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Palladium-catalyzed intramolecular Heck dearomative *gem*-difluorovinylolation of indoles†

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A palladium-catalyzed dearomative reaction of indoles has been developed through a domino Heck/*gem*-difluorovinylolation sequence. By taking advantage of a difluorocarbene precursor (ClCF₂COONa), the palladium difluorocarbene ([Pd]=CF₂) species was formed smoothly. Then, a migratory insertion/ β -H elimination process enabled access to polycyclic indolines containing 1,1-difluoroethylene units in acceptable yields with a broad substrate scope, which also showed dearomative *gem*-difluorovinylolation for the first time. Remarkably, the superb diversified transformations allowed the product to install various functional groups.

Introduction

gem-Difluoroalkenes are widely used in the fields of pharmaceuticals, agrochemicals, materials and fine chemicals (Fig. 1A).^{1–4} Moreover, a number of valuable compounds can be converted by the transformations of *gem*-difluoroalkenes with radicals, carbon-metal species, and nucleophiles.^{5–7} So far, a range of methods have been developed to prepare *gem*-difluoroalkene derivatives.^{7–11} Traditionally, the well-known Julia-Kocienski^{12–14} and Wittig^{15–19} reactions are confined to aldehyde and ketone substrates. In recent years, the defluorinative functionalization of trifluoromethyl olefins has been explored in detail,^{20–22} but the synthesis of trifluoromethyl olefins is cumbersome.²³ Besides, *gem*-difluoroalkenes can also be acquired from diazo compounds,^{24–27} which have potential safety hazards. Consequently, it is necessary to develop a new strategy to get *gem*-difluoroalkenes.

Transition-metal-catalyzed cross-coupling reactions with carbenes have been extensively studied.²⁸ C=C double bonds can be constructed smoothly through general procedures of carbene migratory insertion and β -H elimination.²⁹ Studies mainly focus on nonfluorinated carbenes, and β -H elimination involving difluorocarbene has not been reported. Even the conversion of metal difluorocarbene ([M]=CF₂) is a massive challenge due to limited reaction types.³⁰ In 2015, Zhang and coworkers reported the first metal difluorocarbene coupling

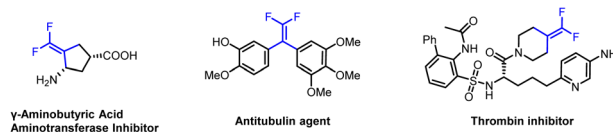
(MeDiC) reaction for synthesizing organofluorine compounds *via* palladium catalysis.³¹ Thereafter, several successful transformations of [Pd]=CF₂ were reported,^{31–37} but most of the coupling reagents are limited to nucleophilic arylboronic acids and esters (Scheme 1a).^{31–35} Furthermore, in the only research involving the coupling of electrophilic aryl halides, the hydrolysis of [Pd]=CF₂ is inevitable (Scheme 1b).³⁸ On this foundation, we expect to inhibit the hydrolysis by the β -H elimination process to prepare *gem*-difluoroalkenes and expand the coupling of aryl halides with difluorocarbene ulteriorly. Meanwhile, considering the operability as a crystalline solid and low cost, ClCF₂COONa is chosen as the difluorocarbene precursor.³⁹

The assembly of polycyclic indoline derivatives remains one of the most interesting subjects in organic synthesis^{40–45} due to the fact that many natural products contain constitutional units (Fig. 1B).^{46–49} At present, the production of polycyclic indoline scaffolds has been established by palladium-catalyzed intramolecular Heck dearomatization of indoles (Scheme 1c).^{50–68} On the one hand, 1,2-difunctionalization of indoles is achieved when the resulting benzyl-Pd species are captured with diverse

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A: difluorovinyl-containing bioactive compounds



