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Alternative Palladium-Catalyzed Vinylic C–H Difluoroalkylation of Ketene Dithioacetals Using Bromodifluoroacetate Derivatives

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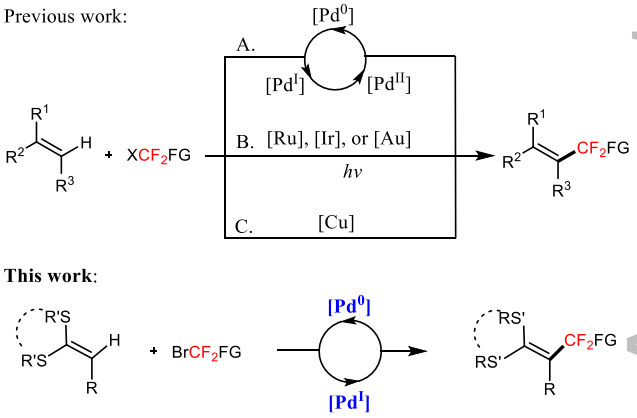
Abstract. A palladium-catalyzed cross-coupling of α-oxo ketene dithioacetals and bromodifluoroacetate derivatives has been developed for the synthesis of a class of CF_2-containing tetra-substituted olefins, which has potential to extend to drug design and material application. The process is proposed to involve two single electron transfer processes accompanied by an alternative loop from palladium(0) to palladium(I), likely due to unique structural properties of ketene dithioacetals with β,β-dialkylthiol substituents on the olefin double bond.

Keywords: cross-coupling; difluoroalkylation; ketene dithioacetals; synthetic methods; tetra-substituted olefins

Poly-substituted olefins are ubiquitous in pharmaceuticals, bioactive molecules, natural products and functional materials.[1] Among them, CF_2-containing alkenes are notable examples due to the particular value of the CF_2 motif,[2] which is considered a bioisostere of oxygen, sulfur and carbonyl groups via increasing dipole moments or enhancing the acidity of its adjacent groups.[3] For instance, arginine vasopressin (AVP) shows enormous potent affinity for recerptors,[4] and talfuprost not only exhibits high compatibility to receptors but also possesses potential for anti-glaucoma drugs.[5] Consequently, many efforts have been made to intruduce CF_2-containing group onto the olefins, among which transition-metal-catalyzed Csp^2-H difluoroalkylations of alkenes provide efficient and direct route to these compounds. Zhang and co-workers reported in 2015 a palladium-catalyzed Heck-type reaction of alkenes with ethyl bromodifluoroacetate for the construction of difluoroalkylated olefins (Scheme 1, Previous work A).[6a] A catalytic cycle from Pd(0) to Pd (II) via Pd(I) was recognized as the key procedure in their reactions. In addition, the difluoroalkylation of alkenes has been developed through visible-light-induced reactions using Ru, Ir or Au catalysts (Scheme 1, Previous work B).[7] Recently, copper-catalysed cross-coupling reactions between alkenes and XCF_2FG (FG: functional group) have successfully been carried out (Scheme 1, Previous work C).[8] Despite considerable progress in this field, there are rare examples related to the difluoroalkylation of tri-substituted olefin substrates.[6-8] In fact, the Csp^2-H functionalization of internal olefins has been an arduous problem in poly-substituted olefin synthesis, especially in the synthesis of fluorine-containing ones. Herein, we wish to disclose a unique Pd-catalyzed Csp^2-H difluoroalkylation of ketene dithioacetals to provide a facile route to CF_2-containing tetra-substituted olefins. An alternative Pd(0)/Pd(I) catalytic cycle pathway is proposed likely due to unique structural properties of ketene dithioacetals (Scheme 1, This work).



Scheme 1. Cross-coupling of alkenes with halodifluoroacetate derivatives

α-Oxo ketene dithioacetals are a kind of special internal alkenes. The push-pull electronic effects of the two β-alkylthio groups and the α-carbonyl make the carbon carbon double bond highly polarized, which endows them unique reactivity and wide

