

Palladium-Catalyzed Intramolecular C–H Difluoroalkylation: Synthesis of Substituted 3,3-Difluoro-2-oxindoles**

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Abstract: The synthesis of 3,3-difluoro-2-oxindoles through a robust and efficient palladium-catalyzed C–H difluoroalkylation is described. This process generates a broad range of difluoro-oxindoles from readily prepared starting materials. The use of BrettPhos as the ligand was crucial for high efficiency. Preliminary mechanistic studies suggest that oxidative addition is the rate-determining step for this process.

The incorporation of fluorinated functional groups into organic molecules has been widely recognized as a general strategy in pharmaceutical research and drug development. Fluorinated analogues of pharmaceutically relevant compounds often possess properties conducive to drug development, such as improved lipophilicity, metabolic stability, and bioavailability relative to their nonfluorinated counterparts.^[1] For these reasons, substantial effort has been devoted to the development of synthetic methods for the assembly of fluorinated small molecules.^[2] The fluorination^[3] and trifluoromethylation^[4] of arenes have been the most prominent targets of these efforts, and as a result, increasingly general and practical methods are now available for these transformations.^[2] In contrast, methods for the synthesis of difluoroalkylated arenes remain limited.^[5] In particular, the synthesis of fluorinated heterocyclic compounds by the difluoroalkylation of arenes is a promising but underutilized strategy.

Derivatives of oxindole and isatin appear in a variety of naturally occurring and synthetic bioactive compounds (Figure 1).^[6] As bioisosteric analogues^[7] of both classes of heterocycles, compounds containing the 3,3-difluoro-2-oxindole ring system have demonstrated considerable promise as potential medicinal agents.^[8] There are, however, only a limited number of approaches for their preparation, each of which suffers from serious drawbacks.^[9] Difluoro-oxindoles have been prepared by the treatment of isatin derivatives with diethylaminosulfur trifluoride (DAST) or by electrophilic fluorination of indoles.^[9a–c] However, the limited stability of

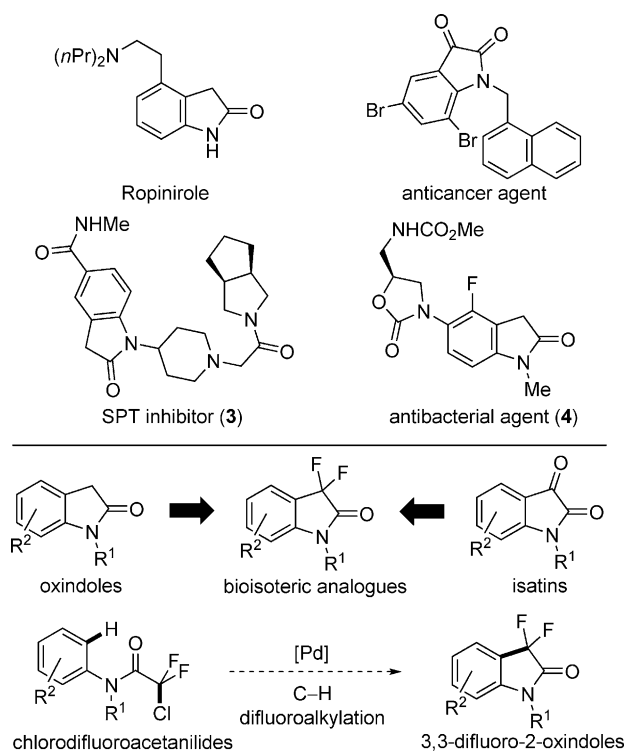


Figure 1. Bioactive oxindoles and isatins (top), 3,3-difluoro-2-oxindoles as bioisosteric analogues of oxindoles and isatins and their proposed synthesis from chlorodifluoroacetanilides (bottom).

the requisite reagents and modest functional-group tolerance diminish the utility and practicality of these procedures.^[10] Moreover, both approaches depend on the availability of the pre-existing bicyclic ring system, whose construction may be nontrivial. The synthesis of the difluoro-oxindole ring system under free-radical conditions^[9a] or in the presence of a stoichiometric amount of copper^[9c] has also been reported. However, these methods are limited by their scope, synthetic efficiency, or the accessibility of the required starting materials. A synthesis of difluoro-oxindoles through a palladium-catalyzed C–H difluoroalkylation process^[11] would constitute a general and practical alternative to these previously reported methods.

