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Carboxylate Directed Cross-Coupling Reactions in the Synthesis of Trisubstituted Benzoic Acids

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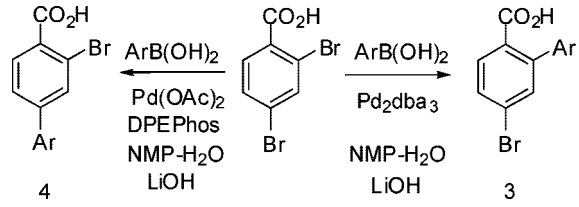
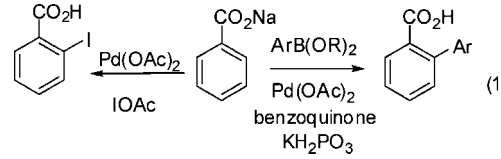
ABSTRACT



The carboxylate anion has been used as a directing group to effect selective ortho-substituted derivatives 3 (>99:1 selectivity 50−80% yield). The solvent, base, and equivalents of base are the determining factors for the success of this reaction. The directing effect can be reversed by the appropriate use of phosphine ligands to prepare the para-substituted 4 selectively (ca. 12:1 selectivity).

Directed processes, i.e., the use of neighboring groups to control either the face-or regioselectivity of organic transformations, have been an indispensable tool for synthetic organic chemists.[1]

More recently, this strategy has been used to provide elegant solutions to the problem of selective C−H activation. A significant number of seminal papers have detailed the use of nitrogen groups to direct the insertion[2] of transition metals to the C−H bond followed by other transformations. Surprisingly, the more synthetically versatile carboxylate function has been under-represented in these processes until Yu et al. published a series of innovative papers demonstrating the powerful directing effect of the carboxylate in cross-coupling and directed halogenation reactions (eq 1).[3]



In our own work,[4] we have discovered that Li-carboxylates also give excellent regioselectivity in Kumada cross-coupling reactions of dihalobenzoic acid derivatives.

We decided to investigate this initial observation further and to apply the concept to the widely used Suzuki cross coupling reaction. We thus hoped to be able to perform selective functionalizations of benzoic acid derivatives to prepare trisubstituted aromatics, still a significant challenge in synthesis.

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(1) Directed orthometalation reactions: (a) Anctil, E.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150. (b) Anctil, E. J.-G.; Snieckus, V. In *Metal-Catalyzed Cross Couping Reactions*, 2nd ed.; Diedrich, F., De Meijere, A., Eds.; Wiley: New York, 2004; pp 761−814. (c) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206. Directed hydrogenations: Crabtree, R. H.; Davies, M. W. *J. Org. Chem.* **1986**, *51*, 2655.

(2) Reviews: (a) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (b) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041.

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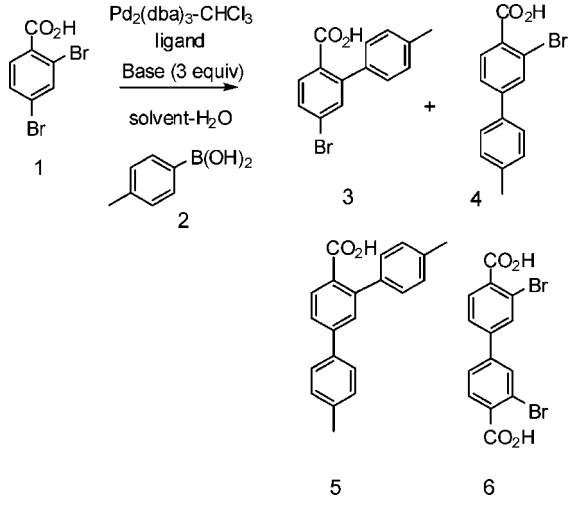
An additional impetus for this work was that, although the Suzuki reaction and its variants are widely used in both total synthesis and pharmaceutical applications, effecting selectivity in the case of isoelectronic coupling sites has not been thoroughly explored.[5]

For the initial exploration, we chose as a model system 2,4-dibromobenzoic acid **1**, where the two halides have similar electronic properties (Scheme 1). Indeed, the ortho

Scheme 1. Reaction of 2,4-Dibromobenzoic Acid and Tolylboronic Acid



substituent is relatively sterically hindered, and we would anticipate that in the absence of any directing effect the para position should be preferred. We also decided to use tolyl boronic acid **2** as the coupling partner to facilitate regiochemical assignment.