B: indoline-containing natural products

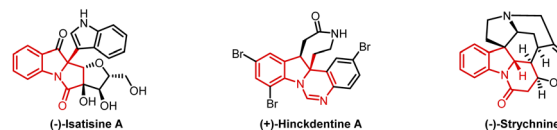
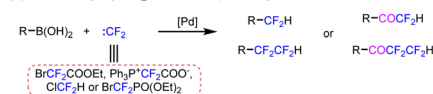
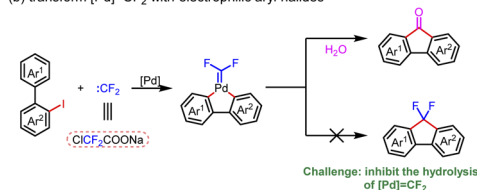


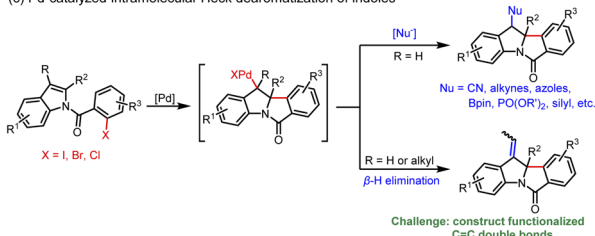
Fig. 1 Molecules containing difluorovinyl and indoline units.



Previous work:

(a) transform [Pd]=CF₂ with nucleophilic arylboronic acids(b) transform [Pd]=CF₂ with electrophilic aryl halides

(c) Pd-catalyzed intramolecular Heck dearomatization of indoles



This work: Pd-catalyzed dearomative gem-difluorovinylations of indoles

Scheme 1 Pd-catalyzed transformations of :CF₂ and dearomatization of indoles.

nucleophiles that can effectively form various C–X (H, C, N, O, P, B, and Si) bonds. On the other hand, the reactions can be terminated by β-H elimination to construct C=C double bonds.^{48,60,64–66} However, limited precursors restrict the installation of functionalized C=C double bonds. Inspired by our first attempt at dearomatization of indoles,⁶⁷ we present herein an innovative idea for synthesizing *gem*-difluoroalkenes from *N*-(2-bromobenzoyl)indoles and ClCF₂COONa. Remarkably, it is the first report of dearomative *gem*-difluorovinylations.

Results and discussion

With this thinking in mind, *N*-acyl indole **1a** and ClCF₂COONa were selected as model substrates in the palladium/ligand catalytic system to explore the optimal conditions (Table 1). As expected, when Pd(OAc)₂/PCy₃ was used as a catalyst with K₂CO₃ in 1,2-dichloroethane (DCE) at 120 °C for 12 h, the process of dearomative *gem*-difluorovinylations was carried out smoothly to afford the expectant product **3a** in 45% yield (Table 1, entry 1). The structure of **3a** was confirmed by X-ray crystallographic analysis (see the ESI†). Then, K₃PO₄ and NEt₃ as bases were tested, but they were unfavorable for the reaction compared to K₂CO₃ (Table 1, entries 2 and 3). And several ligands such as dpppe, PPh₃, and DPEphos were studied, and the results showed that DPEphos was a suitable ligand to get **3a** in 60% yield (Table 1, entries 4–6). Substituting Pd(TFA)₂ for Pd(OAc)₂, the yield of the target product decreased to 42% (Table 1, entry

