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Intermolecular Decarboxylative Direct C-3 Arylation of Indoles with Benzoic Acids

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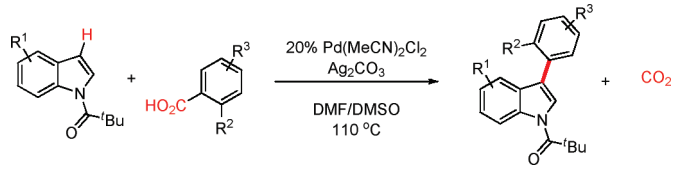
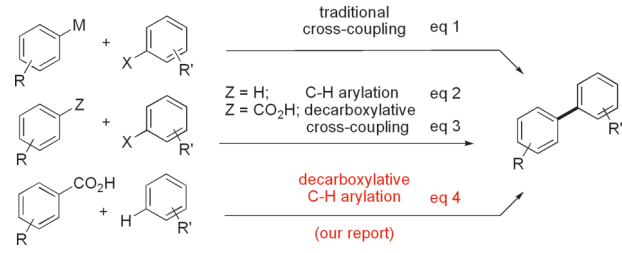
ABSTRACT



A palladium catalyzed C−H activation of indoles and a silver catalyzed decarboxylative C−C activation of ortho substituted benzoic acids are synergistically combined to synthesize indoles arylated exclusively in the C-3 position. This novel decarboxylative C−H arylation methodology is compatible with electron-donating and -withdrawing substituents in both coupling partners.

Palladium catalyzed cross-coupling reactions between organometallic and haloarene moieties are among the most employed methodologies for the synthesis of biaryls (Scheme 1, eq 1).[1] However, these methodologies present intrinsic disadvantages, namely the need for prefunctionalization of both coupling partners and the generation of stoichiometric amounts of often toxic metal salts. In the past few years direct C−H arylation has emerged as an alternative in which one of the coupling partners is not prefunctionalized, thus saving synthetic steps and avoiding waste formation from this substrate (eq 2).[2] Recently, a ground-breaking report from Goossen et al. showed that benzoic acids can be employed as aryl donors in cross-coupling reactions (eq 3), where CO_2 is generated as the leaving group.[3,4] These couplings are proposed to proceed via a Pd/Cu bimetallic catalytic cycle. A related Pd/Ag system had also been reported previously by Myers et al. for Heck-type couplings.[5] Both methodologies, C−H arylation and decarboxylative aryl−aryl cross-couplings, still require the prefunctionalization of one of the coupling partners as an aryl halide.

Scheme 1. Strategies for Biaryl Construction (X = Cl, Br, I, OTf, etc.)



We recently developed a palladium-catalyzed room temperature C-2 selective direct arylation of indoles with iodoarenes, which requires the use of a silver carboxylate

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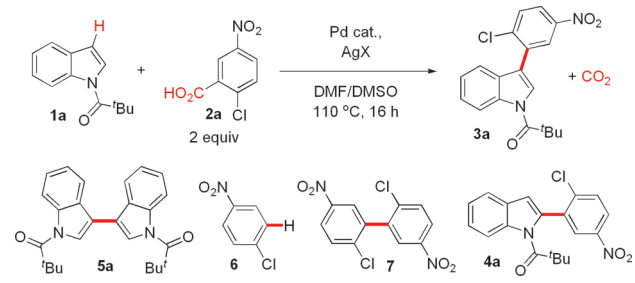
as the base.[6] Interestingly, when we attempted these reactions at higher temperatures, we observed the formation of side products derived from the decarboxylation of the silver carboxylate followed by coupling with either the iodoarene (eq 3) or the indole (eq 4). These results led us to hypothesize that it should be possible to develop an oxidative cross-coupling methodology combining both C−H and decarboxylative activations (eq 4), which, potentially, would only generate water and CO_2 as byproduct if oxygen was used as the terminal oxidant. Such a methodology could allow for excellent control of regio- and chemo-selectivity. As a comparison, these are significant problems in double C−H activation oxidative couplings that are generally overcome by using large excesses of one of the substrates (up to 60 equiv).[7]

During the preparation of this manuscript, Crabtree et al. reported four examples of the decarboxylative coupling of 2,6-dimethoxybenzoic acid with arene donors in low to moderate yields using a Pd/Ag catalyst system at 200 °C.[8] Subsequently, Glorius and co-workers reported the *intramolecular* decarboxylative C−H arylation of 2-phenoxybenzoic acids.[9] Both of these methodologies are restricted to the use of ortho alkoxy benzoic acids. No examples have been reported of the use of benzoic acids bearing electron-withdrawing groups. Here we report the first intermolecular direct arylation of indoles with several benzoic acids bearing ortho electron-withdrawing substituents via a C−H functionalization-decarboxylation process. This process occurs with high chemo- and regio-selectivity in both coupling partners. Furthermore, contrary to the usual C-2 regioselectivity in indole direct arylation with palladium, this methodology affords exclusively the C-3 arylated indole adducts.[7c,10−12]

