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Palladium-catalyzed allylic alkylation dearomatization of β-naphthols and indoles with *gem*-difluorinated cyclopropanes†

Zhiyuan Fu,‡ Jianping Zhu,‡ Songjin Guo* and Aijun Lin *

A palladium-catalyzed allylic alkylation dearomatization of β-naphthols and indoles with *gem*-difluorinated cyclopropanes has been developed. This reaction provided an efficient route to access 2-fluoroallylic β-naphthalenones and indolenines bearing quaternary carbon centers in good yields with high *Z*-selectivity *via* C–C bond activation, C–F bond cleavage and the dearomatization process, benefiting from the wide substrate scope and good functional group tolerance. Moreover, 2-fluoroallylic furanoindoline and pyrroloindolines were achieved in good efficiency *via* cascade allylic alkylation, dearomatization and cyclization processes in the presence of Et_3B.

Naphthols and indoles are abundant and readily available chemical feedstocks, which are widely used in organic synthesis chemistry.[1] The dearomatization of β-naphthols and indoles shows great potential in rapidly accessing highly functionalized β-naphthalenones and indolenines bearing quaternary carbon centers,[2] serving as pivotal scaffolds that are frequently found in biologically active natural products and pharmaceuticals.[3] In the past decades, allylic esters and carbonates,[4] allylic alcohols,[5] allylbenzenes[6] and allenes[7] have been widely employed in transition-metal catalyzed allylic alkylation dearomatization of β-naphthols and indoles (Fig. 1a). Recently, our group described a redox-neutral palladium-catalyzed allylic alkylation dearomatization of β-naphthols and indoles with alkynes in high atom and step economy.[8] Although impressive results were achieved in previous works, it is worth noting that the 2-position of the allyl framework in the products was short of functional groups. Thus, it is of great significance to explore novel allylating reagents, which could enable assembling some functional groups at the 2-position of the allyl fragment to expand the diversity and utility of β-naphthols and indoles.

The incorporation of fluorine or fluorine-containing motifs into organic molecules brings about substantial improvement in bioactivity, and provides unique chemical and physical properties.[9] Moreover, monofluoroalkenes have emerged as ideal peptide bond mimetics, which exhibit a similar steric and electronic profile to amides, and have been extensively applied in the fields of medicinal chemistry and drug-discovery.[10] Recently, *gem*-difluorinated cyclopropanes as fluoro-alkenylating building blocks have attracted increasing attention in the construction of functional monofluoroalkenes.[11] Herein, we describe a palladium-catalyzed allylic alkylation dearomatization of β-naphthols and indoles with *gem*-difluorinated cyclopropanes to the synthesis of β-naphthalenones and indolenines with 2-fluorinated allyl scaffolds in good efficiency for the first time (Fig. 1b).

We started our studies with *gem*-difluorinated cyclopropane **1a** and 1,3-dimethyl-2-naphthol **2a** as the model substrates. After a systematic survey of the reaction conditions (see the ESI† for details), the desired product **3a** was obtained in 92% yield with 5 mol% $[\eta^3\text{-}C_3H_5PdCl]_2$ as the catalyst, XPhos as the

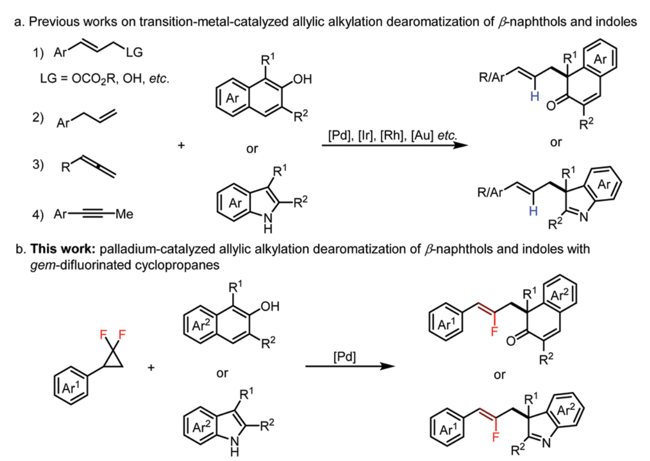

Fig. 1 Strategies for transition-metal-catalyzed allylic alkylation dearomatization of β-naphthols or indoles.

