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

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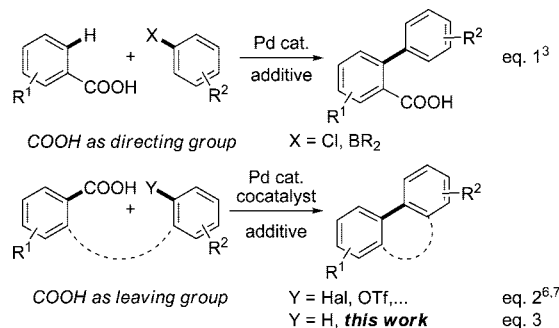
The biaryl moiety is a ubiquitous motif of polymeric materials, ligands, and biologically active compounds. Consequently, many methods have been developed for the formation of unsymmetrical biaryls,¹ the most versatile and powerful ones being transition-metal catalyzed cross-coupling reactions, such 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.

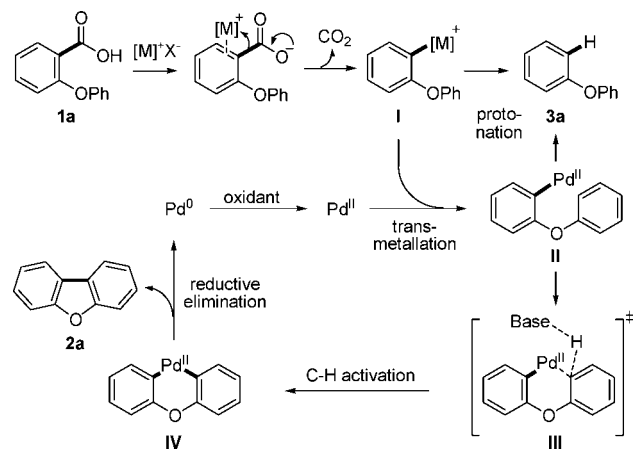
The following mechanism was envisaged (Scheme 2): transition-metal mediated decarboxylation of 2-phenoxybenzoic acid **1a** affords arylmetal species **I**.^{4a} The following transmetalation with a Pd^{II} complex results in the formation of an arylpalladium intermediate **II**, which can undergo intramolecular C–H activation to palladacycle **IV**. Finally, reductive elimination provides dibenzofuran **2a** and Pd⁰, 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 parameters¹⁰

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**)



for substrate **1a**, we obtained the optimal conditions using Pd(TFA)₂ as the catalyst together with stoichiometric amounts of Ag₂CO₃, providing **2a** in 85% isolated yield with the ratio 68:1 of **2a/3a** (Table 1, entry 1).

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

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 ^d (98:1) |
| 6 | 2f : 39 (>99:1) | 13 | 2m : 52 (24:1) |
| 7 | 2g : 70 (>99:1) | 14 | 2n : 51 ^f (53:1) |

^a Reaction conditions: **1** (1 mmol), Pd(TFA)₂ (0.15 mmol), Ag₂CO₃ (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 R¹ = H and R² = *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>.

References

- (1) (a) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (b) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; De Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (c) *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, Germany, 2009. For a survey on the relevance of these reactions in process R&D, see: (d) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.
- (2) For excellent reviews, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (d) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (e) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrich Chim. Acta* **2007**, *40*, 35.
- (3) (a) Wang, D.-H.; Sheng, T.-M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676. (b) Giri, R.; Mangel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (c) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879.
- (4) For excellent reviews, see: (a) Goossen, L. J.; Rodriguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100. (b) Bonesi, S. M.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 10022.
- (5) For lead references on the use of carboxylic acids in decarboxylative Heck reactions, see: (a) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250. (b) Tanaka, D.; Romeril, A. S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323.
- (6) (a) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662. (b) Goossen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7103. (c) Goossen, L. J.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824. (d) Goossen, L. J.; Rodriguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, *130*, 15248.
- (7) For related couplings of aliphatic, aromatic, heteroaromatic carboxylic acids, see: (a) Bi, H.-P.; Zhao, L.; Liang, Y.-M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 792. (b) Becht, J.-M.; Le Drian, C. *Org. Lett.* **2008**, *10*, 3161. (c) Becht, J.-M.; Catala, C.; Le Drian, C.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781. (d) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350.
- (8) (a) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230. (b) Würtz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523. (c) Altenhoff, G.; Würtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925. (d) Altenhoff, G.; Glorius, F. *Adv. Synth. Catal.* **2004**, *346*, 1661. (e) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195. (f) Glorius, F. *Tetrahedron Lett.* **2003**, *44*, 5751.
- (9) During the preparation of this manuscript, Crabtree et al. reported compound **1a** affording **2a** and **3a** in a ratio of 1:1.2 under microwave heating conditions and employing a phosphine ligand. In addition, the results of four intermolecular tandem decarboxylation/C–H activation couplings are given, although with low chemoselectivity and mostly low yields: Voutchkova, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun.* **2008**, 6312.
- (10) For more details, see Supporting Information.
- (11) For some mechanistically insightful examples, see: (a) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. (b) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (c) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (d) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848. (e) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (f) Wen, J.; Zhang, J.; Chen, S.-Y.; Li, J.; Yu, X.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 8897. (g) Özdemir, I.; Demir, S.; Cetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156. (h) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (i) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201. (j) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084.

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