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Cobalt(III)-Catalyzed Regio- and Stereoselective α-Fluoroalkenylation of Arenes with *gem*-Difluorostyrenes

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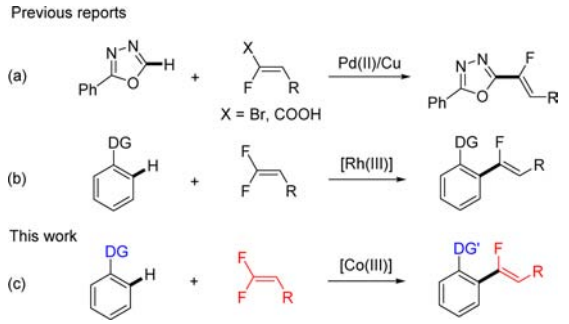
Supporting Information

ABSTRACT: A cobalt(III)-catalyzed α-fluoroalkenylation of different arenes with readily available *gem*-difluorostyrenes has been realized under mild and redox-neutral conditions. This reaction occurs via a C−H activation pathway and offers a step-economical access to various 1,2-diaryl-substituted monofluoroalkenes in excellent *Z* selectivity in moderate to excellent yields.

The incorporation of fluorine atoms into small organic molecules can often drastically enhance the metabolic stability, lipophilicity, and bioavailability. It can also increase the receptor-binding affinity and selectivity relative to the parent molecule.[1] Consequently, fluorine-containing compounds are known to a play an important role in the pharmaceutical/medicinal, agrochemical, and material sciences.[2] Fluoroalkenes represent an important class of olefins owing to their biological properties and also their applications in synthetic organic chemistry.[3] Therefore, considerable efforts have been devoted to the development of efficient methods for their synthesis. Existing effective methods usually require preactivation of substrates or employment of nonreadily available starting materials, and these methods often suffer from low regio- or stereoselectivity and poor functional group tolerance due to the employment of sensitive reagents.[4] Therefore, new synthetic options featuring high efficiency and mild conditions are still under great demand.

In recent years, metal-catalyzed C−H activation has been established as an effective strategy to build C(sp^2)−C bonds.[5] Related studies have been reported for the synthesis of fluoroalkenes via C−H activation. Hoarau reported fluoroalkene synthesis via Pd/Cu-catalyzed C−H activation of heteroarenes and coupling with different fluorinated alkenes (Scheme 1a).[6] Very recently, Loh elegantly reported a rhodium(III)-catalyzed coupling of arenes with *gem*-difluoroalkenes via C−H activation and C−F cleavage (Scheme 1b).[7] Instead of relying on C−H activation, Toste reported access to the same product via a Pd-catalyzed defluorinative coupling between boronic acids and *gem*-difluoroalkenes.[8] Despite the success, these coupling systems have been accomplished using expensive second-row transition-metal catalysts. Thus, the development of comparably or even more efficient systems with earth-abundant first-row transition-metal catalysts is highly desirable. As well-established and efficient catalysts for various organic transformations, Cp*Co(III) complexes have attracted increasing attention owing to its earth-abundance, cost-effectiveness, low toxicity, and unique catalytic reactivity,[9] as

Scheme 1. Fluoroalkenylation of Arenes via C−H Activation



in the reports by Kanai/Matsunaga,[10] Glorius,[11] Ackermann,[12] Ellman,[13] Daugulis,[14] Chang,[15] and others.[16] However, Co(III)-catalyzed C−H activation and coupling with olefins remains largely underexplored.[17] We now report cobalt(III)-catalyzed α-fluoroalkenylation of diverse arenes with *gem*-difluorostyrenes via C−H activation and C−F cleavage.