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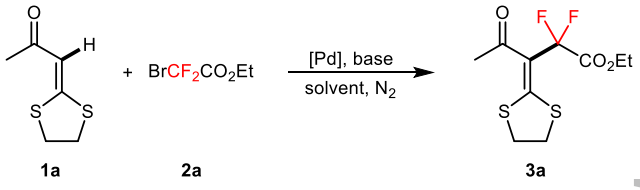
utilizations in synthesis.[9] During our continuing research on the synthesis of multi-substituted alkenes from ketene dithioacetals under the catalysis of transition metal,[10] we recently focused on their α-C-H difluoroalkylation using bromodifluoroacetate derivatives. We started our investigation by reacting 1-(1,3-dithiolan-2-ylidene)propan-2-one (**1a**) with ethyl bromodifluoroacetate (**2a**) under the catalysis of Pd. Delightfully, upon treatment of **1a** with 1.2 equiv of **2a** in the presence of 5 mol % $Pd(PPh_3)_4$ and 2.0 equiv of K_2CO_3 in 1,4-dioxane at 80 °C, the desired ethyl 3-(1,3-dithiolan-2-ylidene)-2,2-difluoro-4-oxopentanoate (**3a**) could be obtained in 49% yield, based on it's NMR and MS analysis (entry 1, Table 1). Besides $Pd(PPh_3)_4$, other Pd catalysts, including $Pd_2(dba)_3$, $Pd(dba)_2$, $PdCl_2(PPh_3)_2$, $PdCl_2(PhCN)_2$, $PdCl_2$(dppe), $PdCl_2$(dppp) or a combination of $PdCl_2$ and dppf as external ligand (entries 2-8, Table 1), could also catalyse the reaction, among which the yield of **3a** reached 69% in the presence of 5 mol% $PdCl_2$(dppp) (entry 7, Table 1). A base screening revealed that K_2CO_3 remained the best choice in our case (entries 9-13, Table1). A screen of other solvents revealed that 1,4-dioxane at 80 °C could provide somewhat more efficiency (entry 7 versus entries 14-18, Table 1). The yield of **3a** was raised to 75% by increasing the amounts of $BrCF_2CO_2Et$ to 2.0 equivalents (entry 19, Table 1). As illustrated in table 1 (entries 20 and 21), the reaction gave higher yield at 120 °C, but led to inferior results with substrate remaining at low temperatures. A control experiment verified the requirement of $PdCl_2$(dppp), K_2CO_3 (entries 22 and 23, Table 1).

With an active catalyst in hand and reliable conditions identified for this Pd-catalyzed reaction, we studied the scope of ketene dithioacetals. In general, a variety of ketene dithioacetals could react with **2a** to give the corresponding cross-coupling products. As described in Table 2, **1a-e**, bearing acyl, ester, amide, and cyano substituents at the α-position, could afford the desired **3a-e** in excellent yields. By comparison, α-benzoyl ketene dithioacetals **1** required more amount of Pd catalyst (7.5 mol% $PdCl_2$(dppp)) along with longer reaction time (12 h) for good conversion. Among them, α-benzoyl ketene dithioacetals bearing electron-donating R on the phenyl ring afforded the desire **3g, 3h**, and **3l** in high yields, respectively, while those with electron-deficient R on the phenyl ring gave **3i-k**, and **3n** in lower yields. By comparison, substrates **1** with an ortho-substituent on the phenyl ring gave **3o-q** in poor to moderate yields. Gratifyingly, the successful formation of **3k**, **3m** and **3p** with an intact bromide also highlighted the advantage of the present reaction. Furthermore, furanyl-bearing and 2-naphthyl-bearing substrates also afforded the corresponding products **3s** and **3t** in acceptable yield, respectively. In the case of piperonyl-containing substrate, **3r** was isolated in 36% yield accompanied by substrate residues. When acyclic ketene dithioacetals reacted with $BrCF_2CO_2Et$ under the identical reaction conditions, potential cross-couplings based on the C-S bond cleavage of ketene dithioacetals[10] usually made the reaction complex. **3u-y** were often obtained in poor yields. Further screening of the reaction conditions could not improve the reaction. Additionally, **1** with six membered ring backbone also afforded **3z** in good yield.

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3a**

Entry	[Pd] (x mol %)	Base	solvent	Yield (%)[b]
1	$Pd(PPh_3)_4$ (5)	K_2CO_3	dioxane	49
2	$Pd_2(dba)_3$ (2.5)	K_2CO_3	dioxane	36
3	$Pd(dba)_2$ (5)	K_2CO_3	dioxane	32
4	$PdCl_2(PPh_3)_2$ (5)	K_2CO_3	dioxane	35
5	$PdCl_2(PhCN)_2$ (5)	K_2CO_3	dioxane	42
6	$PdCl_2$(dppe) (5)	K_2CO_3	dioxane	40
7	$PdCl_2$(dppp) (5)	K_2CO_3	dioxane	69
8	$PdCl_2$ (5), ddpf (7.5)	K_2CO_3	dioxane	60
9	$PdCl_2$(dppp) (5)	NEt_3	dioxane	5
10	$PdCl_2$(dppp) (5)	K_3PO_4	dioxane	63
11	$PdCl_2$(dppp) (5)	KF	dioxane	trace
12	$PdCl_2$(dppp) (5)	Cs_2CO_3	dioxane	50
13	$PdCl_2$(dppp) (5)	Na_2CO_3	dioxane	trace
14	$PdCl_2$(dppp) (5)	K_2CO_3	CH_3CN	26
15	$PdCl_2$(dppp) (5)	K_2CO_3	THF	61
16	$PdCl_2$(dppp) (5)	K_2CO_3	DMF	7
17	$PdCl_2$(dppp) (5)	K_2CO_3	DMSO	trace
18	$PdCl_2$(dppp) (5)	K_2CO_3	toluene	27
19[c]	$PdCl_2$(dppp) (5)	K_2CO_3	dioxane	75
20[c,d]	$PdCl_2$(dppp) (5)	K_2CO_3	dioxane	95
21[c,e]	**$PdCl_2$(dppp) (5)**	**K_2CO_3**	**dioxane**	**98 (96)**[f]
22[c,e]	---	K_2CO_3	dioxane	n.d.[g]
23[c,e]	$PdCl_2$(dppp) (5)	---	dioxane	n.d.[g]

