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Transition metal-catalyzed C(sp^2/sp^3)–H α-fluoroalkenylation from *gem*-(bromo/di) fluoroalkenes to monofluoroalkenes: scope, mechanisms, and synthetic applications

Essam M. Eliwa, [a,b] Ahmed H. Bedair[b] and Jean-Pierre Djukic *[a]

Organofluorines have a broad range of industrial applications, such as pharmaceuticals, liquid crystal displays (LCDs), solar cells, textiles, and construction coatings, and are used in peptidomimetics, surfactants, refrigerants, anesthetics, and agrochemicals. Among them are versatile monofluoroalkenes that play a crucial role in medicinal and synthetic chemistry. The synthetic strategies for this class of molecules are limited, and prior efforts frequently suffered from poor atom- and step-economies. As a surrogate pathway for traditional cross-coupling transformations, transition metal (TM)-catalyzed C–H direct α-fluoroalkenylation overcomes these obstacles and provides straightforward techniques to access monofluoroalkenes. Nevertheless, substrate scope is still a challenge for catalysis, where *gem*-bromofluoroalkene synthons are applicable with electronically biased substrates such as azoles, while *gem*-difluoroalkene-based strategies are limited to substrates containing N-based directing groups. Herein, we review the cutting-edge fluoroalkenylation research for direct synthesis of monofluoroalkenes achieved during the last decade (2013–2023). This review is divided into two main parts: the first part discusses TM-catalyzed direct α-fluoroalkenylation *via* the merging of C–H activation and C(sp^2)–Br cleavage strategies using *gem*-bromofluoroalkenes, and the second part describes the same reaction, albeit with C(sp^2)–F cleavage of highly explored *gem*-difluoroolefins. Our review surveys all previously reported monofluoroalkenes in this research area, including their preparation techniques, stereoselectivity, and yield percentages. Furthermore, optimal conditions, reactant scope, mechanistic investigations, synthetic applications, benefits, and drawbacks of each presented methodology are critically discussed.

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1. Introduction

The realm of transition metal (TM)-based catalysts is of extensive interest in academic and industrial research laboratories as an ultimate solution to the synthesis of high-value organic compounds. TM-based catalysts are applied as supported or not on a solid. These might be a wide range of coordination complexes with significant catalytic activity, organometallic complexes, metal oxides, simple metal salts, or even pure metals.[1–4]

In the organic synthesis community, C–H bond activation and functionalization chemistry has acquired considerable momentum as a powerful tool to access diverse organic frameworks through extraordinary bond cleavage methodologies.[5–12]

Among organohalogens, organofluorine chemicals are relevant to several aspects of daily life and technology. They are essential reagents for the materials science, pharmaceutical,[13] and agrochemical industries,[14] among other fields. Organofluorines are thought to make up about 53% of agrochemicals and 20% of medicines, including some of the most popular drugs. As ligands, they have also been studied in coordination and organometallic chemistry.[15] Fluorine atoms (or C–F bond formation) can be introduced to the organic molecule skeleton through C–H fluorination, fluoroalkylation, or fluoroalkenylation reactions.[16–24]

Monofluoroalkenes are a versatile class of organic molecules; they can be used as fluorinated synthons in synthetic organofluorine chemistry.[17,23,24] They also play a crucial role in chemical biology as precursors of bioactive molecules and impact the medicinal chemistry domain as a bioisostere for peptide linkage because they can impart desirable electronic and steric characteristics as well as enhance lipophilicity, improve recognition, and increase metabolic and conformational stability.[13] As a result, several strategies have been

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deployed to obtain various monofluoroalkene classes. In the last decade (2013–2023), TM-catalyzed C–H fluoroalkenylation has proven to be a successful and promising strategy.[17,23,24] It is endowed with the general advantages of being atom- and step-economical[25] as well as being specifically oxidant-free (redox-neutral), stereoselective and regioselective, with good functional group tolerance, no alkynylated side-product, and a scalable reaction.

Despite the fact that C–H α-fluoroalkenylation has attracted widespread attention in the last decade as a major methodology to access monofluoroalkenes, it is still facing significant challenges such as substrate scope (general applicability) and harsh conditions. Regarding the limitations of substrates, they are either electronically biased or pre-directed substrates. We find that the reported protocols that utilized *gem*-bromofluoroalkene synthons are applicable with "electronically biased" substrates such as azoles,[26–28] and their *gem*-difluoroalkene counterparts are limited to substrates containing N-based directing groups (DG),[29–46] whereas other substrates are still unsuitable, such as ketones, esters, acids, *etc*.

Furthermore, as we will see below, all the reported competition experiments confirmed the superiority of substrates and fluorinated reagents that contain electron-donating groups (EDGs) over the analogues carrying electron-withdrawing groups (EWGs). Though some mild and cost-effective α-fluoroalkenylation procedures (room temperature and abundant TM catalysis) are reported,[28,40–46] harsh conditions are still a significant obstacle that needs to be addressed. According to several experimental and theoretical studies,[30,39,41,43] the α-fluoroalkenylation mechanistic pathway employing *gem*-difluoroalkene synthons proceeds *via* four main steps, including C–H activation, olefin π-coordination, regioselective migratory olefin insertion, and β-fluoride elimination. In contrast with TM-mediated oxidative addition to cleavage C–F bonds, the β-F elimination route proceeds under milder conditions *via* β-fluoroorganometallic intermediates to install C–C coupling products (monofluoroalkenes).[23,24] Additionally, kinetic isotope effect (KIE) tests indicated that either C–H dissociation or alkene migratory insertion is a rate-determining step.[30,37,39]

Given the importance of monofluoroalkenes and the synthetic obstacles of C–H fluoroalkenylation reactions, there was an imperious need to survey recent achievements in this field. Thus, this review summarizes with mechanistic and synthetic details the newly discovered C–H α-fluoroalkenylation approaches for accessing distinct monofluoroalkenes categorized according to their synthetic protocols, which are based on the types of *gem*-halofluoroalkene building blocks and TM catalysts.

