ORGANIC CHEMISTRY
FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2018, **5**, 1978

Ruthenium(II)-catalyzed α-fluoroalkenylation of arenes *via* C–H bond activation and C–F bond cleavage†

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Received 19th March 2018,
Accepted 4th May 2018

DOI: 10.1039/c8qo00297e

rsc.li/frontiers-organic

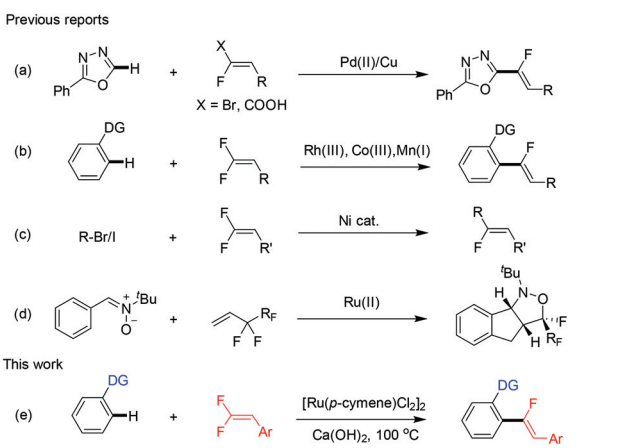
Ru(II)-Catalyzed efficient α-fluoroalkenylation of arenes has been realized with *gem*-difluorostyrene as an olefinating reagent. This coupling system is efficient with a broad substrate scope, providing 1,2-diaryl-substituted monofluoroalkenes with good to excellent regio- and stereoselectivities under silver-free conditions.

Introduction

With the rapid development of organic chemistry, organofluorines have participated flexibly in many research areas ranging from drug discovery to material synthesis.[1,2] Various fluorine-containing compounds are found to be biologically active. Thus, the polarity, lipophilicity and metabolic capacity of drug molecules can be improved with introduction of fluorine atoms, which can enhance the non-covalent binding of the compound to the target molecule, resulting in a significant increase of drug activity.[3] In particular, fluoroalkenes are a class of fluorine-containing compounds[4,5] that are of significant importance. Traditional synthesis of fluoroalkenes generally relies on the coupling of the nucleophilic/electrophilic reagent with fluorinated compounds.[6] However, these methods often suffer from preactivation of fluoroalkanes, employment of stoichiometric amounts of metal reagents, and low regio- and/or stereo-selectivity.[7] Recently, the groups of Hashmi[8] and Fu[9] applied the photoredox catalyzed strategy to access fluoroalkenes. Still, there is a high demand for the development of efficient and cost-effective synthetic methods to access fluoroalkenes.

Transition metal-catalyzed C–H activation has been established as an increasingly important strategy for the construction of C–C bonds.[10,11,18] The synthesis of fluoroalkenes *via* C–H activation has been recently reported. Thus, the groups of Hoarau,[12] Loh,[13] Li,[14] Wang[15] and Fu[16] disclosed fluoroalkenylations of arenes *via* C–H activation using Pd/Cu, Rh(III), Mn(I), Co(III), Fe(III) and Ni(II) catalysts (Scheme 1). On the other hand, ruthenium(II) catalysts have played an important role in the chemistry of C–H activation owing to the relatively low cost of the Rh(II) catalysts.[19] Very recently, we reported a ruthenium(II)-catalyzed coupling of *N*-*tert*-butyl nitrones with perfluoroalkylalkenes *via* a sequence of C–H activation, C–F elimination, and intramolecular dipolar addition (Scheme 1d).[17] However, this reaction failed to stop at the olefination stage. We have now reported ruthenium(II)-catalyzed step-economical access to fluoroalkenes *via* C–H activation of arenes and C–F cleavage (Scheme 1e), which occurred in the absence of any copper(II) or silver(I) additives.

We initiated our studies by exploring the reaction conditions of the coupling of *N*-pyrimidinylindole (**1a**) with a substituted *gem*-difluorostyrene (**2a**) under Ru(II) catalysis (Table 1). Initially, no desired product was observed when catalyzed by $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%)/$AgSbF_6$ (10 mol%) using



Scheme 1 Fluoroalkenylation of arenes *via* C–H activation.

