C–C Coupling

DOI: 10.1002/anie.200904916

Copper-Catalyzed Decarboxylative Cross-Coupling of Potassium Polyfluorobenzoates with Aryl Iodides and Bromides**

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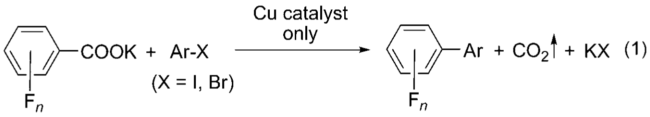
Transition-metal-catalyzed decarboxylative cross-coupling using carboxylic acids as aryl sources is of contemporary interest.[1] This method does not use expensive and sensitive organometallic reagents, and generates CO_2 instead of toxic metal halides. Early studies showed that a stoichiometric quantity of copper could promote the decarboxylative coupling of aromatic carboxylic acids with aryl iodides.[2] Recently, Goossen et al. reported Pd/Cu-catalyzed decarboxylative coupling of benzoic acids and α-oxo carboxylates with aryl halides and triflates.[3] Related studies by the groups of Myers,[4] Forgione,[5] and others[6–9] showed that palladium by itself could also catalyze the decarboxylative coupling of aromatic carboxylic acids. We reported a palladium-catalyzed decarboxylative coupling of oxalate monoesters with aryl halides,[10] and related decarboxylative reactions were also reported recently by the groups of Tunge, Li, Chruma, and others.[11]

Herein we describe the first, copper-only systems that catalyze the decarboxylative coupling of potassium polyfluorobenzoates with aryl iodides and bromides [Eq. (1)].[12] The importance of the study is twofold: 1) The new reactions can replace the use of expensive but often less reactive[13] fluorobenzene organometallics in the synthesis of polyfluorobiaryls, which are important molecules in medicinal chemistry[14] and material science.[15] They also provide a method complementary to that reported by Fagnou and co-workers[16] and Daugulis and co-workers[17] for fluorobiaryl synthesis through C–H arylation of a polyfluoroarene. 2) Recently Goossen et al. reported the copper-catalyzed protodecarboxylation of aromatic carboxylic acids.[18] Nonetheless, there has not been any example for copper-catalyzed decarboxylative coupling of acids with aryl halides. Therefore, the reactions reported herein represent a novel type of copper-catalyzed cross-coupling reactions.[19,20]



(1)

Our work started with the decarboxylative coupling of C_6F_5COOK with PhI. When 10 mol % of CuI/1,10-phenanthroline was used as the catalyst, decarboxylation proceeded rapidly in NMP at 160 °C but the yield of the desired product was only 10 %. To improve the yield we lowered the reaction temperature and found that the best compromise between the reaction rate and yield is achieved at 130 °C. However, the optimal yield remained at about 40 % after we examined many combinations of solvents and ligands. A breakthrough was then made when diglyme was used as the solvent, and the optimal yield obtained was 99 % with or even without the ligand.

A possible explanation for the outstanding performance of diglyme is that diglyme can coordinate to K^+, thereby facilitating the complexation between CuI and $C_6F_5CO_2^-$. Extending the model reaction to other substrates showed that both electron-rich and electron-poor aryl iodides could be successfully converted and a range of functional groups were tolerated (Table 1, entries 2–12). The reaction yields range from good to excellent. Importantly, *ortho* substitution can be well tolerated in the transformation (Table 1, entries 13–16). In addition to phenyl iodides, other aryl substrates including naphthyl, perfluorophenyl, and heteroaryl iodides can also be used to produce the corresponding polyfluorobiaryls (Table 1, entries 18–24).

