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### Palladium-catalyzed decarbonylative and decarboxylative cross-coupling of acyl chlorides with potassium perfluorobenzoates affording unsymmetrical biaryls<sup>†</sup>

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This paper describes the synthesis of unsymmetrical biaryls by the palladium-catalyzed cross-coupling reaction of acyl chlorides with potassium perfluorobenzoates. This transformation is unique in that it involves simultaneous decarbonylation and decarboxylation under redox-neutral conditions. Compared to conventional crosscoupling protocols for the synthesis of unsymmetrical biaryls, the two reactants in this synthetic strategy can be readily prepared from abundant and inexpensive aromatic carboxylic acids.

Over the past few decades, carboxylic acids and their derivatives have aroused wide interest in organic synthesis due to their ready availability, abundance, and environmental friendliness.<sup>1</sup> In this context, benzoic acids and their derivatives have been developed as convenient surrogates for conventional coupling partners through the loss of CO or CO<sub>2</sub>, known as decarbonylative<sup>2</sup> and decarboxylative<sup>3</sup> couplings, respectively. Among these protocols, the development of synthetic methods for biaryls, one of the most versatile units of organic molecules, is of great importance (Scheme 1a).<sup>4–7</sup> As a pioneering example, Gooßen and co-workers developed the Pd/Cu-cocatalyzed intermolecular decarboxylative coupling of benzoic acids or benzoates with aryl (pseudo)halides.<sup>4</sup> In 2018, Sanford and co-workers reported the nickel-catalyzed decarbonylative couplings of acyl fluorides with arylboronic acids under base-free conditions.<sup>7c</sup> Although these synthetic methods utilize substrates derived from naturally abundant carboxylic acids, either organic (pseudo) halides or organometallic reagents are still required. Therefore, a method for the synthesis of unsymmetrical biaryls from benzoic acid derivatives alone via redox-neutral decarbonylative and decarboxylative couplings has not yet been developed (Scheme 1b).<sup>8</sup>

Based on our previous studies on palladium-catalyzed decarbonylative cross-coupling reactions<sup>9</sup> and related mechanisms,<sup>5,7d,10</sup> we hypothesized the possible scenario of biaryl synthesis via decarbonylation and decarboxylation (Scheme 2). First, the acylpalladium(II) complex A is formed by oxidative addition of benzoic acid derivatives 1 to the Pd(0) catalyst. In Path a, decarbonylation occurs prior to transmetalation, affording the arylpalladium(II) species B, which reacts with benzoates 2 to yield the intermediate C. After decarboxylation, the diarylpalladium(II) complex D is formed from C. Finally, reductive elimination of D yields the desired unsymmetrical biaryls 3, and regeneration of palladium(0) completes the catalytic cycle. On the other hand, in Path b, transmetalation between A and benzoates 2 gives the intermediate  $\mathbf{B}'$ . Thus, the loss of  $CO_2$  in  $\mathbf{B}'$ produces complex C', and subsequent decarbonylation gives the same intermediate D, while ketone 4 is a by-product from the direct reductive elimination of C'. Compared to previously reported





Scheme 1 Biaryl synthesis via decarboxylation or/and decarbonylation.



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Scheme 2 A working hypothesis for the synthesis of biaryl from benzoic acid derivative **1** and benzoate **2**.

couplings involving decarboxylation or decarbonylation, this process poses a greater challenge since both processes should occur prior to reductive elimination.