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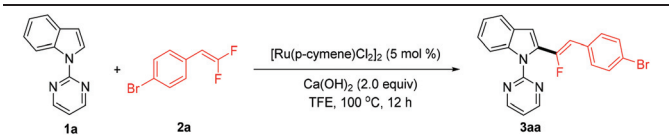
†Electronic supplementary information (ESI) available: Detailed experimental procedures, analytical data and NMR spectra. See DOI: 10.1039/c8qo00297e

Table 1 Optimization studies[a,b]

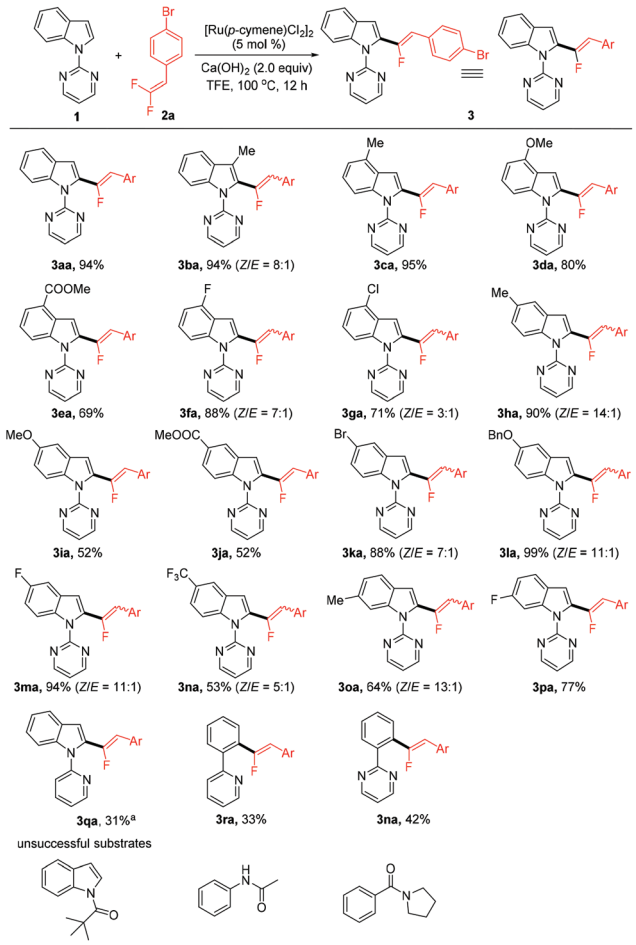


Entry	T (°C)	1a : 2a	Solvent (mL)	Additive (equiv.)	Yield[b] (%)
1	80	1 : 1.2	THF (3)	$AgSbF_6$ (0.2), $Ca(OH)_2$ (2)	n.r.
2	80	1 : 1.2	TFE (3)	$AgSbF_6$ (0.2), $Ca(OH)_2$ (2)	n.r.
3	80	1 : 1.2	TFE (3)	$Ca(OH)_2$ (2)	64
4	80	1 : 1.2	THF (3)	$Ca(OH)_2$ (2)	n.r.
5	80	1 : 1.2	DCE (3)	$Ca(OH)_2$ (2)	n.r.
6	80	1 : 1.2	CH_3OH (3)	$Ca(OH)_2$ (2)	n.r.
7	80	1 : 1.2	CH_3CN (3)	$Ca(OH)_2$ (2)	n.r.
8	80	1 : 1.2	Dioxane (3)	$Ca(OH)_2$ (2)	n.r.
9	80	1 : 1.2	TFE (3)	CaO (2)	44
10	80	1 : 1.2	TFE (3)	$CaCO_3$ (2)	Trace
11	80	1 : 1.2	TFE (3)	$Ca(A_C)_2$ (2)	36
12	80	1 : 1.2	TFE (3)	$Ca(OH)_2$ (0.5)	19
13	80	1 : 1.2	TFE (3)	$Ca(OH)_2$ (1)	35
14	100	1 : 1.2	TFE (3)	$Ca(OH)_2$ (2)	71
15	100	1 : 1.2	TFE (1)	$Ca(OH)_2$ (2)	82
16	100	1 : 1.2	TFE (5)	$Ca(OH)_2$ (2)	62
17	100	1 : 1.4	TFE (1)	$Ca(OH)_2$ (2)	89
18	**100**	**1 : 1.6**	**TFE (1)**	**$Ca(OH)_2$ (2)**	**94**

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24–0.32 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%), additive, solvent, 12 h, under Ar. [b] Isolated yield.

$Ca(OH)_2$ (2 equiv.) as an additive (entries 1 and 2). Interestingly, the desired product **3aa** was obtained in 64% yield with >20 : 1 stereoselectivity when $AgSbF_6$ was omitted (entry 3). Solvent screening revealed that trifluoroethanol (TFE) was the best choice (entries 4–8). The yield decreased by changing the additive to other calcium salts such as CaO, $CaCO_3$, and $Ca(OAc)_2$ (entries 9–11). What's more, reducing the amount of $Ca(OH)_2$ decreased the efficiency of the reaction (entries 12 and 13). To our delight, the isolated yield of **3aa** was dramatically improved to 94% by increasing the temperature to 100 °C, concentrating the reaction system and increasing the loading of **2a** (entries 14–17).

