

Pd-Catalyzed Decarboxylative Cross Coupling of Potassium Polyfluorobenzoates with Aryl Bromides, Chlorides, and Triflates

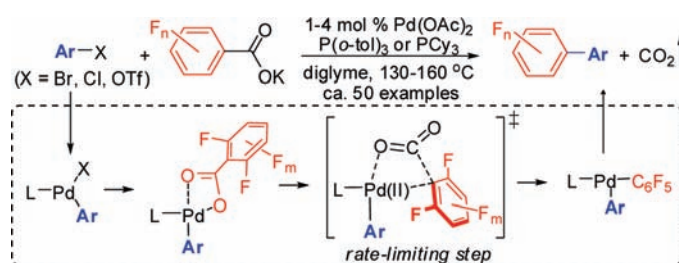
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ABSTRACT



Pd-catalyzed decarboxylative cross coupling of potassium polyfluorobenzoates with aryl bromides, chlorides, and triflates is achieved by using diglyme as the solvent. The reaction is useful for synthesis of polyfluorobiaryls from readily accessible and nonvolatile polyfluorobenzoate salts. Unlike the Cu-catalyzed decarboxylation cross coupling where oxidative addition is the rate-limiting step, in the Pd-catalyzed version decarboxylation is the rate-limiting step.

Transition-metal-catalyzed decarboxylative coupling reactions using carboxylic acids as aryl sources have unique advantages.¹ They do not use expensive and/or sensitive organometallic reagents and generate CO₂ without producing toxic metal halides. Goossen et al. showed that through a Pd/Cu bimetallic catalysis they could accomplish decarboxylative coupling of certain benzoic acids and α -oxo carboxylates with aryl halides and triflates.² Myers,³ Forgiione,⁴ and other groups⁵ found that Pd could catalyze the decarboxylative cross coupling of some carboxylic acids with olefins and aryl iodides or bromides. Other recent studies by Tunge, Li, Miura, Chruma, and other groups also highlighted the synthetic utility of related decarboxylative reactions.⁶

We recently found that some Cu-only catalysts could catalyze the decarboxylative coupling of potassium polyfluorobenzoates with aryl iodides and bromides.⁷ Here we report that certain Pd-only systems can also catalyze the same decarboxylative cross couplings, but importantly, with aryl bromides, chlorides, and even triflates. Like the Cu-catalyzed versions,⁷ the new Pd-catalyzed reactions can replace the

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(1) (a) Baudoin, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 1373. (b) Goossen, L. J.; Rodriguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100.

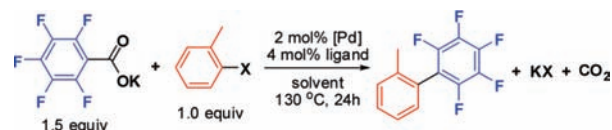
(2) (a) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662. (b) Goossen, L. J.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824. (c) Goossen, L. J.; Melzer, B. *J. Org. Chem.* **2007**, *72*, 7473. (d) Goossen, L. J.; Knauber, T. *J. Org. Chem.* **2008**, *73*, 8631. (e) Goossen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7103. (f) Goossen, L. J.; Rodriguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, *130*, 15248. (g) Goossen, L. J.; Rudolphi, F.; Oppel, C.; Rodriguez, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 3043. (h) Goossen, L. J.; Zimmermann, B.; Linder, C.; Rodriguez, N.; Lange, P. P.; Hartung, J. *Adv. Synth. Catal.* **2009**, *351*, 2667. (i) Goossen, L. J.; Linder, C.; Rodriguez, N.; Lange, P. P. *Chem.—Eur. J.* **2009**, *15*, 9336.

use of expensive but often less reactive⁸ fluorobenzene organometallics in the synthesis of polyfluorobiaryls useful to material⁹ and medicinal¹⁰ sciences. The new reactions also provide a practical method complementary to Fagnou's¹¹ and Daugulis's¹² fluorobiaryl synthesis through direct C–H arylation of polyfluoroarene. Furthermore, through computational analysis we show that the Pd-catalyzed decarboxylative cross coupling has a major mechanistic difference as compared to the Cu-catalyzed versions.