Table 1 Condition optimization^a

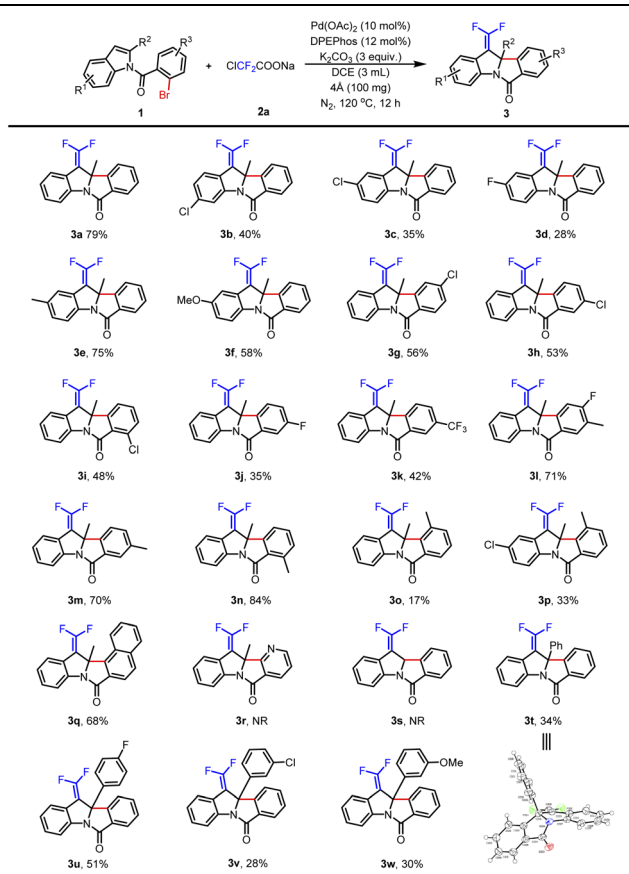
Entry	[Pd]	Ligand	Base	Solvent	Yield ^b (%)
1	Pd(OAc) ₂	PCy ₃	K ₂ CO ₃	DCE	45
2	Pd(OAc) ₂	PCy ₃	K ₃ PO ₄	DCE	20
3	Pd(OAc) ₂	PCy ₃	NEt ₃	DCE	Trace
4	Pd(OAc) ₂	dpppe	K ₂ CO ₃	DCE	39
5	Pd(OAc) ₂	PPh ₃	K ₂ CO ₃	DCE	26
6	Pd(OAc) ₂	DPEphos	K ₂ CO ₃	DCE	60
7	Pd(TFA) ₂	DPEphos	K ₂ CO ₃	DCE	42
8	PdCl ₂	DPEphos	K ₂ CO ₃	DCE	NR
9	Pd(OAc) ₂	DPEphos	K ₂ CO ₃	1,4-Dioxane	Trace
10	Pd(OAc) ₂	DPEphos	K ₂ CO ₃	Toluene	Trace
11 ^c	Pd(OAc) ₂	DPEphos	K ₂ CO ₃	DCE	63
12 ^{c,d}	Pd(OAc) ₂	DPEphos	K ₂ CO ₃	DCE	73
13 ^{c,d,e}	Pd(OAc) ₂	DPEphos	K ₂ CO ₃	DCE	79
14 ^{c,d,e,f}	Pd(OAc) ₂	DPEphos	K ₂ CO ₃	DCE	NR
15 ^{c,d,e,g}	Pd(OAc) ₂	DPEphos	K ₂ CO ₃	DCE	20
16 ^{c,d,e,h}	Pd(OAc) ₂	DPEphos	K ₂ CO ₃	DCE	Trace

^a Reaction conditions: **1a** (0.2 mmol), **2a** (2.0 equiv.), [Pd] (10 mol%), ligand (20 mol%), base (3.0 equiv.) and solvent (2.0 mL) at 120 °C for 12 h under a N₂ atmosphere. ^b Isolated yield. ^c DPEphos (12 mol%). ^d 4 Å MS (100 mg) was added. ^e DCE (3.0 mL). ^f **2a** changed by BrCF₂TMS. ^g **2a** changed by ClCF₂COOEt. ^h Pd(OAc)₂ (5 mol%). NR = no reaction.