State Key Laboratory of Natural Medicines (SKLNM) and Department of Medicinal Chemistry, School of Pharmacy, China Pharmaceutical University, Nanjing 210009, P. R. China. E-mail: yd1029820332@163.com, ajlin@cpu.edu.cn

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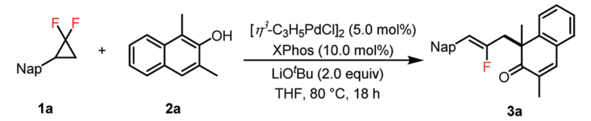
‡ These authors contributed equally to this work.

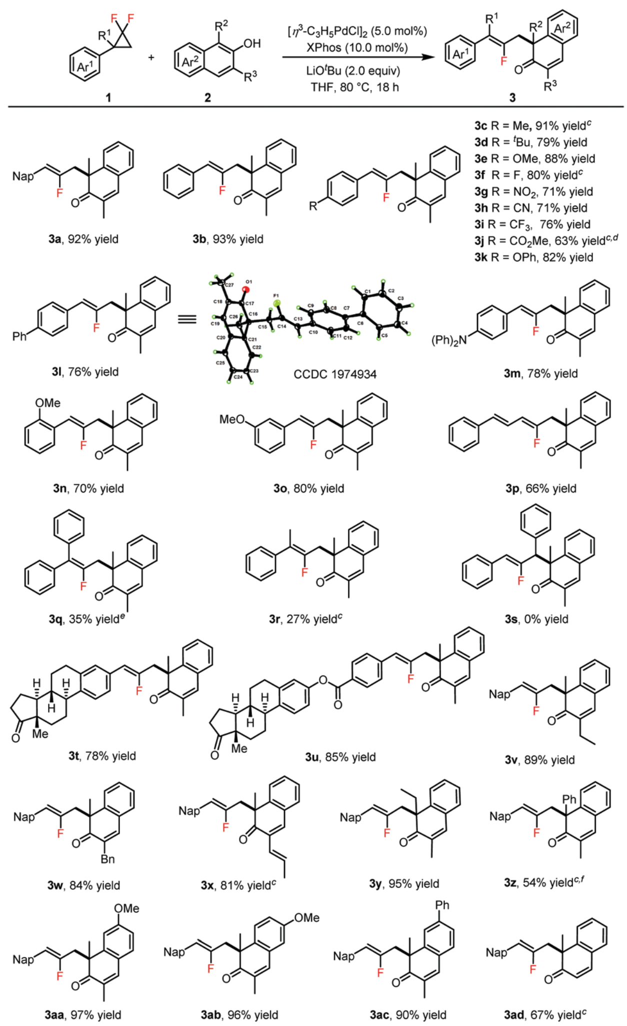
Table 1 Optimization of the reaction conditions



Entry	Deviation of standard conditions[a]	Yield[b]/(%)
1	None	92
2	$Pd(OAc)_2$ instead of $[\eta^3\text{-}C_3H_5PdCl]_2$	83
3	$Pd(OTFA)_2$ instead of $[\eta^3\text{-}C_3H_5PdCl]_2$	86
4	$Pd_2(dba)_3$ instead of $[\eta^3\text{-}C_3H_5PdCl]_2$	85
5	$Pd(PPh_3)_4$ instead of $[\eta^3\text{-}C_3H_5PdCl]_2$	80
6	Cy_3P instead of XPhos	46
7	SPhos instead of XPhos	58
8	XantPhos instead of XPhos	37
9	^{t}Bu-XPhos instead of XPhos	15
10	DavePhos instead of XPhos	40
11	Toluene instead of THF	87
12	Mesitylene instead of THF	90
13	CH_3CN instead of THF	33
14	1,4-Dioxane instead of THF	74
15	Without $[\eta^3\text{-}C_3H_5PdCl]_2$ or XPhos	n.r.

