A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Stereoselective Palladium-Catalyzed C-F Bond Alkynylation of Tetrasubstituted gem-Difluoroalkenes

Authors: Gavin Chit Tsui, Qiao Ma, and Yanhui Wang

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202002219

Link to VoR: https://doi.org/10.1002/anie.202002219

WILEY-VCH

10.1002/anie.202002219

WILEY-VCH

COMMUNICATION

Stereoselective Palladium-Catalyzed C-F Bond Alkynylation of Tetrasubstituted *gem*-Difluoroalkenes

Qiao Ma, Yanhui Wang and Gavin Chit Tsui*

Abstract: A stereoselective $Pd(PPh_3)_4$-catalyzed C-F bond alkynylation of tetrasubstituted *gem*-difluoroalkenes with terminal alkynes has been developed. The method gives access to a great variety of conjugated monofluoroenynes bearing a tetrasubstituted alkene moiety with well-defined stereochemistry. Chelation-assisted oxidative addition of Pd to the C-F bond is proposed to account for the high level of stereocontrol. X-ray structure of a key monofluorovinyl Pd(II) intermediate has been obtained for the first time as evidence for the proposed mechanism.

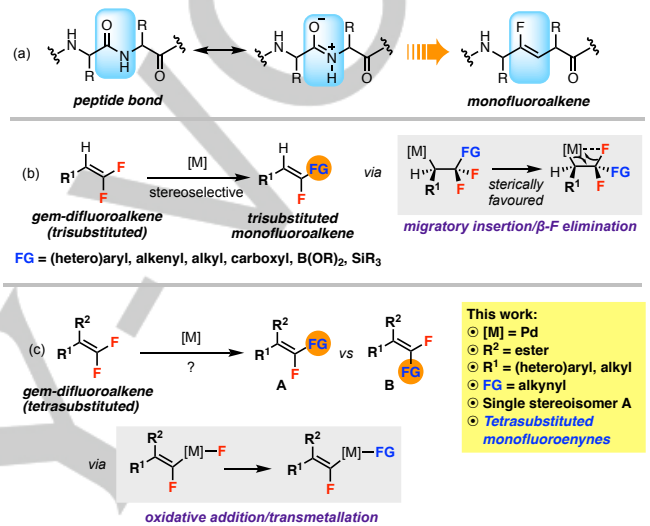
Activation of the carbon-fluorine bond constitutes an important area of research in modern organofluorine chemistry.[1] In contrast to C-F bond formation,[2] selective *cleavage* and *functionalization* of robust C-F bonds in abundant poly- or perfluorinated compounds offers new opportunities for the synthesis of value-added fluorinated molecules.[3] For instance, selective transformation of one C-F bond of *gem*-difluoroalkenes[4] leads to functionalized monofluoroalkenes. Monofluoroalkenes have shown great potential as peptide bond isosteres in drug discovery and as versatile fluorinated synthons in organic synthesis (Scheme 1a).[5] Their preparation has been achieved by efficient and selective transition metal-catalyzed (Cu,[6] Ni,[7] Rh,[8] Co,[9] Mn,[10] Ru,[11] Ir,[12] Fe[13]) C-F bond functionalization of fluoroalkenes.[14] High level of stereocontrol to functionalize a single C-F bond is a key criterion in these reactions. Two factors usually facilitate such control: (1) using trisubstituted *gem*-difluoroalkenes that can be prepared from the corresponding aldehydes;[4a] (2) the steric repulsion between R^1 and FG in the *β*-F elimination step (Scheme 1b).[14] However, the stereoselectivity would be hampered with unsymmetrical tetrasubstituted *gem*-difluoroalkenes (Scheme 1c), especially when R^1 and R^2 have similar steric properties, resulting in a mixture of stereoisomers **A** and **B** that are difficult to separate by conventional chromatographic techniques.[15] Consequently, the scope of current methods[6-13] is largely limited to the synthesis of trisubstituted monofluoroalkenes. We hypothesize that a *selective oxidative addition* of metal to the C-F bond would solve this problem and afford a single diastereomer. The product profiles can therefore be significantly expanded to include densely functionalized *tetrasubstituted* monofluoroalkenes with well-defined alkene geometry.[16]

To the best of our knowledge, this approach has not been reported to date, presumably due to the strong C-F bonds (120-129 kcal/mol for aliphatic and olefinic C-F bonds)[17] and the difficulty in identifying suitable substrates and catalytic systems.

[*] Q. Ma, Y. Wang and Prof. Dr. G. C. Tsui
Department of Chemistry
The Chinese University of Hong Kong
Shatin, New Territories, Hong Kong SAR
E-mail: *gctsui@cuhk.edu.hk

Supporting information for this article is given via a link at the end of the document.