[a] Reaction Condition: **1a** (0.5 mmol), base (1.0 mmol), [Pd] (x mol %), $BrCF_2CO_2Et$ (1.2 equiv), solvent (2.5 mL), 80 °C, 12 h.
[b] Determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.
[c] $BrCF_2CO_2Et$ (2.0 equiv).
[d] 100°C.
[e] 120°C, 6 h.
[f] Isolated yield.
[g] Not detected.

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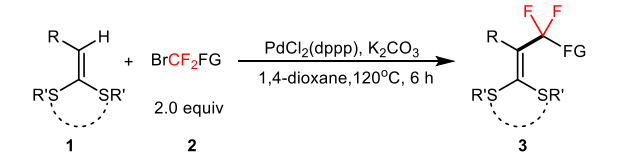
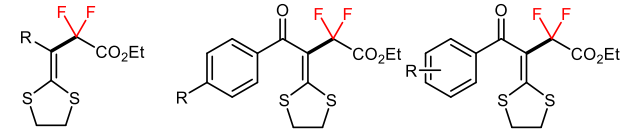
Table 2. Pd-catalyzed C-H difluoroalkylation of ketene dithioacetals using $BrCF_2FG$[a]

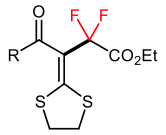




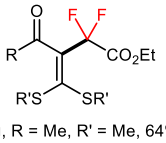
3a, R = COMe, 97%
3b, R = COOEt, 89%[b]
3c, R = COOMe, 92%
3d, R = $CONMe_2$, 64%[c](86%)[d]
3e, R = CN, 74%[b]

3f, R = H, 92 %[b]
3g, R = Me, 99 %[c]
3h, R = OCH_3, 94%[c]
3i, R = F, 62%[c]
3j, R = Cl, 89%[c]
3k, R = Br, 71%[b]

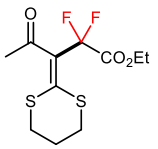
3l, R = 3-OCH_3, 91%[c]
3m, R = 3-Br, 92 %[c]
3n, R = 3-NO_2, 16%[c]
3o, R = 2-F, 46%[c]
3p, R = 2-Br, 36 %[e]
3q, R = 2-Me, 16%[c]



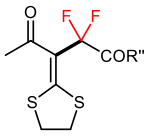
3r, R = 1-piperonyl, 36%[c]
3s, R = 2-furanyl, 58%[c]
3t, R = 2-naphthyl, 67%[c]



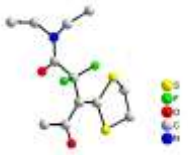
3u, R = Me, R' = Me, 64%[c]
3v, R = Ph, R' = Me, 28%[f](42%)[d]
3w, R = 4-MeC_6H_4, R' = Me, 14%[f](35%)[d]
3x, R = 3-BrC_6H_4, R' = Me, 18%[f](39%)[d]
3y, R = Me, R' = Et, trace[b]



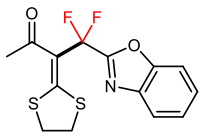
3z, 78%[b]



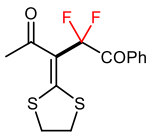
4a, R" = 1-pyrrolidinyl, 73%[g]
4b, R" = 4-morpholinyl,68%[g]
4c, R" = NEt_2,65%[g]



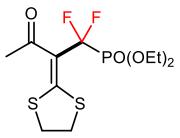
x-ray structure of **4c**



4d, 49%[c]



4e, 28%[c]



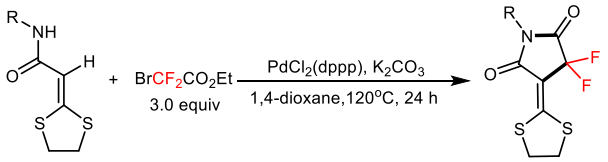
4f, trace[c]

