

Palladium-Catalyzed Decarboxylative Coupling of Isatoic Anhydrides with Arylboronic Acids

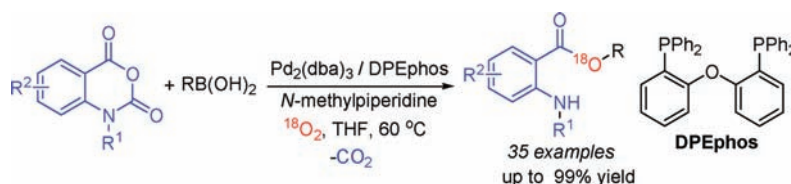
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Received September 27, 2011

ABSTRACT



The decarboxylative coupling of isatoic anhydrides with arylboronic acids was realized for the first time in the presence of $\text{Pd}_2(\text{dba})_3$ and DPEphos, achieving aryl *o*-aminobenzoates with yields ranging from moderate to good. The efficiency of this procedure was demonstrated by good compatibility with fluoro, chloro, bromo, nitro, cyano, trifluoromethyl, formacyl, acetyl, thienyl, and naphthyl groups. Preliminary mechanistic experiments using deuterium labeling showed that the oxygen atom was derived from dioxygen.

Aryl benzoate derivatives are important building blocks for the synthesis of natural products and pharmacologically active compounds.¹ Recently, aryl benzoate derivatives have been used as indicators of fragments of chemiluminescent labels in the field of photochemistry.² Traditional methods for the preparation of these compounds involve esterification³ and transesterification reactions⁴ as well as Baeyer–Villiger oxidation reactions.⁵

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However, the esterification and transesterification reactions were often conducted under strongly acidic or basic conditions, which might limit the scope of functional groups and practicality of the reaction. The regioselectivity of the Baeyer–Villiger oxidation reaction depends on the relative migratory ability of the substituents attached to the carbonyl group, and in cases where the substituent groups have similar migratory rates, the resulting products will be mixtures with low regioselectivity. In 2008, we developed the palladium-catalyzed aromatic esterification of aldehydes with arylboronic acids.⁶ However, the yields of the anticipated aryl benzoates were unsatisfactory. Thus, we still consider it highly desirable to develop milder and more efficient catalytic systems for the synthesis of aryl benzoate derivatives.

Herein, we report a new method for the synthesis of aryl *o*-aminobenzoates by Pd-catalyzed decarboxylative coupling of isatoic anhydrides with arylboronic acids.

Initially, the reaction between isatoic anhydride **1a** and phenylboronic acid **2a** was chosen as a model reaction to screen the optimal reaction conditions, and the results are listed in Table 1. Through the screening process, no target product was detected using Na_2PdCl_4 as the Pd source with

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a variety of parameters. However, we were delighted to find that the yield could be improved to 18% when the combination of Pd(OAc)₂, tricyclohexylphosphine (PCy₃), and Na₂CO₃ was employed in THF under an O₂ atmosphere (Table 1, entry 1).

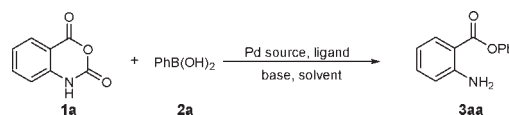
Encouraged by this promising result, we further adjusted reaction parameters including palladium catalysts, bases, and solvents. Among the palladium sources used (e.g., PdCl₂, PdCl₂(PPh₃)₂, PdCl₂(dppf), PdCl₂(PhCN)₂, PdCl₂(cod), PdCl₂(acac)₂, Pd(PPh₃)₄, and Pd₂(dba)₃), Pd₂(dba)₃ exhibited the highest catalytic reactivity in 47% yield (Table 1, entries 2–9). The choice of base was also vital to the success of the catalytic reaction. Screening revealed that the use of 1-methylpiperidine as base achieved the best result. Other bases, including Na₂CO₃, NaOAc, Cs₂CO₃, CsF, KF, ^tBuONa, Et₂NH, Et₃N, DABCO, 1-methylpyrrolidine, and 1-methylmorpholine, were less efficient (Table 1, entries 9–20). Since phosphorus ligands always play important roles in metal-catalyzed chemistry,⁷ we then turned our attention to the screening of ligands (Table 1, entries 21–28). We were pleased to discover that only when the ligand changed to the bis[(2-diphenylphosphino)phenyl] ether (DPEphos) did the yield dramatically increase to 92% yield (Table 1, entries 21–28). Finally, we studied the solvent effect and found that THF was superior to CH₃NO₂, 1,4-dioxane, xylene, DMF, CH₃CN, toluene, and sulfolane (Table 1, entries 28–35). In addition, the reaction failed to give the desired product when the procedure was carried out under a N₂ atmosphere. Therefore, the optimized conditions were defined as follows: under an O₂ atmosphere, Pd₂(dba)₃ (5 mol %) as the catalyst, DPEphos (10 mol %) as the ligand, and 1-methylpiperidine (3 equiv) as the base in THF at 60 °C.