This review is divided into two parts: the first one focuses on relatively less explored direct α-fluoroalkenylation *via* the merging of C–H activation and C(sp^2)–Br cleavage strategies using *gem*-bromofluoroalkenes, and the second part describes the same reaction, albeit with C(sp^2)–F cleavage of easily accessible and commercially available *gem*-difluoroolefins. Each part is subdivided into subsections according to the type of TM-based catalysis. This review covers all the reported monofluoroalkenes in this research area from 2013 up to 2024 with the specific procedures, stereoselectivity, and yields. Moreover, this review reports on the optimal conditions, reactant scope, mechanistic studies, synthetic applications, advantages, and shortcomings of each reported protocol. Furthermore, some related out-of-scope examples are also considered for comparison. Finally, this review critically outlines the achievements in the field of C–H direct α-fluoroalkenylation and draws some perspectives for future advances.

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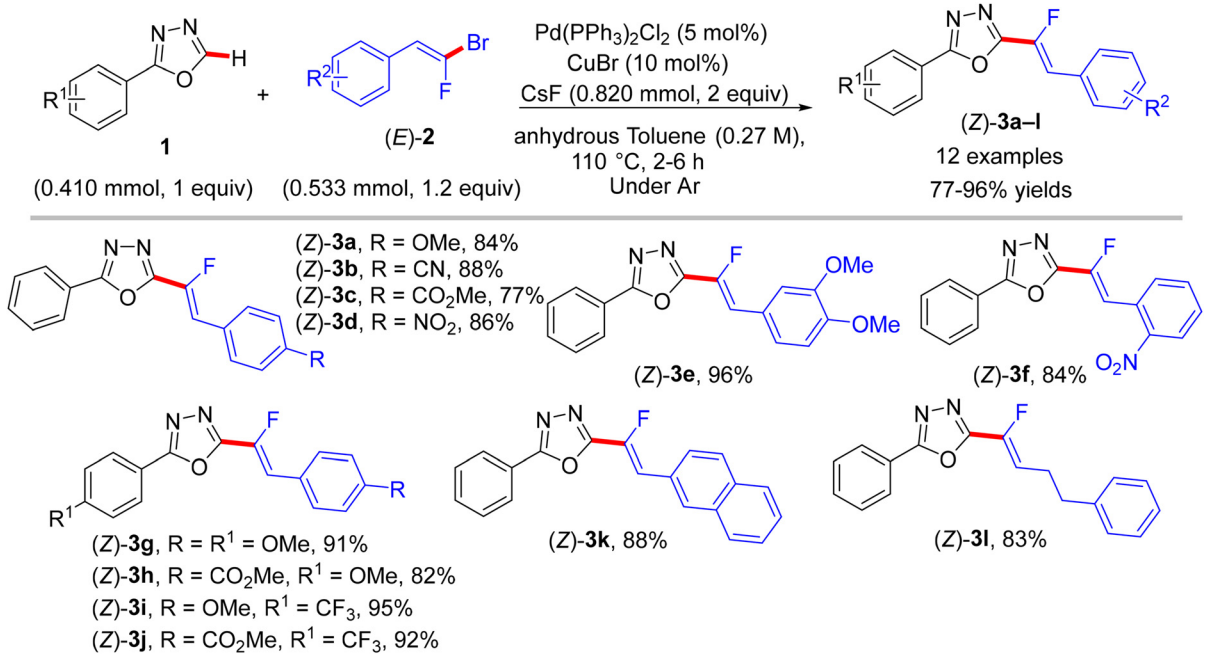

Scheme 1 Direct C(sp^2)–H α-fluoroalkenylation of 1,3,4-oxadiazoles **1** by Pd(0)/Cu(I) catalytic system.

2. Direct α-fluoroalkenylation with *gem*-bromofluoroalkenes

2.1. C–H α-fluoroalkenylation using Pd(0)/Cu(I) bimetallic catalytic system

As mixed 1,1-dihalo-1-alkenes, *gem*-bromofluoroolefins are significant fluorinated substructures and useful building blocks.[19,20] They can be prepared as a mixture of stereoisomers by several methods, such as the Wittig reaction, but some separation protocol-dependent chemoselectivity is reported.[47,48] They were successfully employed as synthons in organic synthesis to access monofluoroalkenes.[49] The paper by Hoarau *et al.* (2013) documented the first use of trisubstituted (*E*)-*gem*-bromofluoroalkenes (**2**) as electrophilic coupling partners in the direct C(sp^2)–H α-fluoroalkenylation of various electronically biased azoles (**1** and **4**) to access the corresponding (*Z*)-monofluoroalkenes (**3a–l** and **5a–o**) in fair to excellent yields (Schemes 1 and 2).[26]

