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Fluoroalkylation

Pd-Catalyzed Difluoromethylation of Vinyl Bromides, Triflates, Tosylates, and Nonaflates

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Abstract: Pd-catalyzed difluoromethylation of di-, tri- or tetra-substituted vinyl bromides, triflates, tosylates and nonaflates under mild conditions is described. The reaction tolerates a wide range of functional groups, such as bromide, chloride, fluoride, ester, amine, nitrile, and protected carbonyl, thus providing a general route for the preparation of difluoromethylated alkenes.

The beneficial "fluorine effect" on drug molecules has been well recognized in the field of medicinal and agro-chemistry, as evidenced by the growing number of fluorinated drugs and agrochemicals on the market and drug candidates at developmental stages.[1] Typically, most of these molecules contain a fluorine or a trifluoromethyl group.[2] In comparison, compounds bearing a difluoromethyl group (-CF_2H) have been much less prominently marketed.[3] Nevertheless, interest in this structural unit is growing rapidly, since the difluoromethyl group is known to be a bioisostere of carbinol or thiol groups in drug design.[4] In addition, the difluoromethyl group can act as a lipophilic hydrogen bond donor that could improve the molecule's binding selectivity and cell membrane permeability. Consequently, these interests in the medicinal chemistry community have stimulated many research groups to develop efficient methods for the incorporation of the difluoromethyl group into organic molecules under mild conditions.[5] In the past five years, several elegant methods for the construction of difluoromethylated arenes or heteroarenes have been achieved either through radical-based fluorination[6] and difluoromethylation[7] processes, or through transition metal-catalyzed direct difluoromethylation of aryl halides or diazonium salts.[8]

Owing to their similar steric and electronic properties, fluoroalkylated alkenes are generally considered to be capable of replacing a peptide bond in peptidomimetics to improve biological activity.[9] Hence, difluoromethylated alkenes could act as a very useful structural component in drug design. In spite of remarkable progress in the development of new methods for difluoromethylation of arenes, protocols for the construction of difluoromethylated alkenes have been much less explored. Only recently, the groups of Hartwig and Surya Prakash have reported copper(I)-mediated reactions of vinyl iodides with nucleophilic difluoromethylated reagents.[8c,d] However, reactions with easily available vinyl sulfates, such as triflates, nonaflates, and tosylates, have not been reported. Liu and coworkers reported an iron-catalyzed decarboxylative difluoromethylation of electron-rich aryl-substituted acrylic acids with moderate yields under mild conditions.[10] However, electron-deficient aryl-substituted acrylic acids gave very low yields under the same reactions conditions. Thus, efficient methods for the introduction of difluoromethyl onto alkenes are highly desirable.[11]

As a part of ongoing efforts on the development of efficient methods for late-stage introduction of fluoroalkyl groups into small molecules through transition metal catalysis,[12] we report herein the first example of palladium-catalyzed direct difluoromethylation of di-, tri-, or tetra-substituted vinyl bromides, triflates, tosylates, and nonaflates under mild reaction conditions, thus providing a general solution for the high efficient synthesis of a wide range of functionalized difluoromethylated alkenes.

We recently reported a cooperative bimetallic Pd/Ag-catalyzed difluoromethylation of aryl bromides and iodides using $TMSCF_2H$ as the difluoromethyl source and NaO*t*Bu as the activator.[8j] We envisaged that, under similar conditions, the palladium-catalyzed difluoromethylation of alkenyl electrophiles might provide a straightforward solution. However, use of a palladium catalyst for the formation of difluoromethylated alkenes is a challenging task, since, in the presence of a palladium catalyst, the allylic C–F bond in difluoromethylated alkenes has been known to undergo an irreversible oxidative addition, and subsequent further transformation will give defluorinated compounds.[13] For example, Gouverneur and co-workers reported that palladium-catalyzed allylic alkylation of monoallylic fluoride occurred at room temperature, whereby a C–F bond is replaced by a C–C bond.[14a] Paquin and co-workers reported that, under palladium-catalyzed conditions, one of the C–F bonds in 3,3-difluoropropenes could be activated and functionalized at slightly increased temperature (70 °C).[14b] Thus, a highly activated palladium catalyst is needed that could promote reductive elimination from a [L_2Pd(vinyl)(CF_2H)] complex to form the difluoromethylated alkene, while, at the same time, prohibiting the allylic C–F bond activation process (Scheme 1).