Initially, we studied the coupling of *N*-pivaloylindole (**1a**) and 2-chloro-5-nitrobenzoic acid (**2a**, Table 1) using catalytic

Table 1. Optimization of the Decarboxylative Direct C−H Arylation of *N*-Pivaloylindole (**1a**) and 2-Chloro-5-nitrobenzoic Acid (**2a**)[a]



entry	Pd cat.	AgX	**3a** (%)[b]
1	$Pd(TFA)_2$	Ag_2O	33
2	$Pd(TFA)_2$	AgOAc	53
3	$Pd(TFA)_2$	Ag_2CO_3	72
4	$Pd(dppf)Cl_2$	Ag_2CO_3	25
5	Pd-PEPPSI-IPr	Ag_2CO_3	62
6	$Pd(MeCN)_2Cl_2$	Ag_2CO_3	77
7	$Pd(MeCN)_2Cl_2$[c]	–	0
8	–	Ag_2CO_3	0

[a] Unless otherwise noted, all reactions were carried out using 20 mol % Pd cat., 3.0 equiv of AgX, 2.0 equiv of **2a**, 2.4 equiv of DMSO and 1.0 equiv of **1a** in a 0.1 M DMF solution, for 16 h at 110 °C. [b] Yield of **3a** was measured by ^{1}H NMR analysis of the crude product using an internal standard. [c] $Pd(MeCN)_2Cl_2$ (100 mol %) was used.

$Pd(TFA)_2$ and a range of silver salts as oxidants (entries 1−3).[13] Gratifyingly, the use of Ag_2CO_3 afforded the C-3 adduct **3a** in good yield (72%, entry 3). A survey of different palladium catalysts identified $Pd(MeCN)_2Cl_2$ as the best catalyst for this transformation increasing the yield to 77% (entry 6). In addition to adduct **3a**, protodecarboxylation product **6**, decarboxylative homocoupling adduct **7** and traces of indole dimer **5a** were observed. The use of molecular sieves to prevent the formation of **6** proved unsuccessful. Remarkably, the reaction is completely regioselective for the

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(7) For selected references on oxidative couplings, see: (a) Brasche, G.; Garcia-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207. (b) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (c) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (d) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (e) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137.

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(9) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194.

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(11) For selected examples of C-2 arylation see: (a) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473. (b) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476. (c) Zhang, Z.; Hu, Z.; Yu, Z.; Lei, P.; Chi, H.; Wang, Y.; He, R. *Tetrahedron Lett.* **2007**, *48*, 2415. (d) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 1970. (e) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (f) Touré, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979. (g) Bellina, F.; Cauteruccio, S.; Rossi, R. *Eur. J. Org. Chem.* **2006**, 1379. (h) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996. (i) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (j) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 4990. (k) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897. For selected examples of C-3 arylation, see: (l) Ackermann, L.; Barfuesser, S. *Synlett* **2009**, 808. (m) Cusati, G.; Djakovitch, L. *Tetrahedron Lett.* **2008**, *49*, 2499. (n) Bellina, F.; Benelli, F.; Rossi, R. *J. Org. Chem.* **2008**, *73*, 5529. (o) Djakovitch, L.; Dufaud, V.; Zaidi, R. *Adv. Synth. Catal.* **2006**, *348*, 715. (p) Djakovitch, L.; Rouge, P.; Zaidi, R. *Catal. Commun.* **2007**, *8*, 1561. (q) Zhang, Z.; Hu, Z.; Yu, Z.; Lei, P.; Chi, H.; Wang, Y.; He, R. *Tetrahedron Lett.* **2007**, *48*, 2415. (r) Akita, Y.; Itagaki, Y.; Takizawa, S.; Ohta, A. *Chem. Pharm. Bull.* **1989**, *37*, 1477.

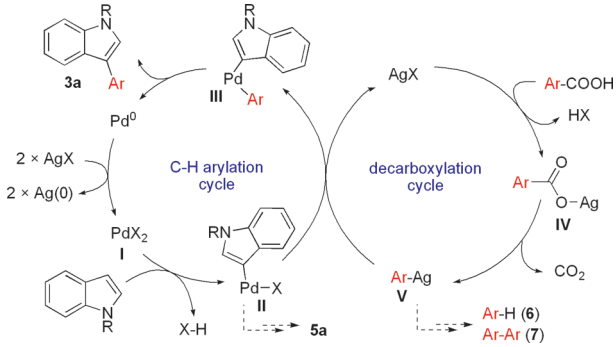
(12) For a C-2/C-3 regioselective indole arylation under copper catalysis see: Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172.