This step-economical reaction proceeds *via* a base-assisted Pd(0)/Cu(I) bimetallic catalytic system at 110 °C under complete control of stereochemistry with functional group tolerance and without alkynylated (dehydrofluorinated) side-products. This protocol can also be scaled up from 0.41 to 2.05 mmol without losing efficiency. C(sp^2)–H α-fluoroalkenylation of oxadiazoles **1** was conducted using CsF as a mild base, while the less acidic 1,3-diazoles **4** needed more basic conditions offered by Cs_2CO_3 or LiO*t*Bu. The $PdCl_2(PPh_3)_2$ pre-catalyst was more effective in this transformation than $Pd(OAc)_2$, and the CuBr co-catalyst dramatically influenced the success of the reaction. Although the

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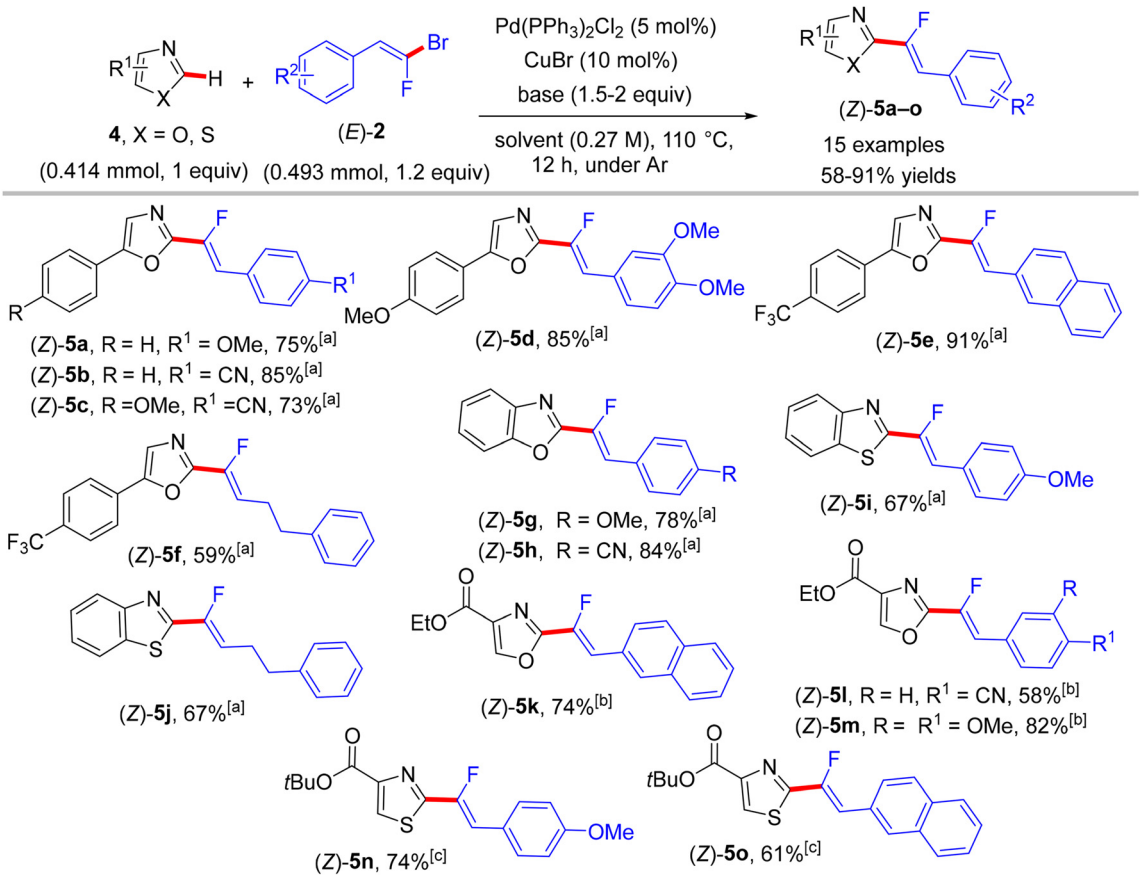
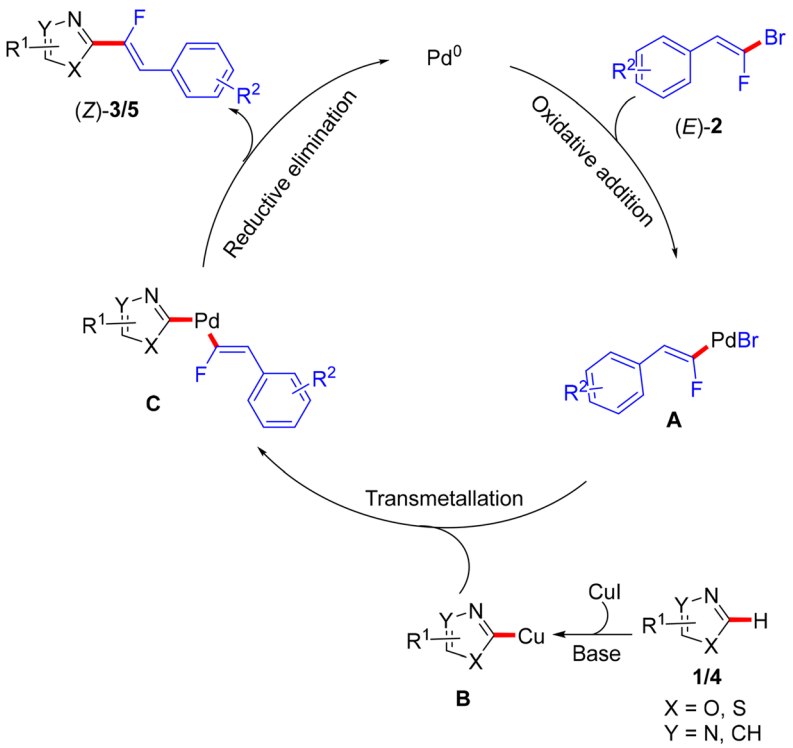