With these thoughts in mind, we initially studied the palladium-catalyzed coupling of β-bromostyrene with trimethylsilyldi-

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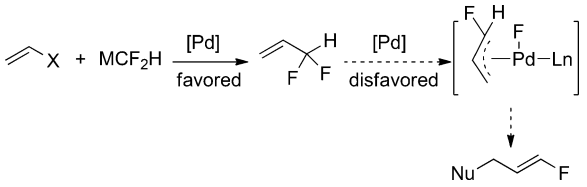


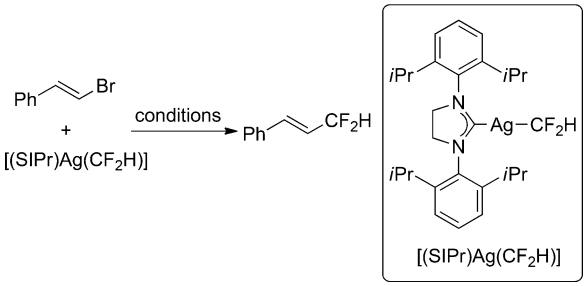
Scheme 1. Palladium-catalyzed difluoromethylation of vinyl electrophiles and possible defluorination side reaction.

fluoromethane ($TMSCF_2H$) at room temperature in the presence of a variety of phosphine ligands, such as XantPhos, DPPF, BINAP, Brettphos, Ruphos, and tBu_3P. Initial attempt to extend our recently published palladium/silver cooperative catalyst with DPPF as the ligand for direct difluoromethylation of aryl bromides and iodides[8j] resulted in a 44% yield when the reaction was conducted in dioxane at room temperature for 24 h. Switching to other phosphine ligands led to lower yields. Interestingly, the yield was decreased when the reaction time was elongated to 48 h or the reaction temperature was increased to 60 °C for 12 h. We attribute this decrease in the yield of the desired product to the palladium-mediated irreversible oxidative addition of the allylic C–F bond in difluoromethylated alkenes under the basic conditions. In fact, only 40% yield of the β-difluoromethylated styrene was detected by ^{19}F NMR spectroscopy when the reaction was carried out in dioxane at 60 °C for 4 h in the presence of 10 mol% $[Pd(dba)_2]$, 20 mol% DPPF and 1.0 equivalent of NaO*t*Bu. When other activators, such as KF, CsF or TBAF, were used, the yields of the desired product were less than 10%.

To facilitate the formation of the difluoromethylated alkenes and to prevent the activation of the allylic C–F bond, we sought to use $[(SIPr)Ag(CF_2H)]$ (SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene), which is not air, moisture, or light sensitive and can be readily prepared on 20 g scale, as the source of difluoromethyl group; thus the reaction could be conducted under neutral conditions.[8i] A combination of various palladium precursors with DPPF was found to promote the difluoromethylation of β-bromostyrene, whereas catalyst generated from $[\{Pd(cinnamyl)Cl\}_2]$ (cinnamyl = 3-phenylallyl)[15] gave the highest yield (Table 1, entries 1–6). The efficacy of the difluoromethylation in the presence of other phosphine ligands was then examined. Reactions using other bidentate or monodentate phosphine ligands gave the difluoromethylated alkenes in 0–73% yields (Table 1, entries 7–11). Increasing the temperature to 80 °C led to slightly lower yield (Table 1, entry 12). The Pd/ligand ratios proved crucial for the reactivity of the catalyst. When 1:1 or 2:1 palladium/DPPF ratio was used, the yields of the reaction dropped significantly (Table 1, entries 15 and 16). Finally, the loading of the catalyst could be decreased to 1.0 mol% without erosion of the yield of the reaction (Table 1, entries 17–19).