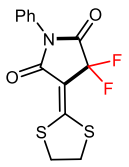
[a] Reaction Condition: **1** (0.5 mmol), $PdCl_2(dppp)$ (5 mmol%), K_2CO_3 (1.0 mmol), $BrCF_2FG$ (1.0 mmol), 1,4-dioxane (2.5 mL), 120 °C, 6 h, isolated yields.
[b] 12 h.
[c] $PdCl_2(dppp)$ 7.5 mol%, K_2CO_3 (1.5 mmol), $BrCF_2FG$ (1.5 mmol), 12 h.
[d] ^1H NMR yield by using 1,3,5-trimethoxybenzene as internal standard.
[e] $PdCl_2(dppp)$ 7.5 mol%, K_2CO_3 (2.0 mmol), $BrCF_2FG$ (3.0 mmol), 12 h.
[f] $Pd(PPh_3)_4$ 15 mol%, K_2CO_3 (1.5 mmol), $BrCF_2FG$ (1.5 mmol), 15 h.
[g] $Pd(PPh_3)_4$ 7.5 mol%, K_2CO_3 (1.5 mmol), $BrCF_2FG$ (1.5 mmol), 12 h.

Encouraged by the above results, we extended the coupling partner from bromodifluoroacetate to bromodifluoroacetamides. It was found in Table 2 that tertiary amides **2b-d** could couple with **1a** to afford **4a-c** in 65-73% yields, respectively, with $Pd(PPh_3)_4$ as the catalyst. The structure of product **4c** was further identified by its X-ray.[11] Then, we investigated the performances of other difluoroalkyl bromides in this catalytic system, including, $BrCF_2Het$ (Het = 2-benzo[*d*]oxazole), $BrCF_2COPh$, and $BrCF_2PO(OEt)_2$. To our delight, $BrCF_2COPh$ and $BrCF_2Het$ (Het = 2-benzo[*d*]oxazole) could couple with **1a** to afford the corresponding products in 49% and 28% yields, respectively. However, only trace amount of the desired product are detected in the Pd-catalyzed reaction of $BrCF_2PO(OEt)_2$ and **1a** under the identical reaction conditions.

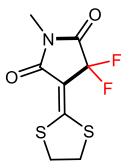
Interestingly, when we selected α-carbamoyl ketene dithioacetals **1aa-ae** as the substrates to couple with $BrCF_2CO_2Et$ under the identical Pd-catalysis, *gem*-difluorosuccinimides **5** were directly isolated in 59-88% yields, as shown in table 3, likely via Pd-catalyzed cross-coupling and further cyclization. Succinimides are a class of important natural product skeleton and widely found in alkaloids or drug molecules.[12] Here, we provided an efficient route to these compounds having the CF_2 motif, which would have potential use in medicine chemistry and biological chemistry.

Table 3. Pd-catalyzed cross-coupling-cyclization of α-carbamoyl ketene dithioacetals with $BrCF_2CO_2Et$.[a]

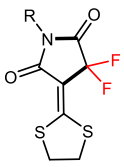




5a, 88%



5b, 77%

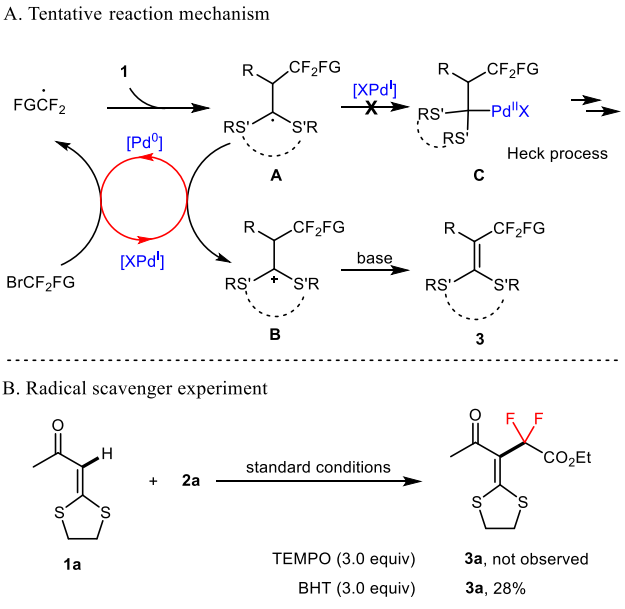


5c, R = 4-MeC_6H_4, 78%
5d, R = 4-ClC_6H_4, 59%
5e, R = 2-MeC_6H_4, 72%

[a] Reaction Condition: **1** (0.5 mmol), $PdCl_2(dppp)$ (7.5 mmol%), K_2CO_3 (1.5 mmol), $BrCF_2CO_2Et$ (1.5 mmol), 1,4-dioxane (2.5 mL), 120 °C, 24 h, isolated yields.

