Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/c5ob02213d

Copper-catalyzed direct C–H fluoroalkenylation of heteroarenes†

Kevin Rousée, Cédric Schneider, Jean-Philippe Bouillon, Vincent Levacher, Christophe Hoarau,* Samuel Couve-Bonnaire* and Xavier Pannecoucke

Received 26th October 2015,
Accepted 13th November 2015

DOI: 10.1039/c5ob02213d

www.rsc.org/obc

Copper-catalyzed direct C–H fluoroalkenylation of heterocycles using various *gem*-bromofluoroalkenes as electrophiles is reported. This efficient method offers step-economical, low-cost and stereocontrolled access to relevant heteroarylated monofluoroalkenes. The synthesis of fluorinated analogues of biomolecules and therapeutic agents for the treatment of Duchenne muscular dystrophy as application is reported.

Introduction

The importance of fluorinated compounds in agrochemicals,[1,2] pharmaceuticals/medicinals,[1,3] and materials science[1,4] has triggered an explosion of research efforts in developing new and efficient methods to introduce a fluorinated functional group into organic molecules. Of particular relevance is the emergence of fluoroalkenes,[5] versatile compounds that have found many applications as, for example, peptidomimetics,[6] drugs[7] and materials.[8] In peptide synthesis and fine organic chemistry, fluoroalkenes are widely looked upon as stable isosteric and isoelectronic mimics of the amide bond,[6] and bioisosteres in the structure/activity relationship studies.

Within the readily available fluorinated building blocks for the construction of fluoroolefins, *gem*-bromofluoroalkenes are easily accessible[9] and versatile reagents for the achievement of highly useful cross-coupling reactions.[10] The development of catalytic direct C–H bond functionalization methodologies using transition metals as catalysts has received considerable attention avoiding thus the preparation of organometallic intermediates as coupling partners.[11] For a realistic catalyst loading of these precious metals, less expensive transition elements such as copper have received significant attention. Indeed, since the breakthroughs made by Daugulis,[12] Miura[13] and Piguel,[14] remarkable advances have been made in copper-catalyzed direct arylation,[15] alkynylation[16] and alkenylation[17,18] of azoles from monohalogenoalkenes (Fig. 1, eqn (1) and (2)). However, no example of copper-catalyzed direct C–H halogenoalkenylation so far has been reported from *gem*-dihalogenoalkenes. Indeed, the latter have been used only for copper-catalyzed C–H alkynylation of heterocycles, the non-coupled second halogen being eliminated during the catalytic process (Fig. 1, eqn (3)).[19] Recently, Cao has described an elegant metal-free base mediated nucleophilic vinylic substitution reaction between tetrasubstituted *gem*-difluoroalkenes and azoles (Fig. 1, eqn (4)).[20a] In this case, only tetrasubstituted *gem*-difluoroalkenes can be used as substrates, and the trisubstituted ones would directly lead to the dehydrofluorination process. This year, Loh have successfully engaged

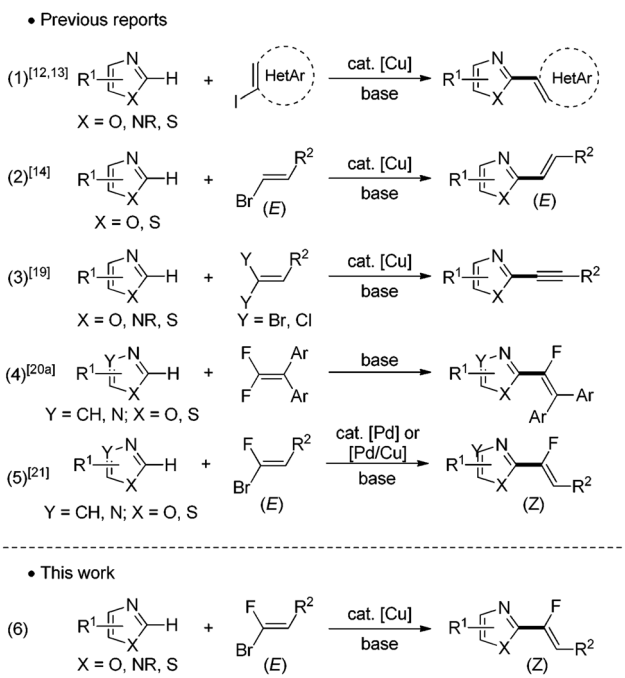


Fig. 1 Direct functionalization of ubiquitous C–H bonds using halogenoaryls/alkenes and *gem*-dihalogenoalkenes.