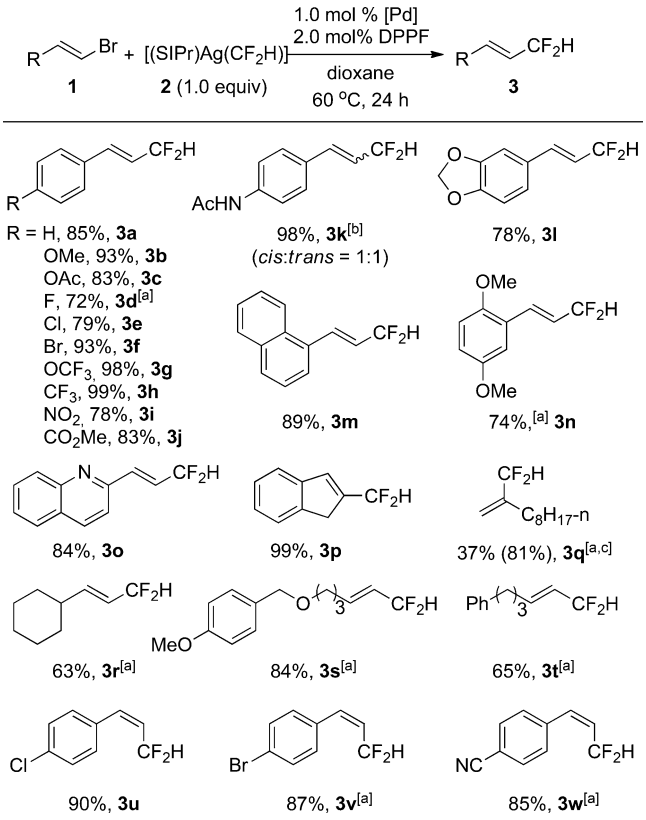
The reaction conditions developed for difluoromethylation of β-bromostyrene were applicable to a variety of alkenyl bromides (Scheme 2). Electron-neutral, electron-poor, or electron-rich *trans*-aryl-substituted alkenyl bromides reacted in high yields. Reactions of *trans*-alkyl-substituted alkenyl bromides were slightly slower and generally required 1.0 mol% $[\{Pd(cinnamyl)Cl\}_2]$ and 4.0 mol% DPPF for full conversion (Scheme 2, **3r–t**). A wide range of substrates, with functional groups such as chloride, bromide, fluoride, ester, amide, protected carbonyl, or nitro groups, underwent efficient difluoromethylation to afford the corresponding products in good to excellent yields (Scheme 2, **3c–f**, **3i–l**). Notably, the aryl bromo group in 1-(2-bromoethenyl)-4-bromobenzene **1f** remained intact, which indicated that vinyl bromides are much more reactive than aryl bromides under the reaction conditions (Scheme 2, **3f**). Reactions of *cis*-aryl-substituted alkenyl bromides also occurred in good to excellent yields with retention of the olefin geometry (Scheme 2, **3u–w**). These results provide evidence that the reaction does not precede via a radical intermediate, since the vinyl radical is known to be configurationally unstable;[16] a mixture of stereoisomers of the difluoromethylated alkenes would be observed if the vinyl radical was formed under the reaction conditions.

Table 1. Optimization of conditions for palladium-catalyzed difluoromethylation of vinyl bromide.[a]