We initiated our investigation by screening of the reaction conditions of the coupling of *N*-pyrimidinylindole (**1a**) with *gem*-difluoroalkene (**2a**) under Co(III) catalysis (Table 1). When the reaction was conducted in TFE using [Cp*Co(CO)I_2]/$AgNTf_2$ (10 mol %/20 mol %) as a catalyst at 80 °C, the desired product **3aa** was obtained in 76% yield but with a poor *Z*/*E* ratio (1.9:1, entry 1). Upon introduction of $Ca(OH)_2$, the yield was dramatically improved to 95% (*Z*/*E* = 3.7), where the $Ca(OH)_2$ likely scavenges the HF coproduct with CaF_2 formation (entry 3). Screening of several other calcium salts revealed that $Ca(OH)_2$ remained superior to $Ca(OAc)_2$ and $CaCO_3$ (entries 4 and 5). To our delight, switching the catalyst to [Cp*Co$(MeCN)_3$][SbF_6]$_2$ even in 5 mol % loading gave rise to an improved *Z*/*E* ratio of 16.6 while maintaining the reaction efficiency (entry 6). Meanwhile,

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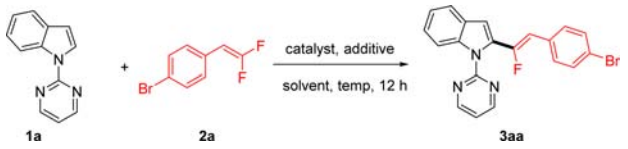
Table 1. Optimization Studies[a]



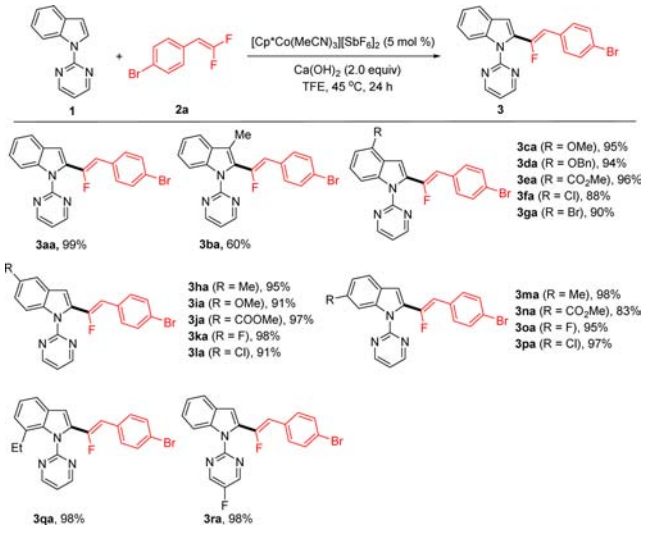
entry	catalyst (mol %)	silver salt (mol %)	additive	t (°C)	solvent	yield (%)[b]
1	$[Cp^*Co(CO)I_2]$ (10)	$AgNTf_2$ (20)	–	80	TFE	76 (1.9:1)[c]
2	$[Cp^*Co(CO)I_2]$ (10)	$AgNTf_2$ (20)	PivOH	80	TFE	61 (2.0:1)[c]
3	$[Cp^*Co(CO)I_2]$ (10)	$AgNTf_2$ (20)	$Ca(OH)_2$	80	TFE	95 (3.7:1)[c]
4	$[Cp^*Co(CO)I_2]$ (10)	$AgNTf_2$ (20)	$Ca(OAc)_2$	80	TFE	70 (2.7:1)[c]
5	$[Cp^*Co(CO)I_2]$ (10)	$AgNTf_2$ (20)	$CaCO_3$	80	TFE	85 (1.6:1)[c]
6	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	–	$Ca(OH)_2$	80	TFE	94 (16.6:1)[c]
7	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	–	$Ca(OH)_2$	80	HFIP	90 (14.1:1)[c]
8	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	–	$Ca(OH)_2$	80	DCE	<5
9	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	–	$Ca(OH)_2$	60[d]	TFE	96 (>20:1)[c]
10	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	–	$Ca(OH)_2$	45[e]	TFE	99 (>20:1)[c]
11	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	–	$Ca(OH)_2$	25[e]	TFE	84 (>20:1)[c]
12	–	–	$Ca(OH)_2$	45	TFE	0

[a]Reaction conditions: indole **1a** (0.1 mmol), **2a** (0.12 mmol), cobalt(III) catalyst, silver salt, and an additive (2.0 equiv) in a solvent (1.5 mL) under nitrogen for 12 h. [b]Isolated yield after chromatography. [c]Ratio of Z/E (determined by ^{19}F NMR spectroscopy). [d]16 h. [e]24 h.

solvent screening demonstrated that TFE was optimal (entries 7 and 8). Extending the reaction time and decreasing the reaction temperature to 45 °C (entries 9–11) improved the stereoselectivity (Z/E > 20/1).