The above protocol can be applied to aryl iodides but not aryl bromides. This problem can be solved by using 1,10-phenanthroline as a ligand. As shown in Table 2, copper-catalyzed decarboxylative cross-couplings between potassium pentafluorobenzoate and a variety of aryl bromides display high yields ranging from 88 to 99 %. These coupling reactions can tolerate both electron-rich and electron-poor substrates (Table 2, entries 1–9) and can also tolerate *ortho* substitution (Table 2, entries 14–16). In addition, heteroaryl bromides are acceptable substrates in the reaction (Table 2, entries 17–20). Notably, copper-catalyzed decarboxylative cross-coupling of potassium pentafluorobenzoate with 1-bromoadamantane produces a $C(sp^3)$–$C(sp^2)$ bond [Eq. (2)]. Moreover, the method can be used to synthesize polyfluorostilbene in high yields from vinyl bromides [Eq. (3)].[24]

The scope of the reaction with respect to fluoroarene is presented in Table 3. Although diglyme is important for the reactions with potassium pentafluorobenzoate, dimethyl acetamide (DMA) affords better results for fluoroarenes

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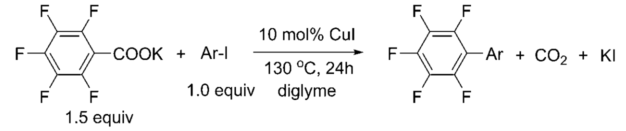
[**] This work was supported by NSFC (20832004, 20802040), and the Li Foundation.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200904916.

Table 1: Copper-catalyzed decarboxylative cross-coupling between potassium pentafluorobenzoate and aryl iodides.[a]



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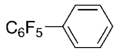
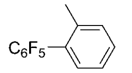
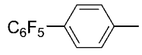
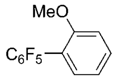
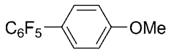
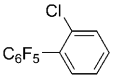
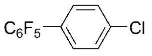
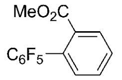
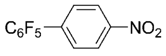
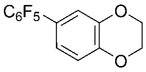
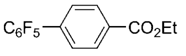
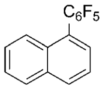
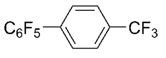
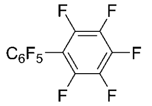
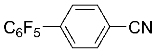
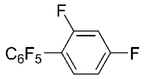
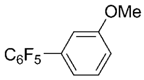
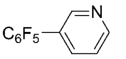
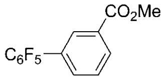
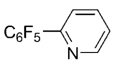
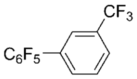
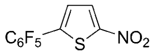
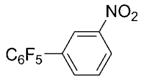
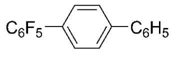
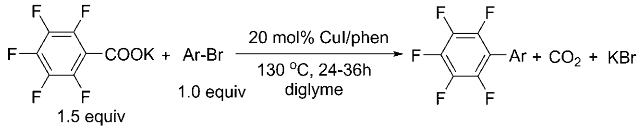
1		99	13[c]		96
2		99	14[c]		97
3		99	15		94
4		95	16		99
5		98	17		99
6		99	18[c]		99
7[b]		99	19[b]		80
8		99	20[b]		94
9		96	21		99
10		98	22		99
11[b]		92	23		61
12		99	24[d]		89

[a] Yields of isolated products were calculated based on the amount of aryl iodide used. [b] 1.2 equiv $C_6F_5CO_2K$ was used. [c] 20 mol% CuI was used. [d] 1,4-diiodobenzene was used as substrate.

Table 2: Copper-catalyzed decarboxylative cross-coupling between potassium pentafluorobenzoate and aryl bromides.[a]



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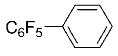
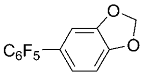
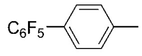
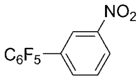
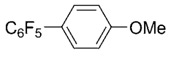
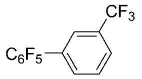
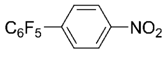
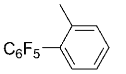
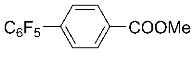
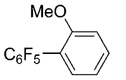
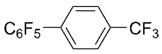
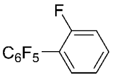
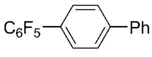
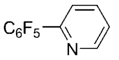
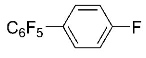
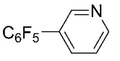
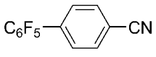
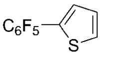
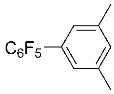
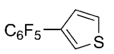
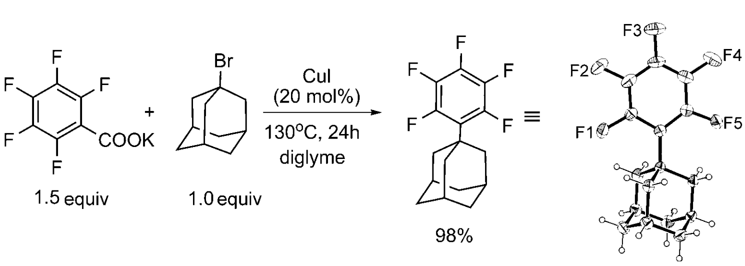
1		88	11		96
2		95	12		99
3		97	13		93
4		89	14		92
5		99	15		94
6		94	16		91
7		92	17		91
8		94	18		94
9		92	19		97
10		95	20		88