[a] Standard reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $[\eta^3\text{-}C_3H_5PdCl]_2$ (5.0 mol%), XPhos (10.0 mol%), LiO^{t}Bu (2.0 equiv.), THF (2.0 mL), at 80 °C under an Ar atmosphere for 18 h, sealed tube. [b] Isolated yield. n.r. = no reaction. Nap = 2-naphthyl.

Table 2 Substrate scope of β-naphthols and *gem*-difluorinated cyclopropanes[ab]



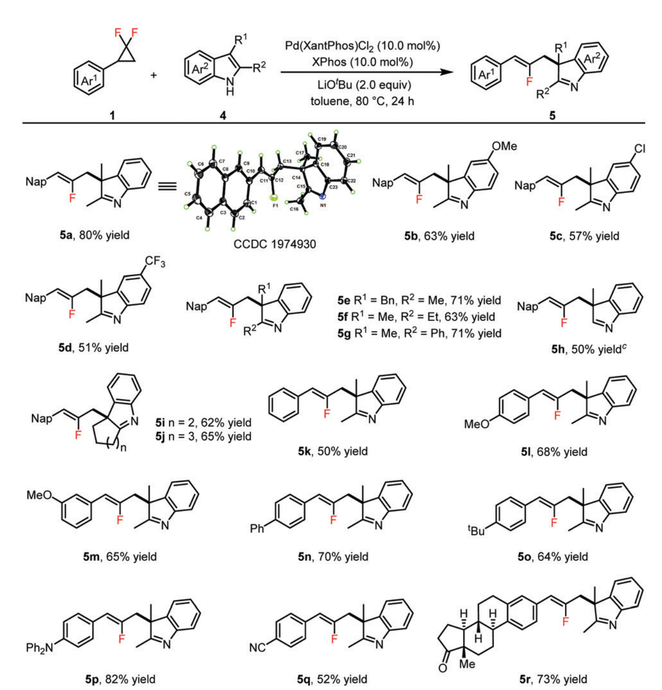
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $[\eta^3\text{-}C_3H_5PdCl]_2$ (5.0 mol%), XPhos (10.0 mol%), LiO^{t}Bu (2.0 equiv.), THF (2.0 mL), 80 °C, Ar atmosphere, 18 h, sealed tube. [b] Isolated yields. [c] Mesitylene (2.0 mL) as solvent. [d] **1j** (0.3 mmol), **2a** (0.2 mmol). [e] K_3PO_4 (2.0 equiv.) as base, mesitylene (2.0 mL) as solvent. [f] 100 °C.

ligand and LiO^{t}Bu as the base in THF at 80 °C under an Ar atmosphere for 18 h (Table 1, entry 1). Other catalysts, such as $Pd(OAc)_2$, $Pd(OTFA)_2$, $Pd_2(dba)_3$ and $Pd(PPh_3)_4$, performed this reaction in 80–86% yields (Table 1, entries 2–5). Other ligands, such as Cy_3P, SPhos, XantPhos, ^{t}Bu-XPhos and DavePhos, offered **3a** in less efficiency (Table 1, entries 6–10). Toluene and mesitylene offered **3a** in 87% and 90% yields, while CH_3CN and 1,4-dioxane gave **3a** in 33% and 74% yields, respectively (Table 1, entries 11–14). No reaction occurred when this transformation was conducted without the Pd catalyst or the ligand (Table 1, entry 15).

