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Pd-Catalyzed Decarboxylative Arylation of Thiazole, Benzoxazole, and Polyfluorobenzene with Substituted Benzoic Acids

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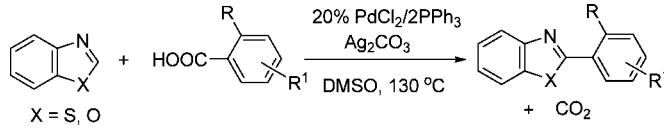
ABSTRACT



A Pd-catalyzed decarboxylative coupling of thiazoles and benzoxazole with various substituted benzoic acids is developed. The reaction is compatible with both electron-rich and electron-poor benzoic acids. It can also be extended to the synthesis of polyfluoro-substituted biaryls using polyfluorobenzenes as the starting materials.

Over the past 30 years, Pd-catalyzed cross-coupling between aryl halides and aryl metals has become one of the most powerful methods for the syntheses of biaryls.[1] However, one fundamental drawback with these coupling reactions is that they require the use of a stoichiometric amount of an expensive organometallic reagent that often has to be prepared either beforehand or in situ. In order to overcome this problem, chemists have strived to develop couplings that use other alternative reagents, and recently, benzoic acids have emerged as viable coupling partners, largely through the efforts of Goossen and others.[2−6] What is interesting is that benzoic acids can be used not only as the source of the aryl electrophile but also as the aryl metal equivalent after undergoing in situ decarboxylation to generate the aryl-Pd species. For instance, Goossen,[2] Larrosa,[3] Becht,[4] and others[5] have all shown that benzoic acids, acting as organometallic reagent equivalents, can be efficiently coupled with aryl halides, diaryliodonium salts, and indoles. On the other hand, Myers[6a−c] and others[6d] have shown that benzoic acids, acting as organohalide equivalents, can efficiently undergo Pd-catalyzed Heck coupling with various olefins. Detailed

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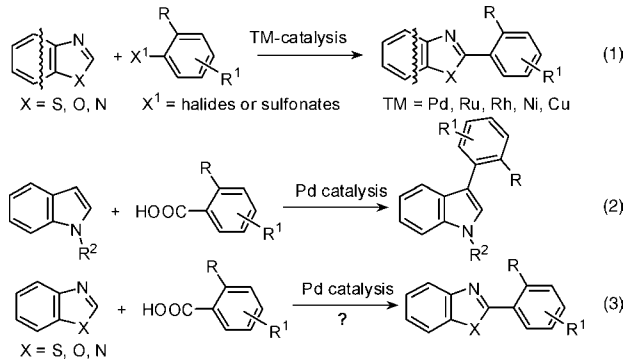
mechanistic investigations by Myers[6a−c] and Kozlowski[7] have shed some light on the mechanism of these reactions. Although some of the basic foundations have been laid, compared with the well-established standard Pd-catalyzed cross-coupling between organic halides and aryl metals, the coupling with benzoic acids is much under-developed, and thus there remains much to be explored. Herein we report that benzoic acids can also efficiently couple with thiazoles, benzoxazole, and polyfluorobenzenes via Pd-catalysis.

Coupling between heteroaromatic compounds and aryl halides through various transition-metal-catalyzed processes is well-documented (Scheme 1, eq 1).[8] In sharp contrast,

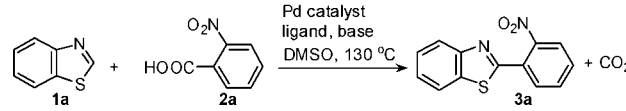
Scheme 1. Strategies for the Arylation of Heterocycles



the coupling of heteroaromatics with benzoic acids is rare. As far as we know, only the Pd-catalyzed decarboxylative coupling between indole and benzoic acids has been reported (Scheme 1, eq 2).[3] The coupling of other heterocycles such as oxazoles and thiazoles with benzoic acids is totally unknown. Because of the widespread presence of heteroaromatic nuclei in drugs and biologically active natural compounds, we sought to extend this protocol to other heterocycles as well (Scheme 1, eq 3).