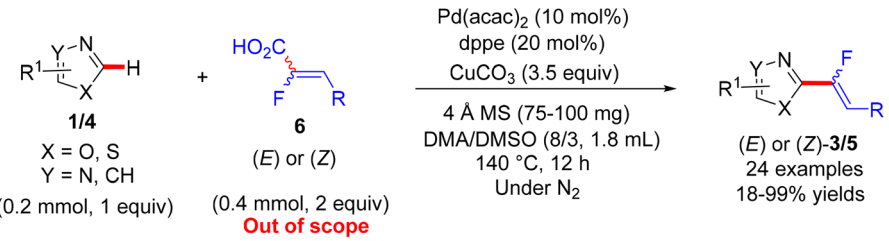
Scheme 2 Direct C(sp^2)–H α-fluoroalkenylation of various 1,3-diazoles **4** by Pd(0)/Cu(I) catalytic system. [a] LiO*t*Bu (1.5–2 equiv.), 1,4-dioxane. [b] Cs_2CO_3 (2 equiv.), 1,4-dioxane. [c] Cs_2CO_3 (2 equiv.), dimethylformamide (DMF).



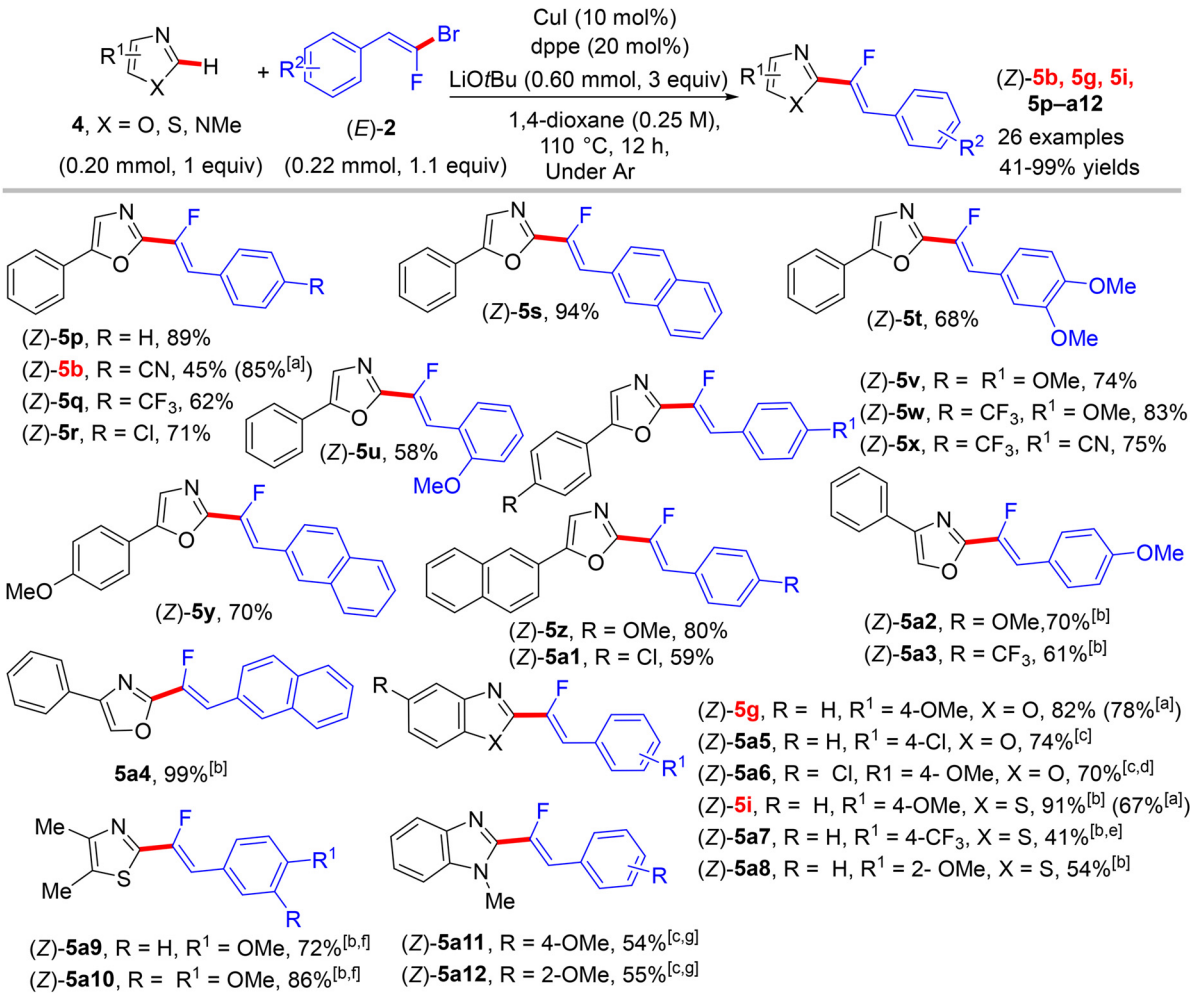
Scheme 3 Proposed catalytic cycle of Pd(0)/Cu(I)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of various azoles **1/4** with **2**.

authors did not perform any mechanistic studies, according to the reported Pd(0)/Cu(I) catalytic cycle,[2,50] the oxidative addition afforded organopalladium intermediate **A**, while the base and Cu(I) mediated the deprotonative metalation of azoles to a 2-azolylcopper intermediate **B** that was combined with **A** *via* transmetalation, yielding **C** followed by reductive elimination to furnish the desired monofluoroalkenes (Scheme 3).