7). When PdCl₂ was used as the catalyst, **3a** was not generated (Table 1, entry 8). Only a trace amount of **3a** was obtained by changing the solvent to 1,4-dioxane or toluene (Table 1, entries 9 and 10). We reduced the amount of ligand to 12 mol%, and the yield of the final product was 63% (Table 1, entry 11). To our delight, when 4 Å molecular sieves (4 Å MS) were added to the reaction, the yield of the desired product improved to 73% (Table 1, entry 12). On this foundation, the amount of DCE was raised to 3 mL, and the yield of product **3a** further increased to 79% (Table 1, entry 13). Afterwards, difluorocarbene precursors such as BrCF₂TMS and ClCF₂COOEt were investigated with unsatisfactory results (Table 1, entries 14 and 15). The result was poor when the amount of Pd(OAc)₂ was lowered to 5 mol% (Table 1, entry 16). Finally, we determined that the best reaction conditions were to use Pd(OAc)₂ (10 mol%), DPEphos (12 mol%), K₂CO₃ (3.0 equiv.), and 4 Å MS (100 mg) in DCE (3 mL) under N₂ at 120 °C for 12 h.

The optimal reaction conditions for the synthesis of **3a** were evaluated by using indole derivatives containing different substituents and ClCF₂COONa. As shown in Table 2, electron-donating and electron-withdrawing groups on indoles' C5 and C6 positions could afford the desired products in 28–79% yields (**3a–3f**), and electron-donating groups helped to get better

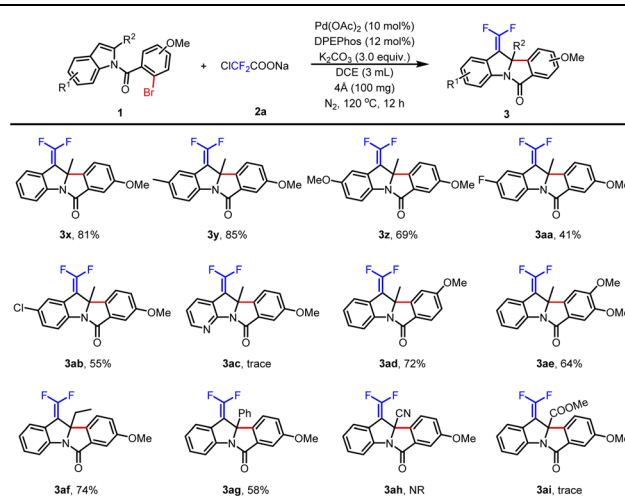


Table 2 Substrate scope^a

^a Reaction conditions: **1** (0.2 mmol), **2a** (2.0 equiv.), Pd(OAc)₂ (10 mol%), DPEPhos (12 mol%), K₂CO₃ (3.0 equiv.), 4 Å MS (100 mg) and DCE (3.0 mL) at 120 °C for 12 h under a N₂ atmosphere. Isolated yield. NR = no reaction.

results (**3e–3f**). Compared with the electron-withdrawing groups that provided related products in 35–56% yields (**3g–3k**), the electron-donating group on *N*-benzoyl was more conducive to the reaction in 70–84% yields (**3l–3n**). However, due to the influence of steric hindrance, the substrate with a methyl group at the C3 position of *N*-benzoyl provided the corresponding product **3o** in only 17% yield. When both indole and *N*-benzoyl were substituted, the desired product **3p** was obtained in 33% yield. A substrate containing a naphthalene ring was tried and led to **3q** in 68% yield, but heteroaromatic bromine (pyridine-containing) and non-substituted indole (R² = H) failed (**3r–3s**). In the cases of phenyl and substituted phenyl (4-fluorophenyl, 3-chlorophenyl, and 3-methoxyphenyl) attached at the C2 position of indoles, the protocol went smoothly with 28–51% yields (**3t–3w**). The structure of **3t** was confirmed by X-ray crystallographic analysis (see the ESI†).