We herein describe the first Pd-catalyzed C-F bond alkynylation of *gem*-difluoroalkenes involving a key stereoselective C-F bond oxidative addition step. The method enables the stereoselective synthesis of tetrasubstituted *monofluoroenynes*, which belong to the class of conjugated 1,3-enynes that are prevalent in natural products and pharmaceuticals.[18]



Scheme 1. Transition metal-catalyzed stereoselective C-F bond activation of *gem*-difluoroalkenes for the synthesis of functionalized monofluoroalkenes.

Despite being one of the most powerful catalysts for cross-coupling reactions,[19] palladium-catalyzed defluorinative coupling of *gem*-difluoroalkenes has been underdeveloped. Heitz and co-workers first reported the Pd-catalyzed coupling of 1,1-difluoroethylene with aryl iodides in 1991.[20a] The stereoselective version, a Pd-catalyzed coupling of difluorostyrenes with arylboronic acids only appeared recently in 2016 by Toste and co-workers.[20b] Both cases invoked the insertion of difluoroalkene into the palladium-aryl bond followed by *β*-F elimination to generate the monofluoroalkene product. Although there is no precedence for the Pd-mediated oxidative addition of a C-F bond of *gem*-difluoroalkenes, the pioneer work by Ogoshi and co-workers in the Pd-catalyzed coupling reactions of tetrafluoroethylene (TFE) with arylzinc reagents, arylboronates and arylsiloxanes provided important evidence.[21] They proposed that the oxidative addition of C-F bond by Pd followed by transmetallation with organometallic reagents is a viable mechanism, as supported by the isolation and X-ray crystal data of the key trifluorovinylpalladium complex.[21a] While these Pd-catalyzed reactions allowed the Csp^2-Csp^2 bond formation of fluoroalkenes (*e.g.* for the synthesis of monofluorostilbenes),[20b] the corresponding Csp^2-Csp bond construction remains unknown.

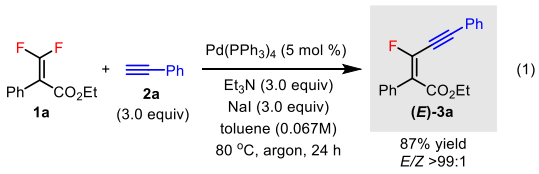
We found that the difluoroacrylate derivative **1a**[4b] underwent smooth Sonogashira-type defluorinative coupling with terminal alkyne **2a** in the presence of catalytic tetrakis(triphenylphosphine)palladium(0) and an additive sodium iodide (eq 1). The tetrasubstituted monofluoroenyne product **(*E*)-**