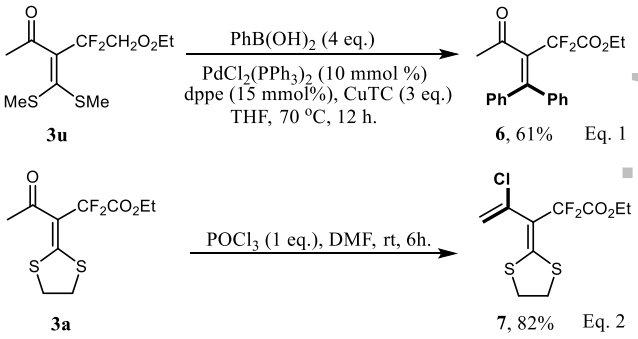
Zhang and his co-workers[6] reported that Pd-catalyzed cross-coupling of mono- or di-substituted alkenes with bromodifluoroacetate likely underwent a $Pd^0/Pd^I/Pd^{II}$ catalytic cycle (Scheme 1, Previous work A), involving a single transfer process followed by a Heck-type reaction. Tri-substituted alkene substrates were proved to be difficult to complete the coupling process in their work. By comparison, we realized the cross-coupling reactions between ketene dithioacetals, a kind of tri-substituted alkenes, and bromodifluoroacetate derivatives under the palladium catalyst. The gigantic steric hindrance of the olefin substrates resulting from the *gem*-dialkylthiol substituents may lead to an alternative catalytic pathway. On the basis of the structural features of the

ketene dithioacetals[9] and a known catalytic cycle from Pd(I) to Pd(0),[13] two single electron transfer (SET) process was suggested for our present reactions. As shown in Scheme 2A, first SET from [Pd^0] to $BrCF_2COR$ generates a free difluoroacetyl radical and [XPd^I] species.[6a,14] Subsequently, the resulting radical reacts with electron-rich olefins to deliver radical **A**[15] along with the formation of a new C-CF_2CO_2R bond. At this moment, the coupling of radical **A** with [Pd^I] leading to Pd-C intermediate **C** seems difficult due to the steric hindrance.[6a] Thus, a second SET pathway may generate cation **B**[15] accompanied with the reduction of [XPd^I] to [Pd^0] for the next catalytic cycle. After the abstraction of a proton with the base, the cation **B** delivers difluoroalkylated product **3**.[15a] In the case of the substrates carrying an α-amido group, further cycloamidations yield *gem*-difluorosuccinimide derivatives **5** as the final products (Table 3). In fact, the suggested intermediate **B** is reasonable due to its stability resulted from the two alkylthiol groups of ketene dithioacetals.[9] Many transformations based on this type of cation are known.[9,10a,15,16] Thus, the efficient formation of **B** is likely another key factor which leads to a different catalytic pathway. Control experiments using radical scavengers support the radical process of the above conversion (Scheme 2B). However, we can not exclude the $Pd^0/Pd^I/Pd^{II}$ catalytic cycle at this stage.



Scheme 2. Tentative reaction mechanism and radical scavenger experiment.

The above cross-coupling reactions provide an efficient route to CF_2-containing tetra-substituted alkenes. Importantly, furhter modifications of these poly-functionalized alkene products are forseeable. To highlight the synthetic potential of our approach, the Pd-catalyzed desulfitative cross-coupling of **3u** with phenylboronic acid was first investigated in the presence of copper(I)-thiophene-2-carboxylate (CuTC).[17] To our delight, *gem*-diphenyl alkene **6** was isolated from the reaction mixture in 61% yield (Scheme 2, Eq. 1). Additionally, upon treatment of **3a** with $POCl_3$ in DMF, the chlorovinyl-substituted ketene dithioacetal **7** was afforded in high yield *via* an enolation-chlorination sequence of the acetyl of **3a** under Vilsmeier-Haack reaction conditions (Scheme 2, Eq. 2).[18]



Scheme 3. Further transformations of **3**.

In summary, we have achieved a series of CF_2-containing tetra-substituted olefins from the cross-coupling reaction of readily available ketene dithioacetals with bromodifluoroacetate derivatives under the catalysis of palladium. The reaction proceeds with good functional group compatibility and broad substrate scope. Different from the known palladium-catalyzed Heck-type reaction of alkenes with fluoroalkyl bromides, unique structural characters of α-oxo ketene dithioacetals likely enables an alternative Pd(0)/Pd(I) catalytic cycle. Further investigations on the reaction mechanism and applications of the method are in progress in our group.