Normandie Univ, COBRA, UMR 6014 & FR 3038, Univ Rouen, INSA Rouen, CNRS, IRCOF, 1 rue Tesnière 76821, Mont-Saint-Aignan Cedex, France.
E-mail: samuel.couve-bonnaire@insa-rouen.fr, christophe.hoarau@insa-rouen.fr

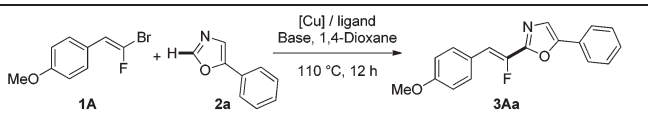
†Electronic supplementary information (ESI) available: Experimental procedures, optimization tables, characterization data and NMR spectra of new compounds. See DOI: 10.1039/c5ob02213d

gem-difluoroalkenes in an innovative Rh(III)-catalyzed *ortho*-directed C–H activation, migratory insertion into the double bond and a defluorination sequence to produce fluoroalkenylated (hetero)aromatics.[20b] Our group has previously reported the first Pd-catalyzed direct C–H halogenoalkenylation of heterocycles demonstrating that *gem*-bromofluoroalkenes are suitable building blocks for this transformation (Fig. 1, eqn (5)).[21] During this study, a combination of copper salt with a palladium catalyst led to a cooperative Pd(0)/Cu(I) catalysis which was found highly performant to achieve the direct C–H alkenylation of a broad range of 1,3-diazoles with any *gem*-bromofluoroalkenes as electrophiles. This efficiency was based upon the catalytic generation of an heteroaryl copper intermediate reacting as a transmetallating agent.[22] In our ongoing project devoted to the production of fluorinated biomolecule analogues, we have recently turned our attention to the evaluation of the reactivity of the heteroaryl copper intermediate towards *gem*-bromofluoroalkenes in view of developing a novel palladium free copper-catalyzed direct C–H fluoroalkenylation of heterocycles offering step-economical, low-cost and stereocontrolled access to heteroarylated monofluoroalkenes (Fig. 1, eqn (6)). Moreover, taking into account that the direct fluoroalkenylation is very scarce in the literature, it could represent an efficient alternative to produce fluorinated fine chemicals. We reported herein this methodology giving access to a wide variety of trisubstituted monofluoroalkene[5,23] derivatives including fluorinated analogues of therapeutic agents.

Results and discussion

We initiated our investigation by probing various reaction conditions for the direct C–H fluoroalkenylation of 5-phenyloxazole (**2a**) with easily accessible (*E*)-*gem*-bromofluoroalkene[9] **1A** (Table 1). Indeed, whereas a set of experiments with our model substrate, phenyloxadiazole, under an optimized previously reported procedure was found unsuccessful without the palladium catalyst,[24] **2a** proved to be a suitable substrate for direct fluoroalkenylation without a palladium source, providing **3Aa** in 63% yield compared to 75% yield under bimetallic Pd/Cu catalysis (entries 1 and 2). Switching the nature of the copper source for CuI led to a slight enhancement of the yield (entry 3). Among the bases, *t*-BuOLi proved to be the most effective without formation of the alkynylated side-product *via* a dehydrofluorination process (entries 4 and 5). Subsequently, common ligands of copper have been screened, such as Phen and derivatives, diamine ligands or mono- and bidendate phosphines (entries 4–10), and surprisingly, dppe revealed considerable efficiency affording the desired product in almost quantitative yield (entry 10). Crucially, formation of **3Aa** was not observed when copper was omitted from the reaction mixture (entry 11). We then performed the reaction with different copper sources (entries 12–14). The best performance of the reaction was thus attained by using CuI as the catalyst; however, we observed that the monofluoroalkenylation was slightly insensitive to the copper source (Cu(I) or Cu(II)).

