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Palladium-catalysed regio- and stereo-controlled C-2  $\beta$ -fluorovinylation of indoles†

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Vinyl-fluorides appended to heterocycles are a broadly underdeveloped family of functionality with potential application in bioactive compounds. Herein, we disclose a C–H functionalisation strategy for the regio- and stereo-controlled synthesis of Z- $\beta$ -fluorovinyl indoles exclusively in the C-2 position. Z-Fluorovinyl iodonium salts, which are formed from alkynes through a Ag-catalysed process, engage in a palladium-catalysed C-2 C–H functionalisation of indoles (and pyrroles) to achieve a broad scope of  $\beta$ -fluorovinyl heterocycles in good to excellent yields. Mechanistic studies and product derivatisations are provided.

## Introduction

Fluorinated moieties are important in drug and agrochemical design,<sup>1,2</sup> as fluorine has the ability to tune physicochemical and biological properties, such as membrane permeability, lipophilicity, and *in vivo* metabolic stability.<sup>3</sup> Monofluoroalkenes are a robust, non-nucleophilic peptide bond bioisostere, and a lipophilic peptidomimetic unit used in the design of protease inhibitors to facilitate *cis/trans* conformational control.<sup>4</sup> Several bioactive compounds with various pharmacological activities (anticancer, antimicrobial, anti-HIV, anti-diabetic) bear this motif, Fig. 1A.<sup>5</sup>

Regio- and stereo-controlled routes to monofluoroalkenes remain broadly underdeveloped,<sup>6–8</sup> which is especially apparent when appended to heteroarenes. There are several methods reported to install the fluoro-vinyl group onto indoles with the fluoride in the  $\alpha$ -position, Fig. 1B; for the most part, *gem*-difluoroalkenes are employed as fluoroalkene surrogates that partner with heteroarenes in transition metal-catalysed coupling reactions.<sup>9–12</sup> In contrast, there are no methods to install the fluorovinyl group with fluoride in the  $\beta$ -position. With the orientation of the monofluoroalkene switched, this moiety should be a bioisostere of an anilide, as opposed to a benzamide derivative, Fig. 1B. Indoles that are vinyllated in the C-2 position are of notable interest because they are present in active pharmaceutical ingredients and this pattern of unsaturation has been derivatised through pericyclic reactions and macrocyclizations.<sup>13</sup> Therefore, the development of a method for direct  $\beta$ -fluorovinylation of indole at C-2 would fill

an important area of currently inaccessible chemical space that should create potential important utility.

The methods reported to vinyllate indoles at C-2 cannot easily be translated to directly access  $\beta$ -fluorovinyl indoles due to several issues, including the use of directing groups and difficulties in achieving high-stereoselectivity.<sup>14</sup> Heck-type coupling reactions of indoles have been reported with Michael acceptors,<sup>14a</sup> but they also do not work with fluoroalkenes, as we show later, *vide infra*.

We have recently reported a highly efficient silver-catalysed strategy for the stereoselective synthesis of Z-fluorovinyl iodonium (FVI) salts (**1**) from unactivated alkynes.<sup>15</sup> These stereo-defined FVI salts are stable tuneable building blocks that can engage in palladium catalysis to create new carbon–carbon bonds, as we,<sup>15</sup> Hara,<sup>16</sup> and Novák<sup>17</sup> have demonstrated. Therefore, we considered whether FVI salts could be effective coupling partners to regio- and stereoselectively deliver the  $\beta$ -fluorovinyl unit to indole, Fig. 1C. We reasoned that a Pd<sup>(II)/(IV)</sup> cycle could be accessed with the use of FVI salts, which should favour the desired C-2 vinylation,<sup>18</sup> as opposed to the more common C-3 vinylation that is readily accessed through the Pd<sup>(0)/(II)</sup> Fujiwara–Moritani reaction.<sup>13</sup> The key challenges associated with this strategy are to maintain exclusive regio- and stereoselectivity, and achieve chemoselectivity by avoiding any competitive arylation *via* cleavage of the Ar–I<sup>(III)</sup> bond.<sup>18–20</sup> With these objectives in mind, we now report on the development of such a process.