Our work started with the decarboxylative coupling of potassium pentafluorobenzoate with aryl chlorides. Note that there were two literature examples^{5d,g} for Pd-catalyzed decarboxylative coupling of pentafluorobenzoic acid with 4-iodoanisole. Through tests (Table 1) it is found that in many solvents (entries 1–4) the desired coupling reaction does not proceed well. Only when diglyme is used as the solvent (entry 5), the reaction takes place readily (yield = 88%) with a simple ligand (PCy₃). The use of more popular Ar–Cl activation ligands such as ^tBu₃P, S-Phos, and Dave-Phos¹³ does not produce a higher yield (entries 6–9), whereas the use of other Pd salts (entries 10–12) gives good

results comparable to that of Pd(OAc)₂. Decrease of the Pd loading to 1 mol % (entry 13) affords a slightly lower yield of 86%. Moreover, the same catalyst system can also be applied to *o*-tolylbromide (entry 14). It is interesting that a less electron-rich ligand (i.e., P(*o*-Tol)₃) is more effective for *o*-tolylbromide than PCy₃ (entry 15).

Table 1. Pd-Catalyzed Decarboxylative Cross Coupling of Potassium Pentafluorobenzoate with *o*-Tolylhalide^a



entry	X	Pd source	ligand	solvent	yield % ^b
1	Cl	Pd(OAc) ₂	P(Cy) ₃	NMP	trace
2	Cl	Pd(OAc) ₂	P(Cy) ₃	DMA	trace
3	Cl	Pd(OAc) ₂	P(Cy) ₃	DMF	11
4	Cl	Pd(OAc) ₂	P(Cy) ₃	Mesitylene	n.r.
5	Cl	Pd(OAc) ₂	P(Cy) ₃	diglyme	88
6	Cl	Pd(OAc) ₂	P(<i>t</i> -Bu) ₃	diglyme	79
7	Cl	Pd(OAc) ₂	S-Phos	diglyme	85
8	Cl	Pd(OAc) ₂	Dave-Phos	diglyme	28
9	Cl	Pd(OAc) ₂	JohnPhos	diglyme	15
10	Cl	Pd ₂ (dba) ₃	P(Cy) ₃	diglyme	84
11	Cl	Pd(TFA) ₂	P(Cy) ₃	diglyme	85
12	Cl	Pd(MeCN) ₂ Cl ₂	P(Cy) ₃	diglyme	73
13 ^c	Cl	Pd(OAc) ₂	P(Cy) ₃	diglyme	86
14	Br	Pd(OAc) ₂	P(Cy) ₃	diglyme	87
15	Br	Pd(OAc) ₂	P(<i>o</i> -Tol) ₃	diglyme	91

^a All the reactions were carried out at 0.25 mmol scale in 0.5 mL of solvent. ^b GC yields using biphenyl as the internal standard. ^c 1 mol % of Pd(OAc)₂ and 2 mol % of ligand were used.

(3) (a) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250. (b) Tanaka, D.; Myers, A. G. *Org. Lett.* **2004**, *6*, 433. (c) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323.

(4) Forgiione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350.

(5) (a) Moon, J.; Jeong, M.; Nam, H.; Ju, J.; Moon, J. H.; Jung, H. M.; Lee, S. *Org. Lett.* **2008**, *10*, 945. (b) Moon, J.; Jang, M.; Lee, S. *J. Org. Chem.* **2009**, *74*, 1403. (c) Becht, J.-M.; Le Drian, C. *Org. Lett.* **2008**, *10*, 3161. (d) Becht, J.-M.; Catala, C.; Le Drian, C.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781. (e) Wang, Z. Y.; Ding, Q. P.; He, X. D.; Wu, J. *Org. Biomol. Chem.* **2009**, *7*, 863. (f) Wang, Z. Y.; Ding, Q. P.; He, X. D.; Wu, J. *Tetrahedron* **2009**, *65*, 4635. (g) Voutchkova, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun.* **2008**, 6312. (h) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194. (i) Shang, R.; Fu, Y.; Li, J. B.; Zhang, S. L.; Guo, Q. X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 5738.