Having the optimized reaction conditions in hand, we next investigated the scope and generality of the coupling reaction using various arylboronic acids and isatoic anhydrides (Table 2). Initially, a variety of arylboronic acids **2b–2u** were examined by the reaction with isatoic anhydride **1a** (Table 2, entries 1–21). The results demonstrated that the optimal conditions were general for arylboronic acids and were compatible with many functional groups, including methyl, methoxy, fluoro, chloro, bromo, formacyl, acetyl, nitro, cyano, trifluoromethyl, naphthyl, and thienyl substituents on the phenyl moiety. For example, arylboronic acids **2b–2h**, with a methyl or methoxy group, smoothly underwent the reaction in excellent yields, although the *o*-methoxy substituents on the phenyl ring decreased the substrate activity (Table 2, entries 1–8).

The electronic properties of the groups on the phenyl ring of arylboronic acids had some effect on the reaction. Generally, the arylboronic acids possessing electron-donating groups produce the corresponding aryl *o*-amino-benzoates **3ab**, **3ad**, **3ae**, and **3ag** with higher yields

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Table 1. Optimization of Reaction Conditions^a



entry	Pd source	ligand	base	solvent	yield (%) ^b
1	Pd(OAc) ₂	PCy ₃	Na ₂ CO ₃	THF	18
2	PdCl ₂	PCy ₃	Na ₂ CO ₃	THF	17
3	PdCl ₂ (PPh ₃) ₂	PCy ₃	Na ₂ CO ₃	THF	11
4	PdCl ₂ (dppf)	PCy ₃	Na ₂ CO ₃	THF	21
5	PdCl ₂ (PhCN) ₂	PCy ₃	Na ₂ CO ₃	THF	16
6	PdCl ₂ (cod)	PCy ₃	Na ₂ CO ₃	THF	25
7	PdCl ₂ (acac) ₂	PCy ₃	Na ₂ CO ₃	THF	27
8	Pd(PPh ₃) ₄	PCy ₃	Na ₂ CO ₃	THF	43
9	Pd ₂ (dba) ₃	PCy ₃	Na ₂ CO ₃	THF	47
10	Pd ₂ (dba) ₃	PCy ₃	NaOAc	THF	23
11	Pd ₂ (dba) ₃	PCy ₃	Cs ₂ CO ₃	THF	<5
12	Pd ₂ (dba) ₃	PCy ₃	CsF	THF	31
13	Pd ₂ (dba) ₃	PCy ₃	KF	THF	32
14	Pd ₂ (dba) ₃	PCy ₃	^t BuONa	THF	0
15	Pd ₂ (dba) ₃	PCy ₃	Et ₂ NH	THF	72 ^c
16	Pd ₂ (dba) ₃	PCy ₃	Et ₃ N	THF	83
17	Pd ₂ (dba) ₃	PCy ₃	DBACO	THF	31
18	Pd ₂ (dba) ₃	PCy ₃	1-methylpyrrolidine	THF	58
19	Pd ₂ (dba) ₃	PCy ₃	1-methylmorpholine	THF	51
20	Pd ₂ (dba) ₃	PCy ₃	1-methylpiperidine	THF	86
21	Pd ₂ (dba) ₃	P(<i>o</i> -Tol) ₃	1-methylpiperidine	THF	29
22	Pd ₂ (dba) ₃	P(<i>p</i> -MeOC ₆ H ₄) ₃	1-methylpiperidine	THF	74
23	Pd ₂ (dba) ₃	P(<i>p</i> -FC ₆ H ₄) ₃ PPh ₃	1-methylpiperidine	THF	68
24	Pd ₂ (dba) ₃	P(1-Nap) ₃	1-methylpiperidine	THF	35
25	Pd ₂ (dba) ₃	P(2-Fur) ₃	1-methylpiperidine	THF	65
26	Pd ₂ (dba) ₃	^t Pr ₂ NPPH ₂	1-methylpiperidine	THF	26
27	Pd ₂ (dba) ₃	Xantphos	1-methylpiperidine	THF	43
28	Pd ₂ (dba) ₃	DPEphos	1-methylpiperidine	THF	92
29	Pd ₂ (dba) ₃	DPEphos	1-methylpiperidine	CH ₃ NO ₂	55
30	Pd ₂ (dba) ₃	DPEphos	1-methylpiperidine	dioxane	69
31	Pd ₂ (dba) ₃	DPEphos	1-methylpiperidine	xylene	62
32	Pd ₂ (dba) ₃	DPEphos	1-methylpiperidine	DMF	61
33	Pd ₂ (dba) ₃	DPEphos	1-methylpiperidine	CH ₃ CN	81
34	Pd ₂ (dba) ₃	DPEphos	1-methylpiperidine	toluene	61
35	Pd ₂ (dba) ₃	DPEphos	1-methylpiperidine	sulfolane	58