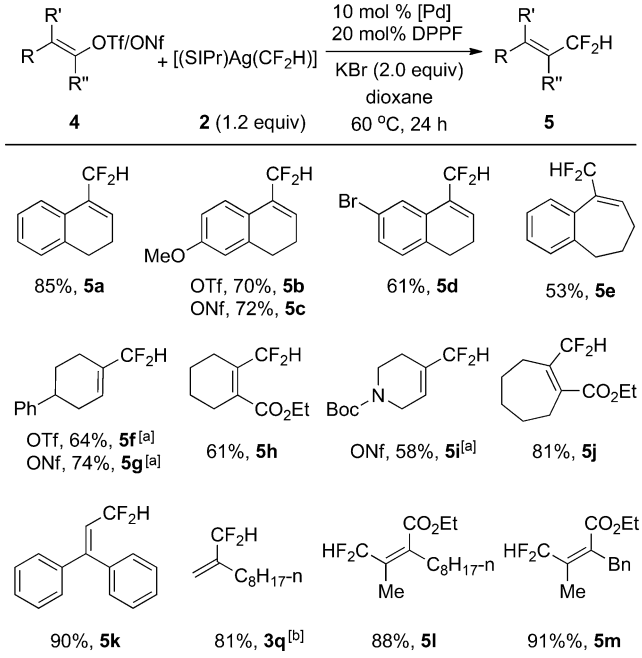
Entry	PdX_2 (mol%)	Ligand (mol%)	*T* [°C]	*t* [h]	Yield [%][b]
1	$[Pd(dba)_2]$ (10)	DPPF (20)	60	24	60
2	$Pd(OAc)_2$ (10)	DPPF (20)	60	24	61
3	$PdCl_2$ (10)	DPPF (20)	60	24	54
4	$[Pd(PPh_3)_4]$ (10)	DPPF (20)	60	24	84
5	$[\{Pd(allyl)Cl\}_2]$ (5)	DPPF (20)	60	24	76
6	$[\{Pd(cinnamyl)Cl\}_2]$ (5)	DPPF (20)	60	24	91
7	$[\{Pd(cinnamyl)Cl\}_2]$ (5)	BINAP (20)	60	24	12
8	$[\{Pd(cinnamyl)Cl\}_2]$ (5)	DPPE (20)	60	24	<2
9	$[\{Pd(cinnamyl)Cl\}_2]$ (5)	DPPP (20)	60	24	43
10	$[\{Pd(cinnamyl)Cl\}_2]$ (5)	XantPhos (20)	60	24	43
11	$[\{Pd(cinnamyl)Cl\}_2]$ (5)	XPhos (20)	60	24	73
12	$[\{Pd(cinnamyl)Cl\}_2]$ (5)	DPPF (20)	80	24	76
13	$[\{Pd(cinnamyl)Cl\}_2]$ (5)	DPPF (20)	60	16	80
14	$[\{Pd(cinnamyl)Cl\}_2]$ (5)	DPPF (20)	60	12	76
15	$[\{Pd(cinnamyl)Cl\}_2]$ (5)	DPPF (10)	60	24	68
16	$[\{Pd(cinnamyl)Cl\}_2]$ (5)	DPPF (5)	60	24	30
17	$[\{Pd(cinnamyl)Cl\}_2]$ (2.5)	DPPF (10)	60	24	88
18	$[\{Pd(cinnamyl)Cl\}_2]$ (0.5)	DPPF (2)	60	24	87
19	$[\{Pd(cinnamyl)Cl\}_2]$ (0.5)	DPPF (1.5)	60	24	76
20	$[\{Pd(cinnamyl)Cl\}_2]$ (0.05)	DPPF (0.2)	60	24	27

[a] Reaction conditions: β-Bromostyrene (0.1 mmol), $[(SIPr)Ag(CF_2H)]$ (0.1 mmol), PdX_2 (0.1–10 mol%), ligand (0.2–20 mol%), dioxane (1.0 mL) at 60–80 °C for 12–24 h; [b] yields were determined by ^{19}F NMR spectroscopy with 1-fluoronaphthalene as the internal standard. DPPF = 1,1′-bis(diphenylphosphino)ferrocene; BINAP = 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl; DPPE = 1,2-bis(diphenylphosphino)ethane; DPPP = 1,3-bis(diphenylphosphino)propane; XantPhos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.