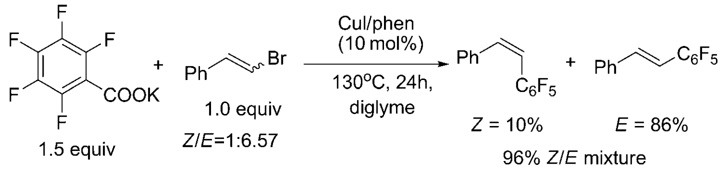
[a] Yields of isolated products were calculated based on the amount of aryl bromide used. phen = 1,10-phenanthroline.

containing fewer fluorine atoms. Under the optimized reaction conditions, potassium monofluorobenzoate cannot be efficiently converted, unless an *ortho*-CF_3 group is added (Table 3, entries 1–3). Once two F atoms are placed at each of the *ortho* positions, the decarboxylative coupling of potassium bis(fluorobenzoate) can proceed smoothly with both electron-rich and electron-poor aryl iodides (Table 3, entries 4–7). Similar reactions are also observed with tri- and tetrafluorobenzoates having two *ortho*-F atoms (Table 3, entries 10–18). In entries 14 and 15 of Table 3 some diarylated by-products are also observed. This means that the direct arylation of acidic C–H bonds of polyfluoroarenes[16–17] is a side reaction in the copper-catalyzed decarboxylative coupling of polyfluorobenzoates.



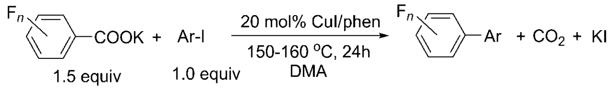
(2)

Goossen et al. previously conducted a theoretical study on the mechanism of copper-mediated decarboxylation of benzoic acids.[21] For the copper-catalyzed decarboxylative coupling described herein, there is a key mechanistic question as to whether decarboxylation occurs on copper(I) before oxidative addition, or at the copper(III) stage. To solve the problem DFT calculations were per-



(3)

Table 3: Copper-catalyzed decarboxylative cross-coupling between aryl iodides and other polyfluorobenzoates.[a]



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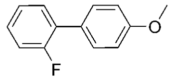
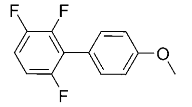
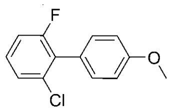
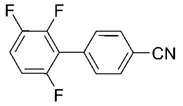
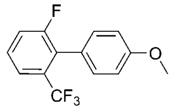
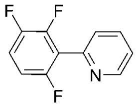
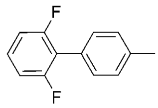
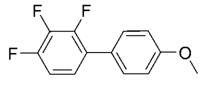
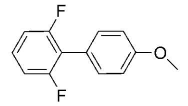
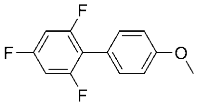
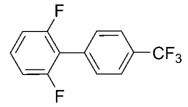
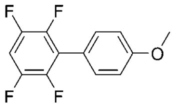
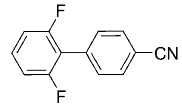
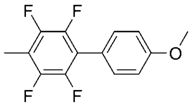
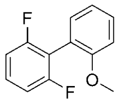
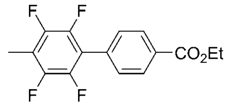
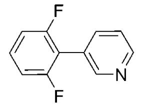
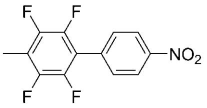
1		trace	10		73
2		trace	11		95
3		68	12		80
4		73	13		21
5		78	14[b]		48
6		86	15[c]		69
7		83	16		97
8		89	17		95
9		88	18		82