Having obtained the optimized reaction conditions, we next investigated the scope of *N*-pyrimidinylindoles in the coupling with **2a** (Scheme 2). Introduction of substituents with different

Scheme 2. Scope of Indole in Olefination Studies[a,b]

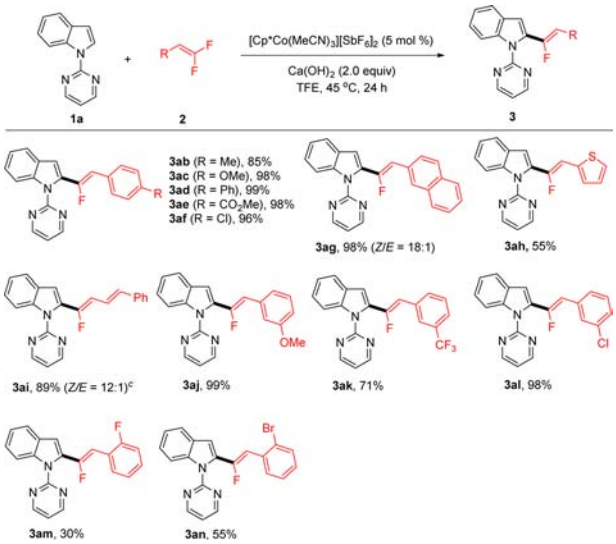


[a]Reaction conditions: indole (0.2 mmol), **2a** (0.24 mmol), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (5 mol %), $Ca(OH)_2$ (2.0 equiv) in TFE (3 mL) at 45 °C for 24 h. [b]Isolated yield, Z/E ratio >20:1.

electronic effects to different positions of the *N*-pyrimidinylindole is fully tolerated. Thus, with electron-donating groups (Me, OMe, and OBn) and -withdrawing groups (F, Cl, Br, and CO_2Me) at the C4-, C5-, and C6-positions of the indole ring, the coupling afforded the corresponding products in excellent yields (**3ca**–**3ga**, **3ha**–**3la**, and **3ma**–**3pa**). Moreover, a C7-substituted indole and variation of the substituent in the pyrimidine ring are tolerated as in the isolation of products **3qa** and **3ra** in 98% yields in both cases. The reaction seems sensitive to steric perturbation at the 3-position in that introduction of a 3-Me group lowered the yield (**3ba,** 60%). In all cases, >20:1 stereoselectivity has been secured.

We next investigated the scope of the *gem*-difluoroalkene in the coupling with *N*-pyrimidinylindole (Scheme 3). *gem*-

Scheme 3. Scope of *gem*-Difluoroalkene in Olefination Studies[a,b]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (5 mol %), and $Ca(OH)_2$ (2.0 equiv) in TFE (3 mL) at 45 °C for 24 h. [b]Isolated yield; Z/E ratio >20:1 unless otherwise mentioned. [c]PivOH (2.0 equiv) was added.