Initial experiments using a Pd:L ratio of 1:4 afforded no reaction (Table 1, entry 1). Popular heterocyclic carbene ligands, represented here by the commercially available (IMES)$PdCl_2$(3-chloropyridine) catalyst),[6] also failed to deliver any product, while **1** and **2** remained unchanged (Table 1, entries 4,5). By changing the Pd/L ratio to 1:2, we were able to obtain some of the desired product; however, the ratio of ortho/para product (**3**:**4**) was 1:1 in an essentially nonselective reaction (Table 1, entries 2 and 3).[7]

Other solvent combinations (DMF−H_2O and THF−H_2O) gave the same unsatisfactory results, particularly in the latter where the undesired **4** was the major component. In our previous Kumada cross-coupling work[3,4] and in the work of the Yu group, external ligands had a detrimental effect on the reactivity and selectivity of our respective reactions. Consequently, we initiated an investigation to examine the selectivity and reactivity of our model reaction using various sources of Pd precatalyst in the absence of external ligands.[8]

In a parallel experimentation mode, we investigated the role of the Pd source, counterion, and base. The most relevant results are shown in Table 1. In a typical screening experiment, the starting materials **1** and **2** and the base were added as solids, followed by the thoroughly degassed solvents. CO_2 (in the case of carbonate bases) was removed by purging the reaction; so as not to affect the pH of the mixture, the precatalyst was added and the mixture was heated to 65 °C. Within a few minutes, the deep purple color of the precatalyst was replaced by a pale-yellow color of the catalytically active species. We were immediately rewarded with an excellent selectivity in favor of the desired ortho-coupled product[9] **3** in DMF−H_2O (Table 1, entry 6); however, only 60% conversion was achieved. NMP and THF aqueous mixtures[10] (Table 1, entries 7−9) afforded no significant improvement in the conversion, with the latter causing the formation of significant amounts of the homo-coupled product **6**. It is assumed that the incomplete conversion was not due to catalyst decomposition, but rather to decomposition of the boronic acid as observed by HPLC analysis. Several other palladium sources were entirely unsuccessful (Table 1, entries 10−12),[11] while other solvent systems offered no improvement in the conversion or in suppressing the formation of **6** (Table 1, entries 13−17). Indeed, for further studies the NMP−H_2O system was chosen as it effectively disfavored the formation of the latter dimer.

Cognisant of the effect of the counterion in these directing processes, we examined Li_2CO_3 as the base (Table 1, entry 18) and discovered that the reaction was substantially improved (>80% conversion). The fact that the decomposition of the boronic acid was the culprit, and that the catalyst was still active, was confirmed by addition of 20% additional boronic acid. Almost complete conversion and 69% isolated yield of **3** was thus obtained after aqueous workup and chromatographic purification. Other solvent combinations were again not effective in suppressing the formation of **6** (Table 1, entries 19−23).

(3) For initial reports of the carboxylate directing effect, see: (a) Maehara, A; Tsurugi, H; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1159. (b) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407. (c) Tanaka, D.; Stuart, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323. (d) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (e) Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 5215. (f) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. Review: (g) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, *15*, 949. (h) For Cu-catalyzed carboxylate-directed aminations, see: Wolf, C.; Liu, S.; Mei, X.; August, A. T.; Casimir, M. D. *J. Org. Chem.* **2006**, *71*, 3270.

(4) Houpis, I. N.; Van Hoeck, J.-P.; Tilstam, U. *Synlett* **2007**, *14*, 2179.

(5) Although there are several examples where the carboxylate and amide functions facilitate the ortho substitution (e.g., refs 1 and 3h), we have not seen any studies in the literature where two electronically similar halides can be differentiated.

(6) The PEPPSI catalyst is marketed by Aldrich and has been used successfully in Suzuki, Negishi, and Kumada coupling reactions.