Table 1 Optimization of the fluoroalkenylation reaction[a]



Entry	[Cu]	Ligand	Base	Yield[b] (%)
1[c]	CuBr	—	*t*-BuOLi	75
2	CuBr	—	*t*-BuOLi	63
3	CuI	—	*t*-BuOLi	65
4	CuI	Phen	*t*-BuOLi	51
5	CuI	Phen	K_2CO_3	—
6	CuI	L_1[d]	*t*-BuOLi	51
7	CuI	L_2[e]	*t*-BuOLi	81
8	CuI	PPh_3	*t*-BuOLi	83
9	CuI	$PCy_3{\cdot}HBF_4$	*t*-BuOLi	51
10	*CuI*	*dppe*	*t*-BuOLi	*96*
11	—	dppe	*t*-BuOLi	—
12	CuBr	dppe	*t*-BuOLi	66
13	$CuCl_2$	dppe	*t*-BuOLi	73
14	$Cu(OTf)_2$	dppe	*t*-BuOLi	65

[a] All reactions were performed using **1A** (1.1 equiv.), **2a** (0.2 mmol, 1.0 equiv.), copper source (10 mol%), ligand (20 mol%), and base (3 equiv.) in 1,4-dioxane (0.25 M) at 110 °C. [b] Yield based on the isolated product after flash chromatography. [c] In the presence of $PdCl_2(PPh_3)_2$ (5 mol%). [d] L_1 = 3,4,7,8-$(Me)_4$-1,10-Phen. [e] L_2 = *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine.

Under these optimized reaction conditions, the heteroarylated fluoroalkene **3Aa** was produced in 96% isolated yield as a pure (*Z*)-isomer, demonstrating that the reaction proceeds with complete retention of the stereochemistry.

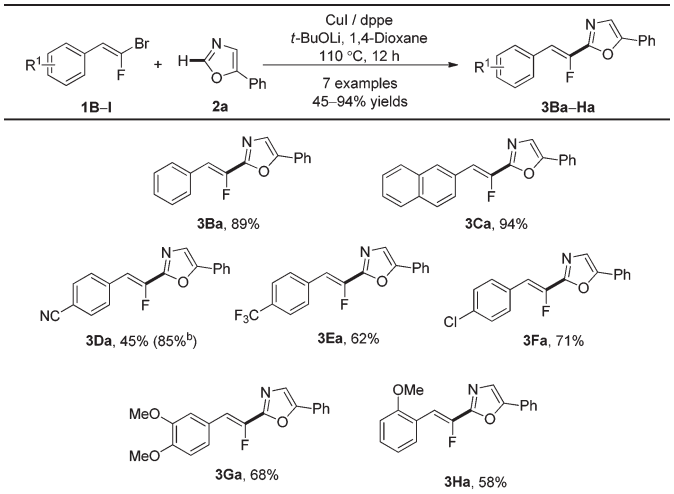
With the optimized conditions in hand, the establishment of the scope of the direct C–H fluoroalkenylation was undertaken on 5-phenyloxazole (**2a**) with various readily accessible (*E*)-*gem*-bromofluoroalkenes[9] (Table 2). The latter flanked indifferently with electron-donating or electron-withdrawing groups on the aromatic unit at the *ortho*, *meta* and *para* positions, reacted at the C-2 position of the 5-phenyloxazole producing the desired product in moderate to excellent yields.