When we treated benzothiazole (**1a**) with 2-nitrobenzoic acid (**2a**, 1.5 equiv) in DMSO at 130 °C in the presence of $PdCl_2$ (20 mol %), PPh_3 (40 mol %), and Ag_2CO_3 (3 equiv) for 12 h (similar to Becht's conditions), we were delighted to see that the desired product **3a** was formed in 68% yield by GC analysis and that the decarboxylative coupling occurred exclusively at the 2-position of the benzothiazole (Table 1, entry 1). After column chromatography, **3a** could

Table 1. Optimization of the Reaction Conditions for the Pd-Catalyzed Decarboxylative Arylation of Benzothiazole with 2-Nitrobenzoic Acid



entry	catalyst (equiv)	ligand (equiv)	base (equiv)	yield (%)[a,b]
1	$PdCl_2$ (0.2)	PPh_3 (0.4)	Ag_2CO_3 (3)	68(60)
2	$PdCl_2$ (0.1)	PPh_3 (0.2)	Ag_2CO_3 (3)	42
3	$PdCl_2$ (0.2)	PPh_3 (0.4)	Ag_2O (3)	33
4	$Pd(OAc)_2$ (0.2)	PPh_3 (0.4)	Ag_2CO_3 (3)	36
5	$PdCl_2$ (0.2)	PPh_3 (0.4)	K_2CO_3 (3)	<5
6	$PdCl_2$ (0.2)	dppe (0.2)	Ag_2CO_3 (3)	63
7	$PdCl_2$ (0.2)	dppp (0.2)	Ag_2CO_3 (3)	65
8	$PdCl_2$ (0.2)	dppb (0.2)	Ag_2CO_3 (3)	59
9	$PdCl_2$ (0.2)	—	Ag_2CO_3 (3)	21
10	—	PPh_3 (0.4)	Ag_2CO_3 (3)	0

[a] GC yields using decane as the internal standard. [b] Isolated yield in parentheses.

be isolated in 60% yield. The yield dropped to 42% when only 10 mol % of Pd-catalyst was used (Table 1, entry 2). Replacing Ag_2CO_3 with Ag_2O gave much lower yield, as was the case when $PdCl_2$ was substituted by $Pd(OAc)_2$ (Table 1, entries 3 and 4). When Ag_2CO_3 was replaced with K_2CO_3, very little **3a** was formed (Table 1, entry 5). This observation is consistent with the reported fact that the use of a silver salt as the base was necessary for the coupling to occur.[4] The use of other phosphine ligands such as dppe, dppp, and dppb or no ligand did not improve the yield either; only comparable or lower yields were obtained (Table 1, entries 6−9). Since the cost of these bidentate ligands is significantly higher than PPh_3, we opted to use the combination of $PdCl_2$/$2PPh_3$/Ag_2CO_3 as our standard conditions.[9] A control reaction also indicated that no product could be formed in the absence of Pd-catalyst (Table 1, entry 10).

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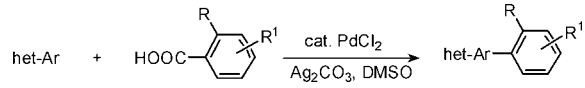
(9) **Representative Procedure.** To a flame-dried, three-neck, round-bottom flask under nitrogen were added benzothiazole (68 mg, 0.5 mmol), 2-nitrobenzoic acid (126 mg, 0.75 mmol), Ag_2CO_3 (414 mg, 1.5 mmol), $PdCl_2$ (18 mg, 0.1 mmol), PPh_3 (53 mg, 0.2 mmol), and DMSO (3 mL). The reaction mixture was heated at 130 °C for 12 h. After cooling to rt, the reaction mixture was diluted with ether and filtered through Celite. The organic phase was washed with saturated NH_4Cl, dried with $MgSO_4$, filtered, and concentrated via vacua. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, 50/1) to afford 77 mg of the desired 2-(2-nitrophenyl)-benzothiazole in 60% yield.

With the standard protocol in hand, we next set out to examine the scope and limitations of this coupling reaction and, the results are shown in Table 2. We found that the coupling was not limited to 2-nitrobenzoic acid. For example, with thiazoles such as benzothiazole and 4,5-dimethylthiazole, other benzoic acids such as 2,6-dimethoxylbenzoic acid, 2,6-difluorobenzoic acid, and 2-fluoro-6-chloro-benzoic acid as well as pentafluorobenzoic acid could also participate in the coupling successfully, affording the desired products in yields ranging from 42% to 63% (Table 2, entries 1−5, 7, and 8). Benzoxazole can also be used (Table 2, entry 6). Unfortunately, the use of *N*-methyl benzimidazole did not furnish any of the desired coupling product, it only produced the *N*-methyl benzimidazole self-dimerization product (Table 2, entry 9).