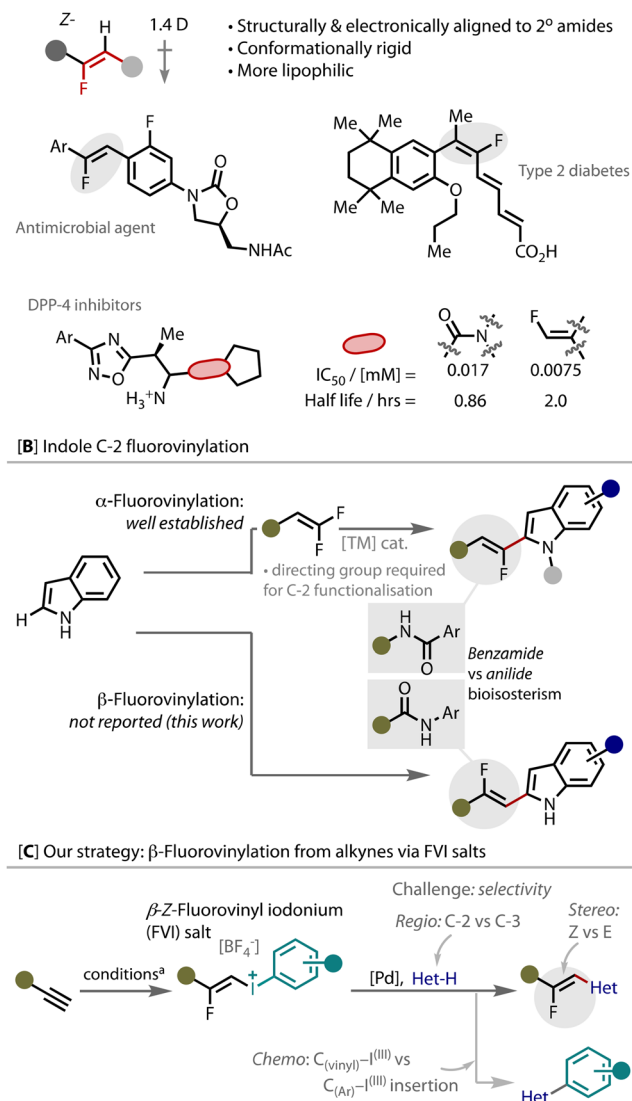
## Results and discussion

We initiated our study by optimising the C-2  $\beta$ -fluorovinylation of *N*-methyl indole **2a**, using mesitylene substituted iodane **1a** as coupling partner. We strategically selected the mesityl (Mes)

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**Fig. 1** The importance of monofluoroalkenes, the fluorovinylation of indoles at C-2 and our strategy for achieving β-fluorovinylation using fluorovinyliodonium (FVI) salts. <sup>a</sup> See ESI† and ref. 15.

substituted iodonium salt due to the steric bulk around the hyper-valent iodine<sup>(III)</sup>, which should aid selective cleavage of the  $C_{(vinyl)}-I^{(III)}$  bond and reduce any competing arylation through cleavage of the  $C_{(Ar)}-I^{(III)}$  bond. A wide range of copper and palladium salts were evaluated as catalysts in the reaction (see ESI† for screening data, and Table 1 for a selected summary). These screening efforts exposed the ability of  $PdBr_2$ ,  $(CH_3CN)_2PdCl_2$  and  $Pd(OCOCF_3)_2$  to catalyse this transformation (entries 1–3), but they proved to be less effective than  $Pd(OAc)_2$ , with the expected product **3a** obtained in 54% yield in acetic acid at room temperature (Table 1, entry 4). The palladium catalyst delivered the β-fluorovinyl unit exclusively to the C-2 position of indole, with no evidence of any reaction at C-3, and with complete retention of stereochemistry (confirmed by 2D NMR and coupling constant analysis).