Interestingly, (*E*)-*gem*-bromofluoroalkenes bearing the cyano group (**1D**) or the chlorine atom (**1F**) on the aromatic ring, both valuable functional groups for further post-functionalizations, displayed good reactivity, even if, in the case of **3Da**, the reaction yield was lower than that obtained under Pd/Cu catalysis.[21]

Alkylated or tetrasubstituted *gem*-bromofluoroalkenes proved to be unreactive under Cu-catalysis whereas the reaction occurred under Pd/Cu catalysis.[21,25] The aromatic ring bearing an electron-withdrawing group at the *ortho* position proved to be unstable under these reaction conditions.[25]

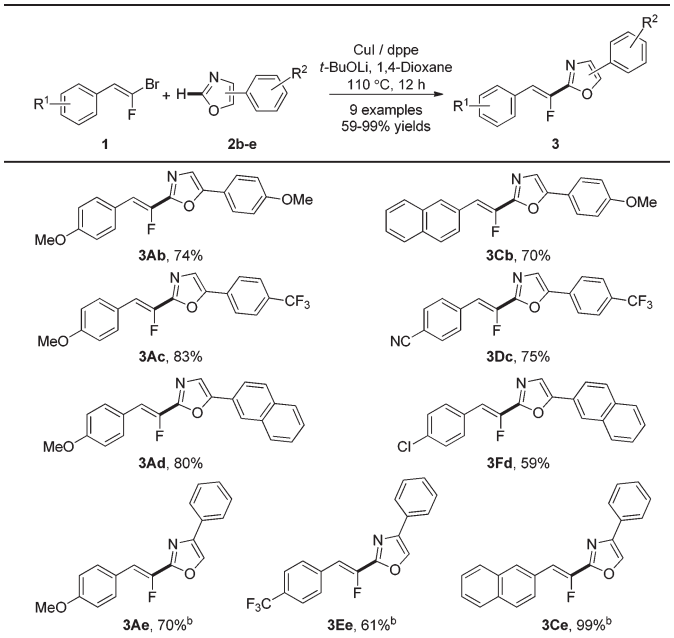
We next examined the substrate scope of various aryloxazoles (**2b–e**) with a panel of *gem*-bromofluoroalkenes in this transformation (Table 3). The reaction was efficient whatever the electronic nature of the substituents on the benzene ring of the 5-phenyloxazole **2b–d**. It is noteworthy that the use of Phen instead of dppe as a ligand with 4-phenyloxazole **2e** as the substrate was crucial to obtain trisubstituted *Z*-fluoroalkenes **3Ae**, **3Ce** and **3Ee** in good yields.[25]

Table 2 Copper-catalyzed C–H fluoroalkenylation of 5-phenyloxazole with various *gem*-bromofluoroalkenes[a]



[a] All reactions were performed using **1** (1.1 equiv.), **2a** (0.2 mmol, 1.0 equiv.), CuI (10 mol%), dppe (20 mol%), *t*-BuOLi (3 equiv.) in 1,4-dioxane (0.25 M) at 110 °C. Yields are based on the isolated product after flash chromatography. [b] Yield obtained under bimetallic Pd/Cu catalysis.

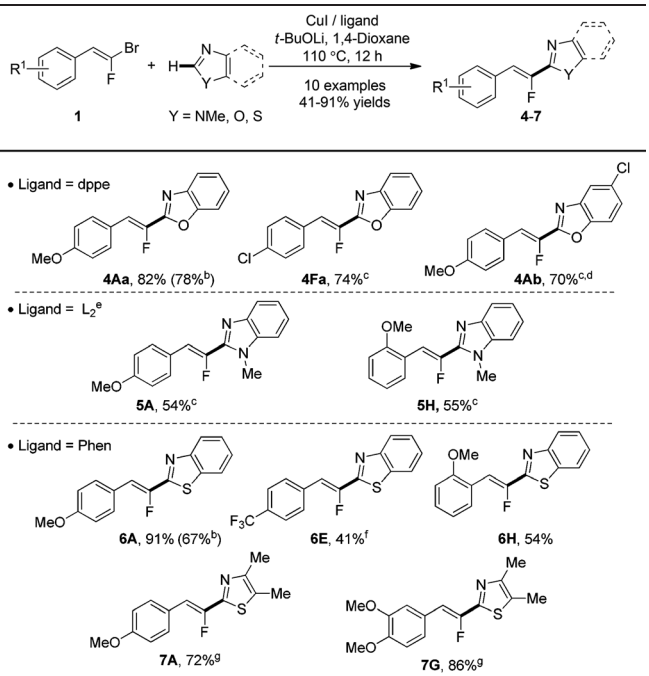
Table 3 Copper-catalyzed C–H fluoroalkenylation of various aryloxazoles[a]