(6) (a) Waetzig, S. R.; Rayabarupu, D. K.; Weaver, J. D.; Tunge, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4977. (b) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 14860. (c) Fields, W. H.; Khan, A. K.; Sabat, M.; Chroma, J. *J. Org. Lett.* **2008**, *10*, 5131. (d) Pi, S.-F.; Tang, B.-X.; Li, J.-H.; Liu, Y.-L.; Liang, Y. *Org. Lett.* **2009**, *11*, 2309. (e) Bi, H.-P.; Zhao, L.; Liang, Y.-M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 792. (f) Bi, H.-P.; Chen, W.-W.; Liang, Y.-M.; Li, C.-J. *Org. Lett.* **2009**, *11*, 3246. (g) Duan, Z.; Ranjit, S.; Zhang, P.; Liu, X. *Chem.—Eur. J.* **2009**, *15*, 3666. (h) Yeagley, A. A.; Lowder, M. A.; Chroma, J. *J. Org. Lett.* **2009**, *11*, 4022. (i) Hu, P.; Kan, J.; Su, W.; Hong, M. *Org. Lett.* **2009**, *11*, 2341. (j) Yu, W.-Y.; Sit, W.; Zhou, Z.; Chan, A. S.-C. *Org. Lett.* **2009**, *11*, 3174. (k) Miyasaka, M.; Fukushima, A.; Satoh, T.; Hirano, K.; Miura, M. *Chem.—Eur. J.* **2009**, *15*, 3674.

(7) Shang, R.; Fu, Y.; Wang, Y.; Xu, Q.; Yu, H.-Z.; Liu, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 9350.

(8) Sakai et al. developed a special protocol for the Suzuki coupling reaction of pentafluorophenylboronic acid, which is an inactive substrate under normal conditions. See: Korenaga, T.; Kosaki, T.; Fukumura, R.; Ema, T.; Sakai, T. *Org. Lett.* **2005**, *7*, 4915.

(9) (a) Nitschke, J. R.; Tilley, T. D. *J. Am. Chem. Soc.* **2001**, *123*, 10183. (b) Zacharias, P.; Gather, M. C.; Rojahn, M.; Nuyken, O.; Meerholz, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4388.

(10) (a) Mewshaw, R. E.; Edsall, R. J., Jr.; Yang, C.; Manas, E. S.; Xu, Z. B.; Henderson, R. A.; Keith, J. C., Jr.; Harris, H. A. *J. Med. Chem.* **2005**, *48*, 3953. (b) de Candia, M.; Liantonio, F.; Carotti, A.; De Cristofaro, R.; Altomare, C. *J. Med. Chem.* **2009**, *52*, 1018.

(11) (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (b) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097.

(12) (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (c) Do, H.-Q.; Kashif Khan, R. M.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185.

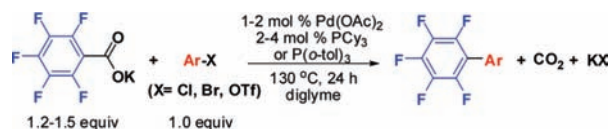
(13) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.

Extending the model reaction to a variety of substrates showed that both electron-rich and electron-poor aryl bromides and chlorides can be successfully converted tolerating a range of functional groups (Table 2). In several cases (entries 1, 4, and 15), aryl triflates (but not aryl tosylates, see entry 13) can also be successfully converted. *Ortho*-substitution can be tolerated in the transformation (entries 3, 5, 7, and 8). In addition, some heteroaryl bromides and chlorides can be used to produce the corresponding polyfluorobiaryls (entries 21 and 22).

The scope of the reaction with respect to fluoroarene is shown in Table 3, where a higher loading of Pd catalyst is required. Under the optimized conditions, potassium monofluorobenzoate cannot be efficiently converted, unless an *ortho*-Cl or *ortho*-CF₃ group is added (entries 1–3). Once two *ortho*-F atoms are added, decarboxylative coupling of potassium bisfluorobenzoate can proceed smoothly with both 4-methoxyphenyl bromide and chloride (entries 4–7). Similar reactions are also observed with tri- and tetrafluorobenzoates carrying two *ortho*-F atoms (entries 9–12), but not with a trifluorobenzoate carrying a single *ortho*-F (entry 8). Note that in entries 9 and 10 some di- or triarylated byproduct are observed. For entry 9, the yields for mono-, di-, and triarylated products are 14%, 21%, and 49%, respectively.

For entry 10, the yields for mono- and diarylated products are 31% and 58%. Thus, the direct arylation of acidic C–H bonds of polyfluoroarenes^{11,12} is a side reaction in Pd-catalyzed decarboxylative coupling of polyfluorobenzoates.