Furthermore, the substrate scope was extended with a methoxyl group substituent at the *N*-benzoyl position (Table 3). Indole without a substituent on the benzene ring produced **3x** in 81% yield. With electron-donating groups (Me- and MeO-) at the C5 position of indoles, the desired products **3y–3z** were

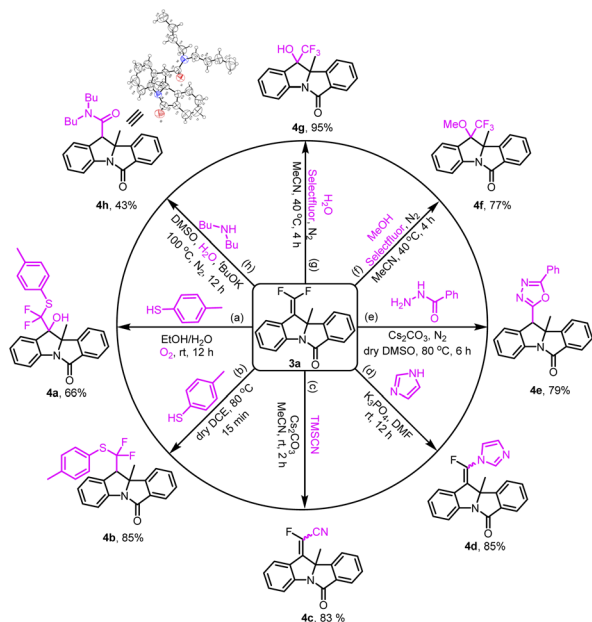
Table 3 Substrate scope^a

^a Reaction conditions: **1** (0.2 mmol), **2a** (2.0 equiv.), Pd(OAc)₂ (10 mol%), DPEPhos (12 mol%), K₂CO₃ (3.0 equiv.), 4 Å MS (100 mg) and DCE (3.0 mL) at 120 °C for 12 h under a N₂ atmosphere. Isolated yield. NR = no reaction.

obtained in 69–85% yields. In contrast, the corresponding products were obtained in lower yields when halogen groups (F- and Cl-) were assembled at the same position (**3aa–3ab**). And then, 7-azaindole was tested but failed to obtain product **3ac**. Next, the desired product **3ad** was smoothly produced in 72% yield by changing the methoxy group at the C4 position of *N*-benzoyl. In addition, a dimethoxy group substituted substrate was also tolerated with this procedure and provided the product **3ae** in 64% yield. Finally, C2-substituted indoles were studied. Although 2-ethyl indole and 2-phenyl indole could afford the anticipated products **3af–3ag** in 58–74% yields, cyano and ester groups were the failed choices (**3ah–3ai**). In short, installing MeO- on the *N*-benzoyl was an excellent choice to improve the yields.

The synthetic transformations of product **3a** indicated the practicability of the method (Scheme 2). *gem*-Difluorovinyl was successfully transformed into eight useful functional groups. Firstly, α -difluoro(thio)methylated alcohol **4a** was obtained in 66% yield by a three-component reaction between compound **3a**, *p*-toluenethiol and oxygen under mild conditions. And the coupling of **3a** with *p*-toluenethiol resulted in α,α -difluoroalkylthioether **4b** in 85% yield in dry DCE at 80 °C for 15 min. When **3a** was treated with trimethylsilyl cyanide and imidazole, the nucleophilic vinylic substitution reaction (S_NV) worked well and afforded the corresponding products **4c** and **4d** in good yields. Moreover, the cyclization of **3a** with benzoyl hydrazine was explored, thus accessing unsymmetrical 2,5-disubstituted 1,3,4-oxadiazole in 79% yield with the assistance of Cs₂CO₃ (**4e**). Besides, the fluoro-functionalization reactions of **3a** with selectfluor and *O*-nucleophiles were conducted smoothly in acetonitrile. Therefore, α -CF₃ derivatives **4f** and **4g** could be synthesized in ideal yields. Remarkably, in the presence of potassium *tert*-butoxide and water, **3a** has successfully worked