10.1002/anie.202002219

WILEY-VCH

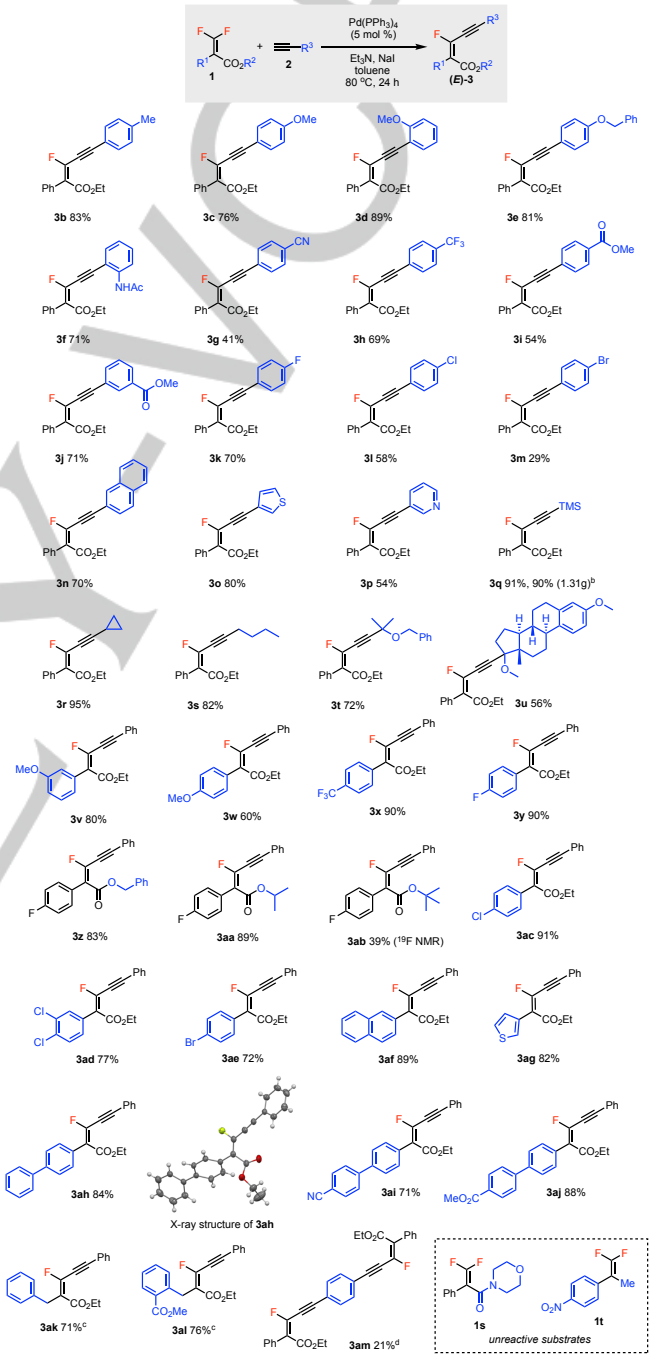
COMMUNICATION

3a was isolated in 87% yield as a single diastereomer and the alkene geometry (*E*) was confirmed by ^{19}F-^{1}H HOESY NMR experiments.[22] The complete stereocontrol in this reaction was remarkable since reported syntheses (Pd-free) of pharmaceutically relevant fluorinated 1,3-enynes by HWE olefination[23a] or the use of alkynyllithium reagents[23b] only gave mixtures of inseparable *E*/*Z* products.



Several trends were observed during the screening of reaction parameters:[22] (1) Phosphine ligands were needed to ensure conversions. Pd(II) catalysts including $PdCl_2(PPh_3)_2$ and $PdCl_2(dppf)\cdot CH_2Cl_2$ were also effective under similar conditions (72-93%). Other Pd(II) pre-catalysts such as $PdCl_2$, $PdCl_2(CH_3CN)_2$ and $Pd(OAc)_2$ required the addition of PPh_3 (Pd:P = 1:2) (74-99%, reactions were shut down without added ligand). The Pd(0) complex $Pd(PPh_3)_4$ was optimal for this reaction due to its straightforward operation (no added ligand) and high reactivity. Control experiment revealed no reaction without Pd catalyst. (2) The additive sodium iodide was crucial for both reactivity and selectivity. Removing NaI from the standard conditions resulted in a low yield (41%). Compared with NaI, the yields decreased when using NaBr, NaCl and KI as additives. We investigated the additive effects of more soluble tetrabutylammonium halides and observed an intriguing anion effect (I^- > Br^- > Cl^-) on the *E*/*Z* selectivity (*E*/*Z* = >99:1, 94:6 and 91:9 for TBAI, TBAB and TBAC, respectively).[24] (3) More dilute concentration (0.067 M) and excess of base and alkyne (3.0 equiv each) were necessary for complete conversions. (4) Good yields and selectivities were also obtained using solvents with different polarities (*e.g.* 1,4-dioxane, DMF). (5) Reactions were sluggish at lower temperatures (23-60 °C) even with increased catalyst loading and longer time. (6) In some cases, $Pd(PPh_3)_4$ loading could be as low as 2 mol % for comparable yields.

The developed method was successfully applied to the synthesis of a great variety of novel monofluoroenynes **3** solely as (*E*)-products (Scheme 2). Terminal alkynes **2** with different substituted (hetero)arenes (R^3) were investigated (products **3b-p**). Generally, electron-rich arenes gave higher yields than electron-poor ones (compare **3c** with **3g-i**). Substituent groups were tolerated at the *para*-, *meta*- and *ortho*-positions of the ring. The bromo-substituted compound (**3m**) was low-yielding due to unreacted starting materials. Thiophene (**3o**) and pyridine (**3p**) moieties were also tolerated. The TMS-substituted compound (**3q**) is a useful precursor for terminal alkyne upon desilylation and it can be obtained on gram-scale using only 2 mol % Pd catalyst. Other alkyl-substituted products (**3r-t**) bearing primary, secondary and tertiary carbons were also synthesized, including a natural product derivative (**3u**) as a demonstration for late-stage functionalization. Variation of the vinylic substituent group (R^1) and the ester substituent group (R^2) of difluoroalkenes **1** was made to probe the reaction scope (products **3v-al**). Electron-withdrawing (4-CF_3, **3x**) aryl substituent gave higher yield than electron-donating (4-OMe, **3w**) group. Aryl chlorides (**3ac**, **3ad**) and bromide (**3ae**), which are known reaction partners in Sonogashira couplings,[19] were tolerated demonstrating the preferential C(vinyl)-F bond over C(aryl)-Cl/Br bond functionalization. Polyaromatic (**3af**) and heteroaromatic (**3ag**) substituents were also tolerated. We compared the effects of R^2 in a series of products **3y-ab**. The trend suggested that the steric hinderance of the substituent group affected the reaction. While ethyl (**3y**), benzyl (**3z**) and isopropyl (**3aa**) groups gave similarly good yields, the bulkier *tert*-butyl group (**3ab**) caused drastic decrease in yield with significant amounts of unreacted starting material.