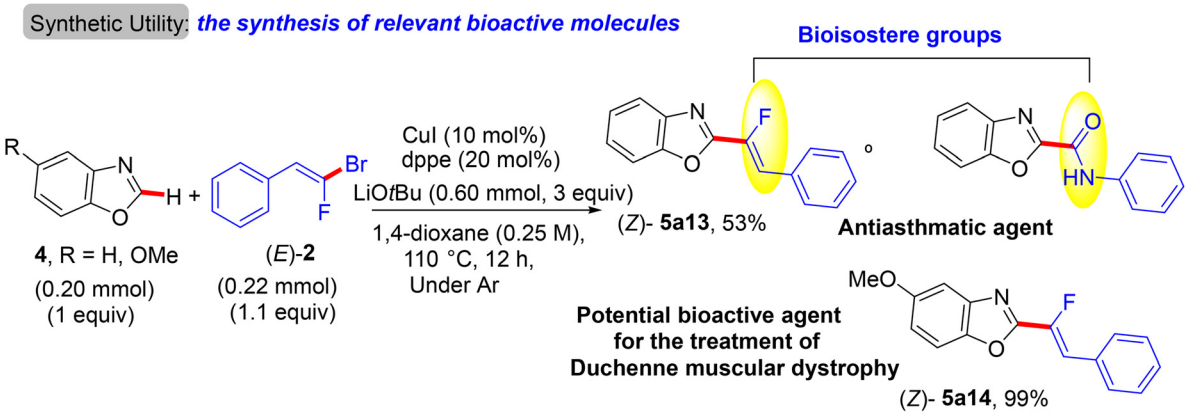
In 2014, the same group reported the synthesis of monofluoroalkenes **3/5** *via* decarboxylative/direct C(sp^2)–H α-fluoroalkenylation of various azoles **1/4** using the same catalytic system (Pd/Cu), albeit with α-fluoroacrylic acid coupling partner **6** that is out of scope of our review. Importantly, this transformation proceeds with complete retention of stereochemistry at the double bond, where the *E* reactant of **6** gives the (*E*)-monofluoroalkenes (Scheme 4).[27]



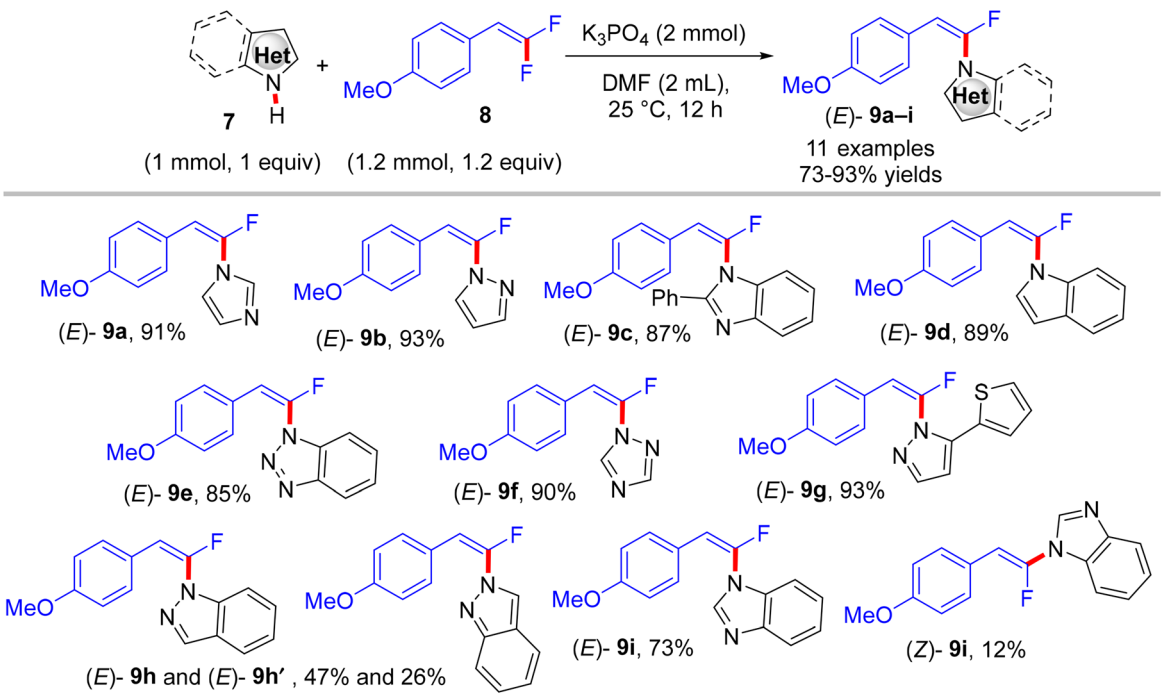
Scheme 4 Direct C(sp^2)–H α-fluoroalkenylation of various azoles **1/4** by Pd(0)/Cu(I) catalytic system using **6** as a coupling partner.