(7) Use of a representative sample of the pioneering ligands developed by the Buchwald and Fu groups (several of them available in ligand kits by Strem) gave either poor conversion and/or poor selectivity: (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411. (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *121*, 2413.

(8) Several studies indicate that a number of cross-coupling reactions proceed via Pd nanoparticles: de Vries, J. *Dalton Trans.* **2006**, 421.

(9) Proof of regiochemistry was performed for all compounds. For representative examples, see the Supporting Information.

(10) In the absence of water, the reaction does not proceed, irrespective of the base or catalyst used.

(11) Pd-black precipitated almost immediately when the reaction reached optimal reaction temperature (ca. 65 °C).

Table 1. Representative Results of the Screening of Different Catalyst, Solvent, and Base Conditions of the Reaction in Scheme 1[a]

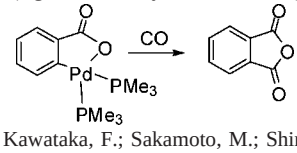
entry	Pd source[b]	base (equiv)	solvent (ratio 1:1)	conv[c] (%)	**3**:**4**	**5** (%)	**6** (%)
1	$Pd(PPh_3)_4$	K_2CO_3 (3)	DMF/H_2O	0			
2	$Cl_2Pd(PPh_3)_2$	K_2CO_3 (3)	DMF/H_2O	60	1:1	7	
3	$Cl_2Pd(PPh_3)_2$	K_2CO_3 (3)	THF/H_2O	40	1:2		
4	PEPPSI	K_2CO_3 (3)	DMF/H_2O	0			
5	PEPPSI	K_2CO_3 (3)	THF/H_2O	0			
6	$Pd_2(dba)_3$	K_2CO_3 (3)	DMF/H_2O	60	99:1	3	
7	$Pd_2(dba)_3$	K_2CO_3 (3)	THF/H_2O	70	99:1	3	13
8	$Pd_2(dba)_3$	K_2CO_3 (3)	THF/H_2O	35	99:1	2	3
9	$Pd_2(dba)_3$	K_2CO_3 (3)	NMP:H_2O	40	99:1	3	0
10	$Pd(OAc)_2$	K_2CO_3 (3)	NMP/H_2O	0			
11	$Pd(acac)_2$	K_2CO_3 (3)	NMP/H_2O	0			
12	$Cl_2Pd(CH_3CN)_2$	K_2CO_3 (3)	NMP/H_2O	0			
13	$Pd_2(dba)_3$	K_2CO_3 (3)	$PhCH_3$/H_2O	30	99:1		19
14	$Pd_2(dba)_3$	K_2CO_3 (3)	Me-THF/H_2O	36	99:1	5	9
15	$Pd_2(dba)_3$	K_2CO_3 (3)	DME/H_2O	30	99:1	4	2
16	$Pd_2(dba)_3$	K_2CO_3 (3)	^{n}PrOH/H_2O	36	99:1	4	0
17	$Pd_2(dba)_3$	Li_2CO_3 (3)	NMP/H_2O	60	99:1	2	2
18	**$Pd_2(dba)_3$**	**Li_2CO_3 (3)**	**NMP/H_2O**	**95**	**99:1 (69%)[d]**	**2**	**0**
19	$Pd_2(dba)_3$	Li_2CO_3 (3)	THF/H_2O	65	99:1	6	12
20	$Pd_2(dba)_3$	Li_2CO_3 (3)	$PhCH_3$/H_2O	30	99:1	2	18
21	$Pd_2(dba)_3$	Li_2CO_3 (3)	Me-THF/H_2O	46	99:1	5	20
22	$Pd_2(dba)_3$	Li_2CO_3 (3)	DME/H_2O	55	99:1	6	4
23	$Pd_2(dba)_3$	Li_2CO_3 (3)	^{n}PrOH/H_2O	53	99:1	1	18
24	$Pd_2(dba)_3$	LiOH (3)	NMP/H_2O	8%[e]			
25	$Pd_2(dba)_3$	LiOH (2)	NMP/H_2O	85	99:1	1.3	0
26	$Pd_2(dba)_3$	LiOH (1)	NMP/H_2O	20[f]	99:1	1	0
27	**$Pd_2(dba)_3$**	**LiOH (2.2)**	**NMP/H_2O**	**>98**	**99:1 (80)[d]**	**3**	**0**
28	$Pd_2(dba)_3$	LiOH (1.8)	NMP/H_2O	78	99:1	1	0
29	$Pd_2(dba)_3$	KOH (2.2)	NMP/H_2O	90	99:1	1	0
30	$Pd_2(dba)_3$	NaOH (2.2)	NMP/H_2O	90	99:1	1	0
31	$Pd_2(dba)_3$	K_2CO_3 (2.2)	NMP/H_2O	88	99:1	3	0
32	Pd/C (10%)	LiOH (2.2)	NMP/H_2O	60	99:1	15	0
33	$Pd(OAc)_2$-dppf	LiOH (2.2)	NMP/H_2O	0			0
34	$Pd(OAc)_2$-Xantphos[g]	LiOH (2.2)	NMP/H_2O	80	12:88	9	0
35	**$Pd(OAc)_2$-DPEPhos**	**LiOH (2.2)**	**NMP/H_2O**	**90**	**8:92 (68)[d]**	**2**	**0**

