possible Reaction Pathway for the Intramolecular Direct Arylation of 2-Phenoxybenzoic Acid (**1a**)

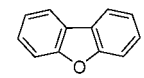
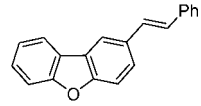
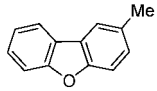
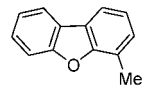
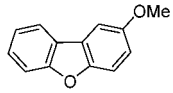
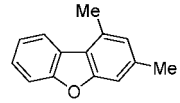
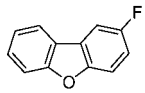
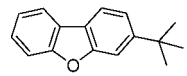
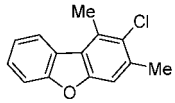
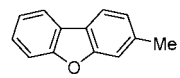
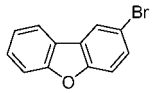
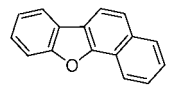
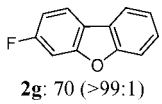
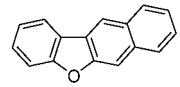


A variety of dibenzofuran derivatives can be generated through this method (Table 1). 2-Phenoxybenzoic acids with both electron-donating and electron-withdrawing substituents afforded the corresponding cyclized products in good isolated yields (entries 1−7). It is important to note that fluoride, chloride, and even bromide groups are tolerated in this process (entries 3−7). These valuable functional groups allow for further synthetic functionalizations, thus providing a distinct advantage of this method over intramolecular direct arylation reactions using aryl halides.[1,2,11] An unsaturated carbon−carbon double bond is also tolerated with retention of configuration (entry 8). The substrates with more steric hindrance with respect to the C−H activation step undergo the desired tandem process as well (entries 9−12). In the case of *meta*-substituted

10.1021/ja8100598 CCC: $40.75

Table 1. Investigations of the Reaction Scope[a]



entry	product yield[b] of **2** [%] (ratio **2**/**3**[c])	entry	product yield[b] of **2** [%] (ratio **2**/**3**[c])
1[d]	 **2a**: 85 (68:1)	8[d]	 **2h**: 55 (48:1)
2	 **2b**: 62 (>99:1)	9	 **2i**: 63 (52:1)
3	 **2c**: 73 (40:1)	10	 **2j**: 59 (53:1)
4[d]	 **2d**: 54 (24:1)	11	 **2k**: 67[e] (35:1)
5[d]	 **2e**: 84 (59:1)	12	 **2l**: 69[f] (98:1)
6	 **2f**: 39 (>99:1)	13	 **2m**: 52 (24:1)
7	 **2g**: 70 (>99:1)	14	 **2n**: 51[g] (53:1)

[a] Reaction conditions: **1** (1 mmol), $Pd(TFA)_2$ (0.15 mmol), Ag_2CO_3 (3 mmol), 5% DMSO/1,4-dioxane (5 mL), 150 °C, 14 h. [b] Yield of the isolated, pure product. [c] Determined by GC−MS analysis. [d] Concentration = 0.1 M. [e] Single regioisomer. [f] The ratio of two regioisomers[c] **2l**/**2l′** = 26:1 (major isomer shown). [g] Combined yield of two regioisomers **2n** and **2n′**; **2n**/**2n′** = 1.8:1[c] (major isomer shown).

substrates, two regioisomeric dibenzofuran products could be produced, though, interestingly, highly selective formation of less sterically hindered regioisomers is observed in all cases (entries 11−12). Substrates with a naphthyl moiety also work well under the same reaction conditions (entries 13−14). Importantly, all the reactions mentioned above proceed with excellent selectivity relative to the proto-decarboxylation side-reactions, which shows the high level of fidelity of this catalytic system. Mechanistic experiments (competition experiments and the determination of an intramolecular isotope effect of 3.9 for substrate **1** with $R^1 = H$ and $R^2 = o$-D) are in agreement with the mechanism depicted in Scheme 2.[10,11]

In summary, we have developed a novel protocol for the highly selective palladium catalyzed intramolecular direct arylation of benzoic acids by tandem decarboxylation/C−H activation. Dibenzofurans are formed in good yields by employing a carefully optimized, albeit simple catalyst system with excellent control of the competing proto-decarboxylation. The extension of this method to intermolecular reactions is currently ongoing.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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