Having optimized the reaction conditions, we then focused on the substrate scope of this method (Table 2). Various *gem*-difluorinated cyclopropanes were all allowed to react with **2a** well, and afforded the corresponding products **3a–3o** in 63–93% yields. The structure of **3l** was confirmed on the basis of a single-crystal X-ray crystallographic analysis (see the ESI,† for details). When **1p** was employed as the substrate, the conjugated fluorodiene **3p** was obtained in 66% yield. The 1,1-disubstituted *gem*-difluorinated cyclopropanes (**1q** and **1r**) could be converted to products **3q** and **3r** in low yields (see the ESI,† for details), but 1,2-diphenyl substituted *gem*-difluorinated cyclopropane **1s** could not offer the desired product **3s**. To further demonstrate the potential utility of this reaction for the late-stage modification of natural products, the estrone derivatives (**1t** and **1u**) were synthesized and tested, offering products **3t** and **3u** in good yields. Subsequently, the compatibility of β-naphthols **2** was examined, and all of them performed smoothly to deliver products **3v–3ad** in good efficiency. Phenyl substituted β-naphthol gave **3z** in 54% yield due to the increased steric bulk. Notably, 1-methylnaphthalen-2-ol converted to product **3ad** in 67% yield with good regioselectivity.

After checking the reactivity of β-naphthols, we then proceeded to explore the generality of indoles (Table 3). All 2,3-disubstituted indoles were found to be compatible with the reaction, and products **5a–5g** were formed in moderate to good yields upon reaction with *gem*-difluorinated cyclopropane **1a** employing $Pd(XantPhos)Cl_2$ as the catalyst, XPhos as the ligand and LiO^{t}Bu as the base in toluene at 80 °C for 24 h (see the ESI,† for details on the optimization of reaction conditions). The structure of **5a** was confirmed on the basis of a single-crystal X-ray crystallographic analysis (see the ESI,† for details). Cyclic olefin-fused indoles could deliver products **5i** and **5j** in 62% and 65% yields. Moreover, *gem*-difluorinated cyclopropanes were investigated upon reaction with 2,3-dimethylindole, offering products **5k–5r** in moderate to good yields. Polycyclic indoline fragments are prevalent in natural products and biologically active molecules.[12] Therefore, tryptophol

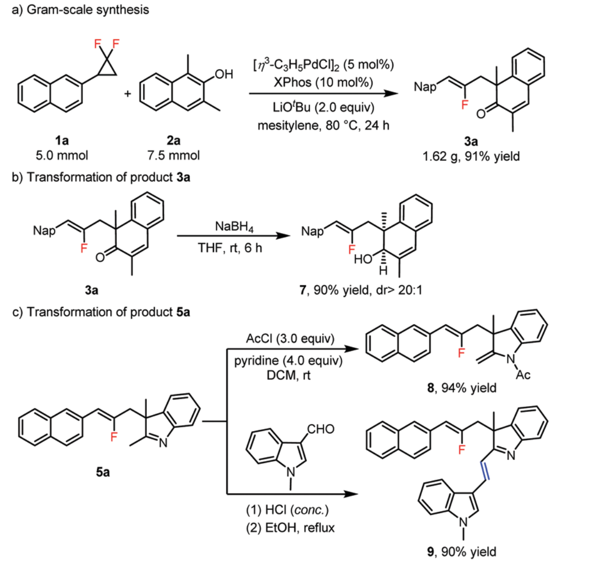
Table 3 Substrate scope of indoles and *gem*-difluorinated cyclopropanes[ab]



[a] Reaction conditions: **1** (0.2 mmol), **4** (0.3 mmol), $Pd(XantPhos)Cl_2$ (10.0 mol%), XPhos (10.0 mol%), LiO^tBu (2.0 equiv.), toluene (2.0 mL), 80 °C, Ar atmosphere, 24 h, sealed tube. [b] Isolated yields. [c] **1** (0.3 mmol), **4** (0.2 mmol), Et_3B (1.1 equiv.).