[a] The reactions were run under Ar with thoroughly degassed solvents. All reactions were performed at 65 °C for 24 h. [b] 0.5 mol % of $Pd_2(dba)_3$−$CHCl_3$, freshly recrystallized, was used for the scouting experiments. Commercial material was found to deliver comparable results. [c] Conversion is reported as the area % ratio of **3** to **1** at 230 nm. Other results are reported as normalized area %. [d] Isolated yield after chromatography (1% MeOH in CH_2Cl_2). [e] There was no decomposition of the boronic acid. [f] Total decomposition of the boronic acid was observed. [g] 9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine).

The final breakthrough came when LiOH was used as the base. Using our standard conditions of 3 equiv of base, there was very little reaction as the color of the precatalyst did not change to the yellow catalytically active species. However, there was also no decomposition of the boronic acid (Table 1, entry 24). To find the balance between reactivity and boronic acid stability, we examined the equivalents of LiOH. After some optimization (Table 1, entries 24−28), we were able to obtain complete conversion and excellent selectivity by employing 2.2 equiv of LiOH (Table 1, entry 27). Remarkably, when the proper amount of base is used, the counterion seems to play a minor role (Table 1, entries 29 and 30) and even carbonate is now an effective base as well (Table 1, entry 31). This was somewhat unexpected compared to our previous observations and those of the Yu group where the counterion played a very important role.

The nature of the catalytically active species is not known at present. While precatalysts devoid of "stabilizing" ligating groups (such as dibenzylidene acetone) were not effective as catalysts, Pd/C is catalytically active. Indeed, it appears to have higher initial reactivity than the catalyst derived from $Pd_2(dba)_3$-$CHCl_3$ as indicated from the increased levels of

(12) The resulting carboxylate palladacycles have only been reported only recently and are not commonly used. They have been shown to be competent catalysts (e.g., for carbonylation reactions):



(a) Nagayama, K.; Kawataka, F.; Sakamoto, M.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 573. Other oxapalladecycles: (b) Fernandez-Rivas, C.; Cardenas, D. J.; Maertin-Matute, B.; Monge, A.; Gutierrez-Puebla, E.; Echavarren, A. M. *Organometallics* **2001**, *20*, 2998. A recent, thorough, review on palladacycles did not report any synthetic utility of carboxylate palladacycle species: (c) Dupont, J.; Consorti, C. S. *Chem. Rev.* **2005**, *105*, 2527.

the bis-coupled product **5** (Table 1, entry 32). However, the productivity of this catalyst is lower with only 60% conversion.

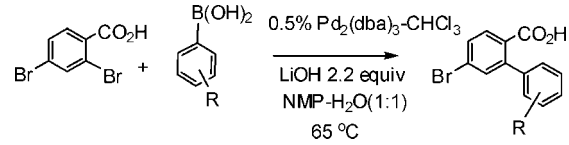
The factor(s) determining the selectivity of our reaction are also not known. Our working hypothesis, however, is that the reaction is controlled by an irreversible oxidative addition at the ortho position which is directed by the carboxylate ion.[12] The resulting oxopalladacycle is also stabilized by the coordinating effect of the carboxylate.