[a] Yields of isolated products were calculated based on the amount of aryl iodide used. [b] 46% of diarylated product was also isolated. [c] 29% of diarylated product was also isolated. See the Supporting Information for more details. DMA = *N*,*N*-dimethyl acetamide.

formed to compare the two plausible mechanisms (Figure 1a).[22] In pathway I, the initial copper(I) complex **1** reacts with perfluorobenzoate to form **2**, which then undergoes decarboxylation via the four-membered-ring transition state $\mathbf{TS_{(2-3)}}$ (Figure 1b), which has an energy barrier of +20.3 kcal mol^{-1}. This step produces a new copper(I) complex **3** which can react with PhBr through oxidative addition (transition state $\mathbf{TS_{(3-3')}}$).[23] The energy barrier of oxidative addition is +30.0 kcal mol^{-1} and therefore, oxidative addition constitutes the rate-limiting step in pathway I. Finally, reductive elimination is found to be a facile step and it finishes the reaction producing C_6F_5Ph.

In pathway II, oxidative addition takes places first on the complex **1**. This step has a relatively low energy barrier of +18.9 kcal mol^{-1}. After oxidative addition the resulting copper(III) species is pentacoordinated and therefore, decarboxylation at copper(III) has to pass through a hexacoordinated transition state. As a result of the strong steric repulsion in the hexacoordinated species, the energy barrier for decarboxylation is calculated to be +51.1 kcal mol^{-1}. Therefore, decarboxylation constitutes the rate-limiting step in pathway II. By comparing pathways I and II we conclude that decarboxylation likely occurs on copper(I) before oxidative addition. This conclusion is in line with the observation by Sheppard et al.[23a,b]

In summary, the decarboxylative cross-coupling of potassium polyfluorobenzoates with aryl iodides and bromides mediated by a copper-only system was discovered. This reaction represents both a new type of copper-catalyzed cross-coupling reaction and a new type of transition-metal-catalyzed decarboxylative coupling reaction. The reaction is practical for the synthesis of polyfluorobiaryls from readily accessible and nonvolatile polyfluorobenzoate salts. In contrast to the previously reported decarboxylative coupling reactions, palladium is not required for the present transformation, meaning that both the decarboxylation and cross-coupling steps in the newly discovered process are catalyzed solely by copper. Theoretical analyses suggest that decarboxylation should occur at first on copper(I) to generate a polyfluorophenylcopper(I) intermediate, which then reacts with aryl halides through oxidative addition and reductive elimination to produce the coupling products.

Experimental Section

Representative procedure (Table 1): CuI (0.05 mmol, 9.5 mg), an appointed amount of potassium pentafluorobenzoate (0.60–0.75 mmol), and aryl iodide (0.50 mmol) (if solid) were placed in an oven-dried 10 mL Schlenk tube. The reaction vessel was evacuated and filled with argon, a process which was repeated three times. Then aryl iodide (0.50 mmol) (if liquid) and diglyme (0.5 mL) were added with a syringe under a counterflow of argon. The vessel was sealed with a screw cap, stirred at room temperature for 10 min, and then connected to the Schlenk line filled with argon. The reaction was stirred at 130 °C for the appointed time (24 h). Upon completion of the reaction, the mixture was cooled to room temperature and diluted with ethyl acetate or petroleum ether (20 mL). The mixture was filtered through a short silica gel column to remove the deposition. The organic layers were washed with water (3 × 20 mL) and then with brine. The combined organic layers were dried over Na_2SO_4 and filtered. The solvents were removed under vacuum. Purification of