^a Unless otherwise noted, the reaction conditions were as follows: **1a** (0.4 mmol), **2a** (1.2 mmol), indicated Pd source (5 mol %), ligand (10 mol %), base (1.2 mmol), dry solvent (2.5 mL), 60 °C, 24 h, O₂. ^b Isolated yield. ^c 2-Amino-*N,N*-diethylbenzamide was obtained in 72% yield.

(Table 2, entries 2, 4, 5, and 7). Electron-withdrawing arylboronic acids, which are less nucleophilic, and hence transmetalate more slowly than their electron-neutral analogues, are prone to homocoupling and protodeboronation side reactions.⁸ However, in our catalytic system, *p*-(trifluoromethyl)phenylboronic acid **2i**, *m*-nitrophenylboronic acid **2j**, and *p*-cyanophenylboronic acid **2k** reacted with **1a** to afford the respective compounds **3ai**, **3aj**, and **3ak** in moderate to good yields (Table 2, entries 9–11). Notably, the fluoro, chloro, and bromo moieties (commonly used for cross-coupling reactions) in arylboronic acids **2l–2o** were all tolerated and afforded a novel route to compounds **3al**, **3am**, **3an**, and **3ao** in good yields,

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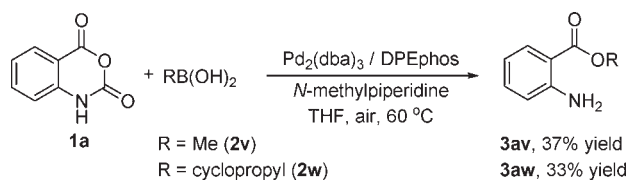
making further elaborations of the corresponding biaryl products possible (Table 2, entries 12–15). Moreover, substrates **2p** and **2q**, possessing the active formacyl or acetyl group, were tolerated well (Table 2, entries 16 and 17).

It is noteworthy that biarylboronic acids such as 4-phenylphenylboronic acid **2r**, 1-naphthylboronic acid **2s**, and 2-naphthylboronic acid **2t** also gave the corresponding **3ar**, **3as**, and **3at** in 99%, 86%, and 84% yields, respectively (Table 2, entries 18–20). Although the heteroatoms in the heteroarylboronic acids may coordinate to palladium, **2u** was still a good partner for the coupling reaction, and the corresponding coupling product **3au** was isolated in 85% yield (Table 2, entry 21).

Next, the decarboxylative coupling reactions of phenylboronic acids with several benzo-substituted isatoic anhydrides were investigated. As expected, the groups on the phenyl ring of isatoic anhydrides, such as methyl, chloro, nitro, and fluoro, were quite compatible under the optimized reaction conditions. Benzo-substituted isatoic anhydrides possessing electron-donating (**1b–1c**) and electron-withdrawing (**1d–1g**) groups on the phenyl ring provided the corresponding aryl *o*-aminobenzoates in good yields (Table 2, entries 22–29). However, benzo-substituted isatoic anhydride containing a strong electron-withdrawing group (—NO₂) on the benzene ring, such as 5-nitroisatoic anhydride (**1h**), achieved the corresponding desired products **3ha** and **3hb** in slightly lower yields (Table 2, entries 30–31). *N*-Methylisatoic anhydride **1e** delivered the corresponding **3ea** and **3eb** in relatively low yields (Table 2, entries 32–33).

Finally, treatment of an alkylboronic acid such as methylboronic acid **2v** or cyclopropylboronic acid **2w** with **1a** under the optimized conditions afforded the desired product **3av** and **3aw** in 37% and 33% yields, respectively (Scheme 1).