Since polyfluorobenzenes are also known to participate in the Cu-catalyzed coupling with aryl halides,[8t] we next examined the possibility of coupling benzoic acids with polyfluorobenzenes (Table 3). Much to our delight, treatment of 2-nitrobenzoic acid with pentafluorobenzene under our standard conditions gave the desired coupled product **5a** in a satisfactory 58% yield (Table 3, entry 1). The decarboxylative coupling took place only at the nonsubstituted position of pentafluorobenzene. The couplings of pentafluorobenzene with other nitrobenzoic acids all proceeded smoothly, furnishing the desired coupled biaryls in yields between 49% and 63% (Table 3, entries 3−5). It should be noted that a chloride substituent can be tolerated in the reaction though aryl chlorides are known to participate in the Pd-catalyzed cross-couplings (Table 3, entry 3). Coupling using 2,6-

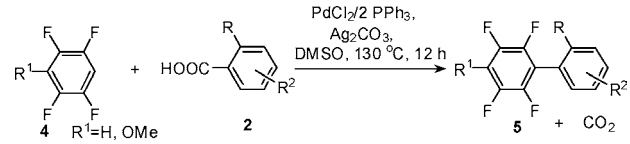
Table 2. Pd-Catalyzed Decarboxylative Arylation of Heteroaromatics with Benzoic Acids



entry	het-Ar	benzoic acid	product	yield (%)[b]
1	**1a**	**2b**	**3b**	61
2	**1a**	**2c**	**3c**	58
3	**1a**	**2d**	**3d**	55
4	**1a**	**2e**	**3e**	42
5	**1a**	**2f**	**3f**	55
6	**1b**	**2c**	**3g**	45
7	**1c**	**2d**	**3h**	63
8	**1c**	**2f**	**3i**	58
9	**1d**	**2a**	**3j**	0

[a] All reactions were carried out using 20 mol % $PdCl_2$, 3 equiv Ag_2CO_3, and 40 mol % PPh_3 in DMSO at 130 °C for 12 h. [b] Isolated yields.

Table 3. Pd-Catalyzed Decarboxylative Arylation of Polyfluorobenzenes with Benzoic Acids



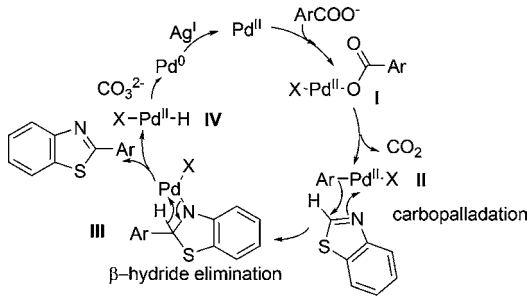
entry[a]	polyfluorobenzene	benzoic acid	product	yield (%)[b]
1	**4a**	**2a**	**5a**	58
2	**4a**	**2c**	**5b**	51
3	**4a**	**2g**	**5c**	53
4	**4a**	**2b**	**5d**	55
5	**4a**	**2h**	**5e**	49
6	**4b**	**2a**	**5f**	63
7	**4b**	**2h**	**5g**	57

[a] All reactions were carried out using 20 mol % $PdCl_2$, 3 equiv Ag_2CO_3, and 40 mol % PPh_3 in DMSO at 130 °C for 12 h. [b] Isolated yields.

dimethoxylbenzoic acid gave slightly lower yields (51%, Table 3, entry 2). Replacing one of the fluorine atoms on pentafluorobenzene with a methoxy group did not affect the coupling either (Table 3, entries 6 and 7).

Though the exact mechanism of this coupling is still not clear, on the basis of results reported by others,[2−8] a plausible mechanism is proposed and shown in Scheme 2 (using benzothiazole as the model). First, Pd(II) catalyst reacts with the carboxylic acid to form a Pd(II)-carboxylate intermediate **I**, which subsequently decarboxylates to form an aryl-Pd(II) species **II**. This aryl-Pd(II) species will undergo carbopalladation with the C−N double bond in the benzothiazole molecule to generate the intermediate **III**. After β-hydride elimination, a Pd-hydride species **IV** is produced besides the desired coupling product. **IV** will react with the carbonate base to give Pd(0) and the Pd(0) catalyst is reoxidized to Pd(II) by the Ag(I) salts, thus closing the catalytic cycle. Alternatively, a mechanism that is similar to what was proposed by Larrosa[3] could be operative here, too.

Scheme 2. Possible Mechanism for the Pd-Catalyzed Decarboxylative Arylation of Benzothiazole with Substituted Benzoic Acids



In summary, we have discovered that, using Pd as the catalyst and Ag_2CO_3 as the base and the oxidant, substituted benzoic acids can be used to arylate thiazoles, benzoxazole and polyfluorobenzenes after in situ decarboxylation. The reaction occurs with high chemo- and regioselectivity, representing an excellent alternative to those Pd-, Ni-, or Cu-catalyzed coupling with aryl halides and sulfonates. Efforts are currently underway to extend this protocol to other types of benzoic acids, and the results will be reported in due course.

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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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