Experimental Section

Typical Procedure

To a dried Schlenk flask, ketene dithioacetals **1a** (0.5 mmol), $PdCl_2$(dppp) (5% mmol), and K_2CO_3 (1.0 mmol) were added under air atmosphere. After evacuated and refilled with nitrogen 3 times, 1,4-dioxane (2.5 mL), $BrCF_2CO_2Et$ **2a** (1.0 mmol) was added in one portion to the mixture by syringe. The resulting mixture was stirred at 120 °C for 6 h. After cooling to room temperature, the reaction mixture was diluted with 5 mL of ethyl acetate and filtered through a plug of celite, followed by washing with 10-20 mL of ethyl acetate. Then, the combined filtrate was washed by brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield the crude product, which was purified by silica gel chromatography (petroleum ether/ethyl acetate: 30/1, v/v) to give **3a** (136.8 mg, 97%) as a yellow oil.

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References

[1] a) C. Chiappe, H. Detert, D. Lenoir, C.-S. Pomelli, M.-F. Ruasse, *J. Am. Chem. Soc.* **2003**, *125*, 2864-2865. b) A.-D. Meijere, S.-I. Kozhushkov, A.-F. Khlebnikov, *Top. Curr. Chem.* **2000**, *207*, 89-147. c) I. Columbus, S.-E. Biali, *J. Org. Chem.* **1994**, *59*, 3402-3407. d) R.-G. Khoury, L. Jaquinod, K.-M. Smith, *Chem. Commun.* **1997**, 1057-1058. e) I.-N. Lykakis, G.-C. Vougioukalakis, M. Orfanopoulos, *J. Org. Chem.* **2006**, *71*, 8740-8747. f) M. Stratakis, R. Nencka, C. Rabalakos, W. Adam, O. Krebs, *J. Org. Chem.* **2002**, *67*, 8758-8795. g) N. Treitel, L. Eshdat, T. Sheradsky, P.-M. Donovan, R.-R. Tykwinski, L.-T. Scott, H. Hopf, M. Rabinovitz, *J. Am. Chem. Soc.* **2006**, *128*, 4703-4709. h) E.-I. Negishi, Z.-H. Huang, G.-W. Wang, S. Mohan, C. Wang, H.-S. Hattori, *Acc. Chem. Res.* **2008**, *41*, 1474-1485.

[2] a) Q.-Q. Min, Z.-S. Yin, Z. Feng, W.-H. Guo, X.-G Zhang, *J. Am. Chem. Soc.* **2014**, *136*, 1230-1233. b) N.-A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529-2591. c) Z. Feng, F. Chen, X.-G. Zhang, *Org. Lett.* **2012,** *14***,** 1938-1941. d) Y.-L. Xiao, W.-H. Guo, G.-Z. He, Q. Pan, X.-G. Zhang, *Angew. Chem.* **2014**, *126*, 10067-10071; *Angew. Chem. Int. Ed.* **2014**, *53*, 9909-9913. e) Z. Feng, Q.-Q. Min, Y.-L. Xiao, B. Zhang, X.-G. Zhang, *Angew. Chem.* **2014**, *126*, 1695-1699; *Angew. Chem. Int. Ed.* **2014**, *53*, 1669-1673.

[3] a) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308-319. b) C.-S. Burgey, K.-A. Robinson, T.-A. Lyle, P.-E.-J. Sanderson, S. Dale-Lewis, B.-J. Lucas, J.-A. Krueger, R. Singh, C. Miller-Stein, R.-B. White, B. Wong, E.-A. Lyle, P.-D. Williams, C.-A. Coburn, B.-D. Dorsey, J.-C. Barrow, M.-T. Stranieri, M.-A. Holahan, G.-R. Sitko, J.-J. Cook, D.-R. McMasters, C.-M. McDonough, W.-M. Sanders, A.-A. Wallace, F.-C. Clayton, D. Bohn, Y.-M. Leonard, T.-J. Detwiler, J.-J. Lynch, Y. Yan, Z. Chen, L. Kuo, S.-J. Gardell, J.-A. Shafer, J.-P. Vacca, *J. Med. Chem.* **2003**, *46*, 461-473. c) J. Li, S.-Y. Chen, B.-J. Murphy, N. Flynn, R. Seethala, D. Slusarchyk, M. Yan, P. Sleph, H. Zhang, W.-G. Humphreys, W.-R. Ewing, J.-A. Robl, D. Gordon, J.-A. Tino, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4072-4074. d) C.-L. Lynch, C.-A. Willoughby, J.-J. Hale, E.-J. Holson, R.-J. Budhu, A.-L. Gentry, K.-G. Rosauer, C.-G. Caldwell, P. Chen, S.-G. Mills, M. MacCoss, S. Berk, L. Chen, K.-T. Chapman, L. Malkowitz, M.-S. Springer, S.-L. Gould, J.-A. DeMartino, S.-J. Siciliano, M.-A. Cascieri, A. Carella, G. Carver, K. Holmes, W.-A. Schleif, R. Danzeisen, D. Hazuda, J. Kessler, J. Lineberger, M. Miller, E.-A. Eminic, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 119-123.