[a]Standard conditions: **1** (0.2 mmol), **2** (0.6 mmol), Et_3N (0.6 mmol), NaI (0.6 mmol), toluene (3.0 mL), under argon. Isolated yields of **3** (*E*/*Z* ratio >99:1). [b]5.0 mmol scale using 2 mol % Pd catalyst. [c]Conditions: $Pd(PPh_3)_4$ (10 mol %), DIPEA (3.0 equiv), NaI (3.0 equiv), toluene (0.2 M), 90 °C, argon, 24-36 h. [d]Conditions: diyne (0.2 mmol), **1a** (0.4 mmol), $Pd(PPh_3)_4$ (10 mol %), Et_3N (0.4 mmol), NaI (1.2 mmol), toluene (3.0 mL), 80 °C, argon, 24 h.

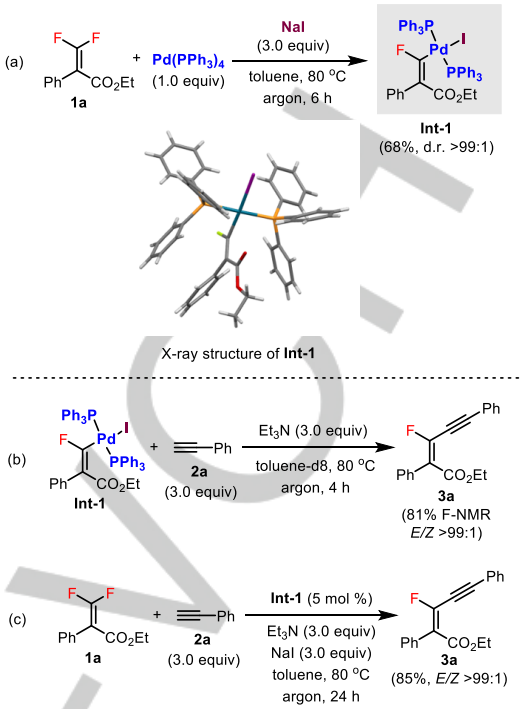
Scheme 2. Scope of tetrasubstituted *gem*-difluoroalkenes and terminal alkynes for the stereoselective synthesis of monofluoroenynes.[a]

10.1002/anie.202002219

The structure and *E*-alkene configuration of the monofluoroenynes **3** were unambiguously confirmed by X-ray crystallography *via* the biphenyl product **3ah**.[25] Remote substituents such as nitrile (**3ai**) and methyl ester (**3aj**) on the biphenyl framework were compatible. Benzyl-substituted difluoroalkenes were not as reactive as their (hetero)aryl counterparts under standard conditions. However, increasing Pd loading (10 mol %) and changing base (DIPEA) could improve the yield significantly (**3ak**). Even the sterically encumbering *ortho*-ester group on the ring was tolerated (**3al**). Finally, reacting 1,4-diethynylbenzene with 2.0 equiv of **1a** afforded an intriguing extensively conjugated product (**3am**) as a single isomer bearing two monofluoroenyne units. Overall, the reaction conditions displayed a broad functional group tolerability for both carbon-based and heteroatom-containing (N, O, S, Si, halogen) functionalities. More importantly, despite the differences in the steric and electronic environments of R^1, R^2 and R^3 groups, excellent *E*/*Z*-selectivities (>99:1) were obtained for all the products **3**. The reaction was unique for difluoroacrylate-type substrates, the corresponding tetrasubstituted *gem*-difluoroalkenes bearing amide (**1s**) and methyl (**1t**) groups were unreactive under these conditions.

Mechanistic studies were conducted to probe the reaction pathway and origin of stereoselectivity (Scheme S1, see Supporting Information). We tested a range of commonly used difluorostyrene (trisubstituted) derivatives **4**[14] containing electron-donating/-withdrawing groups at various positions of the ring under standard conditions (Scheme S1a). However, no reaction took place with these substrates showing the necessity of the difluoroacrylate-type system. Alkene **1a** was susceptible to nucleophilic addition-elimination by *in situ* generated alkynyllithium reagent resulting in a mixture of stereoisomeric products **3a** (*E*/*Z* = 1:1) (Scheme S1b). This shows that **1a** has no intrinsic bias to influence the *E*/*Z*-selectivity (sterically or electronically), therefore, the stereocontrol should be exerted by the Pd catalytic system.[26] A side product, the α-trifluoromethyl ester **s1**, was obtained in an appreciable amount (37% yield) when the reaction was conducted without the additive NaI (Scheme S1c). Adding water to **1a** in the presence of Pd led to a protodefluorinated product **s2** (48% yield, *E*/*Z* >99:1) (Scheme S1d), hinting the presence of a vinylpalladium intermediate that was protodemetallated by H_2O to give **s2**.