[a] All reactions were performed using **1** (1.1 equiv.), **2** (0.2 mmol, 1.0 equiv.), CuI (10 mol%), dppe (20 mol%), and *t*-BuOLi (3 equiv.) in 1,4-dioxane (0.25 M) at 110 °C. Yields are based on the isolated product after flash chromatography. [b] Phen (20 mol%) has been used as a ligand instead of dppe.

We then applied our reaction conditions to various relevant 1,3-diazoles (Table 4). A first set of experiments engaging benzoxazole **4a** with the (*E*)-*gem*-bromofluoroalkenes **1A** and **1F**, as

Table 4 Extension of the reaction to various heterocycles[a]

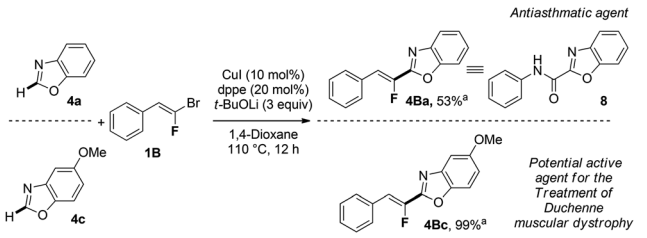


[a] All reactions were performed using **1** (1.1 equiv.), heterocycle (0.2 mmol, 1.0 equiv.), CuI (10 mol%), ligand (20 mol%), and *t*-BuOLi (3 equiv.) in 1,4-dioxane (0.25 M) at 110 °C. Yields are based on the isolated product after flash chromatography. [b] Yield obtained under bimetallic Pd/Cu catalysis. [c] Reaction performed at 130 °C. [d] Reaction performed on a 1 mmol scale. [e] L_2 = *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine. [f] Reaction performed at 90 °C. [g] CuI (20 mol%) and Phen (40 mol%) were used.

coupling partners was addressed. Through the expected monofluoroalkenes, **4Aa** was obtained in good (82%) yield whereas the chlorinated benzoxazolylfluoroalkene **4Fa** was produced in poor (20%) yield (^{19}F NMR yield). Nevertheless, when the temperature was increased from 110 to 130 °C, full completion of benzoxazole **4a** was attained to provide product **4Fa** in 74% yield. The reaction performed with chlorinated benzoxazole **4b** at the same 130 °C temperature delivered the expected benzoxazolylfluoroalkene **4Ab** in good (70%) yield and importantly, the reaction could be scaled up from 0.2 mmol to 1 mmol without any loss of efficiency.

We then examined the selective C–H monofluoroalkenylation with *N*-methyl-benzimidazole **5** as a heterocycle under our optimized conditions and, unfortunately no desired product was obtained. A careful screening of bases, solvents and ligands at different reaction temperatures[25] led to select *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine as a ligand and a reaction temperature of 130 °C to produce fluoroalkenes **5A** and **5H** in optimized 54 and 55% yields, respectively.

Finally, the reaction was investigated in a thiazole series. In this case, the phenanthroline ligand was found highly performant to achieve the cross-coupling at 110 °C of *para*-, *ortho*- or disubstituted *gem*-bromofluoroalkenes **1A**, **1G** and **1H** with benzothiazole **6** and 4,5-dimethythiazole **7** giving the



Scheme 1 Synthesis of fluorinated therapeutic agents. [a] Yields based on the isolated product after flash chromatography.

fluoroalkenes in fair 54% to excellent 91% yields. However, the reaction performed with the trifluoromethylated (*E*)-*gem*-bromofluoroalkenes **1E** provided the desired product **6E** in poor 20% isolated yield mainly due to the degradation of the coupling partner **1E**. Fortunately, the yield was significantly improved to 41% when operating at lower temperature, 90 °C. It has to be noted that the yields obtained for **4Aa** and **6A** under these experimental conditions were better than the yields obtained under bimetallic catalysis.[21]