Scheme 1. Reaction of Alkylboronic Acid with Isatoic Anhydride

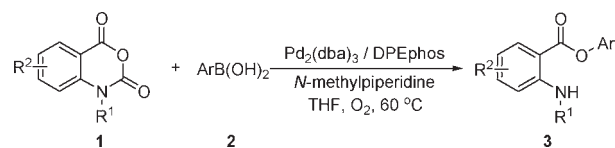


To elucidate the mechanism of this coupling reaction, the following control experiments were performed under our standard conditions as shown in Scheme 2. According to relevant reports in the literature⁹ and our recent report,¹⁰ we initially thought that the oxygen atom of **3aa** might be derived from water present in the solvent

(9) (a) Simon, J.; Salzbrunn, S.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *J. Org. Chem.* **2001**, *66*, 633. (b) Xu, J.; Wang, X.; Shao, C.; Su, D.; Cheng, G.; Hu, Y. *Org. Lett.* **2010**, *12*, 1964.

(10) Zheng, X. W.; Ding, J. C.; Chen, J. X.; Gao, W. X.; Liu, M. C.; Wu, H. Y. *Org. Lett.* **2011**, *13*, 1726.

Table 2. Scope of Arylboronic Acids and Isatoic Anhydrides in the Pd-Catalyzed Coupling Reaction^a

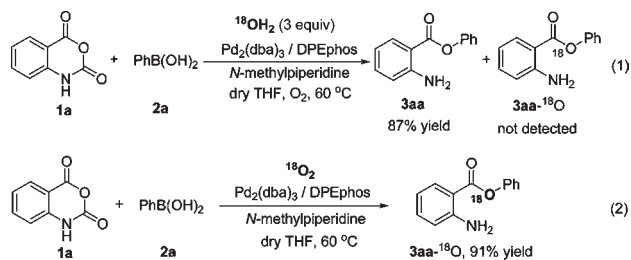


entry	isatoic anhydride (1)	Ar (2)	product	yield (%) ^b
1	1a	Ph (2a)	3aa	92
2	1a	<i>p</i> -(Me)C ₆ H ₄ (2b)	3ab	95
3	1a	<i>o</i> -(Me)C ₆ H ₄ (2c)	3ac	92
4	1a	<i>m</i> -(Me)C ₆ H ₄ (2d)	3ad	93
5	1a	<i>p</i> -(MeO)C ₆ H ₄ (2e)	3ae	96
6	1a	<i>o</i> -(MeO)C ₆ H ₄ (2f)	3af	67
7	1a	<i>m</i> -(MeO)C ₆ H ₄ (2g)	3ag	92
8	1a	3,5-(Me) ₂ C ₆ H ₃ (2h)	3ah	91
9	1a	<i>p</i> -(CF ₃)C ₆ H ₄ (2i)	3ai	83
10	1a	<i>m</i> -(NO ₂)C ₆ H ₄ (2j)	3aj	57
11	1a	<i>p</i> -(CN)C ₆ H ₄ (2k)	3ak	83
12	1a	<i>p</i> -(F)C ₆ H ₄ (2l)	3al	95
13	1a	<i>p</i> -(Cl)C ₆ H ₄ (2m)	3am	92
14	1a	<i>p</i> -(Br)C ₆ H ₄ (2n)	3an	81
15	1a	<i>o</i> -(Br)C ₆ H ₄ (2o)	3ao	80
16	1a	<i>p</i> -(CHO)C ₆ H ₄ (2p)	3ap	77
17	1a	<i>p</i> -(Ac)C ₆ H ₄ (2q)	3aq	85
18	1a	<i>p</i> -(Ph)C ₆ H ₄ (2r)	3ar	99
19	1a	1-naphthyl (2s)	3as	86
20	1a	2-naphthyl (2t)	3at	84
21	1a	3-thienyl (2u)	3au	85
22	1b	Ph (2a)	3ba	92
23	1c	<i>p</i> -(Me)C ₆ H ₄ (2b)	3bb	86
24	1d	Ph (2a)	3ca	91
25	1e	Ph (2a)	3da	84
26	1f	<i>p</i> -(Me)C ₆ H ₄ (2b)	3db	80
27	1g	Ph (2a)	3ea	89
28	1h	Ph (2a)	3fa	87
29	1i	Ph (2a)	3ga	89
30	1j	Ph (2a)	3ha	62
31	1k	<i>p</i> -(Me)C ₆ H ₄ (2b)	3hb	66
32	1l	Ph (2a)	3ia	39
33	1m	<i>p</i> -(Me)C ₆ H ₄ (2b)	3ib	42