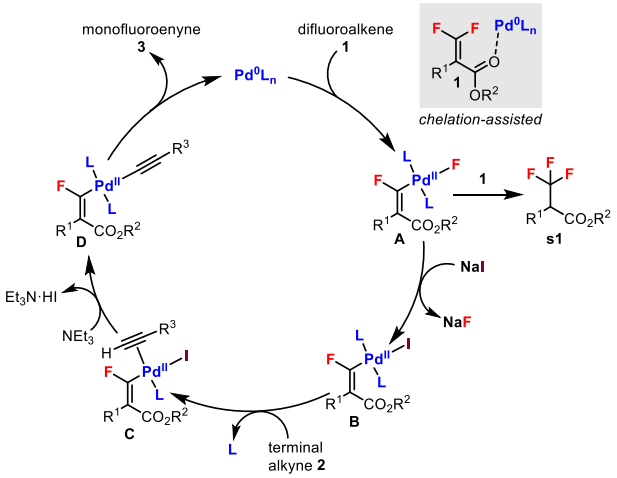
Stoichiometric reaction between **1a** and $Pd(PPh_3)_4$ in the presence of NaI was conducted (Scheme 3a). We were able to isolate and characterize a novel monofluorovinylpalladium(II) iodide intermediate **Int-1** as a single diastereomer. Its structure was unambiguously confirmed by X-ray crystallography,[25] showing that the Pd adopts a square-planar geometry with two PPh_3 ligands in a *trans* manner. To the best of our knowledge, this is the first report of a Pd complex derived from *gem*-difluoroalkenes. Furthermore, the Pd complex **Int-1** reacted with terminal alkyne **2a** to afford desired product **(*E*)-3a** in good yield, proving its intermediacy in the catalytic cycle (Scheme 3b). A catalytic amount of **Int-1** was also efficient in producing **(*E*)-3a** under standard conditions, demonstrating its turnover capability (Scheme 3c).



Scheme 3. Preparation and reaction of the monofluorovinylpalladium(II) iodide complex.

Based on the above evidence and literature supports,[27] we proposed the following plausible catalytic cycle (Scheme 4). First, *oxidative addition* of Pd(0) to one of the C-F bonds of *gem*-difluoroalkene **1** takes place selectively generating R-Pd(II)-F complex **A**. We believe this *stereodifferentiating* step occurs through the chelation of the ester group to Pd centre.[27a] Esters as directing groups (DGs) in Pd-catalyzed C-H functionalization has been well-documented.[27b] Examples of metal-catalyzed DG-assisted C-F bond activation of polyfluoroarenes also exist.[1b] The ester group of **1** is not only important for stereoselectivity, but also for reactivity, possibly due to two reasons: (1) the α,β-unsaturated ester system **1** (electron-deficient alkene) is more reactive than the difluorostyrene system **4**; (2) the chelation effect enhances the oxidative addition of Pd to the C-F bond by bringing the metal centre in close proximity.

While complex **A** is capable of reacting with terminal alkynes to give the desired products to certain extent, it can also undergo migratory insertion with another molecule of **1** to deliver a fluorine atom resulting in the major side product **s1**. However, this side reaction is inhibited by *halide exchange* with NaI generating R-Pd(II)-I complex **B** and eliminating NaF. The elimination of NaF could actually be the driving force for the C-F bond cleavage due to the stronger NaF bond and poorer solubility of NaF in the solvent system.[28] We have direct proof for the existence of complex **B** (X-ray structure) and its reactivity downstream in the catalytic cycle. Next, complexation of terminal alkyne **2** to Pd centre leads to complex **C**.[27c] Increased acidity of acetylenic proton of alkyne **2** due to complexation allows *deprotonation* by a weak base (*e.g.* NEt_3), then *ligand exchange* with iodide (overall eliminating a molecule of HI) affords R-Pd(II)-alkyne complex **D**. Finally, *reductive elimination* provides monofluoroenyne product **3** and regenerates Pd(0) to complete the catalytic cycle.



Scheme 4. Proposed catalytic cycle for stereoselective C-F bond alkynylation.