Acyl chlorides, one of the most fundamental and commercially available carboxylic acid derivatives, have been widely used as electrophiles in organic synthesis.<sup>11</sup> However, despite their widespread existence, there are relatively few reports on the use of acyl chlorides as any sources via decarbonylative cross-coupling reactions.<sup>12</sup> As a recent example, Szostak and co-workers reported a decarbonylative Suzuki-Miyaura-type cross-coupling reaction of acyl chlorides using arylboronic acids as the nucleophiles.<sup>7d</sup> On the other hand, perfluorophenyl groups present unique reactivity and properties.<sup>13</sup> Due to the widespread use of the biaryl skeleton with perfluorophenyl moieties in pharmaceutical<sup>14</sup> and materials<sup>15</sup> chemistry, a series of decarboxylative cross-coupling reactions of perfluorobenzoates with aryl (pseudo)halides have been developed under copper, palladium, and nickel catalysis.<sup>5</sup> Recently, we also reported that spontaneous decarboxylation occurs in transitionmetal-free cross-coupling reactions of acyl fluorides with potassium perfluorobenzoates, leading to unsymmetrical ketones.16 Although this method is an efficient and environmentally friendly route to the synthesis of perfluorinated ketones, the synthesis of perfluorinated biaryls from perfluorobenzoates and benzoic acid derivatives still poses a major challenge. Hence, we herein report the palladium-catalyzed cross-coupling reaction of acyl chlorides with potassium perfluorobenzoates, involving both decarbonylation and decarboxylation.

Our investigation was initiated using 2-naphthoyl chloride (1a) and potassium pentafluorobenzoate (2a), which is not only a coupling partner, but also a base to generate  $PCy_3$  from  $PCy_3 \cdot HBF_4$ . After extensive optimization, the use of  $Pd(OAc)_2$  (10 mol%) and  $PCy_3 \cdot HBF_4$  (20 mol%) in toluene at 150 °C for 20 h was found to be the optimal condition, providing a 72% GC yield of the desired product **3aa** and 5% ketone **4** as a by-product (Table 1, entry 1). Notably, no ester product was observed, suggesting that the decarboxylation proceeded sufficiently. When  $PdCl_2(cod)$  was employed instead of  $Pd(OAc)_2$ , the yield of **3aa** decreased to 62% (entry 2), but when  $Pd(dba)_2$  was used, the yield increased to 74% (entry 3). Changing the

Table 1 Optimization of the reaction conditions<sup>a</sup>

		Pd Cat (10 mol%) Ligand (20 mol%) toluene 150 °C, 20 h	C <sub>6</sub> F <sub>5</sub>	C <sub>6</sub> F <sub>5</sub>
1a (1.0 equiv)	2a (1.5 equiv)		3aa	4
Entry	Catalyst	Ligand	$3aa^{b}$ (%)	$4^{b}$ (%)
1	$Pd(OAc)_2$	PCy <sub>3</sub> ·HBF <sub>4</sub>	72	5
2	PdCl <sub>2</sub> (cod)	PCy <sub>3</sub> ·HBF <sub>4</sub>	62	3
3	Pd(dba) <sub>2</sub>	PCy <sub>3</sub> ·HBF <sub>4</sub>	74	4
4	Pd(dba) <sub>2</sub>	$PPh_3$	10	10
5	Pd(dba) <sub>2</sub>	DCYPE	15	2
6 <sup><i>c</i></sup>	Pd(dba) <sub>2</sub>	PCy <sub>3</sub> ·HBF <sub>4</sub>	26	3
$7^d$	Pd(dba) <sub>2</sub>	PCy <sub>3</sub> ·HBF <sub>4</sub>	1	0
8 <sup>e</sup>	Pd(dba) <sub>2</sub>	PCy <sub>3</sub> ·HBF <sub>4</sub>	71	5
$9^f$	Pd(dba) <sub>2</sub>	PCy <sub>3</sub> ·HBF <sub>4</sub>	48	4
10 <sup><i>g</i></sup>	Pd(dba) <sub>2</sub>	PCy <sub>3</sub> ·HBF <sub>4</sub>	68	7
$11^h$	Pd(dba) <sub>2</sub>	PCy <sub>3</sub> ·HBF <sub>4</sub>	49	5
12		PCy <sub>3</sub> ·HBF <sub>4</sub>	0	3
13	Pd(dba) <sub>2</sub>		0	9
14 <sup><i>i</i></sup>	Pd(dba) <sub>2</sub>	$PCy_3 \cdot HBF_4$	74 (69)	4