In 2003, we disclosed the palladium-catalyzed synthesis of oxindoles from α -chloroacetanilides.^[12] The application of this method to the kilogram-scale synthesis of two drug candidates, a serine palmitoyl transferase inhibitor (3; Figure 1)^[13] and a long-term oxazolidinone antibacterial (4)^[14] illustrate the practicality and atom- and step-economical advantages of this C–H functionalization protocol. An

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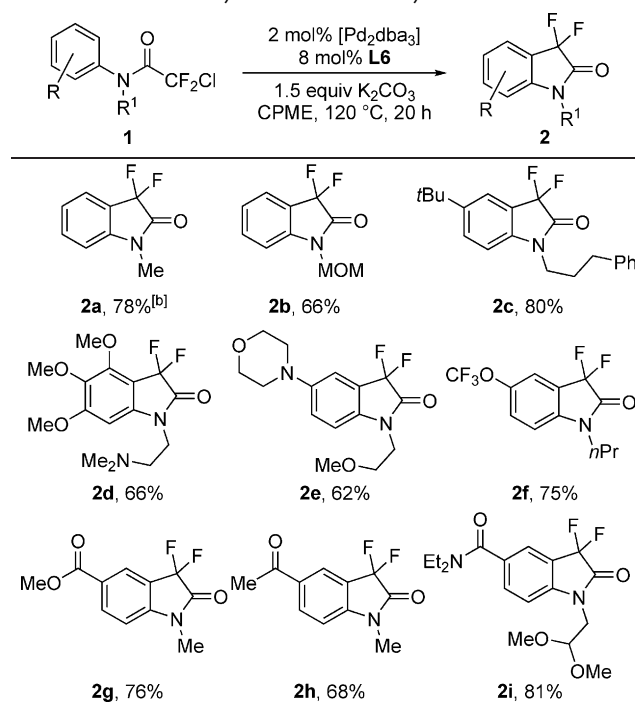
analogous process wherein chlorodifluoroacetanilides are transformed into difluorooxindoles would similarly enable the rapid construction of these compounds from readily available starting materials. Chlorodifluoroacetanilides can be prepared in one step by acylation of the corresponding (hetero)arylamines with inexpensive chlorodifluoroacetic anhydride. Although the oxidative addition^[15] of palladium(0) to the analogous C–Cl bond of chlorodifluoroacetanilides, as well as the subsequent C–C bond-forming reductive elimination^[4a,16] are expected to be challenging processes, we posited that the use of bulky biarylphosphine ligands would facilitate these elementary steps. We disclose herein the successful development of an efficient palladium-catalyzed C–H difluoroalkylation reaction for the synthesis of 3,3-difluoro-2-oxindoles.

We began our investigation of the proposed transformation by exposing the chlorodifluoroacetanilide **1a** to base (K_2CO_3) and palladium catalysts generated from premixing^[17] 1 mol % of $[Pd_2dba_3]$ and 4 mol % of a variety of phosphine ligands (Table 1). The use of JohnPhos (**L1**), the optimal ligand for the previous oxindole synthesis, provided **2a** in low yield (entry 1). Catalysts derived from CyJohnPhos (**L2**), RuPhos (**L3**), XPhos (**L4**), and *t*BuXPhos (**L5**) were more effective, but still only provided the desired oxindole in low to moderate yields (entries 2–5). However, when BrettPhos (**L6**) was employed as the ligand, the difluorinated oxindole **2a** was isolated in high yield (78%; entry 6). The use of other monophosphine ligands, as well as bidentate phosphine ligands, such as PPh_3 , PCy_3 , $P(tBu)_3$, dppe, binap, and Xantphos, resulted in low to no conversion to the desired

product (entries 7–12). No conversion of the starting material was observed in the absence of either a phosphine ligand or palladium source (entries 13 and 14). Lastly, exposure of **1a** to Friedel–Crafts cyclization conditions (1.2 equiv $AlCl_3$) led to the decomposition of the starting material without formation of the desired product.