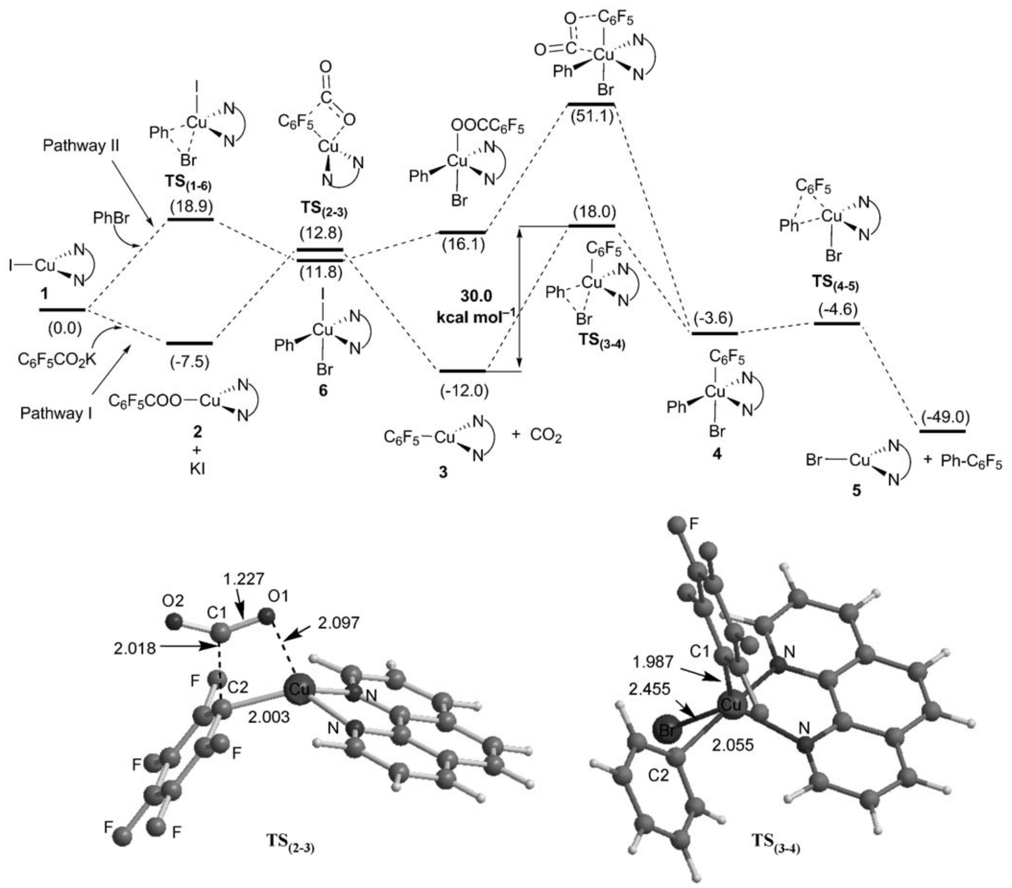


Figure 1. Comparison of two plausible mechanisms for copper-catalyzed decarboxylative cross-coupling (B3LYP method. SDD basis set for I, 6-31G(d) for C, H, O, F, Cu, and Br. Solvation = CPCM/Bondi). All energies (in parentheses) are given in kcal mol^{-1}. a) Energy diagram for the two plausible mechanisms. b) Minimized structure of the proposed transitions states showing some bond lengths and distances (in Å).

the residue by column chromatography on silica gel (EtOAc/*n*-hexane 1:1) yielded the corresponding fluoroarene.

Received: September 2, 2009

Keywords: copper · cross-coupling · homogeneous catalysis · reaction mechanisms · polyfluoroarenes

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[1] a) O. Baudoin, *Angew. Chem.* **2007**, *119*, 1395; *Angew. Chem. Int. Ed.* **2007**, *46*, 1373; b) L. J. Goossen, N. Rodriguez, K. Goossen, *Angew. Chem.* **2008**, *120*, 3144; *Angew. Chem. Int. Ed.* **2008**, *47*, 3100.

[2] a) M. Nilsson, *Acta Chem. Scand.* **1966**, *20*, 423; b) C. Björklund, M. Nilsson, *Acta Chem. Scand.* **1968**, *22*, 2585; c) A. Cairncross, J. R. Roland, R. M. Henderson, W. A. Shepard, *J. Am. Chem. Soc.* **1970**, *92*, 3187; d) T. Cohen, R. A. Schambach, *J. Am. Chem. Soc.* **1970**, *92*, 3189.