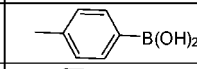
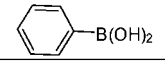
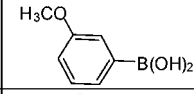
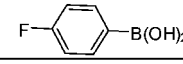
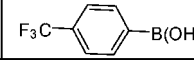
Based on these assumptions, we can now understand why this coordination effect seems to be reversed in the presence of phosphine ligands. Presumably, the superior ligating properties of the phosphine, compared to the carboxylate, disrupts coordination of the carboxylate. In addition, the increase in steric bulk of the $Pd(0)L_n$ species (L = phosphine ligand) directs the oxidative addition to the less hindered para position. We reasoned that perhaps the selectivity of the reaction could be totally reversed in favor of the para-substituted derivative **4** (Scheme 1) by the appropriate choice of ligand. This would allow us to choose the order of introduction of the aromatic substituents as desired (Table 1, entries 33−35). In a brief study, we were pleased to find that a palladium catalyst incorporating the diphosphine DPEPhos [2,2′-oxybis(2,1-phenylene)bis(diphenylphosphine)] was successful in reversing the selectivity to afford ca. 68% isolated yield of the para-substituted **4**. In this case, the conversion was incomplete, and we are now optimizing the reaction parameters to remedy this issue.

We next sought to understand the scope of the reaction and examined a number of electronically different boronic acids (Table 2).[13] Interestingly, electron-deficient substrates give poorer reactivity as indicated by the longer reaction times which in turn reduce the yields of the desired isomers due to boronic acid decomposition. The reactivity of heteroaromatic boronic acids in these directed processes will be reported in due course.

(13) General procedure: A flame-dried and argon-filled Schlenk tube was charged in sequence with **1** (1.0 equiv), **2** (1.1 equiv), and LiOH−H_2O (2.2 equiv). Freshly degassed NMP (3 mL/mmol) was added followed by degassed, deionized water (3 mL/mmol). The precatalyst, Pd_2dba−$CHCl_3$ (0.5−1 mol % depending on the substrate) was added under an argon blanket, and the reaction mixture was heated to 65 °C for ca. 16−36 h (depending on substrate). After ca. 30 min, the deep purple color of the precatalyst turned pale yellow. This color persisted throughout the reaction. Alternatively, the catalyst can be added at the reaction temperature without major differences in the reaction outcome. Upon completion (as judged by HPLC analysis at 230 nm), the reaction mixture was subjected to an acidic aqueous workup (2-Me-THF or MTBE were used), and the organic layer was concentrated in vacuo. Flash chromatography using the appropriate mixture of ethyl acetate and heptane (depending on the substrate) afforded the product.

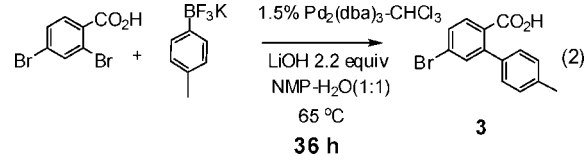
Table 2. Scope of the Reaction[a]



entry	substrate	time	isolated yield[a]
1		16 h	80%
2		16 h	75%
3		25 h	72%
4		32 h	64%
5		42 h	55%

[a] Reactions performed on multigram scale. Yields are after chromatographic isolation.

Finally, we were pleased to see that this directing effect extends to fluoroborate derivatives (eq 2). Not surprisingly, the reaction is considerably slower and it required a higher catalyst loading (1.5 mol % compared to 0.5 mol % for the boronic acids) due to the increased stability of the fluoroborates. However, the ratio of **3**:**4** remained unchanged (>99:1) affording 72% yield of **3** while very little of the bis-adduct **5** was detected. This opens up the possibility of introducing alkyl derivatives or heteroaromatics of which the corresponding boronic acid is unstable, and we are actively pursuing these possibilities.



Supporting Information Available: Compound characterization, evidence supporting the regiochemical assignment, structures of the precatalysts used in Table 1, and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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