In conclusion, a highly stereoselective Pd-catalyzed C-F bond alkynylation of tetrasubstituted *gem*-difluoroalkenes has been developed. The origin of stereoselectivity presumably stems from a chelation-assisted oxidative addition of Pd to the C-F bond. X-ray structure of the monofluorovinyl Pd(II) intermediate has been obtained for the first time as proof. This method gives access to a great variety of novel conjugated monofluoroenynes bearing a tetrasubstituted alkene unit with well-defined geometry. Their pharmaceutical and materials applications are under investigation. We are currently exploring other C-C and C-X bond formations through Pd-catalyzed C-F bond activation involving a stereoselective oxidative addition process.

Acknowledgements

This work was supported by the Research Grants Council of Hong Kong (CUHK 24301217) and the Chinese University of Hong Kong (the Faculty Strategic Fund for Research from the Faculty of Science and the Direct Grant for Research). We also thank the Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences for funding. Prof. Jinbo Hu is thanked for the access of some reagents.

Keywords: C-F bond • palladium • stereoselective • fluoroalkenes • fluoroenynes

[1] For representative reviews on C-F bond activation, see: a) G. Coates, F. Rekhroukh, M. Crimmin, *Synlett* **2019,** *30,* 2233-2246; b) T. Ahrens, J. Kohlmann, M. Ahrens, T. Braun, *Chem. Rev.* **2015,** *115,* 931-972; c) H. Amii, K. Uneyama, *Chem. Rev.* **2009,** *109,* 2119-2183; d) T. Stahl, H. Klare, M. Oestreich, *ACS Catal.* **2013,** *3,* 1578-1587; e) E. Clot, O. Eisenstein, N. Jasim, S. Macgregor, J. McGrady, R. Perutz, *Acc. Chem. Res.* **2011,** *44,* 333-348; f) J. Kiplinger, T. Richmond, C. Osterberg, *Chem. Rev.* **1994,** *94,* 373-431.

[2] For representative reviews on C-F bond formation, see: a) C. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2015,** *54,* 3216-3221; b) T. Liang, C. Neumann, T. Ritter, Angew. Chem. Int. Ed. **2013,** *52,* 8214-8264; c) P. Champagne, J. Desroches, J. Hamel, M. Vandamme, J. Paquin, *Chem. Rev.* **2015,** *115,* 9073-9174.

[3] For selected reviews on fluorinated molecules in pharmaceuticals, see: a) H. Mei, J. Han, S. Fustero, M. Medio-Simon, D. Sedgwick, C. Santi, R. Ruzziconi, V. Soloshonok, *Chem. Eur. J.* **2019,** *25,*11797-11819; b) J. Wang, M. Sánchez-Roselló, J. Aceña, C. Pozo, A. Sorochinsky, S. Fustero, V. Soloshonok, H. Liu, *Chem. Rev.* **2014,** *114,* 2432-2506; c) K. Muller, C. Faeh, F. Diederich, *Science* **2007,** *317,* 1881-1886.

[4] For a review on the preparation of *gem*-difluoroalkenes, see: a) G. Chelucci, *Chem. Rev.* **2012,** *112,* 1344-1462; For practical synthesis of tetrasubstituted *gem*-difluoroalkenes from diazo compounds, see: b) M. Hu, C. Ni, L. Li, Y. Han, J. Hu, *J. Am. Chem. Soc.* **2015,** *137,* 14496-14501; c) M. Hu, Z. He, B. Gao, L. Li, C. Ni, J. Hu, *J. Am. Chem. Soc.* **2013,** *135,* 17302-17305; d) M. Hu, C. Ni, J. Hu, *J. Am. Chem. Soc.* **2012,** *134,* 15257-15260; e) J. Zheng, J. Lin, L. Yu, Y. Wei, X. Zheng, J. Xiao, *Org. Lett.* **2015,** *17,* 6150-6153.

[5] For reviews on the synthesis and applications of monofluoroalkenes, see: a) T. Taguchi, H. Yanai, *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley-Blackwell, Chichester, 2009; b) G. Landelle, M. Bergeron, M. Turcotte-Savard, J. Paquin, *Chem. Soc. Rev.* **2011,** *40,* 2867-2908; c) H. Yanai, T. Taguchi, *Eur. J. Org. Chem.* **2011,** 5939-5954.