<sup>*a*</sup> Reactions were carried out with catalyst (0.02 mmol, 10 mol%), ligand (0.04 mmol, 20 mol%), **1a** (0.2 mmol, 1.0 equiv.) and **2a** (0.3 mmol, 1.5 equiv.) in toluene (1 mL) at 150 °C for 20 h under Ar. <sup>*b*</sup> GC yields using *n*-tetradecane as an internal standard and an isolated yield is shown in parentheses. <sup>*c*</sup> C<sub>6</sub>F<sub>5</sub>COONa instead of C<sub>6</sub>F<sub>5</sub>COOK. <sup>*d*</sup> C<sub>6</sub>F<sub>5</sub>COOLi instead of C<sub>6</sub>F<sub>5</sub>COOK. <sup>*e*</sup> Toluene/1,4-dioxane (10:1). <sup>*f*</sup> Toluene/diglyme (10:1). <sup>*g*</sup> 140 °C. <sup>*h*</sup> Pd(dba)<sub>2</sub> (0.01 mmol, 5 mol%), PCy<sub>3</sub>·HBF<sub>4</sub> (0.02 mmol, 10 mol%). <sup>*i*</sup> 12 h.

ligand resulted in a decrease in the yield of the desired product (entries 4 and 5), indicating that the ligand properties have a significant effect on the present reaction. The similar trend was observed for the variation from potassium pentafluorobenzoate to lithium and sodium salts, leading to lower yields (entries 6 and 7). The employment of co-solvent also reduced the yield of **3aa** (entries 8 and 9). Furthermore, decreasing the temperature (entry 10) and the amount of catalyst loading (entry 11) resulted in the product yields of 68% and 49%, respectively. The control experiments indicated both the palladium precursor and the phosphine ligand were necessary for the formation of the target product (entries 12 and 13). Fortunately, the yield of **3aa** was still 74% in the 12 h reaction, providing a 69% isolated yield (entry 14).

With optimized conditions in hand, a range of acyl chlorides were examined in reactions with potassium pentafluorobenzoate (2a) (Scheme 3). Both 2- and 1-naphthoyl chlorides afforded the desired products 3aa and 3ba in good yields. The use of benzoyl chloride (1c) also generated the corresponding product 3ca in 49% yield. Substrates bearing electron-donating groups such as 3-methyl, 4-methyl, 4-tert-butyl, and 4-phenyl moieties could also be applicable to provide coupling products 3da, 3ea, 3fa, and 3ga in moderate yields. In addition, the ester group and the electronwithdrawing trifluoromethyl group furnished the desired products 3ha and 3ia in 61% and 48% yields, respectively. The highly reactive chlorobenzene moiety was also tolerated in this manner, providing 3ja in 34% yield. Finally, the probenecid-derived acyl chloride 1k underwent decarbonylation and decarboxylation to give the desired product 3ka in 52% yield, demonstrating the synthetic potential of this protocol for late-stage functionalization.



In a further study, the reactions of various potassium perfluorobenzoates 2 with 1a was investigated (Scheme 4). As a result, two fluorine atoms located in the *ortho*-position of benzoates 2 appeared to be the key point in this reaction.<sup>17</sup> Decarbonylative and decarboxylative couplings of potassium 2,6-difluorobenzoate (2b) and 2,4,6-trifluorobenzoate (2c) proceeded smoothly to give the desired products 3ab and 3ac in 63% and 42% yields, respectively. While 2,3,5,6-tetrafluoro-4methylbenzoates (2d) afforded the corresponding product 3ad in 54% yield, no coupling product 3ae was observed when 2,3,4,5-tetrafluorobenzoate (2e) was employed. Only 20% of the desired product 3af was obtained, probably due to competition from the C-H bond activation reaction at the 2,3,5, 6-tetrafluorobenzene moiety.<sup>18</sup>

To gain insights into the mechanism of this reaction, the reaction was conducted without perfluorobenzoates 2 (Scheme 5a).