[3] a) L. J. Goossen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 662; b) L. J. Goossen, N. Rodriguez, B. Melzer, C. Linder, G. Deng, L. M. Levy, *J. Am. Chem. Soc.* **2007**, *129*, 4824; c) L. J. Goossen, B. Melzer, *J. Org. Chem.* **2007**, *72*, 7473; d) L. J. Goossen, T. Knauber, *J. Org. Chem.* **2008**, *73*, 8631; e) L. J. Goossen, B. Zimmermann, T. Knauber, *Angew. Chem.* **2008**, *120*, 7211; *Angew. Chem. Int. Ed.* **2008**, *47*, 7103; f) L. J. Goossen, N. Rodriguez, C. Linder, *J. Am. Chem. Soc.* **2008**, *130*, 15248; g) L. J. Goossen, F. Rudolphi, C. Oppel, N. Rodriguez, *Angew. Chem.* **2008**, *120*, 3085; *Angew. Chem. Int. Ed.* **2008**, *47*, 3043.

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

[5] P. Forgione, M.-C. Brochu, M. St-Onge, K. H. Thesen, M. D. Bailey, F. Bilodeau, *J. Am. Chem. Soc.* **2006**, *128*, 11350.

[6] a) J. Moon, M. Jeong, H. Nam, J. Ju, J. H. Moon, H. M. Jung, S. Lee, *Org. Lett.* **2008**, *10*, 945; b) J. Moon, M. Jang, S. Lee, *J. Org. Chem.* **2009**, *74*, 1403.

[7] a) J.-M. Becht, C. Le Drian, *Org. Lett.* **2008**, *10*, 3161; b) J.-M. Becht, C. Catala, C. Le Drian, A. Wagner, *Org. Lett.* **2007**, *9*, 1781.

[8] a) Z. Y. Wang, Q. P. Ding, X. D. He, J. Wu, *Org. Biomol. Chem.* **2009**, *7*, 863; b) Z. Y. Wang, Q. P. Ding, X. D. He, J. Wu, *Tetrahedron* **2009**, *65*, 4635; c) A. Voutchkova, A. Coplin, N. E. Leadbeater, R. H. Crabtree, *Chem. Commun.* **2008**, 6312.

[9] C. Wang, I. Piel, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 4194.

[10] R. Shang, Y. Fu, J. B. Li, S. L. Zhang, Q. X. Guo, L. Liu, *J. Am. Chem. Soc.* **2009**, *131*, 5738.

[11] a) S. R. Waetzig, D. K. Rayabarupu, J. D. Weaver, J. A. Tunge, *Angew. Chem.* **2006**, *118*, 5099; *Angew. Chem. Int. Ed.* **2006**, *45*, 4977; b) S. R. Waetzig, J. A. Tunge, *J. Am. Chem. Soc.* **2007**, *129*, 14860; c) W. H. Fields, A. K. Khan, M. Sabat, J. J. Chruma, *Org. Lett.* **2008**, *10*, 5131; d) S.-F. Pi, B.-X. Tang, J.-H. Li, Y.-L. Liu, Y. Liang, *Org. Lett.* **2009**, *11*, 2309; e) H.-P. Bi, L. Zhao, Y.-M. Liang, C.-J. Li, *Angew. Chem.* **2009**, *121*, 806; *Angew. Chem. Int.*

Ed. **2009**, *48*, 792; f) H.-P. Bi, W.-W. Chen, Y.-M. Liang, C.-J. Li, *Org. Lett.* **2009**, *11*, 3246; g) Z. Duan, S. Ranjit, P. Zhang, X. Liu, *Chem. Eur. J.* **2009**, *15*, 3666; h) A. A. Yeagley, M. A. Lowder, J. J. Chruma, *Org. Lett.* **2009**, *11*, 4022; i) P. Hu, J. Kan, W. Su, M. Hong, *Org. Lett.* **2009**, *11*, 2341; j) W.-Y. Yu, W. Sit, Z. Zhou, A. S.-C. Chan, *Org. Lett.* **2009**, *11*, 3174; k) M. Miyasaka, A. Fukushima, T. Satoh, K. Hirano, M. Miura, *Chem. Eur. J.* **2009**, *15*, 3674.

[12] There are two literature examples for palladium-catalyzed decarboxylative coupling of perfluorobenzoic acid with 4-iodoanisole; see references [7b,8c].