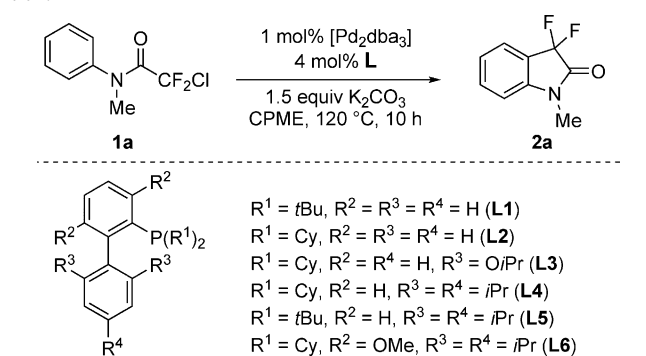
Under optimized reaction conditions (Table 2), we explored the substrate scope of this transformation. A series of chlorodifluoroacetanilides with electron-rich, electron-neutral, and electron-deficient substituents on the aryl

Table 2: Palladium-catalyzed C–H difluoroalkylation of arenes.^[a]



[a] Yields of isolated product are an average of two runs on a 1.0 mmol scale. [b] Reaction conditions: $[Pd_2dba_3]$ (1 mol %), **L6** (4 mol %), 10 h.

Table 1: Palladium-catalyzed C–H difluoroalkylation: Ligand identification.^[a]



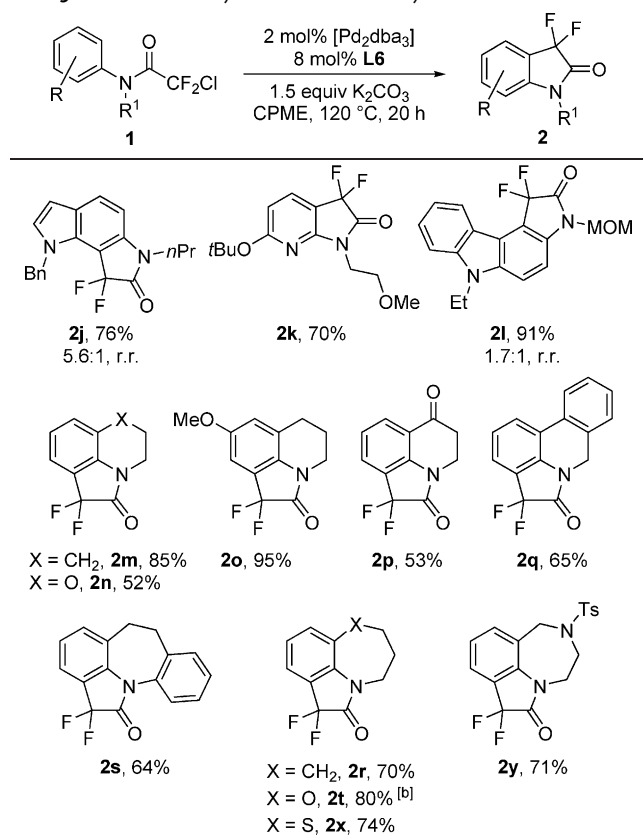
Entry	Ligand	Yield [%] ^[b]	Entry	Ligand	Yield [%] ^[b]
1	L1	7	8	PCy_3	16
2	L2	17	9	$PtBu_3$	16
3	L3	13	10	dppe	13
4	L4	38	11	binap	4
5	L5	53	12	Xantphos	0
6	L6	85 (78) ^[c]	13 ^[d]	L6	0
7	PPh_3	6	14 ^[e]	–	0

[a] Reactions were run in 0.2 mmol scale. [b] Determined by ^{19}F NMR analysis of the crude reaction mixture using $PhCF_3$ as an internal standard. [c] Yield of isolated product. [d] Without $[Pd_2dba_3]$. [e] Without ligand. binap = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, CPME = cyclopentyl methyl ether, dba = dibenzylidene acetone, dppe = 1,2-bis(diphenylphosphino)ethane, Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

group were found to undergo the desired transformation to afford the corresponding difluorooxindoles in good yield. This process was found to be compatible with ketone (**2h**), ester (**2g**), amide (**2i**), acetal (**2i**), hemiaminal (**2b**), amino (**2d**, **2e**), and trifluoromethoxy (**2f**) functional groups.