The corresponding ketone was formed as a side-product when acetic acid was used as a solvent, which could be

**Table 1** Optimization of reaction conditions<sup>a</sup>

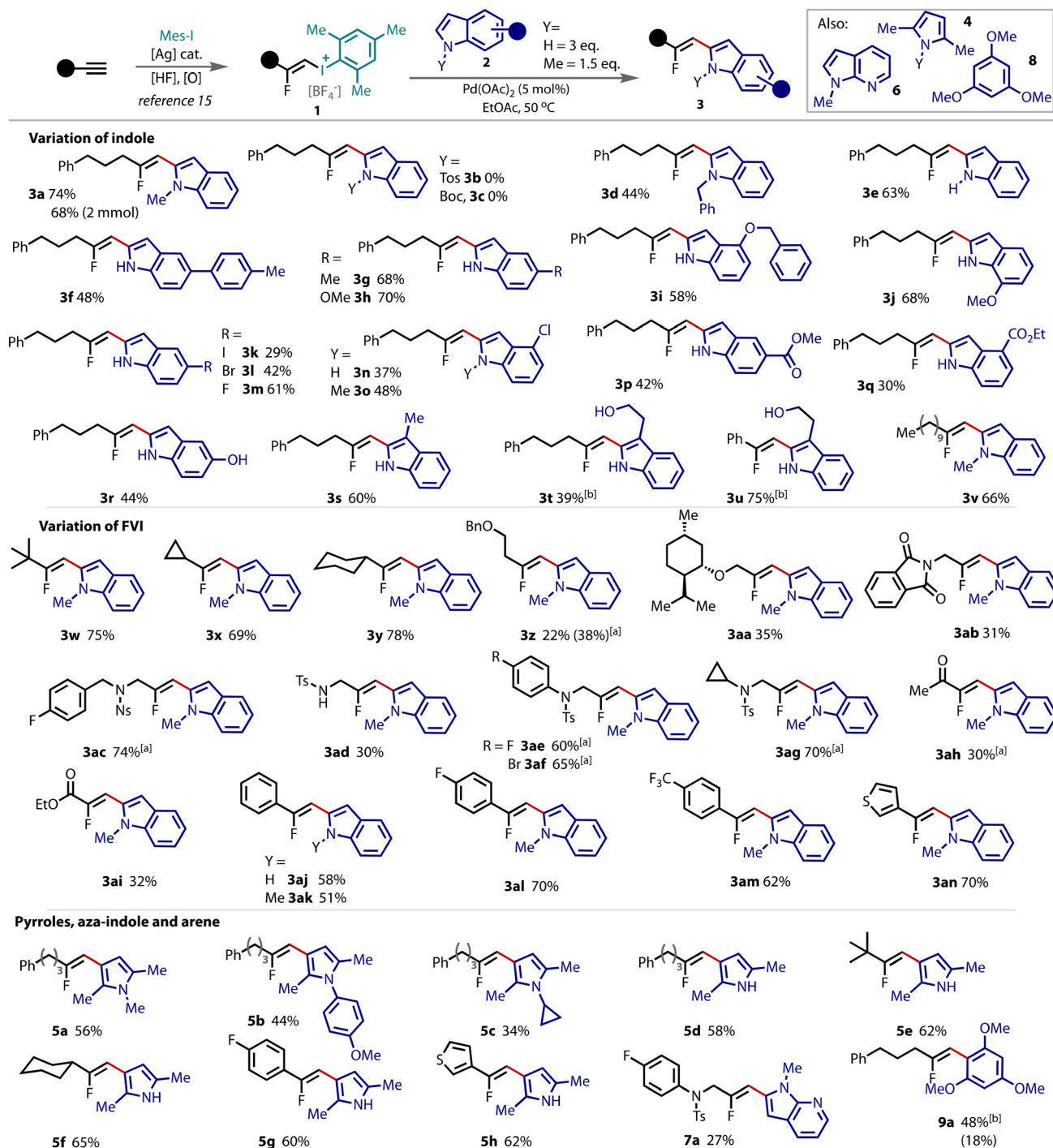
| Entry           | Catalyst (x mol%)      | Solvent | Yield <sup>b</sup> |
|-----------------|------------------------|---------|--------------------|
| 1               | $PdBr_2$ (5)           | AcOH    | 50                 |
| 2               | $(CH_3CN)_2PdCl_2$ (5) | AcOH    | 30                 |
| 3               | $Pd(OCOCF_3)_2$ (5)    | AcOH    | 32                 |
| 4               | $Pd(OAc)_2$ (5)        | AcOH    | 54                 |
| 5               | $Pd(OAc)_2$ (5)        | DCE     | 29                 |
| 6               | $Pd(OAc)_2$ (5)        | MeOH    | 12                 |
| 7               | $Pd(OAc)_2$ (5)        | HFIP    | 35                 |
| 8               | $Pd(OAc)_2$ (5)        | EtOAc   | 64                 |
| 9               | $Pd(OAc)_2$ (10)       | EtOAc   | 65                 |
| 10              | $Pd(OAc)_2$ (2)        | EtOAc   | 42                 |
| 11 <sup>c</sup> | $Pd(OAc)_2$ (5)        | EtOAc   | 74                 |
| 12 <sup>d</sup> | $Pd(OAc)_2$ (5)        | EtOAc   | 68                 |
| 13 <sup>e</sup> | $Pd(OAc)_2$ (5)        | EtOAc   | 80                 |