Table 2. Pd-Catalyzed Decarboxylative Cross Coupling of C₆F₅COOK with Aryl Bromides, Chlorides, and Triflates^a



entry	substrate	yield ^b	entry	substrate	yield ^b
1		Cl 91		Cl 86	
		Br 89			
		OTf 76			
2		Br 96	13		Br 88
		Cl 92			Cl 85
3		Cl 84	14		Br 93
		Br 86			
4		OTf 79	15		OTf 89
		Cl 85			Br 97
5		Cl 94	16		Cl 83
6		Cl 96	17		Cl 99
7		Br 81	18		Cl 97
8		Cl 83	19		Cl 98
9		Br 93	20		Cl 95
10		Cl 89	21		3-Br 81
		Br 84			2-Br trace
11		Br 87	22		2-Cl 75
					3-Cl 52

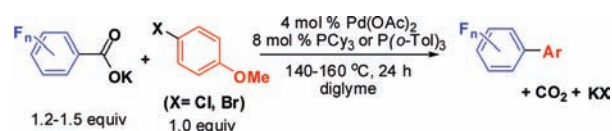
^a All the reactions were carried out at 0.25 mmol scale in 0.5 mL of diglyme. For more details, see the Supporting Information. ^b Isolated yields were calculated based on the quantity of aryl halide.

To understand the mechanism of the Pd-catalyzed decarboxylative cross coupling, we carried out DFT calculations (Figure 1).¹⁴ Through the analysis, we first concluded that it is Pd(II), but not Pd(0), that promotes the decarboxylation of the carboxylic acid. Accordingly, we proposed that in a catalytic cycle a monocoordinated Pd(0) complex first activates the aryl halide.^{15,16} When PMe₃ is used as a model ligand, the Pd(0) complex forms a complex with PhCl (**IN1**), which undergoes oxidative addition through **TS1** to produce a Pd(II) intermediate (**IN2**). The energy barrier for oxidative addition is +14.5 kcal/mol. **IN2** then exchanges the anionic

(14) For the previous theoretical analysis on the related subject, see: (a) Goossen, L. J.; Thiel, W. R.; Rodriguez, N.; Linder, C.; Melzer, B. *Adv. Synth. Catal.* **2007**, *349*, 2241. (b) Zhang, S.-L.; Fu, Y.; Shang, R.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 638.

ligand to form **IN3** and its coordination isomer **IN4**. Note that the barrier between **IN3** and **IN4** is only +16.8 kcal/mol meaning that they can readily isomerize to each other. From **IN4**, the decarboxylation transition state (**TS3**) is identified as a four-coordinate Pd(II) species. From **IN3** to **TS3**, the free energy increases by +24.0 kcal/mol, and therefore, decarboxylation is the rate-limiting step. The immediate product of decarboxylation is a three-coordinate Pd(II) complex (**IN5**), which undergoes reductive elimination readily to form the biaryl product through **TS4** with a low barrier of +11.7 kcal/mol.

Table 3. Pd-Catalyzed Decarboxylative Cross Coupling of Various Potassium Polyfluorobenzoates^a



entry	product	yield ^b	entry	product	yield ^b
1		Cl trace	7		Br 73
2		Br 68	8		Cl trace
3		Cl 81	9 ^c		Cl 14
		Br 74			
4		Cl 85	10 ^c		Cl 31
		Br 82			
5		Cl 96	11		Cl 89
		Br 92			Br 96
6		Cl 51	12		Cl 85

^a All the reactions were carried out at 0.25 mmol scale in 0.5 mL of diglyme. For more details, see the Supporting Information. ^b Isolated yields were calculated based on the quantity of aryl halide. ^c Di- and triarylations were observed.

The above results reveal a major difference between Cu- and Pd-catalyzed decarboxylative couplings. In Cu-catalyzed

(15) Oxidative addition is not a rate-limiting step in the decarboxylative cross coupling because a mechanistic related Pd-catalyzed cross coupling reaction (e.g. Suzuki coupling) does not require a high temperature to proceed. Therefore, we do not discuss the detailed mechanism of the oxidative addition step, which may be complicated by many factors. For oxidative addition of an aryl halide to monoligated Pd(0), see: (a) Ahlquist, M.; Fristrup, P.; Tanner, D.; Norrby, P.-O. *Organometallics* **2006**, *26*, 2066. (b) Li, Z.; Fu, Y.; Guo, Q.-X.; Liu, L. *Organometallics* **2008**, *27*, 4043.

(16) For oxidative addition to an anionic Pd(0) species, see: (a) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531. (b) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.