Scheme 4 Substrate scope of perfluorobenzoates 2. <sup>a</sup> Reaction conditions: Pd(dba)<sub>2</sub> (0.02 mmol, 10 mol%), PCy<sub>3</sub>·HBF<sub>4</sub> (0.04 mmol, 20 mol%), 2-naphthoyl chloride **1a** (0.2 mmol), potassium perfluorobenzoates **2** (0.3 mmol, 1.5 equiv.), and toluene (1 mL) at 150 °C for 20 h. Isolated yields. <sup>b</sup> 140 °C.



Reaction of **1c** with Pd(dba)<sub>2</sub> in the presence of stirred PCy<sub>3</sub> at room temperature gave complex **5**, corresponding to intermediate **A** in Scheme 2, and reaction at 140 °C for 3 h yielded complex **6**, corresponding to intermediate **B** in Scheme 2.<sup>7d</sup> Reaction with **2a** using the separately prepared and isolated palladium complex **6** gave the product **3ca** in 77% GC yield, with no esters observed (Scheme 5b). These results suggest that Path a is a plausible reaction pathway. However, the possibility of Path b cannot be ruled out at this stage. Although the decarboxylation of potassium perfluorobenzoates **2** could proceed under transition-metal-free conditions, we propose that the decarboxylation in this transformation is caused by palladium, since Liu's work<sup>5b</sup> and our previous reports<sup>16</sup> indicate that decarboxylation cannot proceed in toluene without palladium, and that only a small amount of ketone **4** was obtained in the absence of palladium catalyst, as shown in entry **12** of Table **1**.

In summary, we have developed the palladium-catalyzed cross-coupling reaction of acyl chlorides with potassium perfluorobenzoates to synthesize perfluorinated biaryls. This protocol realized the first cross-coupling involving simultaneous decarbonylation and decarboxylation under redoxneutral conditions, and both starting materials can be prepared directly from carboxylic acids, providing an environmentally friendly and sustainable cross-coupling reaction. We are currently conducting experiments to achieve a wide substrate scope under even milder conditions.

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#### Conflicts of interest

There are no conflicts to declare.

#### References

- (a) L. J. Gooßen, N. Rodriguez and K. Gooßen, Angew. Chem., Int. Ed., 2008, 47, 3100; (b) N. Rodriguez and L. J. Gooßen, Chem. Soc. Rev., 2011, 40, 5030; (c) W. I. Dzik, P. P. Lange and L. J. Gooßen, Chem. Sci., 2012, 3, 2671.
- 2 (a) L. Guo and M. Rueping, Acc. Chem. Res., 2018, 51, 1185; (b) L. Guo and M. Rueping, Chem. Eur. J., 2018, 24, 7794; (c) N. Blanchard and V. Bizet, Angew. Chem., Int. Ed., 2019, 58, 6814; (d) Y. Ogiwara and N. Sakai, Angew. Chem., Int. Ed., 2020, 59, 574; (e) Z. Wang, X. Wang and Y. Nishihara, Chem. Asian. J., 2020, 15, 1234; (f) H. Lu, T.-Y. Yu, P.-F. Xu and H. Wei, Chem. Rev., 2021, 121, 365.