Finally, we applied this copper-catalyzed fluoroalkenylation to the synthesis of relevant biomolecules as depicted in Scheme 1. Taking into account the similarities between the fluoroolefin moiety and the amide bond,[6] we first synthesized a fluorinated analogue **4Ba**, in 53% yield, of the antiasthmatic agent **8**,[26] starting from benzoxazole **4a** and *gem*-bromofluoroalkene **1B**. Then, we decided to apply our methodology as an alternative pathway to produce potential active molecules used in the treatment of Duchenne muscular dystrophy exemplified by the molecule **4Bc**[27] which was produced in quantitative yield by reacting 5-methoxybenzoxazole **4c** with *gem*-bromofluoroalkene **1B** (Scheme 1). Interestingly, a library of compounds may be readily produced for further SAR study introducing various substituents on both aromatic rings bearing heterocycle **4** or *gem*-bromofluoroalkene partner **1**.

Conclusions

In summary, an efficient Cu(I)/*t*-BuOLi catalyst has been employed for direct C–H fluoroalkenylation of 1,3-diazoles with readily available *gem*-bromofluoroalkenes as coupling partners. Although phenyloxadiazole remained unreactive as well as the use of alkylated *gem*-bromofluoroalkenes as electrophiles were unsuitable under these experimental conditions compared to the bimetallic Pd/Cu catalysis, the palladium free copper catalyzed fluoroalkenylation proved to be very efficient with *gem*-bromofluorostyrenes. Remarkably, a broad scope of 1,3-diazoles was accomplished modulating the nature of the ligand. Notably, the (benzo)oxazole, (benzo)thiazole and benzimidazole series were successfully coupled with various *gem*-bromofluoroalkenes using diarylphosphine, phenanthroline and diamine ligands. The methodology gave access to innovative and valuable heteroarylated fluoroalkenes **3–7** produced in fair to excellent yields. It was finally applied to the synthesis of valuable benzoxazolylfluoroalkenes **4Ba**, a fluorinated analogue of an antiasthmatic agent, and **4Bc** which is potentially active in the treatment of Duchenne muscular dystrophy.

Acknowledgements

This work has been partially supported by INSA Rouen, Rouen University, CNRS EFRD, Labex SynOrg (ANR-11-LABX-0029).

Notes and references

1 (*a*) T. Hiyama in *Organofluorine Compounds: Chemistry and Applications*, *ed* H. Yamamoto, Springer-Verlag, Berlin, 2000; (*b*) Approximately 30–40% of agrochemicals and 20–25% of pharmaceuticals on the market are estimated to contain fluorine: A. M. Thayer, *Chem. Eng. News*, 2006, **84**, 15.
2 P. Jiechke, *ChemBioChem*, 2004, **5**, 570.
3 (*a*) J.-P. Bégué and D. Bonnet-Delphon, *J. Fluorine Chem.*, 2006, **127**, 992; (*b*) K. L. Kirk, *J. Fluorine Chem.*, 2006, **127**, 1013; (*c*) K. Muller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (*d*) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359; (*e*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (*f*) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432.
4 M. Pagliaro and R. Ciriminna, *J. Mater. Chem.*, 2005, **15**, 4981.
5 (*a*) G. Landelle, N. Bergeron, M.-O. Turcotte-Savard and J.-F. Paquin, *Chem. Soc. Rev.*, 2011, **40**, 2867; (*b*) H. Yanai and T. Taguchi, *Eur. J. Org. Chem.*, 2011, 5939; (*c*) S. Hara, *Top. Curr. Chem.*, 2012, **327**, 59.
6 (*a*) K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, 2006; (*b*) S. Couve-Bonnaire, D. Cahard and X. Pannecoucke, *Org. Biomol. Chem.*, 2007, **5**, 1151 and references therein; (*c*) C. Pierry, S. Couve-Bonnaire, L. Guilhaudis, C. Neveu, A. Marotte, B. Lefranc, D. Cahard, I. Segalas-Milazzo, J. Leprince and X. Pannecoucke, *ChemBioChem*, 2013, **14**, 1620.
7 Monofluoroalkenes as (*a*) Antitumoral: S. Osada, S. Sano, M. Ueyama, Y. Chuman, H. Kodama and K. Sakaguchi, *Bioorg. Med. Chem.*, 2010, **18**, 605; (*b*) Antimicrobial: Y. Asahina, K. Iwase, F. Iinuma, M. Hosaka and T. Ishizaki, *J. Med. Chem.*, 2005, **48**, 3194; (*c*) Anti-HIV: S. Oishi, H. Kamitani, Y. Kodera, K. Watanabe, K. Kobayashi, T. Narumi, K. Tomita, H. Ohno, T. Naito, R. Kodama, M. Matsuoka and N. Fujii, *Org. Biomol. Chem.*, 2009, **7**, 2872; (*d*) Antidiabetic: S. D. Edmondson, L. Wei, J. Xu, J. Shang, S. Xu, J. Pang, A. Chaudhary, D. C. Dean, H. He, B. Leiting, K. A. Lyons, R. A. Patel, S. B. Patel, G. Scapin, J. K. Wu, M. G. Beconi, N. A. Thornberry and A. E. Weber, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2409.