<sup>a</sup> Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol),  $Pd(OAc)_2$  (5 mol%) in 1 mL solvent at room temperature for 12 h. <sup>b</sup> <sup>19</sup>F NMR yield using 4,4'-difluorobiphenyl as internal standard. <sup>c</sup> Reaction performed at 50 °C for 4 h. <sup>d</sup> 1.5 equiv. **1a**. <sup>e</sup> 1.5 equiv. of **2a**.

decreased by employing a suitably dry solvent. DCE, methanol and HFIP each afforded lower yields (entries 5–7), however, EtOAc improved the yield to 64% (entry 8). Further screening of the catalyst loading, temperature and equivalents of coupling partner revealed that 5 mol% catalyst loading was adequate (entries 8 vs. 9 vs. 10), 50 °C was optimum (entry 11) and a slight excess of indole led to the highest yield of **3a** (entries 12 vs. 13). Different arenes in the iodonium salts were trialed under these optimal conditions. The influence of electronics was found to be significant, as a large range of yields were observed for different *para*-substitution (see ESI† for details) however, the bulky mesityl displayed the best balance of yield and selectivity, and hence was retained for subsequent studies.

We proceeded to examine the generality of the substrate scope with respect to both FVI **1** and indole **2**, Fig. 2. The model substrates were coupled, and product **3a** isolated in very good yield, and without an appreciable drop in yield on larger scale. *N*-Tosyl and *N*-boc protected indoles did not react, however, *N*-benzylated and unprotected *N*-H indoles were both suitable coupling partners, as products **3d** and **3e**, were successfully formed. The unprotected *N*-H indoles led to higher yields when used in an excess (3 equiv.). Substitution on the indole was accommodated with electron withdrawing and donating substituents in different positions around the ring, including aryl (**3f**), alkyl (**3g**), alkoxy (**3h–j**), halogen (**3k–o**), ester (**3p,q**) and alcohol (**3r**) moieties. The tolerance to iodo- and bromo-substitution on the ring is noteworthy considering the opportunity for oxidative addition with a palladium catalyst. Substitution on the C-3 position did not affect the coupling at the C-2 position to give **3s**. This result rules out a mechanism that involves initial vinylation at C-3 with a subsequent migration to C-2.<sup>19</sup> The natural product, tryptophol, was found to transform better using a copper catalyst to selectively yield the C-2 fluorovinylated indoles **3t** and **3u**.





**Fig. 2** Isolated yields given, with <sup>19</sup>F NMR yields given in parentheses. Reactions conducted on a 0.1 mmol scale of FVI **1** with either *N*-Me indole (0.15 mmol, 1.5 equiv.) **2a** or *N*-H indole (0.3 mmol, 3 equiv.) **2b** and Pd(OAc)<sub>2</sub> (5 mol%) in EtOAc at 50 °C for 2–6 h. <sup>a</sup> Reaction ran at room temperature (20 °C). <sup>b</sup> Reaction performed with Cu(OTf)<sub>2</sub> (10 mol%) in DCM from 0 °C–rt for 30 minutes.

The generality of the reaction was then explored with different FVIs (**1**). Although the *N*-Me indole was used for this scope, the unprotected *N*-H indoles (3 equiv.) work comparably well under the conditions (*cf.* **3a** vs. **3e**). Cyclic, acyclic and (hetero)aryl FVIs were transformed efficiently under the optimised conditions, delivering the corresponding β-fluorovinyl

indoles (**3v–am**) in moderate to very good yields. Ethers (**3z,aa**) and amines (**3ab–ag**) were tolerated, several of which furnished the corresponding products in better yields at room temperature, rather than elevated temperatures. Ketone **3ah** and α,β-unsaturated ester **3ai** were both compatible with this Pd-catalysed strategy, as were styrenyl-FVIs **3aj–am** and thienyl



containing **3an**, which were all transformed successfully to  $\beta$ -fluorovinyl indoles.