Given the prevalence of heterocycles in medicinal chemistry, we also investigated the scope of heterocyclic substrates (Table 3).^[18] A broad array of heterocycle substrates featuring monocyclic, bicyclic, and tricyclic rings were compatible with the optimized reaction conditions. The scope included heterocycles such as pyridine (**2k**), tetrahydroquinoline (**2m**, **2o**), 1,4-benzoxazine (**2n**), dihydrophenanthridine (**2q**), dihydroquinolinone (**2p**), tetrahydrobenzazepine (**2r**), dihydrodibenzoazepine (**2s**), tetrahydrobenzooxazepine (**2t**), tetrahydrobenzothiazepine (**2x**), and tetrahydrobenzodiazepine (**2y**) ring systems. Unsymmetrical indole and carbazole substrates provided products **2j** and **2l** as chromatographically separable regioisomers with moderate selectivity. Interestingly, the cyclization occurred preferentially at the

Table 3: Palladium-catalyzed C–H difluoroalkylation of heteroarenes.^[a]



[a] Yields of isolated product are an average of two runs in 1.0 mmol scale. [b] Reaction was conducted in 5.0 mmol scale. r.r. = regioisomeric ratio. MOM = methoxymethyl.

more sterically hindered position of these substrates, in contrast to our previous palladium-catalyzed oxindole synthesis.^[12] To demonstrate the robustness of our reaction conditions, the synthesis of **2t** was also conducted on a 5 mmol scale to afford the desired product in undiminished isolated yield.

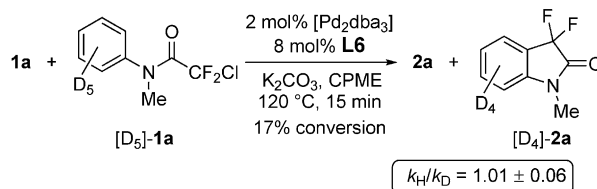
To probe the mechanism of this transformation, we synthesized the isotopically labeled substrates **[D₁]-1a** and **[D₅]-1a** (Scheme 1) for the determination of the intra- and intermolecular kinetic isotope effects, respectively. An inverse kinetic isotope effect was observed when **[D₁]-1a** was subjected to standard reaction conditions ($k_H/k_D = 0.79$; Scheme 1 a). On the other hand, no kinetic isotope effect was observed upon exposure of a 1:1 mixture of **1a** and **[D₅]-1a** to the standard reaction conditions ($k_H/k_D = 1.01$; Scheme 1 b).

Based on these data, a plausible mechanism for this transformation is shown in Scheme 2. The initial step of this process is likely the oxidative addition of the chlorodifluoro amide to Pd⁰ to generate a Pd^{II} enolate. The absence an intermolecular isotope effect indicates that the rate-determining step occurs prior to a C–H bond cleavage or rehybridization event, thus suggesting that oxidative addition is rate-determining.^[19] Subsequently, electrophilic aromatic substitution of the arene furnishes a six-membered palladacycle, which then undergoes reductive elimination to provide the observed product and regenerate the Pd⁰ species. The

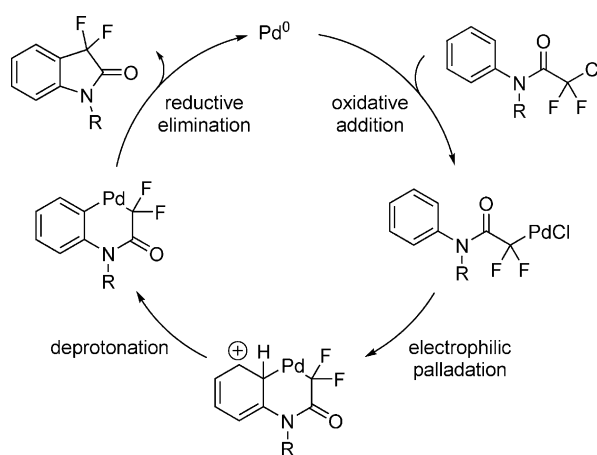
a) Intramolecular



b) Intermolecular



Scheme 1. Observed kinetic isotope effects.