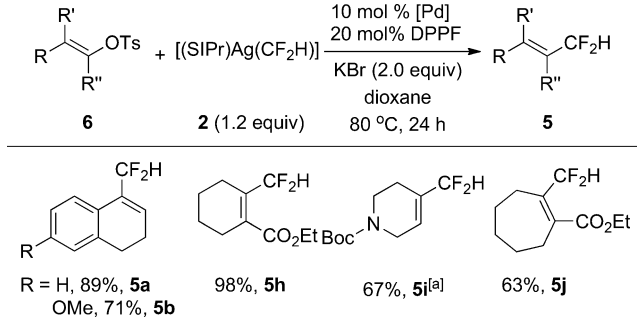
Scheme 2. Scope of palladium-catalyzed difluoromethylation of vinyl bromides. Reaction conditions (unless otherwise stated): Alkenyl bromide (1.0 mmol), [(SIPr)Ag(CF_2H)] (1.0 mmol), [{Pd(cinnamyl)Cl}$_2$] (0.5 mol%), DPPF (2.0 mol%), dioxane (10.0 mL) at 60 °C for 24 h, yield of isolated product. [a] The reaction was conducted in the presence of 1.0 mol% [{Pd(cinnamyl)Cl}$_2$]/4.0 mol% DPPF; [b] a 1:1 mixture of alkenyl bromides was used; [c] yield shown in parentheses was determined by ^{19}F NMR spectroscopy with 1-fluoronaphthalene as the internal standard.

Multi-substituted vinyl bromides, particularly cyclic vinyl bromides, generally require several steps to be synthesized. In these cases, vinyl triflates that are easily synthesized from enolizable carbonyl compounds and often referred to as pseudohalides, can be employed as alternatives to vinyl halides in many cross-coupling reactions.[17] Interestingly, reaction of triflate **4a**, derived from tetralone, with [(SIPr)Ag(CF_2H)] under the conditions optimized for vinyl bromides resulted in less than 5% yield for the formation of difluoromethylated alkenes. The yield was slightly increased to 16% when the catalyst loading was increased to 10 mol%. Addition of tetrabutylammonium chloride or bromide is known to accelerate the rate of the Heck reaction.[18] We then decided to study whether addition of halogenated salts could also accelerate the difluoromethylation process. Indeed, addition of 2.0 equivalents of KBr to the catalytic reaction resulted in full conversion after 24 h at 60 °C when a combination of 5 mol% of [{Pd(cinnamyl)Cl}$_2$] and 20 mol% of DPPF was used as the catalyst (see the Supporting Information for details). Because the halogen anion is capable of binding easily to [(dppf)Pd(vinyl)(OTf)] to form more stable [(dppf)Pd(vinyl)Br], it is likely that the addition of KBr facilitates the transmetalation step and the catalytic cycle thereafter. Various multi-substituted cyclic and acyclic vinyl triflates were difluoromethylated in good to excellent yields under these conditions (Scheme 3). Likewise, reactions of vinyl nonaflates[19] occurred smoothly under these conditions in good yields (Scheme 3, **5c** and **5g**).



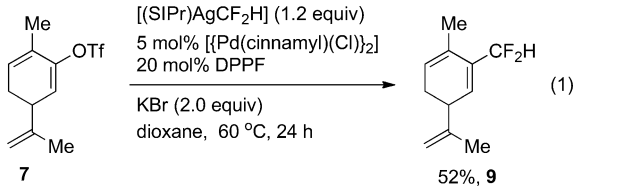
Scheme 3. Scope of palladium-catalyzed difluoromethylation of vinyl triflates and nonaflates. Reaction conditions (unless otherwise stated): Alkenyl triflate or nonaflate (1.0 mmol), [(SIPr)Ag(CF_2H)] (1.0 mmol), [{Pd(cinnamyl)Cl}$_2$] (5 mol%), DPPF (20 mol%), KBr (2.0 mmol) in dioxane (10.0 mL) at 60 °C for 24 h, yield of isolated product. [a] CsF was used instead of KBr; [b] 40 °C for 24 h.

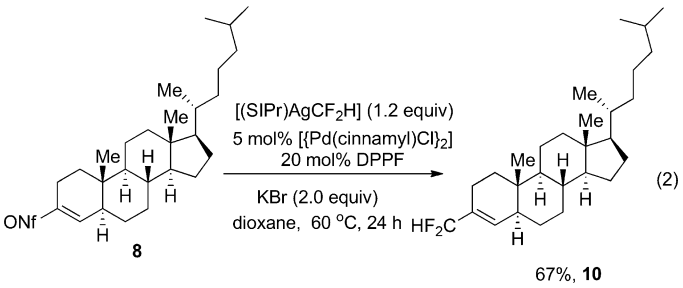
Vinyl tosylates are crystalline solids that are easily handled in the air. In addition, vinyl tosylates are generally less expensive than vinyl triflates. Thus, it is more attractive to use vinyl tosylates for coupling reactions.[20] The difluoromethylation of vinyl tosylates was found to be slightly slower than that of vinyl triflates. Reactions of vinyl tosylates required heating at 80 °C for 24 h for full conversion to give the corresponding difluoromethylated alkenes in good to excellent yields (Scheme 4).