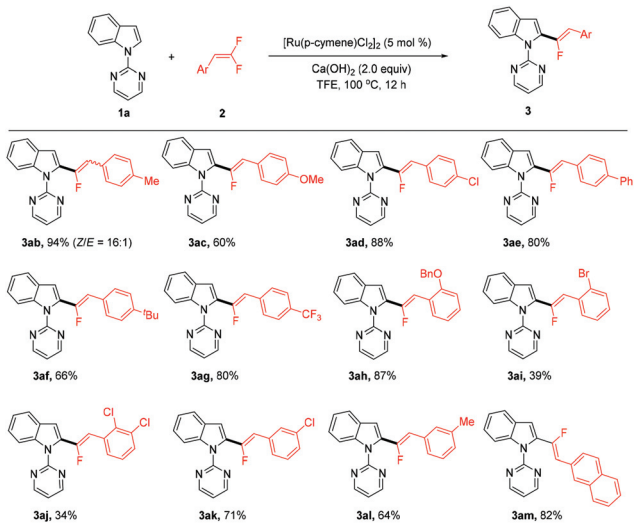
With the optimized conditions in hand, we next examined the applicability of various *N*-pyrimidinylindole substrates (**1a–1p**) in the coupling with **2a** (Scheme 2), and the corresponding α-fluoroalkenylation products (**3aa–3pa**) were obtained. Thus, *N*-pyrimidylindoles bearing electron-donating (Me, OMe, and OBn) or -withdrawing groups (F and CO_2Me) at the C4-, C5-, and C6-positions were coupled to give the corresponding products in 52–99% yields with moderate to high *Z*/*E* selectivity. Notably, >20 : 1 stereoselectivity has been achieved in many cases such as **3ca**, **3da**, **3ea**, **3ia**, **3ja**, and **3pa**. The steric effect was next explored with installation of a 3-methyl group, and the corresponding product **3ba** was obtained in a high yield of 94% (*Z*/*E* = 8 : 1), indicating that the reaction was insensitive to steric perturbation. The arene substrate was not limited to *N*-pyrimidinylindole. The α-fluoroalkenylation of several other arenes assisted by a *N*-pyridyl/pyrimidyl group also proceeded



Scheme 2 Scope of indole in fluoroalkenylation studies. Reaction conditions: **1** (0.2 mmol), **2a** (0.32 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%), and $Ca(OH)_2$ (2.0 equiv.) in TFE (1 mL) at 100 °C for 12 h. Isolated yield. *Z*/*E* ratio determined by ^{1}H NMR spectroscopy after flash column chromatography. *Z*/*E* ratio > 20 : 1 unless otherwise mentioned. Ar = 4-Br(C_6H_4). [a] 24 h.

in moderate yield (**3qa–3ra**). In contrast, 1-(1*H*-indol-1-yl)-2-dimethylpropan-1-one, phenyl(pyrrolidin-1-yl)methanone and *N*-phenylacetamide all failed to undergo any desired coupling (Scheme 2).

The scope of *gem*-difluorostyrene was next investigated, and the results are summarized in Scheme 3. *gem*-Difluorostyrene bearing electron-donating groups such as methyl (**3ab**), methoxy (**3ac**), and *tert*-butyl (**3af**) or electron-withdrawing groups such as trifluoromethyl (**3ag**) and chlorine (**3ad**) at the *para* position all proved to be viable (60–94% yield) with good stereoselectivity (*Z*/*E* > 16 : 1). Introduction of Br (**3ai**) and OBn (**3ah**) to the *ortho* position in the *gem*-difluoroalkene still gave the corresponding products in 39% and 87% yields, respectively. *meta*-Substituted substrates were also well-tolerated (**3ak** and **3al**). This system also accommodates 2-naphthyl-substituted *gem*-difluoroethylene (**3am**). A multi-substituted substrate (**3aj**) was also amenable to the coupling conditions. In most cases, >20 : 1 *Z*-selectivity was obtained.