Scheme 2. Proposed catalytic cycle (the ligand was omitted for clarity).

inverse kinetic isotope effect observed in the intramolecular experiment is likely a secondary isotope effect resulting from the sp² to sp³ rehybridization of the arene carbon atom to which the proton or deuteron is attached.^[20] The observation of an inverse isotope effect implies that palladation is slow relative to C–H bond cleavage in the electrophilic aromatic substitution process, and is in contrast to our previously reported palladium-catalyzed oxindole synthesis from α -chloroacetanilides.^[12] Alternative mechanisms in which palladation occurs through concerted either a metalation/deprotonation or σ -bond metathesis pathway are excluded on the basis of the observed inverse intramolecular isotope effect.^[21]

In summary, we have developed a practical palladium-catalyzed aromatic C–H difluoroalkylation reaction using readily available chlorodifluoroacetanilides. The bulky biarylphosphine ligand, BrettPhos, was found to be the only phosphine ligand capable of efficiently providing the desired difluoro-oxindole product. This method allows the straightforward and efficient preparation of a wide range of substituted 3,3-difluoro-2-oxindoles. The high level of functional-group tolerance and ready availability of starting materials should make this protocol broadly useful and attractive in academic and industrial settings.

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- [1] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; b) T. Hiyama, *Fluorine Compounds: Chemistry and Applications*, Springer, Berlin, **2000**; c) T. Yamazaki, T. Taguchi, I. Ojima in *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley-Blackwell, Chichester, **2009**, pp. 3–46; d) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; e) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506.
- [2] For selected reviews, see: a) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214–8264; *Angew. Chem.* **2013**, *125*, 8372–8423; b) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475–4521; c) T. Besset, C. Schneider, D. Cahard, *Angew. Chem. Int. Ed.* **2012**, *51*, 5048–5050; *Angew. Chem.* **2012**, *124*, 5134–5136; d) X.-F. Wu, H. Neumann, M. Beller, *Chem. Asian J.* **2012**, *7*, 1744–1754; e) R. J. Lundgren, M. Stradiotto, *Angew. Chem. Int. Ed.* **2010**, *49*, 9322–9324; *Angew. Chem.* **2010**, *122*, 9510–9512; for selected examples of arene fluorination and trifluoromethylation, see: f) D. A. Nagib, D. W. C. MacMillan, *Nature* **2011**, *480*, 224–228; g) Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond, P. S. Baran, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 14411–14415; h) P. Tang, T. Furuya, T. Ritter, *J. Am. Chem. Soc.* **2010**, *132*, 12150–12154; i) X. Wang, L. Truesdale, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3648–3649; j) N. D. Ball, J. W. Kampf, M. S. Sanford, *J. Am. Chem. Soc.* **2010**, *132*, 2878–2879; k) L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2012**, *134*, 1298–1304.
- [3] a) D. A. Watson, M. Su, G. Teverovskiy, Y. Zhang, J. García-Fortanet, T. Kinzel, S. L. Buchwald, *Science* **2009**, *325*, 1661–1664; b) H. G. Lee, P. J. Milner, S. L. Buchwald, *Org. Lett.* **2013**, *15*, 5602–5605; c) H. G. Lee, P. J. Milner, S. L. Buchwald, *J. Am. Chem. Soc.* **2014**, *136*, 3792–3795.