Scheme 4. Scope of palladium-catalyzed difluoromethylation of vinyl tosylates. Reaction conditions: alkenyl tosylate (1.0 mmol), [(SIPr)Ag(CF2H)] (1.2 mmol), [{Pd(cinnamyl)Cl}$_2$] (5 mol%), DPPF (20 mol%), KBr (2.0 mmol) in dioxane (10.0 mL) at 80 °C for 24 h, yield of isolated product. [a] CsF was used instead of KBr.

As a demonstration of the utility of the current method, we studied the difluoromethylation of two derivatives of natural compounds. Compound **9**, a difluoromethylated derivative of the terpenoid carvone, was generated in 52% yield [Equation (1)]. Likewise, triflate derivative of the steroid cholestanone could be converted easily into its difluoromethylated derivative **10** in 67% yield [Equation (2)]. These results suggest that the palladium-catalyzed difluoromethylation of vinyl sulfonates is applicable for late-stage difluoromethylation of drug-like compounds for new drug discovery.





In summary, we have developed a Pd-catalyzed method for direct difluoromethylation of vinyl bromides, triflates, nonaflates, and tosylates under mild conditions. The reaction exhibits a broad substrate scope and excellent functional group tolerance. In addition, reactions of vinyl sulfonates were found to be dramatically accelerated by addition of 2.0 equivalents of KBr. Studying the mechanism of the reaction and further expanding the scope of the reaction to other electrophilic substrates, such as alkyl halides and sulfonates, are currently underway in our laboratory.

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Keywords: alkenes · cross-coupling · fluoroalkylation · fluorine · palladium

[1] a) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, Germany, **2004**; b) K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; c) J.-P. Bégué, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, Hoboken, NJ, **2008**; d) I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*. Wiley-Blackwell, Chichester, U.K., **2009**; e) V. A. Petrov, *Fluorinated Hetericyclic Compounds: Synthesis Chemistry and Applications*, Wiley, Hoboken, NJ, **2009**; f) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; g) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359.

[2] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; b) R. Filler, R. Saha, *Future Med. Chem.* **2009**, *1*, 777; c) D. O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071; d) 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.

[3] a) N. Chauret, D. Guay, C. Li, S. Day, J. Silva, M. Blouin, Y. Ducharme, J. A. Yergey, D. A. Nicoll-Griffith, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2149; b) E. L. Williams, T.-C. Wu, PCT Int. Appl. WO2004033430A2; Chem. Abstr. 2004, 140, 339200; c) G. W. Rewcastle, S. A. Gamage, J. U. Flanagan, R. Frederick, W. A. Denny, B. C. Baguley, P. Kestell, R. Singh, J. D. Kendall, E. S. Marshall, C. L. Lill, W.-J. Lee, S. Kolekar, C. M. Buchanan, S. M. F. Jamieson, P. R. Shepherd, *J. Med. Chem.* **2011**, *54*, 7105; d) J.-N. Desrosiers, C. B. Kelly, D. R. Fandrick, L. Nummy, S. J. Campbell, X. Wei, M. Sarvestani, H. Lee, A. Sienkiewicz, S. Sanyal, X. Zeng, N. Grinberg, S. Ma, J. J. Song, C. H. Senanayake, *Org. Lett.* **2014**, *16*, 1724.

[4] a) N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529; b) J. A. Erickson, J. I. McLoughlin, *J. Org. Chem.* **1995**, *60*, 1626; c) F. Narjes, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 701; d) Y. Xu, G. D. Prestwich, *J. Org. Chem.* **2002**, *67*, 7158.

[5] a) J. Hu, W. Zhang, F. Wang, *Chem. Commun.* **2009**, 7465; b) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214; *Angew. Chem.* **2013**, *125*, 8372.