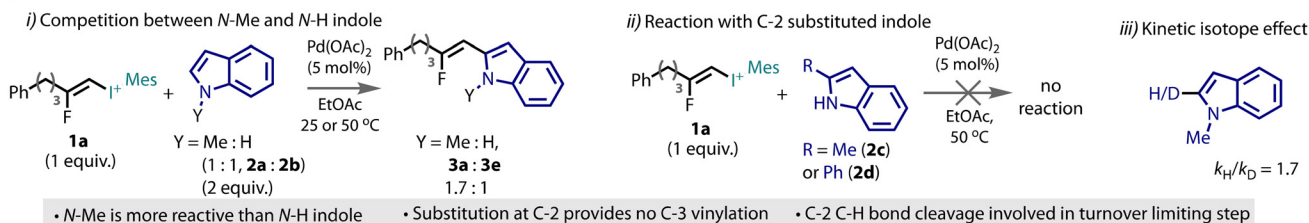
The suitability of pyrroles (**4**) as coupling partners in place of indoles was then scrutinised under the catalytic conditions, Fig. 2. The use of unsubstituted *N*-methyl pyrrole created an inseparable mixture of compounds (see ESI† for details) due to the high reactivity of this heterocycle, however, the dimethylated *N*-methyl pyrrole (**4a**) provided the 3-fluorovinylated pyrrole **5a** in good yield. Variation of the *N*-substituent to an arene or cyclopropyl group successfully led to the desired products **5b** and **5c**, respectively. The unprotected *N*-H pyrrole **5d** fared well under the optimised conditions. Acyclic and cyclic alkyl, styrenyl and thienyl FVIs were all competent coupling partners that furnished the  $\beta$ -fluorovinyl pyrroles in good yields (**5e–5h**). Aza-indole **6** delivered the desired coupled product **7a**, but an enhanced temperature of 90 °C was required. Trimethoxybenzene **8** gave the fluorovinylated arene **9a** in enhanced yield using copper catalysis in place of palladium.

To gain insight into the reactivity, we conducted a series of control experiments. The *N*-Me (**2a**) and unprotected *N*-H (**2b**)

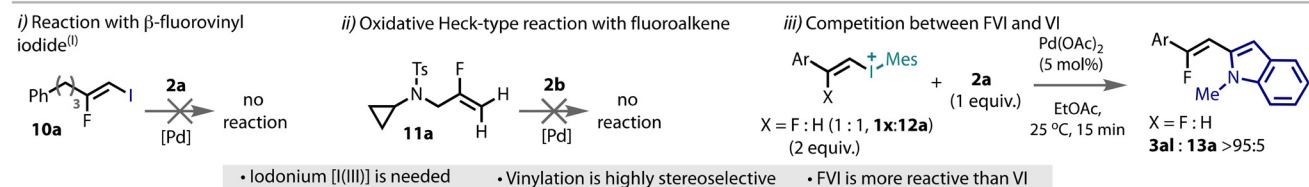
indoles were competed for limiting FVI **1a**, Fig. 3Ai, which revealed the *N*-Me indole to be more reactive. When the indole was substituted in the C-2 position with either a methyl (**2c**) or phenyl (**2d**) group, there was no reaction, neither to a C-2 fluorovinylated species nor the C-3 fluorovinylated product, Fig. 3Aii. This evidence further excludes a mechanism that involves initial reaction at the C-3 position. Independent yield measurements at partial conversion for both indole **2a** and [ $^2\text{H}$ ]<sub>0.7</sub>-**2a** revealed a kinetic isotope effect of 1.7 at the C-2 position, Fig. 3Aiii, indicating cleavage of this bond is involved in the turnover limiting step.

Concerning the FVI coupling partner, the  $\beta$ -fluorovinyl iodide(*i*) (**10a**) was tested in place of the  $\beta$ -fluorovinyl iodonium (I(III)) salt **1a**, Fig. 3Bi. This I(*i*) building block was unreactive under the conditions. When a fluoroalkene **11a** was reacted under typical oxidative Heck conditions, there was also no reaction, Fig. 3Bii. Together, this evidence demonstrates the absolute necessity for a hypervalent I(III) and that other, Heck-type conditions are not suitable to install fluorinated alkenes. The vinyl iodonium(vi) **12a** was reacted in place of the fluoro-vinyl iodonium (FVI) **1j**, which successfully led to the desired

#### [A] Control reactions of the indole

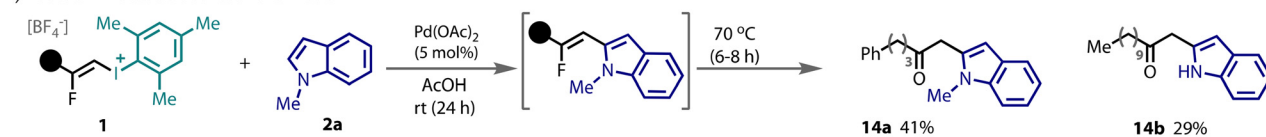


#### [B] Control reactions of the FVI

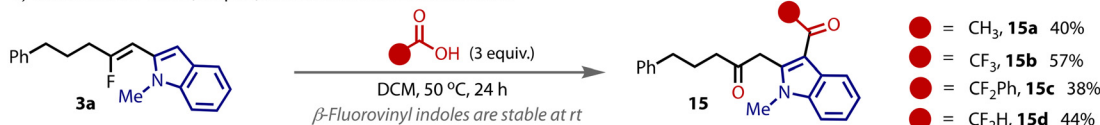


#### [C] Derivatisations of $\beta$ -fluorovinyl indoles: at elevated temperatures

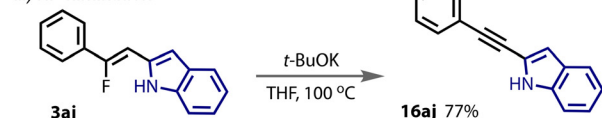
##### i) Reaction in acetic acid: ketone formation