8 (*a*) F. Babudri, G. M. Farinola, F. Naso and R. Ragni, *Chem. Commun.*, 2007, 1003; (*b*) F. Babudri, A. Cardone, G. M. Farinola, C. Martinelli, R. Mendichi, F. Naso and M. Striccoli, *Eur. J. Org. Chem.*, 2008, 1977.

9 All *gem*-bromofluoroalkenes were prepared following our optimized olefination procedure: (*a*) X. Lei, G. Dutheuil, X. Pannecoucke and J.-C. Quirion, *Org. Lett.*, 2004, **6**, 2101; (*b*) L. Zoute, G. Dutheuil, J.-C. Quirion, P. Jubault and X. Pannecoucke, *Synthesis*, 2006, 3409; (*c*) For other preparation see: D. J. Burton, Z.-Y. Yang and W. Qiu, *Chem. Rev.*, 1996, **96**, 1641.

10 (*a*) F. Legrand, K. Jouvin and G. Evano, *Isr. J. Chem.*, 2010, **50**, 588; (*b*) G. Chelucci, *Chem. Rev.*, 2012, **112**, 1344 and references therein.

11 For recent reviews see: (*a*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (*b*) B. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173; (*c*) K. Fagnou, *Top. Curr. Chem.*, 2010, **292**, 35; (*d*) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy and J. F. Hartwig, *Chem. Rev.*, 2010, **110**, 890; (*e*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (*f*) C. L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Commun.*, 2010, **46**, 677; (*g*) M. Wasa, K. M. Engle and J.-Q. Yu, *Isr. J. Chem.*, 2010, **50**, 605; (*h*) C. Liu, H. Zhang, W. Sui and A. Lei, *Chem. Rev.*, 2011, **111**, 1780; (*i*) P. Herrmann and T. Bach, *Chem. Soc. Rev.*, 2011, **40**, 2022; (*j*) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315; (*k*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*l*) W. Shi, C. Liu and A. Lei, *Chem. Soc. Rev.*, 2011, **40**, 2761; (*m*) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788; (*n*) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960; (*o*) T. Besset, T. Poisson and X. Pannecoucke, *Chem. – Eur. J.*, 2014, **20**, 16830.

12 (*a*) H.-Q. Do and O. Daugulis, *J. Am. Chem. Soc.*, 2007, **129**, 12404; (*b*) H.-Q. Do, R. K. M. Khan and O. Daugulis, *J. Am. Chem. Soc.*, 2008, **130**, 15185.

13 (*a*) M. Yamashita, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2009, **11**, 2337; (*b*) T. Yoshizumi, H. Tsurugi, T. Satoh and M. Miura, *Tetrahedron Lett.*, 2008, **49**, 1598.