- Communication
- 3 (a) R. Shang and L. Liu, Sci. China: Chem., 2011, 54, 1670;
  (b) J. Cornella and I. Larrosa, Synthesis, 2012, 653; (c) T. Patra and D. Maiti, Chem. Eur. J., 2017, 23, 7382; (d) Y. Wei, P. Hu, M. Zhang and W. Su, Chem. Rev., 2017, 117, 8864; (e) T. Zhang, N.-X. Wang and Y. Xing, J. Org. Chem., 2018, 83, 7559; (f) J. Schwarz and B. König, Green Chem., 2018, 20, 323.
- 4 For selected reports, see: (a) L. J. Gooßen, G. Deng and L. M. Levy, *Science*, 2006, 313, 662; (b) L. J. Gooßen, N. Rodríguez, B. Melzer, L. Linder, G. Deng and L. M. Levy, *J. Am. Chem. Soc.*, 2007, 129, 4824; (c) L. J. Gooßen, N. Rodríguez and C. Linder, *J. Am. Chem. Soc.*, 2008, 130, 15248; (d) L. J. Gooßen, N. Rodríguez, P. P. Lange and C. Linder, *Angew. Chem., Int. Ed.*, 2010, 49, 1111.
- 5 (a) R. Shang, Y. Fu, Y. Wang, Q. Xu, H.-Z. Yu and L. Liu, Angew. Chem., Int. Ed., 2009, 48, 9350; (b) R. Shang, Q. Xu, Y.-Y. Jiang, Y. Wang and L. Liu, Org. Lett., 2010, 12, 1000; (c) L. W. Sardzinski, W. C. Wertjes, A. M. Schnaith and D. Kalyani, Org. Lett., 2015, 17, 1256; (d) Q. Chen, A. Wu, S. Qin, M. Zeng, Z. Le, Z. Yan and H. Zhang, Adv. Synth. Catal., 2018, 360, 3239; (e) R. A. Daley, E.-C. Liu and J. J. Topczewski, Org. Lett., 2019, 21, 4734.
- 6 For selected reports of decarboxylative cross-couplings, see:
  (a) P. Forgione, M.-C. Brochu, M. St-Onge, K. H. Thesen, M. D. Bailey and F. Bilodeau, J. Am. Chem. Soc., 2006, 128, 11350;
  (b) J.-M. Becht, C. Catala, C. Le Drian and A. Wagner, Org. Lett., 2007, 9, 1781;
  (c) X. Li, D. Zou, F. Leng, C. Sun, J. Li, Y. Wu and Y. Wu, Chem. Commun., 2013, 49, 312.
- 7 For selected reports of decarbonylative cross-couplings, see:
  (a) K. Muto, J. Yamaguchi, D. G. Musaev and K. Itami, *Nat. Commun.*, 2015, 6, 7508; (b) S. Shi, G. Meng and M. Szostak, *Angew. Chem., Int. Ed.*, 2016, 55, 6959; (c) C. A. Malapit, J. R. Bour, C. E. Brigham and M. S. Sanford, *Nature*, 2018, 563, 100; (d) T. Zhou, P. Xie, C. Ji, X. Hong and M. Szostak, *Org. Lett.*, 2020, 22, 6434.
- 8 To the best of our knowledge, three works on tandem radical decarboxylation and decarbonylation reactions under oxidative conditions have been reported, see: (a) C. Pan, Y. Chen, S. Song, L. Li and J.-T. Yu, J. Org. Chem., 2016, 81, 12065; (b) Z. Luo, X. Han, Y. Fang, P. Liu, C. Feng, Z. Lia and X. Xu, Org. Chem. Front., 2018, 5, 3299; (c) F. Zhou, L. Li, K. Lin, F. Zhang, G.-J. Deng and H. Gong, Chem. Eur. J., 2020, 26, 4246.
- 9 (a) L. Fu, Q. Chen, Z. Wang and Y. Nishihara, Org. Lett., 2020,
   22, 2350; (b) Q. Chen, L. Fu and Y. Nishihara, Chem. Commun., 2020,
   56, 7977.
- (a) T. Kashiwabara and M. Tanaka, Organometallics, 2006, 25, 4648;
   (b) F. Pan, G. B. Boursalian and T. Ritter, Angew. Chem., Int. Ed., 2018, 57, 16871.
- 11 (a) B. M. Trost and I. Fleming, Comprehensive Organic Synthesis, Pergamon Press, 1991; (b) M. B. Smith and J. March, Advanced Organic Chemistry, Wiley, 2007; (c) W. H. Brown, B. L. Iverson, E. V. Anslyn and C. S. Foote, Organic Chemistry, Cengage, 2018.