and tryptamines were then subjected to the reaction with *gem*-difluorinated cyclopropane **1a.** To our delight, furanoindoline **6a** and pyrroloindolines **6b–6d** were achieved in 80–90% yields *via* cascade allylic alkylation, dearomatization and cyclization processes in the presence of Et_3B (Scheme 1).[13]

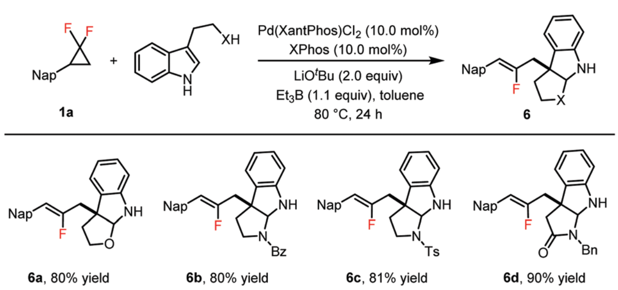
To demonstrate the synthetic utility of this method, the scale-up synthesis and further transformations of products were conducted as shown in Scheme 2. Product **3a** (1.62 g) was achieved in 91% yield on the 5.0 mmol scale under the standard reaction conditions (Scheme 2a). The ketone group could be selectively reduced by $NaBH_4$ to afford compound **7** in 90% yield, and the relative configuration was confirmed by the NOE spectra analysis (see the ESI† for details) (Scheme 2b). Product **5a** reacted with AcCl to deliver compound **8** in 94% yield. Bisindole **9** bearing an ethylene bridge, a potent antitumor activity skeleton,[14] could be synthesized by Aldol-type condensation (Scheme 2c).



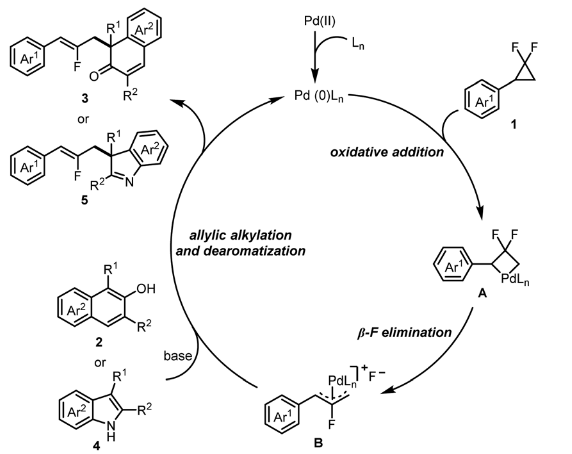
Scheme 2 Further study of the reaction.

Based on previous works,[11] a plausible catalytic cycle of this reaction is shown in Scheme 3. Initially, the activated Pd(0) catalyst reacts with the *gem*-difluorinated cyclopropanes **1** through oxidative addition to generate the four-membered palladacycle intermediate **A**, which undergoes β-F elimination to form the π-allylpalladium species **B.** Subsequent nucleophilic attack of β-naphthols **2** or indoles **4** at the sterically less hindered carbon atom of intermediate **B** affords the products 2-fluoroallylic β-naphthalenones **3** or indolenines **5**, and regenerates Pd(0) catalysts for the next catalytic cycle.

In conclusion, we have developed a palladium-catalyzed allylic alkylation dearomatization of β-naphthols and indoles with *gem*-difluorinated cyclopropanes for the first time. This reaction provided an efficient approach to prepare 2-fluoroallylic β-naphthalenones and indolenines in good to excellent yields. In addition, functional furanoindoline and pyrroloindolines could



Scheme 1 Construction of polycyclic indoline.



Scheme 3 Proposed mechanism.

also be synthesized *via* cascade allylic alkylation, dearomatization and cyclization processes from tryptophol and tryptamines. Further study on the asymmetrical process of this reaction is currently underway in our laboratory (see the ESI† for details).

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Conflicts of interest

There are no conflicts to declare.

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