Difluoroalkenes bearing methyl (**3ab**), methoxy (**3ac** and **3aj**), phenyl (**3ad**), CO_2Me (**3ah**), CF_3 (**3ak**), and halogen groups (**3ai**, **3al-an**) at both the *para* and *meta* positions proved to be a viable coupling partner (30–98% yield). Notably, a heterocycle-based *gem*-difluoroalkene is also applicable, leading to the formation of corresponding product (**3af**) in moderate yield. Moreover, this protocol also accommodates a naphthyl

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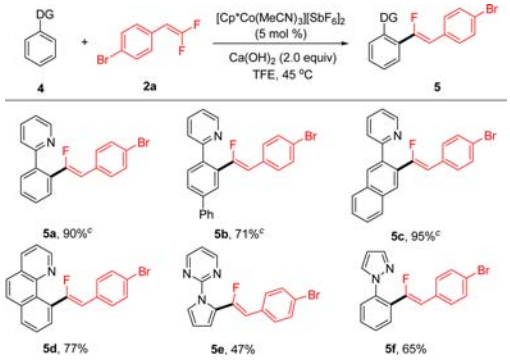
(**3ae**) and an alkenyl (**3ag**) group in the *gem*-difluoroakene with high isolated yield and good to high selectivity (18:1 and 12:1, respectively). Introduction of an *ortho* substituent to the benzene ring of the *gem*-difluorostyrene retarded the reaction, and only a low to moderate yield was realized (**3am** and **3an**). In most cases, >20:1 *Z*-selectivity was obtained.

The arene substrate is not limited to *N*-pyrimidinylindoles (Scheme 4). Under mild conditions, the α-fluoroalkenylation of

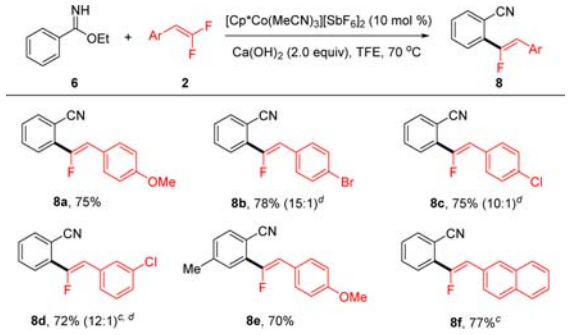
Scheme 4. Scope of Arenes Bearing a Heterocycle Directing Group[a,b]



[a]Reaction conditions: arene **4** (0.2 mmol), **2a** (0.24 mmol), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (5 mol %), and $Ca(OH)_2$ (2.0 equiv) in TFE (3 mL) at 45 °C for 24 h. [b]Isolated yield. [c]25 °C.

arenes assisted by pyridine, benzo[*h*]quinoline, pyrimidine, and pyrazole also proceeded smoothly in good to excellent yield (**5a**−**5f**). When we moved to ethyl benzimidate as an arene substrate (Scheme 5), (*Z*)-2-(1-fluoro-2-phenylvinyl)-

Scheme 5. Coupling of ethyl benzimidates and *gem*-difluoroalkenes[a,b,c,d]

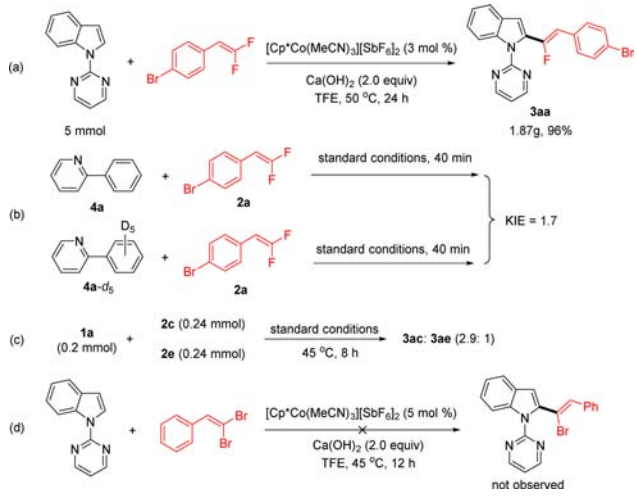


[a]Reaction conditions: imidate ester **6** (0.2 mmol), **2** (0.24 mmol), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (5 mol %), and $Ca(OH)_2$ (2.0 equiv) in TFE (3 mL) at 70 °C for 24 h. [b]Isolated yield, > 20:1 Z/E ratio unless otherwise mentioned. [c]Imidate ester **6** (0.24 mmol) and **2** (0.2 mmol) were used. [d]The ratio of *Z*/*E* was determined by ^{19}F NMR spectroscopy.

benzonitrile was obtained in good yield, where the imidate functionality acts *in situ* as a transformable directing group.[18] The scope of this reaction was then briefly explored. *gem*-Difluoroalkenes bearing a methoxy (**8a** and **8e**), halogen (**8b**−**8d**), and naphthyl group (**8f**) consistently coupled smoothly, and the corresponding products were isolated in 70−78% yield as a single stereoisomer.