[4] Y. Shimada, N. Taniguchi, A. Matsuhisa, K. Sakamoto, T. Yatsu, A. Tanaka, *Chem. Pharm. Bull.* **2000**, *48*, 1644-1651.

[5] X.-D. Han, Z.-Z. Yue, X.-F. Zhang, Q. He, C.-H. Yang, *J. Org. Chem.* **2013**, *78*, 4850-4856.

[6] a) Z. Feng, Q.-Q. Min, H.-Y. Zhao, J.-W. Gu, X.-G. Zhang, *Angew. Chem.* **2015**, *127*, 1286-1290; *Angew. Chem. Int. Ed.* **2015**, *54*, 1270-1274. b) F. Zhang, Q.-Q. Min, X.-G. Zhang, *Synthesis* **2015**, *47*, 2912-2923. c) Z. Feng, Y.-L. Xiao, X.-G. Zhang, *Org. Chem. Front.* **2016**, *3*, 466-469.

[7] a) H.-Y. Xiang, Q.-L. Zhao, Z.-Y. Tang, J.-A. Xiao, P.-J. Xia, C.-M. Wang, C.-H. Yang, X.-Q. Chen, H. Yang, *Org. Lett.* **2017**, *19*, 146-149. b) C. Yu, N. Iqbal, S. Park, E.-J. Cho, *Chem. Commun.* **2014**, *50*, 12884-12887. c) H. Jiang, C.-M. Huang, J.-J. Guo, C.-Q. Zeng, Y. Zhang, S.-Y. Yu, *Chem. Eur. J.* **2012**, *18*, 15158-15166. c)C.-Y. He, J.-J. Kong, X.-F. Li, X.-F. Li, Q.-L. Yao, F.-M. Yuan, *J. Org. Chem.* **2017**, *82*, 910-917. d) Q.-Y. Lin, L.-L. Chu, F.-L. Qing, *Chin. J. Chem.* **2013**, *31*, 885-891. e) J. Xie, J. Li, V. Weingand, M. Rudolph, A.-S. Hashmi, *Chem. Eur. J.* **2016**, *22*, 12646-12650. f) A. Najib, S. Tabuchi, K. Hirano, M. Miura, *Heterocycles.* **2016**, *92*, 1187-1203.

[8] a) M.-C. Belhomme, T. Poisson, X. Pannecoucke, *Org. Lett.* **2013**, *15*, 3428-3431. b) G. Caillot, J. Dufour, M.-C. Belhomme, T. Poisson, L. Grimaud, X. Pannecoucke, I. Gillaizeau, *Chem. Commun.*, **2014**, *50*, 5887-5890. c) X.-Y. Wang, S. Zhao, J. Liu, D.-S. Zhu, M.-J Guo, X.-Y Tang, G.-W. Wang, *Org. Lett.* **2017**, *19*, 4187-4190. d) I. Fabre, T. Poisson, X. Pannecoucke, I. Gillaizeau, I. Ciofini, L. Grimaud, *Catal. Sci. Technol.* **2017**, *7*, 1921-1927. e) M.-M. Belhomme, D. Dru, H.-Y. Xiong, D. Cahard, T. Besset, T. Poisson, X. Pannecoucke, *Synthesis* **2014**, *46*, 1859-1870.

[9] a) L. Pan, X.-H. Bi, Q. Liu, *Chem. Soc. Rev.* **2013**, *42*, 1251-1286. b) L.-D. Wang, W. He, Z.-K. Yu, *Chem Soc. Rev.* **2013**, *42*, 599-621. c) H. Junjappa, H. Ila, C.-V. Asokan, *Tetrahedron*, **1990**, *46*, 5423-5506. d) R.-K. Dieter, *Tetrahedron*, **1986**, *42*, 3029-3096.