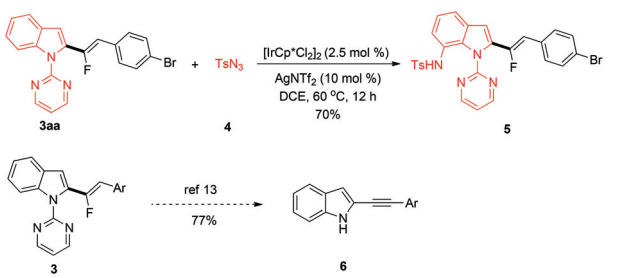


Scheme 3 Scope of *gem*-difluoroalkene in fluoroalkenylation. Reaction conditions: **1a** (0.2 mmol), **2** (0.32 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), $Ca(OH)_2$ (2.0 equiv.) in TFE (1 mL) at 100 °C for 12 h. Isolated yield. *Z*/*E* ratio determined by ^1H NMR spectroscopy after flash column chromatography. *Z*/*E* ratio > 20 : 1 unless otherwise mentioned.

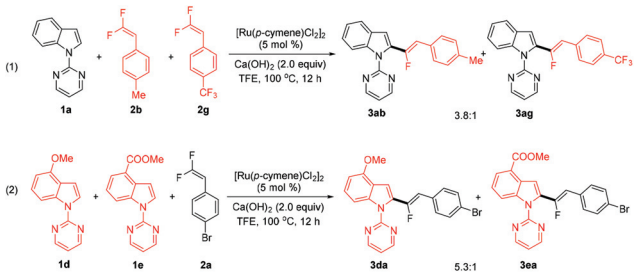
The scale-up synthesis of **3aa** (2 mmol) has also been performed, which was isolated in 85% yield. Derivatization reactions were also examined to demonstrate the synthetic utility of this reaction. Treatment of **3aa** (0.25 mmol) with azide **4** (0.5 mmol) in the presence of an Ir(III) catalyst afforded the C(7) amidation product **5**. In addition, base treatment of **3aa** afforded an alkyne **6** *via* HF elimination, as has been documented in a literature report (Scheme 4).[13]

To understand the electronic effects of this coupling system, two competition experiments have been carried out (Scheme 5). In one experiment, competitive coupling of **2b** and **2g** with **1a** revealed that the electron-rich olefin reacted at a higher rate. In the other experiment using indoles **1d** and **1e** that differ in the electronic effect at the 4-position, the same conclusion holds true. In both cases, the substrates were very responsive to electronic perturbation.

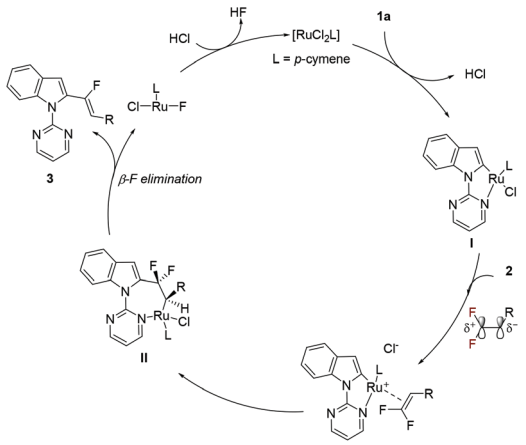
On the basis of our above experimental results and literature precedents of Rh(III) and Co(III)-catalyzed C–H fluoroalkenylation systems, a proposed catalytic cycle is shown in Scheme 6.[12–14,19] A five-membered metallacyclic intermediate **I** is produced *via* cyclometalation of *N*-pyrimidinylindole, together with the formation of HCl. The C(aryl)–Ru bond of **I** undergoes migratory insertion into a ligated *gem*-difluoroalkene to form a Ru–C(alkyl) species **II**. Intermediate **II** then undergoes selective β-*F* elimination *via* a *syn*-coplanar transition state[5c,19] to give the product **3**, together with a Ru(II) fluoride. Subsequent anion exchange with a chloride regenerates the active Ru(II) catalyst for the next catalytic cycle.



Scheme 4 Derivatization reactions.



Scheme 5 Mechanistic studies. Reaction conditions: (1) **1a** (0.2 mmol), **2b**/**2g** (0.2 mmol each), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), $Ca(OH)_2$ (2.0 equiv.) in TFE (1 mL) at 100 °C for 12 h. (2) **1d**/**1e** (0.2 mmol each), **2a** (0.4 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), $Ca(OH)_2$ (2.0 equiv.) in TFE (1 mL) at 100 °C for 12 h.



Scheme 6 Proposed mechanism.

Conclusions

In summary, we have demonstrated ruthenium(II)-catalyzed α-fluoroalkenylation of indoles *via* C–H bond activation and C–F bond cleavage under mild redox-neutral reaction conditions. This method is simple and efficient with a broad substrate scope. Future studies will be directed to metal-catalyzed coupling of arenes with other fluoro-containing coupling partners.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The NSFC (No. 21525208 and 21472186) and the research fund from the Henan Normal University (5101034011009) are gratefully acknowledged.

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