- 12 (a) T. Sugihara, T. Satoh, M. Miura and M. Nomura, Angew. Chem., Int. Ed., 2003, 42, 4672; (b) C. A. Malapit, N. Ichiishi and M. S. Sanford, Org. Lett., 2017, 19, 4142; (c) Z. Wang, X. Wang, Y. Ura and Y. Nishihara, Org. Lett., 2019, 21, 6779.
- 13 For selected reports and reviews, see: (a) M. Weck, A. R. Dunn, K. Matsumoto, G. W. Coates, E. B. Lobkovsky and R. H. Grubbs, Angew. Chem., Int. Ed., 1999, 38, 2741; (b) F. Babudri, G. M. Farinola, F. Naso and R. Ragni, Chem. Commun., 2007, 1003; (c) H. Amii and K. Uneyama, Chem. Rev., 2009, 109, 2119; (d) T. H. Chen, I. Popov, O. Zenasni, O. Daugulis and O. S. Miljanic, Chem. Commun., 2013, 49, 6846.
- 14 (a) R. E. Mewshaw, R. J. Edsall Jr., C. Yang, E. S. Manas, Z. B. Xu, R. A. Henderson, J. C. Keith Jr. and H. A. Harris, *J. Med. Chem.*, 2005, 48, 3953; (b) B. J. Backes, K. Longenecker, G. L. Hamilton, K. Stewart, C. Lai, H. Kopecka, T. W. von Geldern, D. J. Madar, Z. Pei, T. H. Lubben, B. A. Zinker, Z. Tian, S. J. Ballaron, M. A. Stashko, A. K. Mika, D. W. A. Beno, A. J. Kempf-Grote, C. Black-Schaefer, H. L. Sham and J. M. Trevillyan, *Bioorg. Med. Chem. Lett.*, 2007, 17, 2005; (c) M. de Candia, F. Liantonio, A. Carotti, R. De Cristofaro and C. Altomare, *J. Med. Chem.*, 2009, 52, 1018; (d) S. Preshlock, M. Tredwell and V. Gouverneur, *Chem. Rev.*, 2016, 116, 719.
- 15 (a) Y. Sakamoto, T. Suzuki, A. Miura, H. Fujikawa, S. Tokito and Y. Taga, J. Am. Chem. Soc., 2000, 122, 1832; (b) T. Tsuzuki, N. Shirasawa, T. Suzuki and S. Tokito, Adv. Mater., 2003, 15, 1455; (c) A. Facchetti, M. H. Yoon, C. L. Stern, H. E. Katz and T. J. Marks, Angew. Chem., Int. Ed., 2003, 42, 3900; (d) M. L. Tang, A. D. Reichardt, N. Miyaki, R. M. Stoltenberg and Z. Bao, J. Am. Chem. Soc., 2008, 130, 6064; (e) T. Okamoto, K. Nakahara, A. Saeki, S. Seki, J. H. Oh, H. B. Akkerman, Z. Bao and Y. Matsuo, Chem. Mater., 2011, 23, 1646; (f) H. Shin, D. Kim, H. J. Kim, J. Kim, K. Char, C. T. Yavuz and J. W. Choi, Chem. Mater., 2019, 31, 7910.
- 16 L. Fu, Q. Chen and Y. Nishihara, Org. Lett., 2020, 22, 6388.
- 17 According to previous reports, the acidity of R-H has a linear relationship with the decarboxylative reactivity of R-COOH. Hence, the number and position of fluorine atoms strongly affect the reactivity. (a) S.-L. Zhang, Y. Fu, R. Shang, Q.-X. Guo and L. Liu, J. Am. Chem. Soc., 2010, 132, 638; (b) J. Shi, X.-Y. Huang, J.-P. Wang and R. Li, J. Phys. Chem. A, 2010, 114, 6263; (c) S. I. Gorelsky, Coord. Chem. Rev., 2013, 257, 153.
- 18 Activation of C-H bonds in perfluorobenzenes is considered a major side reaction due to their high acidity, see ref. 5a and 5b. Also, (a) M. Lafrance, C. N. Rowley, T. K. Woo and K. Fagnou, J. Am. Chem. Soc., 2006, 128, 8754; (b) M. Lafrance, D. Shore and K. Fagnou, Org. Lett., 2006, 8, 5097; (c) Z. Lian, S. D. Friis and T. Skrydstrup, Chem. Commun., 2015, 51, 1870.