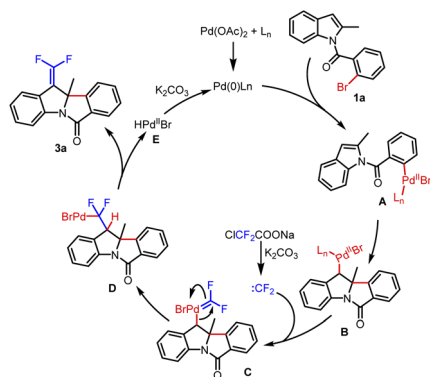




Scheme 2 Synthetic transformations of **3a**: (a) **3a** (0.2 mmol), 4-methylbenzenethiol (0.4 mmol), and EtOH/H₂O (2.0 mL, v/v = 2 : 1) at rt for 12 h under an O₂ atmosphere; (b) **3a** (0.2 mmol), 4-methylbenzenethiol (0.24 mmol), and dry DCE (40 μL) at 80 °C for 15 min; (c) **3a** (0.3 mmol), Cs₂CO₃ (0.03 mmol), TMSCN (0.9 mmol), and dry MeCN (1.0 mL) at rt for 2 h; (d) **3a** (0.6 mmol), K₃PO₄ (1 mmol), imidazole (0.5 mmol), and DMF (1 mL) at rt for 12 h; (e) **3a** (0.2 mmol), benzoyl hydrazide (0.24 mmol), Cs₂CO₃ (0.4 mmol), and dry DMSO (1 mL) at 80 °C for 6 h under a N₂ atmosphere; (f) **3a** (0.2 mmol), selectfluor (0.3 mmol), dry MeOH (1 mmol), and dry CH₃CN (0.8 mL) at 40 °C for 4 h under N₂ atmosphere; (g) **3a** (0.2 mmol), selectfluor (0.3 mmol), H₂O (1.6 mmol), and dry CH₃CN (0.8 mL) at 40 °C for 4 h under a N₂ atmosphere; (h) **3a** (0.2 mmol), ^tBuOK (0.6 mmol) and dibutylamine (0.4 mmol), H₂O (0.02 mL), and DMSO (1.2 mL) at 100 °C for 12 h under a N₂ atmosphere. Isolated yield.

with dibutylamine to provide arylacetamide **4h** in 43% yield. And we confirmed the structure of **4h** by X-ray crystallographic analysis (see the ESI[†]).

Based on previous research and our understanding on palladium-catalyzed Heck dearomatization of indoles, a possible reaction process is shown in Scheme 3. The Pd(0)



Scheme 3 Plausible reaction mechanism.

species was formed under the action of the ligand, and the reaction was initiated by the oxidative addition of Pd(0) to aryl bromide to afford the Pd(II) species **A**. The benzyl-Pd(II) intermediate **B** was generated by the intramolecular coordination and migratory insertion of the Pd(II) species into indole. Difluorocarbene, which formed from ClCF₂COONa *in situ* in the presence of bases, was captured by intermediate **B** to provide the Pd(II)=CF₂ species **C**. Following carbene migratory insertion,³⁴ the σ-alkyl-Pd(II) species **D** was obtained. Then, the β-hydride elimination of the species **D** resulted in the final product **3a** and Pd(II) species **E**. Finally, with the assistance of a base, Pd(0) was regenerated for the next catalytic cycle.

Conclusions

In summary, polycyclic indoline derivatives containing 1,1-difluoroethylene units are prepared by palladium-catalyzed intramolecular Heck dearomatization of indoles with ClCF₂COONa. β-H elimination involving [Pd]=CF₂ provides a new synthetic course for *gem*-difluoroalkenes. In addition, it is the first report of dearomative *gem*-difluorovinylolation, which has a broad substrates scope and acceptable yields. Further diversified transformations of the product show the practicability of this methodology.

Data availability

All data associated with this study are available in the article and ESI.[†]

Author contributions

G. Wang, W. Q. Li, T. X. Liu, B. Wang, and C. Y. Ma carried out the methodology, synthesis, characterization, and analysis. Y. Xia and G. Wang prepared the manuscript. W. W. Jin, Y. H. Zhang, and F. Xue revised the manuscript. C. J. Liu and Y. Xia directed the project and supervised the whole experiment. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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