[6] a) S. Yan, D. Wu, J. Ye, L. Gong, X. Zeng, C. Ran, Y. Gui, J. Li, D. Yu, *ACS Catal.* **2019,** *9,* 6987-6992; b) D. Tan, E. Lin, W. Ji, Y. Zeng, W. Fan, Q. Li, H. Gao, H. Wang, *Adv. Synth. Catal.* **2018,** *360,* 1032-1037; c) J. Hu, X. Han, Y. Yuan, Z. Shi, *Angew. Chem. Int. Ed.* **2017,** *56,* 13342-13346; d) R. Kojima, K. Kubota, H. Ito, Chem. Commun. **2017,** *53,* 10688-10691; e) J. Zhang, W. Dai, Q. Liu, S. Cao, *Org. Lett.* **2017,** *19,* 3283-3286; f) H. Sakaguchi, Y. Uetake, M. Ohashi, T. Niwa, S. Ogoshi, T. Hosoya, *J. Am. Chem. Soc.* **2017,** *139,* 12855-12862; g) W. Dai, H. Shi, X. Zhao, S. Cao, *Org. Lett.* **2016,** *18,* 4284-4287.

[7] a) Y. Watabe, K. Kanazawa, T. Fujita, J. Ichikawa, *Synthesis* **2017,** *49,* 3569-3575; b) X. Lu, Y. Wang, B. Zhang, J. Pi, X. Wang, T. Gong, B. Xiao, Y. Fu, *J. Am. Chem. Soc.* **2017,** *139,* 12632-12637; c) Y. Xiong, T. Huang, X. Ji, J. Wu, S. Cao, *Org. Biomol. Chem.* **2015,** *13,* 7389-7392.

[8] a) L. Kong, B. Liu, X. Zhou, F. Wang, X. Li, *Chem. Commun.* **2017,** *53,* 10326-10329; b) J. Wu, S. Zhang, H. Gao, Z. Qi, C. Zhou, W. Ji, Y. Liu, Y. Chen, Q. Li, X. Li, H. Wang, *J. Am. Chem. Soc.* **2017,** *139,* 3537-3545; c) P. Tian, C. Feng, T. Loh, *Nat. Commun.* 2015, 6, 7472.

[9] a) D. Zell, V. Müller, U. Dhawa, M. Bursch, R. Presa, S. Grimme, L. Ackermann, *Chem. Eur. J.* **2017,** *23,* 12145-12148; b) L. Kong, X. Zhou, X. Li, *Org. Lett. 2016,* **18,** 6320-6323.

[10] D. Zell, U. Dhawa, V. Müller, M. Bursch, S. Grimme, L. Ackermann, *ACS Catal.* **2017,** *7,* 4209-4213.

[11] N. Li, J. Chang, L. Kong, X. Li, *Org. Chem. Front.* **2018,** *5,* 1978-1982.

[12] J. Xie, J. Yu, M. Rudolph, F. Rominger, A. Hashmi, *Angew. Chem. Int. Ed.* **2016,** *55,* 9416-9421.

[13] L. Yang, W. Ji, E. Lin, J. Li, W. Fan, Q. Li, H. Wang, *Org. Lett.* **2018,** *20,* 1924-1927.

[14] For reviews on transition metal-catalyzed C-F bond activation of *gem*-difluoroalkenes, see: a) T. Fujita, K. Fuchibe, J. Ichikawa, *Angew. Chem. Int. Ed.* **2019,** *58,* 390-402; b) X. Zhang, S. Cao, *Tetrahedron Letters* **2017,** *58,* 375-392.

[15] Y. Zhao, F. Jiang, J. Hu, *J. Am. Chem. Soc.* **2015**, *137*, 5199-5203.

[16] Stereocontrolled synthesis of tetrasubstituted alkenes is a challenging topic, for a review, see: A. Flynn, W. Ogilvie, *Chem. Rev.* **2007,** *107,* 4698-4745.

[17] J. Vela, J. Smith, Y. Yu, N. Ketterer, C. Flaschenriem, R. Lachicotte, P. Holland, *J. Am. Chem. Soc.* **2005,** *127,* 7857-7870, and the references therein.

[18] For reviews on the synthesis and applications of conjugated 1,3-enynes, see: a) R. Chinchilla, C. Nájera, *Chem. Rev.* **2013**, *114*, 1783-1826; b) B. M. Trost, J. T. Masters, *Chem. Soc. Rev.* **2016**, *45*, 2212-2238; c) K. Nicolaou, P. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005,** *44,* 4442-4489, and the references therein.

[19] For a recent review on Pd-catalyzed cross-couplings, see: A. Biffis, P. Centomo, A. Zotto, M. Zecca, *Chem. Rev.* **2018,** *118,* 2249-2295.

[20] For intermolecular Pd-catalyzed defluorinative coupling of *gem*-difluoroalkenes, see: a) W. Heitz, A. Knebelkamp, *Makromol. Chem. Rapid Commun.* **1991,** *12,* 69-75; b) R. Thornbury, F. Toste, *Angew. Chem.* **2016,***128,*11801-11804. For an intramolecular example, see: c) K. Sakoda, J. Mihara, J. Ichikawa, *Chem. Commun.* 2005, 4684-4686.