##### ii) Reaction with acids (3 equiv.): ketone formation and addition



##### iii) HF elimination



##### iv) Grignard addition

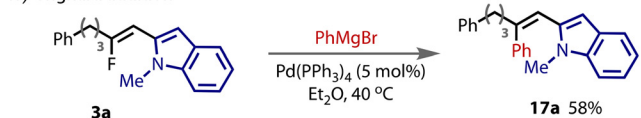


Fig. 3 Mechanistic control reactions for  $\beta$ -fluorovinyl indole synthesis and preliminary derivatisation studies.





product, see ESI† for details. However, when the two were in competition for limiting indole **2a**, Fig. 3Biii, only the product derived from the fluorinated FVI **12a** was observed, thus indicating the superior reactivity of this coupling partner.

A Pd(0)/(II) cycle that proceeds through oxidative addition, indole coordination, migratory insertion and  $\beta$ -hydride elimination was considered. However, preliminary kinetic studies and reaction analysis using Pd(0) pre-catalysts revealed greatly attenuated reaction conversion and lower yields compared to the use of Pd(II)(OAc)<sub>2</sub> (see ESI†). In addition, this mechanism was deemed unlikely considering the tolerance to aryl-bromides, as well as the necessity to proceed through a highly unfavourable anti- $\beta$ -hydride elimination step. Two *E*-FVIs were tested to determine the stereochemistry of the coupling, see ESI,† and a single stereoisomer, aligned to the stereochemistry in the starting material was observed, indicating a stereo-specific, or a highly stereoselective, vinylation. The combined evidence provided therefore supports a Pd(II)/Pd(IV) catalytic cycle that involves electrophilic C-2 palladation, oxidative addition and reductive elimination, which is consistent with that reported for indole arylation.<sup>18</sup>

The reactivity of  $\beta$ -fluorovinyl indole was explored. Conducting the Pd-catalyzed coupling reaction in acetic acid solvent initially formed the  $\beta$ -fluorovinyl indole (<sup>19</sup>F NMR), but when the temperature was raised to 70 °C hydrolysis to ketones (**14a,b**) was observed, Fig. 3Ci. This hydrolysis was not observed without strong heating under any other conditions (see ESI†). When  $\beta$ -fluorovinyl indoles (**3**) were heated with carboxylic acids in reagent quantities (3 equiv.), as opposed to solvent-level quantities, the corresponding diketones (**15a-d**) were afforded in moderate yields, Fig. 3Cii. Dehydrodefluorination of **3aj** was achieved to afford the alkyne **16aj** in excellent yield with *t*-BuOK in THF,<sup>9</sup> Fig. 3Ciii. The defluorinative coupling of **3a** under palladium catalysis with a Grignard reagent (PhMgBr) delivered arylated product **17a** in good yield,<sup>21</sup> Fig. 3Civ.

## Conclusions

In summary, we have developed a Pd(II)-catalysed C–H fluorovinylation of indoles and other pyrroles. This reaction proceeds with exquisite stereo-selectively under ligand-free, directing-group-free and base-free conditions from fluorovinyl iodonium salts, which themselves are formed easily from alkynes in a single silver-catalysed process. The reaction proved to be general, as a wide range of heteroarenes and *Z*-FVIs were successfully employed in the reaction.

## Data availability

The data supporting this article have been included as part of the ESI.†

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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## References

- 1 D. O'Hagen, Understanding Organofluorine Chemistry. An Introduction to the C–F Bond, *Chem. Soc. Rev.*, 2008, **37**, 308–319.
- 2 (a) M. Shimizu and T. Hiyama, Modern Synthetic Methods for Fluorine-Substituted Target Molecules, *Angew. Chem., Int. Ed.*, 2005, **44**, 214–231, (*Angew. Chem.*, 2005, **117**, 218–234); (b) T. Furuya, A. S. Kamlet and T. Ritter, Catalysis for Fluorination and Trifluoromethylation, *Nature*, 2011, **473**, 470–477; (c) T. Besset, C. Schneider and D. Cahard, Tamed Arene and Heteroarene Trifluoromethylation, *Angew. Chem., Int. Ed.*, 2012, **51**, 5048–5050, (*Angew. Chem.*, 2012, **124**, 5134–5136); (d) T. Liang, C. N. Neumann and T. Ritter, Introduction of Fluorine and Fluorine-Containing Functional Groups, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214–8264, (*Angew. Chem.*, 2013, **125**, 8372–8423); (e) T. Besset, T. Poisson and T. X. Pannecoucke, Recent Progress in Direct Introduction of Fluorinated Groups on Alkenes and Alkynes by means of C–H Bond Functionalization, *Chem. – Eur. J.*, 2014, **20**, 16830–16845; (f) E. Merino and C. Nevado, Addition of CF<sub>3</sub> Across Unsaturated Moieties: A Powerful Functionalization Tool, *Chem. Soc. Rev.*, 2014, **43**, 6598–6608; (g) X. Liu, C. Xu, M. Wang and Q. Liu, Trifluoromethyltrimethylsilane: Nucleophilic Trifluoromethylation and Beyond, *Chem. Rev.*, 2015, **115**, 683–730; (h) X. Yang, T. Wu, R. J. Phipps and F. D. Toste, Advances in Catalytic Enantioselective Fluorination, Mono-, Di-, and Trifluoromethylation, and Trifluoromethylthiolation Reactions, *Chem. Rev.*, 2015, **115**, 826–870; (i) P. K. Mykhailiuk, Fluorinated Pyrazoles: From Synthesis to Applications, *Chem. Rev.*, 2021, **121**, 1670–1715; (j) C. M. Marshall, J. G. Federice, C. N. Bell, P. B. Cox and J. T. Njardarson, An Update on the Nitrogen Heterocycle Compositions and Properties of U.S. FDA-Approved Pharmaceuticals (2013–2023), *J. Med. Chem.*, 2024, **67**, 11622–11655.
- 3 (a) J.-P. Bégué and D. Bonnet-Delphon, Recent Advances (1995–2005) in Fluorinated Pharmaceuticals Based on Natural Products, *J. Fluorine Chem.*, 2006, **127**, 992–1012; (b) K. L. Kirk, Fluorine in Medicinal Chemistry: Recent Therapeutic Applications of Fluorinated Small Molecules,