14 F. Besselièvre, S. Piguel, F. Mahuteau-Betzer and D. S. Grierson, *Org. Lett.*, 2008, **10**, 4029.

15 (*a*) A. A. Kulkarni and O. Daugulis, *Synthesis*, 2009, 4087; (*b*) O. Daugulis, H.-Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **41**, 1074; (*c*) O. Daugulis, *Top. Curr. Chem.*, 2010, **292**, 57; (*d*) K. Hirano and M. Miura, *Synlett*, 2011, 294; (*e*) K. Hirano and M. Miura, *Chem. Commun.*, 2012, **48**, 10704; (*f*) K. Hirano and M. Miura, *Top. Catal.*, 2014, **57**, 878.

16 (*a*) F. Besselièvre and S. Piguel, *Angew. Chem., Int. Ed.*, 2009, **48**, 9553; (*b*) N. Matsuyama, M. Kitahara, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2010, **12**, 2358; (*c*) T. Kawano, N. Matsuyama, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2010, **75**, 1764.

17 For recent reviews of C–H alkenylation see: (*a*) S. Messaouidi, J. –D. Brion and M. Alami, *Eur. J. Org. Chem.*, 2010, 6495; (*b*) R. Rossi, F. Bellina and M. Lessi, *Synthesis*, 2010, 4131.

18 (*a*) Q. Liao, L. Zhang, S. Li and C. Xi, *Org. Lett.*, 2011, **13**, 228; (*b*) B. Das, G. C. Reddy, P. Balasubramanyam and N. Salvanna, *Tetrahedron*, 2012, **68**, 300; (*c*) W. Zhang, Y. Tian, N. Zhao, Y. Wang, J. Li and Z. Wang, *Tetrahedron*, 2014, **70**, 6120.

19 (*a*) B. P. Berciano, S. Lebrequier, F. Besselièvre and S. Piguel, *Org. Lett.*, 2010, **12**, 4038; (*b*) G. C. Reddy, P. Balasubramanyam, N. Salvanna and B. Das, *Eur. J. Org. Chem.*, 2012, 471; (*c*) K. Jouvin, A. Coste, A. Bayle, F. Legrand, G. Karthikeyan, K. Tadiparthi and G. Evano, *Organometallics*, 2012, **31**, 7933; (*d*) L. Ackermann, C. Kornhaass and Z. Yingjun, *Org. Lett.*, 2012, **14**, 1824.

20 (*a*) X. Zhang, Y. Lin, J. Zhang and S. Cao, *RSC Adv.*, 2015, **5**, 7905; (*b*) P. Tian, C. Feng and T.-P. Loh, *Nat. Commun.*, 2015, **6**, 7472.

21 C. Schneider, D. Masi, S. Couve-Bonnaire, X. Pannecoucke and C. Hoarau, *Angew. Chem., Int. Ed.*, 2013, **52**, 3246.

22 F. Bellina, S. Cauteruccio and R. Rossi, *Curr. Org. Chem.*, 2008, **12**, 774.

23 K. Rousée, C. Schneider, S. Couve-Bonnaire, X. Pannecoucke, V. Levacher and C. Hoarau, *Chem. – Eur. J.*, 2014, **20**, 15000.

24 Reaction of **1A** with phenyloxadiazole in 1,4-dioxane with *t*-BuOLi as a base gave 83% yield under $PdCl_2(PPh_3)_2$/CuBr catalysis, 0% under CuBr catalysis and 20% under CuI catalysis.

25 See the ESI† for more details.

26 B. Loev, R. E. Brown, F. –C. Huang and H. Jones, *Patent*, EP0127066 (A2), USV Pharmaceutical Corporation, 1984.

27 (*a*) S. P. Wren, G. M. Wynne, F. X. Wilson and S. D. Poignant, *Patent*, WO2010/112093 (A1), BioMarin IGA, Ltd, 2010; (*b*) S. P. Wren, G. M. Wynne and F. X. Wilson, *Patent*, WO2010/112092 (A1), BioMarin IGA, Ltd, 2010.