[13] For a special protocol for the Suzuki–Miyaura coupling reaction of pentafluorophenylboronic acid, which is an inactive substrate under normal conditions, see: T. Korenaga, T. Kosaki, R. Fukumura, T. Ema, T. Sakai, *Org. Lett.* **2005**, *7*, 4915.

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

[15] a) J. R. Nitschke, T. D. Tilley, *J. Am. Chem. Soc.* **2001**, *123*, 10183; b) P. Zacharias, M. C. Gather, M. Rojahn, O. Nuyken, K. Meerholz, *Angew. Chem.* **2007**, *119*, 4467; *Angew. Chem. Int. Ed.* **2007**, *46*, 4388.

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

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

[18] L. J. Goossen, F. Manjolinho, B. A. Khan, N. Rodriguez, *J. Org. Chem.* **2009**, *74*, 2620.

[19] Reviews for copper-catalyzed cross-couplings: a) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400; b) W. Deng, L. Liu, Q.-X. Guo, *Chin. J. Org. Chem.* **2004**, *24*, 150; c) D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450; d) F. Monnier, M. Taillefer, *Angew. Chem.* **2008**, *120*, 3140; *Angew. Chem. Int. Ed.* **2008**, *47*, 3096; e) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054.

[20] For selected examples of copper-catalyzed cross-couplings, see: a) A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727; b) R. A. Altman, A. M. Hyde, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 9613; c) D. Ma, Y. Zhang, J. Yao, S. Wu, F. Tao, *J. Am. Chem. Soc.* **1998**, *120*, 12459; d) D. Ma, S. Xie, P. Xue, X. Zhang, J. Dong, Y. Jiang, *Angew. Chem. Int. Ed.* **2009**, *48*, 4222; e) M. B. Thathagar, J. Beckers, G. Rothenberg, *J. Am. Chem. Soc.* **2002**, *124*, 11858; f) V. del Amo, S. R. Dubbaka, A. Krasovskiy, P. Knochel, *Angew. Chem.* **2006**, *118*, 8002; *Angew. Chem. Int. Ed.* **2006**, *45*, 7838; g) X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790; h) J. M. Villalobos, J. Srogl, L. S. Libeskind, *J. Am. Chem. Soc.* **2007**, *129*, 15734; i) H. Prokopcova, C. O. Kappe, *Angew. Chem.* **2008**, *120*, 3732; *Angew. Chem. Int. Ed.* **2008**, *47*, 3674; j) P. H. Fuller, J.-W. Kim, S. R. Chemler, *J. Am. Chem. Soc.* **2008**, *130*, 17638; k) A. E. King, T. C. Brunold, S. S. Stahl, *J. Am. Chem. Soc.* **2009**, *131*, 5044; l) R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593.

[21] L. J. Goossen, W. R. Thiel, N. Rodriguez, C. Linder, B. Melzer, *Adv. Synth. Catal.* **2007**, *349*, 2241.

[22] Some previous studies on the mechanism of copper-catalyzed cross-couplings: a) A. Ouali, J.-F. Spindler, A. Jutand, M. Taillefer, *Adv. Synth. Catal.* **2007**, *349*, 1906; b) S.-L. Zhang, L. Liu, Y. Fu, Q.-X. Guo, *Organometallics* **2007**, *26*, 4546; c) A. Ouali, M. Taillefer, J.-F. Spindler, A. Jutand, *Organometallics* **2007**, *26*, 65; d) J. W. Tye, Z. Weng, A. M. Johns, C. D. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 9971; e) L. M. Huffman, S. S. Stahl, *J. Am. Chem. Soc.* **2008**, *130*, 9196; f) H. Kaddouri, V. Vicente, A. Ouali, F. Ouazzani, M. Taillefer, *Angew. Chem.* **2009**, *121*, 339; *Angew. Chem. Int. Ed.* **2009**, *48*, 333; g) E. R. Strieter, B. Bhayana, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 78.

[23] Earlier studies already showed that pentafluorophenylcopper can react with aryl iodides producing coupling products in high yield. See: a) A. Cairncross, W. A. Sheppard, *J. Am. Chem. Soc.* **1968**, *90*, 2186; b) W. A. Sheppard, *J. Am. Chem. Soc.* **1970**, *92*, 5419.

[24] Thermal ellipsoids shown at 50% probability. CCDC-752845 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.