^a Unless otherwise noted, the reactions conditions were as follows: isatoic anhydride **1** (0.4 mmol), arylboronic acid **2** (1.2 mmol), Pd₂(dba)₃ (5 mol %), DPEphos (10 mol %), 1-methylpiperidine (1.2 mmol), dry THF (2.5 mL), 60 °C, 24 h, O₂. ^b Isolated yield.

and in the ambient environment. Therefore, we carried out the reaction of isatoic anhydride **1a** with phenylboronic

Scheme 2. Isotope Labeling Studies



acid **2a** in the presence of $^{18}\text{OH}_2$ in dry THF under our standard conditions [eq 1]. However, **3aa** was obtained in 87% yield, and no **3aa- ^{18}O** was detected. To understand the mechanism more clearly, labeling studies were conducted using $^{18}\text{O}_2$ [eq 2]. Surprisingly, the reaction proceeded smoothly under an $^{18}\text{O}_2$ atmosphere to provide the aryl *o*-aminobenzoate product **3aa- ^{18}O** containing ^{18}O in 91% yield. The ^{18}O -atom-containing product **3aa- ^{18}O** was determined by GC/MS and HRMS (ESI) analysis. This result confirmed that dioxygen took part in this reaction and was essential for the transformation. Finally, the reaction of 2-aminobenzoic acid¹¹ with phenylboronic acid **2a** failed to deliver the desired product **3aa**.

We therefore propose a plausible formation mechanism of aryl *o*-aminobenzoate derivatives (Scheme 3) based on the results above and relevant reports in the literature.^{12–14} It is known that the reaction of $[\text{Pd}_2(\text{dba})_3]$ with oxygen affords the reactive palladium–peroxo species $[(\eta^2\text{-O}_2)\text{PdL}_2]$ complex **A** in the presence of ligand.¹³ Jutand, Amatore and co-workers investigated the transmetalation between the $[(\eta^2\text{-O}_2)\text{PdL}_2]$ complex **A** and $\text{ArB}(\text{OH})_2$, and a fast reaction generated the *trans*- $[\text{ArPd}(\text{OH})\text{L}_2]$ complex **B**.¹⁴ Next, decarboxylation and transmetalation of *trans*- $[\text{ArPd}(\text{OH})\text{L}_2]$ complex

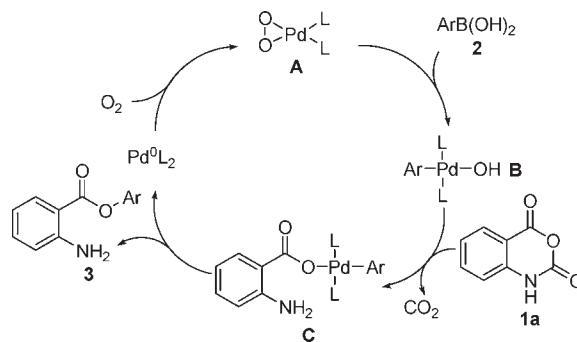
(11) Isatoic anhydride was converted presumably to 2-aminobenzoic acid in the presence of water, please see: Chiu, S.-J.; Chou, C.-H. *Tetrahedron Lett.* **1999**, *40*, 9271.

(12) Liu, Q.; Li, G.; He, J.; Liu, J.; Li, P.; Lei, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 3371.

(13) Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188.

(14) Adamo, C.; Amatore, C.; Ciofini, I.; Jutand, A.; Lakmini, H. *J. Am. Chem. Soc.* **2006**, *128*, 6829 and references cited therein.

Scheme 3. Plausible Mechanism



B in the presence of isatoic anhydride **1** would result in the liberation of carbon dioxide and the formation of the corresponding Pd(II) intermediate **C**, which undergoes reductive elimination to give the desired product **3** and regenerates the starting Pd(0).

In summary, an unprecedented palladium-catalyzed decarboxylative coupling of isatoic anhydrides with arylboronic acids was developed. The present method affords only the *o*-amino benzoate derivatives as products; however, these compounds, as anthranilic acid derivatives, are important structural motifs in natural products, and this new process provides a straightforward method to access these compounds. Preliminary mechanistic experiments using deuterium labeling showed that dioxygen took part in this reaction and was essential for the transformation. Further efforts to expand the scope of the chemistry and studies of the detailed mechanism are currently underway in our laboratories.

Acknowledgment. We thank the National Natural Science Foundation of China (Nos. 21102105 and 21072153) for financial support.

Supporting Information Available. Experimental procedures along with copies of spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.