(13) (a) Other protecting groups for the indole were also examined. See Supporting Information for more details. (b) Other oxidants tested in the presence of catalytic amounts of silver and copper salts included: O2, Oxone, Cu(OTf)2, AgOTf and TEMPO. Adduct **3a** was not observed in any of these experiments.

C-3 position of the indole (the C-2 adduct **4a** was not detected by GCMS or NMR). In contrast, palladium catalyzed oxidative C−H arylations of *N*-pivaloyl protected indoles have previously been reported to afford the C-2 arylated adducts instead.[7c] In the absence of palladium catalyst (entry 8), indole **1a** and *p*-chloronitrobenzene (**6**) were the only observed products. In the absence of silver salts no coupling product **3a** was observed even when using 100 mol % $Pd(MeCN)_2Cl_2$ (entry 7), indicating that both metals are required in the reaction. To further explore the role of each metal, acid **2a** was stirred for 16 h in DMF/DMSO at 110 °C in the presence of 1.5 equiv of Ag_2CO_3, leading to quantitative formation of arene **6**.[14] On the other hand, when 20 mol % $Pd(TFA)_2$ was used instead of the silver salt, benzoic acid **2a** was recovered unreacted, indicating that the Pd catalyst is not responsible for the decarboxylation step.

A working hypothesis for this transformation, consistent with these observations, is outlined in Scheme 2. In two

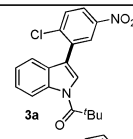
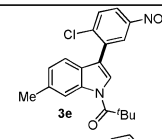
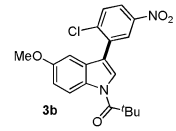
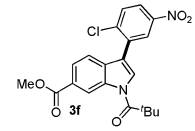
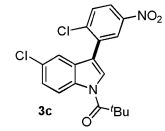
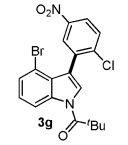
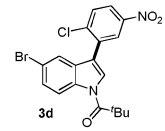
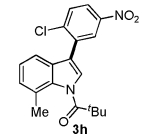
Scheme 2. Working Hypothesis for the Intermolecular Decarboxylative C−H Arylation Strategy (R = ^{t}BuCO-, Ar = 2-Cl-5-NO_2−C_6H_3-)



intertwined catalytic cycles, a palladium catalyst performs an electrophilic palladation (**I** to **II**) and the biaryl formation through reductive elimination (**III** to **3a**), whereas a silver species mediates the decarboxylative activation step (**IV** to **V**) followed by transmetalation to arylpalladium **III**. Finally, oxidation of Pd^0 to Pd^{II} (**I**), also performed by the silver salt, completes the arylation cycle. By-products **5a** and **6**−**7** are formed from palladium and silver arenes **II** and **V**, respectively. Silver arenes have been reported to readily undergo protodemetalation and radical formation at high temperatures.[15] A radical pathway for this transformation was also considered.[16] When a reaction was carried out under the standard conditions in the presence of 1.0 equiv of TEMPO, a radical trap,[17] the same yield of adduct **3a** was obtained, suggesting that a radical mechanism is not in place for this transformation. The rates of both catalytic cycles require a fine balance to maximize transmetalation and minimize the formation of byproduct. Obviously, such rates could be highly dependent on the substrates, and therefore we were concerned that a change in the substrates may require a reoptimization of the reaction conditions.

We next examined the scope of the reaction with a variety of indoles **1** bearing electron-withdrawing and donating substituents (Table 2, **3b**−**h**). Pleasingly, no adjustments on

Table 2. Scope of Decarboxylative Direct C-3 Arylation of *N*-Pivaloyl Indoles (**1**) and 2-Chloro-5-nitrobenzoic Acid (**2a**)[a]

product	yield (%)[b]	product	yield (%)[b]
 **3a**	76	 **3e**	74
 **3b**	67	 **3f**	66
 **3c**	71	 **3g**	44
 **3d**	62	 **3h**	55

[a] All reactions were carried out using 20 mol % $Pd(MeCN)_2Cl_2$, 3.0 equiv of Ag_2CO_3, 2.0 equiv of **2a**, 2.4 equiv of DMSO and 1.0 equiv of indole **1** in a 0.1 M DMF solution, for 16 h at 110 °C. [b] Isolated yields after column chromatography.

the reaction conditions were necessary to afford good yields of the coupled products **3**, showing that the reaction tolerates changes in the indole core. Substituents such as an ester (**3f**), a Cl (**3c**) and a Br (**3d** and **3g**) were compatible with the reaction conditions, allowing for further cross-coupling reactions to be performed on the products. It is noteworthy that even highly hindered indoles substituted in C4 and C7 (which are rarely reported to undergo C−H arylation),[10] afforded moderate to good yields of the C3 coupling adducts **3g** and **3h** without further optimization of the reaction conditions. Furthermore, to the best of our knowledge, no examples have been reported of a C3 selective direct arylation on a C4 substituted indole. In all cases the C-3 adducts were obtained with excellent regioselectivities (>99:1 by GCMS) even when having substituents in C4 and C7.