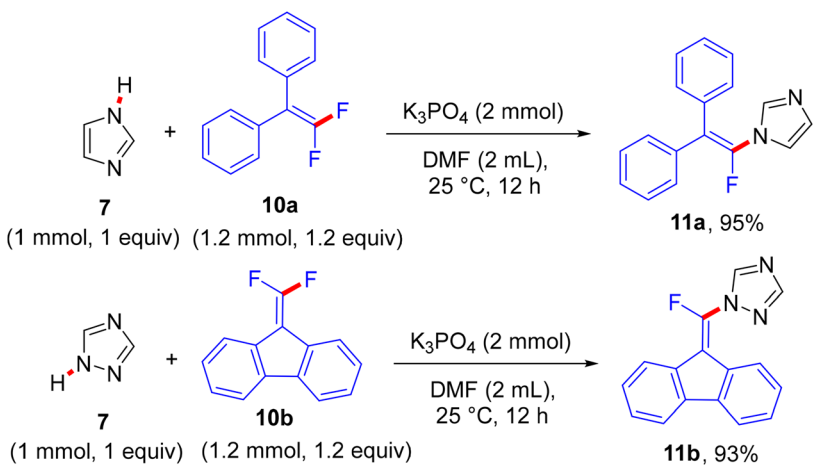
Scheme 5 Direct C(sp^2)–H α-fluoroalkenylation of various 1,3-diazoles **4** by CuI. [a] Yield produced by bimetallic Pd(0)/CuBr catalysis[26] for product numbers colored in red. [b] 1,10-Phenanthroline (phen) (20 mol%) was used as a ligand instead of *dppe*. [c] Reaction was performed at 130 °C. [d] Reaction was performed on a 1 mmol scale. [e] Reaction was performed at 90 °C. [f] CuI (20 mol%) and Phen (40 mol%) were used. [g] Ligand = *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine.



Scheme 6 Direct C(sp^2)–H α-fluoroalkenylation of benzoxazoles by CuI to access relevant bioactive molecules **5a13** and **5a14**.



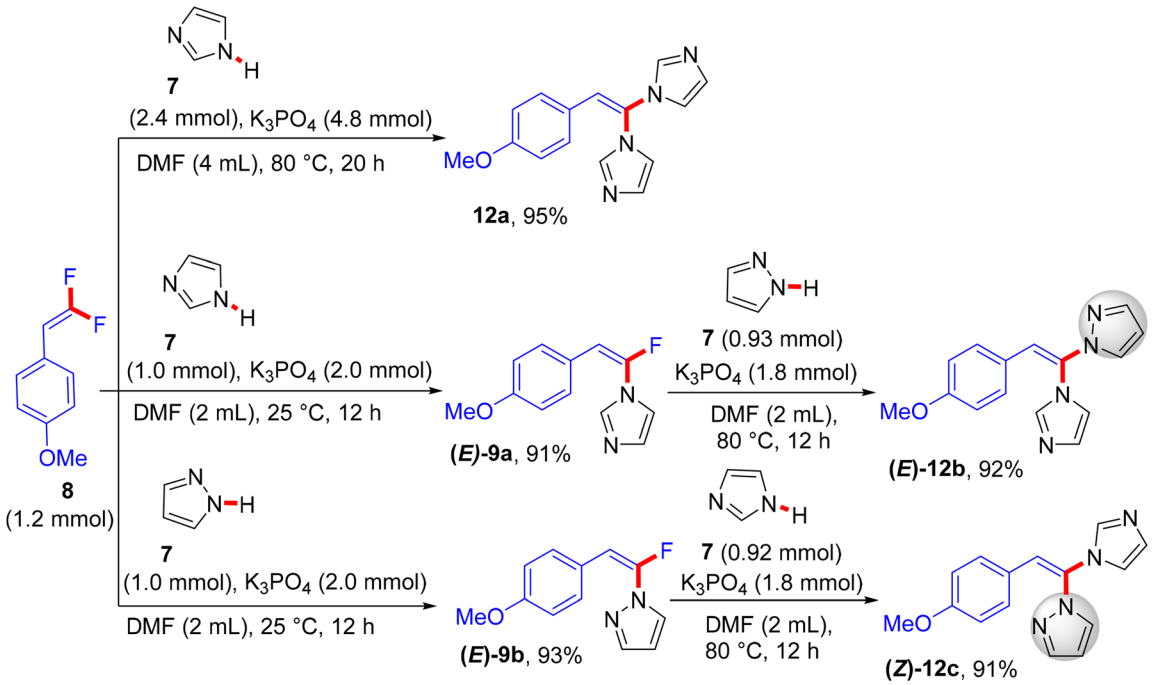
Scheme 7 Metal-free K_3PO_4-mediated direct N–H α-fluoroalkenylation of various NH-containing azoles **7**.