- J. Fluorine Chem.*, 2006, **127**, 1013–1029; (c) K. Muller, C. Faeh and F. Diederich, Fluorine in Pharmaceuticals: Looking Beyond Intuition, *Science*, 2007, **317**, 1881–1886; (d) W. K. Hagmann, The Many Roles for Fluorine in Medicinal Chemistry, *J. Med. Chem.*, 2008, **51**, 4359–4369; (e) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, Fluorine in Medicinal Chemistry, *Chem. Soc. Rev.*, 2008, **37**, 320–330; (f) E. P. Gillis, K. J. Eastman and M. D. Hill, *J. Med. Chem.*, 2015, **58**, 8315–8359; (g) M. Inoue, Y. Sumii and N. Shibata, Contribution of Organofluorine Compounds to Pharmaceuticals, *ACS Omega*, 2020, **5**, 10633–10640.
- 4 (a) M. Drouin and J. F. Paquin, Recent Progress in the Racemic and Enantioselective Synthesis of Monofluoroalkene-based Dipeptide Isosteres, *Beilstein J. Org. Chem.*, 2017, **13**, 2637–2658; (b) N. A. Meanwell, Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design, *J. Med. Chem.*, 2018, **61**, 5822–5880.
- 5 (a) S. Osada, S. Sano, M. Ueyama, Y. Chuman, H. Kodama and K. Sakaguchi, Fluoroalkene Modification of Mercaptoacetamide-based His-tone Deacetylase Inhibitors, *Bioorg. Med. Chem.*, 2010, **18**, 605–611; (b) R. J. Sciotti, M. Pliushchev, P. E. Wiedeman, D. Balli, R. Flamm, A. M. Nilius, K. Marsh, D. Stolarik, R. Jolly, R. Ulrich and S. W. Djuric, The Synthesis and Biological Evaluation of a Novel Series of Antimicrobials of the Oxazolidinone Class, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2121–2123; (c) Y. Asahina, Y. Iwase, F. Iinuma, M. Hosaka and T. Ishizaki, Synthesis and Antibacterial Activity of 1-(2-Fluorovinyl)-7-substituted-4-quinolone-3-carboxylic Acid Derivatives, Conformationally Restricted Analogues of Fleroxacin, *J. Med. Chem.*, 2005, **48**, 3194–3202; (d) 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, Fluoroolefins as Amide Bond Mimics in Dipeptidyl Peptidase IV Inhibitors, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2409–2413; (e) S. Oishi, H. Kamitani, Y. Kodera, K. Watanabe, K. Kobayashi, T. Narumi, K. Tomita, H. Ohno, T. Naito, E. Kodama, M. Matsuoka and N. Fujii, Peptide Bond Mimicry by (*E*)-Alkene and (*Z*)-Fluoroalkene Peptide Isosteres: Synthesis and Bioevaluation of  $\alpha$ -Helical anti-HIV Peptide Analogues, *Org. Biomol. Chem.*, 2009, **7**, 2872–2877.
- 6 (a) A. K. Ghosh and B. Zajc, High-Yield Synthesis of Fluorinated Benzothiazolyl Sulfones: General Synthons for Fluoro-julia Olefinations, *Org. Lett.*, 2006, **8**, 1553–1556; (b) M.-H. Yang, S. S. Matikonda and R. A. Altman, Preparation of Fluoroalkenes via the Shapiro Reaction: Direct Access to Fluorinated Peptidomimetics, *Org. Lett.*, 2013, **15**, 3894–3897; (c) O. E. Okoromoba, J. Han, G. B. Hammond and B. Xu, Designer HF-Based Fluorination Reagent: Highly Regioselective Synthesis of Fluoroalkenes and *gem*-Difluoromethylene Compounds from Alkynes, *J. Am. Chem. Soc.*, 2014, **136**, 14381–14384.
- 7 (a) G. Chelucci, Synthesis and Metal-Catalyzed Reactions of *gem*-Dihalovinyl Systems, *Chem. Rev.*, 2012, **112**, 1344–1462; (b) V. Zhang, S. Geng and Z. Feng, Advances in Silylation and Borylation of Fluoroarenes and *gem*-Difluoroalkenes via C–F Bond Cleavage, *Chem. Commun.*, 2021, **57**, 11922–11934; (c) J. Wang, H. Gao, C. Shi, G. Chen, X. Tan, X. Chen, L. Xu, X. Cai, B. Huang and H. Li, Recent Advances in Radical-based C–F Bond Activation of Polyfluoroarenes and *gem*-Difluoroalkenes, *Chem. Commun.*, 2021, **57**, 12203–12217; (d) M. Z. Lu, J. Goh, M. Maraswami, Z. Jia, J. S. Tian and T. P. Loh, Recent Advances in Alkenyl  $sp^2$  C–H and C–F Bond Functionalizations: Scope, Mechanism, and Applications, *Chem. Rev.*, 2022, **122**, 17479–17646.
- 8 (a) W. Dai, J. Xiao, G. Jin, J. Wu and S. Cao, Palladium- and Nickel-Catalyzed Kumada Cross-Coupling Reactions of *gem*-Difluoroalkenes and Monofluoroalkenes with Grignard Reagents, *J. Org. Chem.*, 2014, **79**, 10537–10546; (b) W. Dai, H. Shi, X. Zhao and S. Cao, Sterically Controlled Cu-Catalyzed or Transition-Metal-Free Cross-Coupling of *gem*-Difluoroalkenes with Tertiary, Secondary, and Primary Alkyl Grignard Reagents, *Org. Lett.*, 2016, **18**, 4284–4287; (c) R. T. Thornbury and D. F. Toste, Palladium-Catalyzed Defluorinative Coupling of 1-Aryl-2,2-Difluoroalkenes and Boronic Acids: Stereoselective Synthesis of Monofluorostilbenes, *Angew. Chem., Int. Ed.*, 2016, **55**, 11629–11632; (d) Y. Wang, X. Qi, Q. Ma, P. Liu and G. C. Tsui, Stereoselective Palladium-Catalyzed Base-Free Suzuki–Miyaura Cross-Coupling of Tetrasubstituted *gem*-Difluoroalkenes: An Experimental and Computational Study, *ACS Catal.*, 2021, **11**, 4799–4809.
- 9 P. Tian, C. Feng and T.-P. Loh, Rhodium-Catalysed C( $sp^2$ )–C( $sp^2$ ) Bond Formation via C–H/C–F Activation, *Nat. Commun.*, 2015, **6**, 7472.
- 10 L. Kong, X. Zhou and X. Li, Cobalt(III)-Catalyzed Regio- and Stereoselective  $\alpha$ -Fluoroalkenylation of Arenes with *gem*-Difluorostyrenes, *Org. Lett.*, 2016, **18**, 6320–6323.
- 11 (a) C. Schneider, D. Masi, S. Couve-Bonnaire, X. Pannecoucke and C. Hoarau, Palladium- and Copper-Catalyzed Stereocontrolled Direct C–H Fluoroalkenylation of Heteroarenes using *gem*-Bromofluoroalkenes, *Angew. Chem., Int. Ed.*, 2013, **52**, 3246–3249; (b) K. Rousée, C. Schneider, S. Couve-Bonnaire, X. Pannecoucke, V. Levacher and C. Hoarau, Pd- and Cu-Catalyzed Stereo- and Regiocontrolled Decarboxylative/C–H Fluoroalkenylation of Heteroarenes, *Chem. – Eur. J.*, 2014, **20**, 15000–15004.
- 12 D. Zell, U. Dhawa, V. Müller, M. Bursch, S. Grimme and L. Ackermann, C–F/C–H Functionalization by Manganese(I) Catalysis: Expedient (Per)Fluoro-Allylations and Alkenylations, *ACS Catal.*, 2017, **7**, 4209–4213.
- 13 M. Petrini, Regioselective Direct C–Alkenylation of Indoles, *Chem. – Eur. J.*, 2017, **23**, 16115–16151.
- 14 (a) N. P. Grimster, C. Gauntlett, C. R. A. Godfrey and M. J. Gaunt, Palladium-Catalyzed Intermolecular Alkenylation of Indoles by Solvent-Controlled