[6] a) J.-B. Xia, C. Zhu, C. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 17494; b) S. Mizuta, I. S. R. Stenhagen, M. O Duill, J. Wolstenhulme, A. K. Kirjavainen, S. J. Forsback, M. Tredwell, G. Sandford, P. R. Moore, M. Huiban, S. K. Luthra, J. Passchier, O. Solin, V. Gouverneur, *Org. Lett.* **2013**, *15*, 2648; c) P. Xu, S. Guo, L.-Y. Wang, P.-P. Tang, *Angew. Chem. Int. Ed.* **2014**, *53*, 5955.

[7] a) W. R. Dolbier Jr., M. Médebielle, S. Ait-Mohand, *Tetrahedron Lett.* **2001**, *42*, 4811; b) 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; c) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herlé, N. Sach, M. R. Collins, Y. Ishihara, P. S. Baran, *Nature* **2012**, *492*, 95.

[8] a) K. Fujikawa, Y. Fujioka, A. Kobayashi, H. Amii, *Org. Lett.* **2011**, *13*, 5560; b) K. Fujikawa, Y. Fujioka, A. Kobayashi, H. Amii, *Synlett* **2012**, 3015; c) P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 5524; d) G. K. Surya Prakash, S. K. Ganesh, J. P. Jones, A. Kulkarni, K. Masood, J. K. Swabeck, G. A. Olah, *Angew. Chem. Int. Ed.* **2012**, *51*, 12090; *Angew. Chem.* **2012**, *124*, 12256; e) S. Ge, W. Chaładaj, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 4149; f) X.-L. Jiang, Z.-H. Chen, X.-H. Xu, F.-L. Qing, *Org. Chem. Front.* **2014**, *1*, 774; g) X.-Y. Sun, S.-Y. Yu, *Org. Lett.* **2014**, *16*, 2938; h) Y.-M. Su, Y. Hou, F. Yin, Y.-M. Xu, Y. Li, X.-Q. Zheng, X.-S. Wang, *Org. Lett.* **2014**, *16*, 2958; i) C. Matheis, K. Jouvin, L. J. Goossen, *Org. Lett.* **2014**, *16*, 5984; j) Y. Gu, X.-B. Leng, Q. Shen, *Nat. Commun.* **2014**, *5*, 5405, DOI: 10.1038/ncomms6405.

[9] a) P. Wipf, T. C. Henninger, S. J. Geib, *J. Org. Chem.* **1998**, *63*, 6088; b) J. Lin, P. J. Toscano, J. T. Welch, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 14020; c) J. Xiao, B. Weisblum, P. Wipf, *J. Am. Chem. Soc.* **2005**, *127*, 5742; d) E. Inokuchi, T. Narumi, A. Niida, K. Kobayashi, K. Tomita, S. Oishi, H. Ohno, N. Fujii, *J. Org. Chem.* **2008**, *73*, 3942; e) C. Couve-Bonnaire, D. Cahard, X. Pannecoucke, *Org. Biomol. Chem.* **2007**, *5*, 1151; f) T. Narumi, R. Hayashi, K. Tomita, K. Kobayashi, N. Tanahara, H. Ohno, T. Naito, E. Kodama, M. Matsuoka, S. Oishi, N. Fujii, *Org. Biomol. Chem.* **2010**, *8*, 616.

[10] Z.-J. Li, Z.-L. Cui, Z.-Q. Liu, *Org. Lett.* **2013**, *15*, 406.

[11] Methods for the preparation of difluoromethyled alkenes via difluoromethyl surrogates: a) Z.-B. He, M.-Y. Hu, T. Luo, L.-C. Li, J.-B. Hu, *Angew. Chem. Int. Ed.* **2012**, *51*, 11545; *Angew. Chem.* **2012**, *124*, 11713; b) N. Surapanich, C. Kuhakarn, Pohmakotr, V. Reutrakul, *Eur. J. Org. Chem.* **2012**, 5943; c) W.-J. Miao, C. F. Ni, Y.-C. Zhao, J.-B. Hu, *J. Fluorine Chem.* **2014**, *167*, 231.