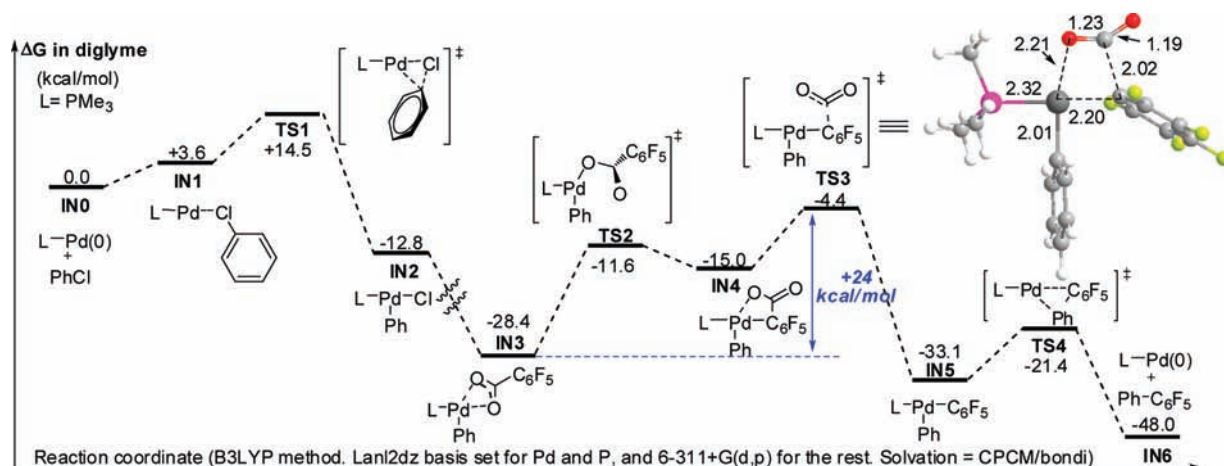


Figure 1. Proposed mechanism for Pd-catalyzed decarboxylative cross-coupling.

versions, the rate-limiting step is oxidative addition of the Cu(I) intermediate to aryl halide.⁸ This conclusion is consistent with the observation that aryl chlorides cannot be converted by the Cu catalyst. By comparison, in Pd-catalyzed versions the rate-limiting step should be decarboxylation. To support this mechanistic proposal, we compared the Pd-catalyzed decarboxylative couplings of potassium 2,6-difluorobenzoate with 4-methoxyphenyl bromide and chloride (Scheme 1). For the bromide, the more electron-rich ligand (PCy₃) affords a worse result due to the side reaction, whereas the less electron-rich ligand P(*o*-Tol)₃ does not show

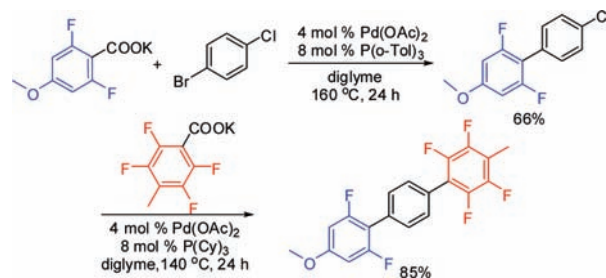
Scheme 1. Effects of the Ligands on the Cross Coupling



this problem. The explanation is presumably that the more electron-rich ligand causes a faster oxidative addition and therefore produces the aryl-Pd(II) intermediate too rapidly to be effectively consumed by the benzoate. On the other hand, for the aryl chloride that will undergo oxidative addition less rapidly, the use of the PCy₃ ligand does not cause much side reaction. Thus, a good balance between the decarboxylation and oxidative addition steps is critical to the success of decarboxylative cross couplings. One method to control the balance was to use a bimetallic catalyst (e.g., Pd for oxidative addition and Cu for decarboxylation).³ We showed here that under some circumstances a strategic change of ligand can also control the balance.

Note that the ligand effects can be used for selective decarboxylative cross couplings. A good example is shown in Scheme 2, where two different polyfluorophenyl groups are sequentially coupled to an aryl halide.

Scheme 2. Selective Decarboxylative Cross Couplings



In summary, we report Pd-catalyzed decarboxylative cross coupling of potassium polyfluorobenzoates with aryl bromides, chlorides, and triflates. The reaction is practical for synthesis of polyfluorobiaryls from readily accessible and nonvolatile polyfluorobenzoate salts. Unlike the Cu-catalyzed decarboxylation cross coupling where oxidative addition is the rate-limiting step, in the Pd-catalyzed version decarboxylation is the rate-limiting step.

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

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