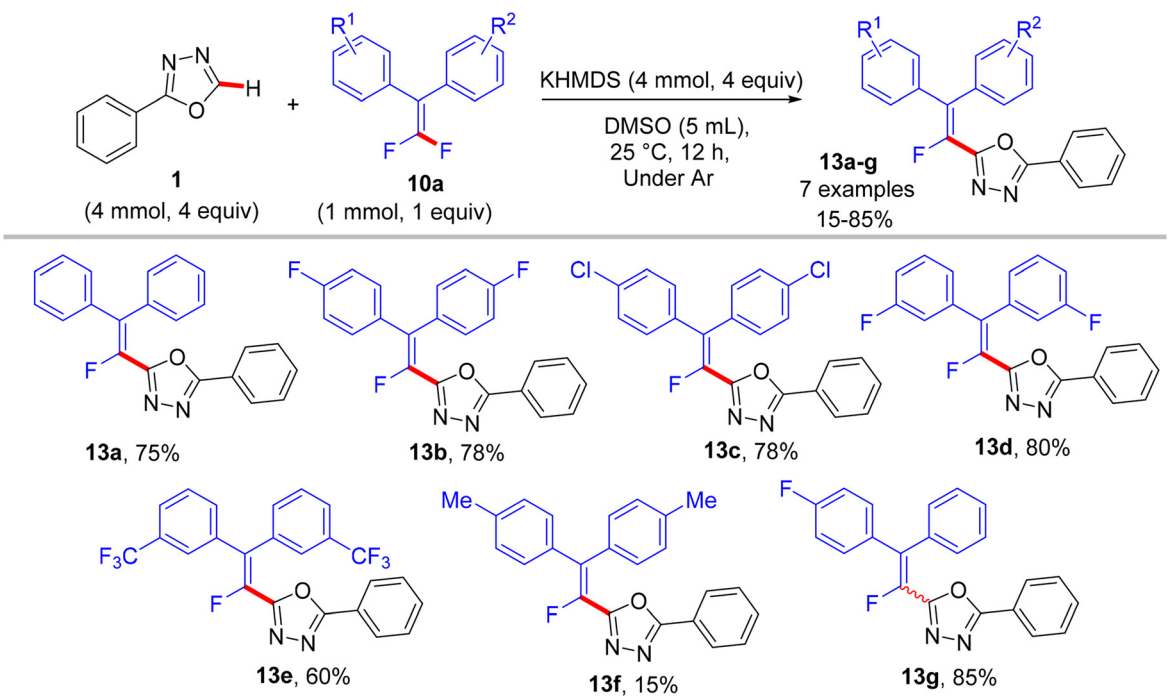
Scheme 8 Metal-free K_3PO_4-mediated direct N–H α-fluoroalkenylation of NH-containing azoles **7** with **10a,b**.

2.2. C–H α-Fluoroalkenylation using Cu(I)

Two years later (2016), the prior research group published an article defining a low-cost protocol for the direct C(sp^2)–H α-fluoroalkenylation of various 1,3-diazoles.[26,27] This pioneering study describes for the first time the use of Cu(I) alone (Pd-free) to catalyze this type of reaction.[28] 5-Phenyloxazole (**4**) was used as a model substrate with (*E*)-1-(2-bromo-2-fluorovinyl)-4-methoxybenzene (**2**) to obtain the optimum conditions. The above conditions without Pd were tested,[26] but the best performance was generated by CuI, 1,2-bis(diphenylphosphino) ethane (*dppe*) ligand, and sublimated LiO*t*Bu in refluxing



Scheme 9 Synthesis of *N*,*N*′-α,α′-dihetaryl-substituted olefins **12a–c** at 80 °C.



Scheme 10 Metal-free KHMDS-mediated direct C(sp^2)–H α-fluoroalkenylation of **1** with **10a**.

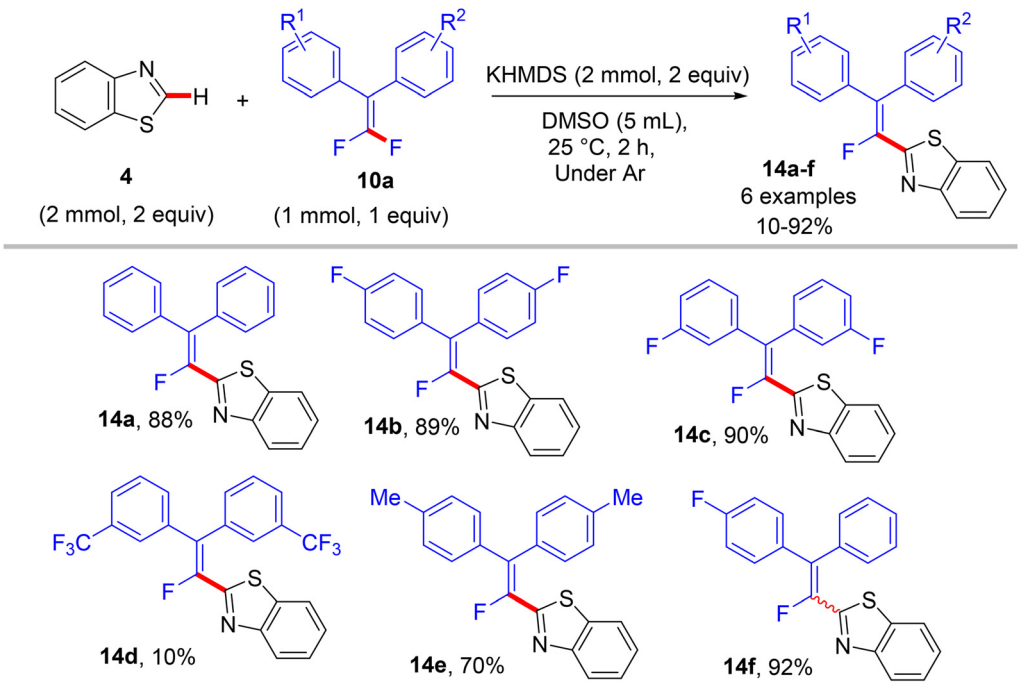
anhydrous 1,4-dioxane under argon at 110 °C for 12 hours. Under these conditions, a variety of 1,3-diazoles **4** were coupled with **2** to afford the corresponding (*Z*)-monofluoroalkenes **5a–o** in moderate to excellent yields (Scheme 5).[28] Importantly, in the absence of Cu, the reaction's outcome was negative and faintly sensitive to the Cu precursor types [Cu(I) or Cu(II)]. This procedure had the same advantages as the prior one as well as being less expensive. Unfortunately, in comparison with the above protocol,[26] the alkylated or tetrasubstituted *gem*-bromofluoroalkenes were unreactive, and the *ortho*-substituted counterparts with an EWG were unstable. A drawback was that the substrate scope in these protocols was limited to azoles, and there was no suggested interpretation for why the activation occurred on the C–H bond that is flanked by two heteroatoms rather than the C–H bond of the phenyl ring (4/5-phenyl azoles) *via* some metallocyclic intermediates. This protocol was employed to synthesize bioactive compounds, as shown in Scheme 6.[28] One of them, **5a13**, is an analogue of a known amide-based antiasthmatic reagent, and the second, **5a14**, is a potential bioactive agent for the treatment of Duchenne muscular dystrophy.[28]