[12] a) T.-F. Liu, Q. Shen, *Org. Lett.* **2011**, *13*, 2342; b) Q.-Q. Qi, Q. Shen, L. Lu, *J. Am. Chem. Soc.* **2012**, *134*, 6548; c) T.-F. Liu, X.-X. Shao, Y.-M. Wu, Q. Shen, *Angew. Chem. Int. Ed.* **2012**, *51*, 540; *Angew. Chem.* **2012**, *124*, 555.

[13] L. Hintermann, F. Läng, P. Maire, A. Togni, *Eur. J. Inorg. Chem.* **2006**, 1397.

[14] a) A. Hazari, V. Gouverneur, J. M. Brown, *Angew. Chem. Int. Ed.* **2009**, *48*, 1296; *Angew. Chem.* **2009**, *121*, 1322; b) X. Pigeon, M. Bergeron, F.

Barabé, P. Dubé, H. N. Frost, J.-f. Paquin, *Angew. Chem. Int. Ed.* **2010**, *49*, 1123; *Angew. Chem.* **2010**, *122*, 1141.

[15] N. Marion, O. Navarro, J.-G. Mei, E. D. Stevens, N. M. Scott, S. P. Nolan, *J. Am. Chem. Soc.* **2006**, *128*, 4101.

[16] P. R. Jenkins, M. C. r. Symons, S. E. Booth, C. J. Swain, *Tetrahedron Lett.* **1992**, *33*, 3543.

[17] a) K. Ritter, *Synthesis* **1993**, 735; b) P. J. Stang, *Acc. Chem. Res.* **1978**, *11*, 107.

[18] T. Jeffery, *Tetrahedron* **1996**, *52*, 10113.

[19] Selected examples for the formation of vinyl tosylates and their transition metal-catalyzed coupling reactions: a) L. R. Subramanian, M. Hanack, *Chem. Ber.* **1972**, *105*, 1465; b) E. Hirsch, S. Hünig, H.-U. Reißig, *Chem. Ber.* **1982**, *115*, 3687; c) M. A. K. Vogel, C. B. W. Stark, I. M. Lyapkalo, *Synlett* **2007**, *18*, 2907; d) M. A. K. Vogel, C. B. W. Stark, I. M. Lyapkalo, *Adv. Synth. Catal.* **2007**, *349*, 1019; e) I. M. Lyapkalo, M. A. K. Vogel, *Angew. Chem. Int. Ed.* **2006**, *45*, 4019; *Angew. Chem.* **2006**, *118*, 4124.

[20] Selected examples for transition metal-catalyzed coupling of vinyl tosylates: a) A. L. Hansen, J.-P. Ebran, M. Ahlquist, P.-O. Norrby, T. Skrydstrup, *Angew. Chem. Int. Ed.* **2006**, *45*, 3349; *Angew. Chem.* **2006**, *118*, 3427; b) M. E. Limmert, A. H. Roy, J. F. Hartwig, *J. Org. Chem.* **2005**, *70*, 9364; c) H. Zhang, C.-B. Zhou, Q.-Y. Chen, J. C. Xiao, R. Hong, *Org. Lett.* **2011**, *13*, 560; d) D. C. Reeves, S. Rodriguez, H. Lee, N. Haddad, D. Krishnamurthy, C. H. Senanayake, *Tetrahedron Lett.* **2009**, *50*, 2870.

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Fluoroalkylation

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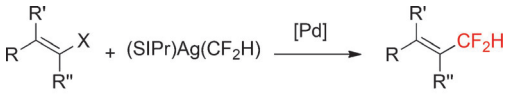
Pd-Catalyzed Difluoromethylation of Vinyl Bromides, Triflates, Tosylates, and Nonaflates



X = Br, OTf, ONf, OTs

46 examples
37-99%

Vinyl fantasy: Pd-catalyzed difluoromethylation of di-, tri- or tetra-substituted vinyl bromides, triflates, tosylates and nonaflates under mild conditions is described. The reaction tolerates a wide range of functional groups, such as bromide, chloride, fluoride, ester, amine, nitrile, and protected carbonyl, thus providing a general route for the preparation of difluoromethylated alkenes.