[21] For Pd-catalyzed defluorinative coupling reactions of tetrafluoroethylene (TFE), see: a) M. Ohashi, T. Kambara, T. Hatanaka, H. Saijo, R. Doi, S. Ogoshi, *J. Am. Chem. Soc.* **2011,** *133,* 3256-3259; b) M. Ohashi, H. Saijo,

10.1002/anie.202002219

M. Shibata, S. Ogoshi, *Eur. J. Org. Chem.* **2013,** 443-447; c) H. Saijo, H. Sakaguchi, M. Ohashi, S. Ogoshi, *Organometallics* **2014,** *33,* 3669-3672; For a review, see: d) M. Ohashi, S. Ogoshi, *J. Synth. Org. Chem. Jpn.* **2016,** *74,* 1047-1057.

[22] See the Supporting Information (SI) for details.

[23] For examples of Pd-free syntheses of 2-fluoro 1,3-enynes, see: a) A. J. Zapata, Y. Gu, G. B. Hammond, *J. Org. Chem.* **2000**, *65*, 227-234; b) G. Jin, J. Zhang, W. Wu, S. Cao, *J. Fluorine Chem.* **2014**, *168*, 240-246.

[24] This reaction is an example of copper-free Sonogashira-type coupling. In the initial screening, adding catalytic CuI (10 mol %) was not as effective as adding excess NaI, see SI for details. For a recent report on the mechanism of copper-free Sonogashira reaction, see: M. Gazvoda, M. Virant, B. Pinter, J. Košmrlj, *Nat. Commun.* **2018,** *9,* 4814.

[25] CCDC 1969313 (**3ah**) and CCDC 1969315 (**Int-1**) contain 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.

[26] Contrastingly, trisubstituted *gem*-difluoroalkenes such as difluorostyrene derivatives have shown intrinsic bias to influence *E*/*Z*-selectivity (*E*/*Z* = 84:16 to 94:6) in the alkynylation with terminal alkynes using ^{n}BuLi, due to electronic repulsion in the elimination step, see reference 23b. However, this influence is absent in tetrasubstituted *gem*-difluoroalkenes such as **1a**.

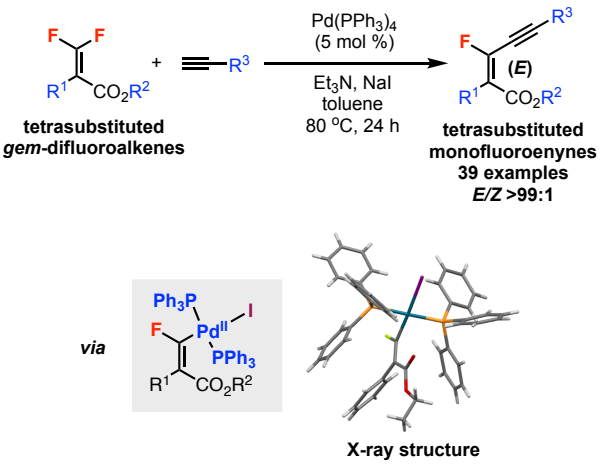
[27] For an example of chelation-assisted Pd-catalyzed C-F bond activation of polyfluoroarenes, see: a) Z. Chen, C. He, Z. Yin, L. Chen, Y. He, X. Zhang, *Angew. Chem. Int. Ed.* **2013,** *52,* 5813-5817; For a recent review on esters as DGs in metal-catalyzed C-H functionalization, see: b) C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. Zia, J. Wencel-Delord, T. Besset, B. Maes, M. Schnürch, *Chem. Soc. Rev.* **2018,** *47,* 6603-6743; For mechanistic discussion of analogous Pd-catalyzed Cu-free Sonogashira cross-coupling of aryl fluorides with terminal alkynes, see: c) J. He, K. Yang, J. Zhao, S. Cao, *Org. Lett.* **2019,** *21,* 9714-9718.

[28] Lithium iodide was shown to be crucial for the C-F bond cleavage of tetrafluoroethylene (TFE) to afford a trifluorovinylpalladium(II) iodide species (*via* oxidative addition of Pd to the C-F bond), see reference 21a.

10.1002/anie.202002219

WILEY-VCH

COMMUNICATION



*Qiao Ma, Yanhui Wang and Gavin Chit Tsui**

Page 1. – Page 5.

Stereoselective Palladium-Catalyzed C-F Bond Alkynylation of Tetrasubstituted *gem*-Difluoroalkenes