[10] For selected examples, see, a) L.-J. Wang, X.-C. Liu, M. Wang, J. Liu, *Org. Lett.* **2016**, *18*, 2162-2165. b) Y. Dong, B.-Y. Liu, P. Chen, Q. Liu, M. Wang, *Angew. Chem.* **2014**, *126*, 3510-3514; *Angew. Chem. Int. Ed.* **2014**, *53*, 3442-3446. c) C. Xu, J.-X. Liu, W.-B. Ming, Y.-J. Liu, J. Liu, M. Wang, Q. Liu, *Chem. Eur. J.* **2013**, *19*, 9104-9109. d) X.-N. Song, S.-Q. Tian, Z.-M. Zhao, D.-S. Zhu, M. Wang, *Org. Lett.* **2016**, *18*, 3414-3417. e) B.-Y. Liu, G. Zheng, X.-C. Liu, C. Xu, J.-X. Liu, M. Wang, *Chem. Commun.* **2013**, *49*, 2201-2203. f) W.-W. Jin, W.-M. Du, Q. Yang, H.-F. Yu, J.-P. Chen, Z.-K Yu, *Org. Lett.* **2011**, *13*, 4272-4275.

[11] Crystal data for **4c**: $C_{12}H_{17}F_2NO_2S_2$, colorless, crystal size 0.85 x 0.62 x 0.40 mm, M = 309.07, triclinic, wavelength 0.71073 Å, calculated density 1.412 mg/m$_3$, absorption coefficient 0.385 mm^{-1}, theta range for data collection 2.145 to 28.413 ^{o} space group P-1, a = 7.8245(10) Å, b = 10.2582(13) Å, c = 10.3207(14) Å, V = 727.54(16) Å^3, α = 68.857(2), β = 71.568(2), γ = 89.641(2), Z = 2, T = 296 (2) K, F000 = 324, 2814 reflections collected, data / restraints / parameters 3623 / 0 / 175, final R indices [I>2sigma(I)] R_1 = 0.0552, wR_2 = 0.1230, R indices (all data) R_1 = 0.0417, wR_2 = 0.1317, largest diff. peak and hole, 0.265 and -0.352 e. Å^{-3}. CCDC

1531370 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.

[12] a) J. Needham, M.-T. Kelly, M. Ishige, R. Andemen, *J. Org. Chem.* **1994**, *59*, 2058-2063. b) J. Uddin, K. Ueda, E.-R.-O. Siwu, M. Kitac, D. Uemurab, *Bioorg. Med. Chem.* **2006**, *14*, 6954-6961. c) F. Robert, H.-Q. Gao, M. Donia, W.-C. Merrick, M.-T. Hamann, J. Pelletier, *RNA*, **2006**, *12*, 717-725. d) M. Kabata, T. Suzuki, K. Takabe, H. Yoda, *Tetrahedron Lett.* **2006**, *47*, 1607-1611.

[13] a) C.-J. Seechurn, T. Sperger, T.-G. Scrase, F. Schoenebeck, T.-J. Colacot, *J. Am. Chem. Soc.* **2017**, *139*, 5194. b) W.-J. Zhou, G.-M. Cao, G. Shen, X.-Y. Zhu, Y.-Y. Gui, J.-H. Ye, L. Sun, L.-L. Liao, J. Li, D.-G. Yu, *Angew. Chem.* **2017**, *129*, 15889-15893; *Angew. Chem. Int. Ed.* **2017**, *56*, 15683-15687.

[14] a) T.-L. Andersen, S. Kramer, J. Overgaard, T. Skrydstrup, *Organometallics* **2017**, *36*, 2058-2066. b) T.-L. Andersen, M.-W. Frederiksen, K. Domino, T. Skrydstrup, *Angew. Chem.* **2016**, *128*, 10552-10556; *Angew. Chem. Int. Ed.* **2016**, *55*, 10396-10400. c) H.-Y. Zhao, Z. Feng, Z.-J. Luo, X.-G. Zhang, *Angew. Chem.* **2016**, *128*, 10557-10561; *Angew. Chem. Int. Ed.* **2016**, *55*, 10401-10405.

[15] a) Q.-N. Wang, J. Lou, P. Wu, K.-K. Wu, Z.-K. Yu, *Adv. Synth. Catal.* **2017**, *359*, 2981-2998. b) J.-W. Wen, F. Zhang, W.-Y. Shi, A.-W. Lei, *Chem. Eur. J.* **2017**, *23*, 8814-8817.

[16] J. Liu, D. Liang, M. Wang, Q. Liu, *Synthesis* **2008**, 3633-3638.

[17] H. Prokopcova, C. O. Kappe, *Angew. Chem.* **2009**, *121*, 2312-3222; *Angew. Chem. Int. Ed.* **2009**, *48*, 2276-2286.

[18] Q. Liu, G. Che, H. Yu, Y. Liu, J. Zhang, Q. Zhang, D. Dong, *J. Org. Chem.* **2003**, *68*, 9148-9150.

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COMMUNICATION

Alternative Palladium-Catalyzed Vinylic C–H Difluoroalkylation of Ketene Dithioacetals Using Bromodifluoroacetate Derivatives

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