To demonstrate the synthetic utility of this reaction, gram-scale coupling of **1a** and **2a** has been performed, and the product **3aa** was also isolated in excellent yield (96%) even under a reduced catalyst loading (Scheme 6a). To briefly probe

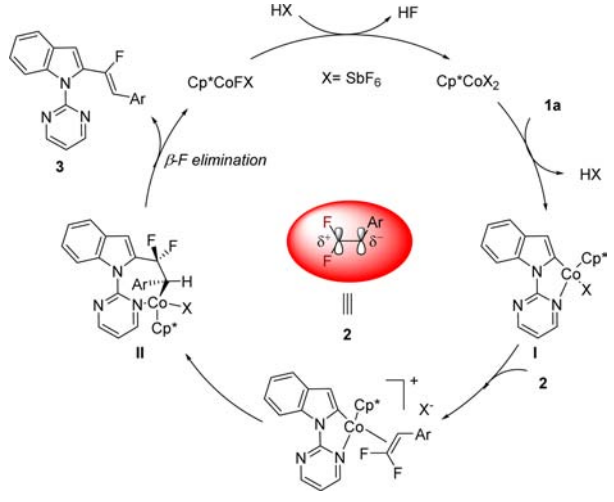
Scheme 6. Gram-Scale Synthesis and Mechanistic Studies



the reaction mechanism, the kinetic isotopic effect was measured in two side-by-side reactions using **4a** and **4a**-d_5 at a low conversion under the standard conditions, from which a k_H/k_D value of 1.7 was obtained on the basis of ^1H NMR analysis (Scheme 6b). This small value indicates that C−H activation is probably not involved in the turnover-limiting step. To further investigate the electronic preference of this reaction, competition between two olefins **2c** and **2h** differing in electronic effects was performed in the coupling with indole **1a**, and the coupling was favored for the more electron-rich one (Scheme 6c). In contrast to the high reactivity of *gem*-difluorostyrenes, no reaction was observed for a *gem*-dibromostyrene under the same reaction conditions, which indicates the uniqueness of the *gem*-difluorostyrene in terms of olefin insertion and C−F cleavage.

A working hypothesis was proposed to account for the above transformations (Scheme 7).[7] Cyclometalation of *N*-pyrimidinylindole affords a five-membered metallacyclic intermediate **I** together with an acid HX. Coordination of *gem*-difluoroalkene is followed by regioselective migratory insertion of the aryl

Scheme 7. Proposed Mechanism



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group to give intermediate **II**. The insertion is governed by electronic effect in that the terminal carbon of the olefin is partially positively charged. Intermediate **II** then undergoes selective β-F elimination (likely via a syn-coplanar transition state) to give the product **3**, together with a Rh(III) fluoride. Further interaction with the HX then regenerates the active Co(III) catalyst for the next catalytic cycle.

In summary, we have demonstrated cobalt(III)-catalyzed α-fluoroalkenylation of (hetero)arenes through C−H activation and C−F cleavage. The reactions are highly efficient and proceeded stereoselectively under mild and redox-neutral reaction conditions to afford a series of *Z*-alkenyl fluorides, which are known to be useful in the synthesis of fluorinated biomolecules. The scopes of the protocols were investigated and found to be satisfactory. Given the mild conditions, broad scope, stereoselectivity, and high catalytic efficiency, this method may find applications in the synthesis of functionalized fluoroalkene derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03203.

Detailed experimental procedures, characterization of new compounds, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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