(14) Catalytic amounts of Ag(I) salts have been recently shown to promote the protodecarboxylation of ortho substituted benzoic acids: Cornella, J.; Sanchez, C.; Banawa, D.; Larrosa, I. *Chem. Commun.* 2009, DOI:10.1039/B916646G.

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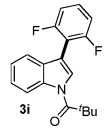
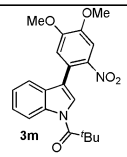
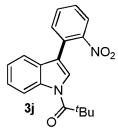
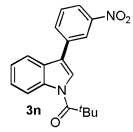
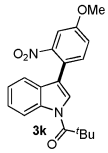
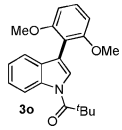
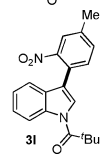
(16) Yu, W.-Y.; Sit, W. N.; Zhou, Z.; Chan, A. S.-C. *Org. Lett.* **2009**, *11*, 3174.

(17) For an example of the use of TEMPO as a radical trap, see: (a) Sibbald, P. A.; Michael, F. E. *Org. Lett.* **2009**, *11*, 1147. (b) Albeniz, A. C.; Espinet, P.; Lopez-Fernandez, R.; Sen, A. *J. Am. Chem. Soc.* **2002**, *124*, 11278.

Having demonstrated the generality of our decarboxylative C−H arylation procedure toward changes in the indole core, we then examined the effect of the substitution pattern of the benzoic acid coupling partner (Table 3). As expected, due to the variations in rates of decarboxylation of **IV** and decomposition/transmetalation of **V**, a small degree of optimization was required for each new carboxylic acid. Gratifyingly, by slightly adjusting concentration, temperature and reaction times, good yields of the coupling adducts **3** were obtained for a variety of substituted benzoic acids (Table 3). We observed that for the reaction to occur smoothly, an electron-withdrawing group, such as NO_2, Cl or F, is necessary in the ortho position (**3a** and **3i**−**m**), whereas no product was observed when in meta (**3n**) or para position. Furthermore, while electron-donating substituents are tolerated in meta and para positions (**3k**−**m**), the ortho substituted 2,6-dimethoxybenzoic acid did not afford any coupling product (**3o**) showing the complementary nature of our methodology when compared with the previously reported decarboxylative C−H arylation procedures.[8,9] Since 2,6-dimethoxybenzoic acid has been shown to undergo decarboxylation promoted by Ag_2CO_3,[14] its lack of reactivity toward the cross-coupling could be due to both catalytic cycles being out of phase as a consequence of a step change in reactivity for intermediate **V.**

Table 3. Scope of Decarboxylative Direct C-3 Arylation of *N*-Pivaloyl Indole (**1a**) and Benzoic Acids (**2**)[a]

product	yield (%)[b]	product	yield (%)[b]
 **3i**	70[c]	 **3m**	44
 **3j**	58	 **3n**	0
 **3k**	63[d]	 **3o**	0
 **3l**	57[d]		

[a] Unless otherwise noted, all reactions were carried out using 20 mol % $Pd(MeCN)_2Cl_2$, 3.0 equiv of Ag_2CO_3, 2.0 equiv of **2**, 2.4 equiv of DMSO and 1.0 equiv of indole **1a** in a 0.1−0.4 M DMF solution, for 3−16 h at 110−120 °C. See Supporting Information for further details. [b] Isolated yields after column chromatography. [c] 2,6-Difluorobenzoic acid (3.0 equiv) and 4.5 equiv of Ag_2CO_3 were used. [d] $Pd(TFA)_2$ was used as the catalyst.

In summary, we have developed a decarboxylative direct C−H arylation methodology that allows the intermolecular coupling of a variety of electron-poor benzoic acids with indoles to give C-3 arylated adducts, based on a Pd/Ag bimetallic system. This transformation occurs with high regio- and chemo-selectivity, representing an excellent alternative to double C−H activation oxidative couplings. Ongoing studies are being directed toward performing the coupling with electron-rich benzoic acids, understanding the mechanism of this new transformation and its regioselectivity, and developing a C-2 arylation procedure.

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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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