- [4] a) E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson, S. L. Buchwald, *Science* **2010**, *328*, 1679–1681; b) T. D. Senecal, A. T. Parsons, S. L. Buchwald, *J. Org. Chem.* **2011**, *76*, 1174–1176; c) E. J. Cho, S. L. Buchwald, *Org. Lett.* **2011**, *13*, 6552–6555; d) M. Chen, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 11628–11631; *Angew. Chem.* **2013**, *125*, 11842–11845.
- [5] a) Y. Guo, J. M. Shreeve, *Chem. Commun.* **2007**, 3583–3585; b) K. Fujikawa, Y. Fujioka, A. Kobayashi, H. Amii, *Org. Lett.* **2011**, *13*, 5560–5563; c) P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 5524–5527; d) G. K. S. Prakash, S. K. Ganesh, J.-P. Jones, A. Kulkarni, K. Masood, J. K. Swabeck, G. A. Olah, *Angew. Chem. Int. Ed.* **2012**, *51*, 12090–12094; *Angew. Chem.* **2012**, *124*, 12256–12260; e) K. Araki, M. Inoue, *Tetrahedron* **2013**, *69*, 3913–3918; f) Q. Qi, Q. Shen, L. Lu, *J. Am. Chem. Soc.* **2012**, *134*, 6548–6551; during the preparation of this manuscript, the following metal-catalyzed difluoroalkylation reactions were reported: g) Q.-Q. Min, Z. Yin, Z. Feng, W.-H. Guo, X. Zhang, *J. Am. Chem. Soc.* **2014**, *136*, 1230–1233; h) S. Ge, W. Chaladaj, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 4149–4152; i) Z. Feng, Q.-Q. Min, Y.-L. Xiao, B. Zhang, X. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 1669–1673; *Angew. Chem.* **2014**, *126*, 1695–1699; j) Y.-L. Xiao, W.-H. Guo, G.-Z. He, Q. Pan, X. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 9909–9913; *Angew. Chem.* **2014**, *126*, 10067–10071; k) Y.-B. Yu, G.-Z. He, X. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 10457–10461; *Angew. Chem.* **2014**, *126*, 10625–10629; l) S. Ge, S. I. Arlow, M. G. Mormino, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 14401–14404; m) C. Matheis, K. Jouvin, L. J. Goossen, *Org. Lett.* **2014**, *16*, 5984–5987; n) Y. Gu, X. Leng, Q. Shen, *Nat. Commun.* **2014**, *5*:5405 DOI: 10.1038/ncomms6405.
- [6] a) Y.-J. Wu in *Heterocyclic Scaffolds II, Topics in Heterocyclic Chemistry*, Vol. 26. (Ed.: G. W. Gribble), Springer, Berlin, **2010**, p. 1–30; b) J. J. Badillo, N. V. Hanhan, A. K. Franz, *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758–776.
- [7] For a discussion on bioisosteres, see: N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529–2591.
- [8] For examples of 3,3-difluoro-2-oxindole analogues in biological studies, see: a) N. Zhou, A. M. Polozov, M. O'Connell, J. Burgeson, P. Yu, W. Zeller, J. Zhang, E. Onua, J. Ramirez, G. A. Palsdottir, G. V. Halldorsdottir, T. Andresson, A. S. Kiselyov, M. Gurney, J. Singh, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2658–2664; b) G. D. Zhu, V. B. Gandhi, J. C. Gong, Y. Luo, X. S. Liu, Y. Shi, R. Guan, S. R. Magnone, V. Klinghofer, E. F. Johnson, J. Bouska, A. Shoemaker, A. Oleksijew, K. Jarvis, C. Park, R. De Jong, T. Oltersdorf, Q. Li, S. H. Rosenberg, V. L. Giranda, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3424–3429; c) A. K. Podichetty, A. Faust, K. Kopka, S. Wagner, O. Schober, M. Schäfers, G. Haufe, *Bioorg. Med. Chem.* **2009**, *17*, 2680–2688.
- [9] a) W. J. Middleton, E. M. Bingham, *J. Org. Chem.* **1980**, *45*, 2883–2887; b) R. P. Singh, U. Majumder, J. M. Shreeve, *J. Org. Chem.* **2001**, *66*, 6263–6267; c) Y. H. Lim, Q. Ong, H. A. Duong, T. M. Nguyen, C. W. Johannes, *Org. Lett.* **2012**, *14*, 5676–5679; d) Y. Ohtsuka, T. Yamakawa, *Tetrahedron* **2011**, *67*, 2323–2331; e) J. Zhu, W. Zhang, L. Zhang, J. Liu, J. Zheng, J. Hu, *J. Org. Chem.* **2010**, *75*, 5505–5512.