- Regioselective C-H Functionalization, *Angew. Chem., Int. Ed.*, 2005, **44**, 3125–3129; (b) A. Garcia-Rubia, R. G. Arrayas and J. C. Carretero, Palladium(II)-Catalyzed Regioselective Direct C2 Alkenylation of Indoles and Pyrroles Assisted by the *N*-(2-Pyridyl)sulfonyl Protecting Group, *Angew. Chem., Int. Ed.*, 2009, **48**, 6511–6515; (c) D. J. Schipper, M. Hutchinson and K. Fagnou, Rhodium(III)-Catalyzed Intermolecular Hydroarylation of Alkynes, *J. Am. Chem. Soc.*, 2010, **132**, 6910–6911; (d) Z. Ding and N. Yoshikai, Mild and Efficient C2-Alkenylation of Indoles with Alkynes Catalyzed by a Cobalt Complex, *Angew. Chem., Int. Ed.*, 2012, **51**, 4698–4701; (e) H. Ikemoto, T. Yoshino, K. Sakata, S. Matsunaga and M. Kanai, Pyrroloindolone Synthesis via a Cp\*CoIII-Catalyzed Redox-Neutral Directed C-H Alkenylation/Annulation Sequence, *J. Am. Chem. Soc.*, 2014, **136**, 5424–5431; (f) L. Liang, S. Fu, D. Lin, X.-Q. Zhang, Y. Deng, H. Jiang and W. Zeng, Ruthenium(II)-Catalyzed Direct Addition of Indole/Pyrrole C2-H Bonds to Alkynes, *J. Org. Chem.*, 2014, **79**, 9472–9480; (g) S. Sharma, S. Han, Y. Shin, N. K. Mishra, H. Oh, J. Park, J. H. Kwak, B. S. Shin, Y. H. Jung and I. S. Kim, Rh-Catalyzed Oxidative C2-Alkenylation of Indoles with Alkynes: Unexpected Cleavage of Directing Group, *Tetrahedron Lett.*, 2014, **55**, 3104–3107; (h) W. Zhang, J. Wei, S. Fu, D. Lin, H. Jiang and W. Zeng, Highly Stereoselective Ruthenium(II)-Catalyzed Direct C2-*syn*-Alkenylation of Indoles with Alkyne, *Org. Lett.*, 2015, **17**, 1349–1352.
- 15 A. T. Sedikides and A. J. J. Lennox, Silver-Catalyzed (Z)- $\beta$ -Fluoro-vinyl Iodonium Salts from Alkynes: Efficient and Selective Syntheses of Z-Monofluoroalkenes, *J. Am. Chem. Soc.*, 2024, **146**, 15672–15680.
- 16 (a) S. Hara, K. Yamamoto, M. Yoshida, T. Fukuhara and N. Yoneda, Stereoselective Synthesis of (E)- $\beta$ -Fluoro- $\alpha,\beta$ -Unsaturated Esters by Carbonylation of (E)-2-Fluoro-1-iodo-1-Alkenyliodonium Salts, *Tetrahedron Lett.*, 1999, **40**, 7815–7818; (b) M. Yoshida, S. Hara, T. Fukuhara and N. Yoneda, Stereo- and Regioselective Synthesis of (E,E)- $\delta$ -Fluoro- $\alpha,\beta,\gamma,\delta$ -Unsaturated Carbonyl Compounds by Heck-type Reaction of Fluoroalkenyliodonium Salts, *Tetrahedron Lett.*, 2000, **41**, 3887–3890; (c) M. Yoshida, D. Nagahara, T. Fukuhara, N. Yoneda and S. Hara, Regio- and Stereoselective Synthesis of Fluoroalkadienes using  $\beta$ -Fluoroalkenyliodonium Salt, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2283–2288; (d) M. Yoshida, A. Komata and S. Hara, Stereoselective Synthesis of (Z)- $\beta$ -Fluoro- $\alpha,\beta$ -Unsaturated Esters from (Z)-2-Fluoro-1-Alkenyliodonium Salts, *J. Fluor. Chem.*, 2004, **125**, 527–529.
- 17 (a) J. T. Csenki and Z. Novák, Iodonium based regioselective double nucleophilic alkene functionalization of a hydrofluoroolefin scaffold, *Chem. Commun.*, 2024, **60**, 726–729; (b) B. L. Tóth, G. Sályi, A. Domján, O. Egyed, A. Bényei, Z. Gonda and Z. Novák, Z-Selective Fluoroalkenylation of (Hetero) Aromatic Systems by Iodonium Reagents in Palladium-Catalyzed Directed C-H Activation, *Adv. Synth. Catal.*, 2022, **364**, 348–354.
- 18 N. R. Deprez, D. Kalyani, A. Krause and M. S. Sanford, Room Temperature Palladium-Catalyzed 2-Arylation of Indole, *J. Am. Chem. Soc.*, 2006, **128**, 4972–4973.
- 19 R. J. Phipps, N. P. Grimster and M. J. Gaunt, Cu(II)-Catalyzed Direct and Site-Selective Arylation of Indoles Under Mild Conditions, *J. Am. Chem. Soc.*, 2008, **130**, 8172–8174.
- 20 (a) Q. Yang, J. Chang, Q. Wu and B. Zhang, A Simple Phenylation of Heteroaromatic Compounds using Diphenyliodonium Triflate, *Res. Chem. Intermed.*, 2012, **38**, 1335–1340; (b) J. Malmgren, A. Nagendiran, C.-W. Tai, J.-E. Bäckvall and B. Olofsson, Selective Arylation of Indoles with Heterogeneous Nanopalladium and Diaryliodonium Salts, *Chem. – Eur. J.*, 2014, **20**, 13531–13535; (c) S. G. Modha and M. F. Greaney, Atom-Economical Transformation of Diaryliodonium Salts: Tandem C-H and N-H Arylation of Indoles, *J. Am. Chem. Soc.*, 2015, **137**, 1416–1419; (d) A. J. Reay, T. J. Williams and I. J. S. Fairlamb, Unified Mild Reaction Conditions for C2-Selective Pd-Catalysed Tryptophan Arylation, Including Tryptophan-containing Peptides, *Org. Biomol. Chem.*, 2015, **13**, 8298–8309; (e) L. Duan, R. Fu, B. Zhang, W. Shi, S. Chen and Y. Wan, An Efficient Reusable Mesoporous Solid-Based Pd Catalyst for Selective C2 Arylation of Indoles in Water, *ACS Catal.*, 2016, **6**, 1062–1074; (f) A. M. Prendergast, R. Shanahan, A. Hickey, F. Harrington, D. Schönbauer, P. A. Byrne, M. Schnürch and G. P. McGlacken, Synthesis of a Diaryliodonium Salt and Its Use in the Direct Arylation of Indole: A Two-Step Experiment for the Organic Teaching Laboratory, *J. Chem. Educ.*, 2020, **97**, 200–206.
- 21 X. Li, Y. Li, W. Shan, Z. Wang, R. Liu, Z. Zhang, X. Li and D. Shi, Nickel-Catalyzed Stereoselective Reductive Cross-Coupling of *gem*-Difluoroalkenes with Alkenyl Electrophiles, *Chem. Commun.*, 2023, **59**, 6893–6896.