- [10] a) L. N. Markovskij, V. E. Pahinnik, A. V. Kirsanov, *Synthesis* **1973**, 787–789; b) W. J. Middleton, *J. Org. Chem.* **1975**, *40*, 574–578; c) P. A. Messina, K. C. Mange, W. J. Middleton, *J. Fluorine Chem.* **1989**, *42*, 137–143.
- [11] a) Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond, P. S. Baran, *J. Am. Chem. Soc.* **2012**, *134*, 1494–1497; b) Q. Zhou, A. Ruffoni, R. Gianatassio, Y. Fujiwara, E. Sella, D. Shabat, P. S. Baran, *Angew. Chem. Int. Ed.* **2013**, *52*, 3949–3952; *Angew. Chem.* **2013**, *125*, 4041–4044; c) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95–99; d) Y.-M. Su, Y. Hou, F. Yin, Y.-M. Xu, Y. Li, X. Zheng, X.-S. Wang, *Org. Lett.* **2014**, *16*, 2958–2961; e) J. Jung, E. Kim, Y. You, E. J. Cho, *Adv. Synth. Catal.* **2014**, *356*, 2741–2748; f) L. Wang, X.-J. Wei, W.-L. Jia, J.-J. Zhong, L.-Z. Zhong, L.-Z. Wu, Q. Liu, *Org. Lett.* **2014**, *16*, 5842–5845. For recent examples of C–H trifluoroethylation, see: g) W. Song, S. Lackner, L. Ackermann, *Angew. Chem. Int. Ed.* **2014**, *53*, 2477–2480; *Angew. Chem.* **2014**, *126*, 2510–2513; h) H. Zhang, P. Chen, G. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 10174–10178; *Angew. Chem.* **2014**, *126*, 10338–10342.
- [12] E. J. Hennessy, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 12084–12085.
- [13] E. J. Kiser, J. Magano, R. J. Shine, M. H. Chen, *Org. Process Res. Dev.* **2012**, *16*, 255–259.
- [14] A. Choy, N. Colbry, C. Huber, M. Pamment, J. V. Duine, *Org. Process Res. Dev.* **2008**, *12*, 884–887.
- [15] To the best of our knowledge, the oxidative addition of palladium to a C–Cl bond of a difluoroalkyl chloride has not been described in the literature. The palladium-catalyzed difluoroalkylation reactions using difluoroalkyl bromides have been reported. See Ref. [5g,i,k].
- [16] a) V. V. Grushin, W. J. Marshall, *J. Am. Chem. Soc.* **2006**, *128*, 4632–4641; b) V. V. Grushin, W. J. Marshall, *J. Am. Chem. Soc.* **2006**, *128*, 12644–12645.
- [17] The beneficial effects of catalyst premixing have been reported previously. See: a) J. P. Wolfe, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1144–1157; b) S. Ueda, M. Su, S. L. Buchwald, *Angew.*

- Chem. Int. Ed.* **2011**, 50, 8944–8947; *Angew. Chem.* **2011**, 123, 9106–9109; c) S. Ueda, M. Su, S. L. Buchwald, *J. Am. Chem. Soc.* **2012**, 134, 700–706.
- [18] a) J. A. Joule, K. Mills in *Heterocyclic Chemistry*, 5th ed., Wiley, Chichester, **2010**; b) R. Leurs, R. A. Bakker, H. Timmerman, I. J. P. de Esch, *Nat. Rev. Drug Discovery* **2005**, 4, 107–120.
- [19] For a useful discussion on analyzing KIE, see: E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, 51, 3066–3072; *Angew. Chem.* **2012**, 124, 3120–3126.
- [20] An inverse secondary intramolecular KIE of similar magnitude has been reported for a hydroarylation reaction and was attributed to sp^2 - to sp^3 -carbon atom rehybridization in an arene dearomatization step: J. A. Tunge, L. N. Foresee, *Organometallics* **2005**, 24, 6440–6444.
- [21] An alternative mechanism in which C–C bond formation proceeds by carbopalladation of the aromatic ring followed by β -hydride elimination cannot be excluded. See Ref. [12].
-