3. Direct α-fluoroalkenylation with *gem*-difluoroalkenes

3.1. Metal-free, base-mediated direct C(N)–H α-fluoroalkenylation at room temperature

gem-Difluoroalkenes are readily accessible and valuable synthetic building blocks that may be functionalized to produce a diverse range of fluorinated products.[17–24] In addition, they are significant alkenyl bidentate electrophiles for organometallic reagents; their oxidative insertion in cross-coupling reactions is rather easy.[23,24] Biologically, they have been employed as irreversible electrophilic inhibitors of numerous enzymes.[51] As examples for comparison, Cao *et al.*'s study (2014) effectively detailed a high stereoselective, metal-free, and straightforward C–N coupling approach giving access to a variety of (*E*)-*N*-(α-fluorovinyl)azoles **9a–i** in good to excellent yields through a direct N–H α-fluoroalkenylation reaction between NH-containing azoles **7** and trisubstituted *gem*-difluoroalkenes **8**.[52]

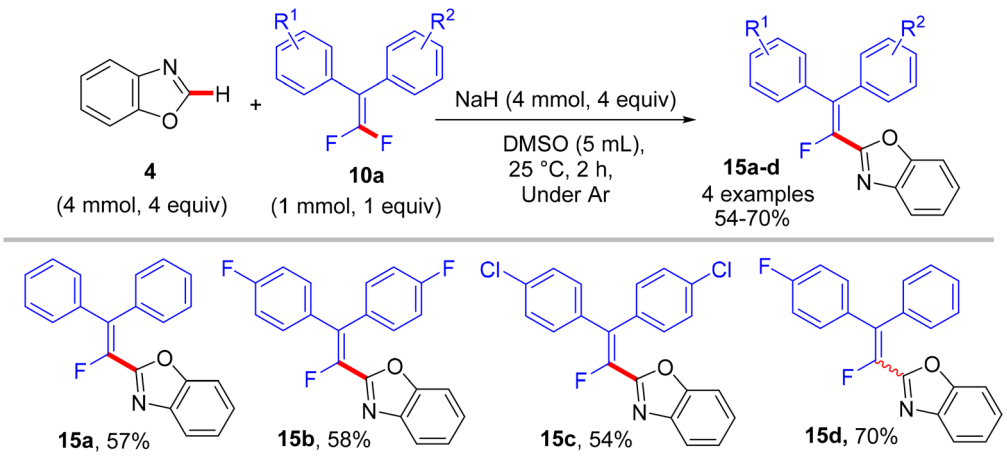
The reaction proceeds *via* a K_3PO_4-mediated vinylic nucleophilic substitution (S_NV) mechanism[53] under rather mild conditions without the formation of alkynylated side-products. Optimal conditions were reported as follows: azole (1 mmol), *gem*-difluoroalkene (1.2 equiv.), K_3PO_4 (2 equiv.), and dried dimethylformamide (DMF, 2 mL), stirring for 12 h at 25 °C (Scheme 7).[52] Under these conditions, the authors succeeded in achieving the same reaction with tetrasubstituted symmetrical *gem*-difluoroalkenes **10a,b** to obtain the corresponding *N*-vinylation products **11a,b** in excellent yields (Scheme 8).[52] In a tunable stereoselective pathway, the produced monofluoroalkenes (*e.g.*, **9a,b**) can be converted to *N*,*N*′-α,α′-dihetaryl-substituted olefins **12a–c** in excellent yields *via* two-fold C–F cleavages by treatment with another equivalent of **7** at 80 °C, establishing the difficult cleavage of the second C–F bond. Worthy of note, 1,1′-(2-(4-methoxyphenyl)ethene-1,1-diyl)bis(1*H*-imidazole) (**12a**) was obtained *via* this one-step method in a nearly quantitative yield (95%) (Scheme 9).[52] In contrast with the aforementioned studies,[26–28] the azoles considered here contain a more acidic proton (N–H group) that a suitable base can abstract. Worthy of note, the optimal base K_3PO_4 did not



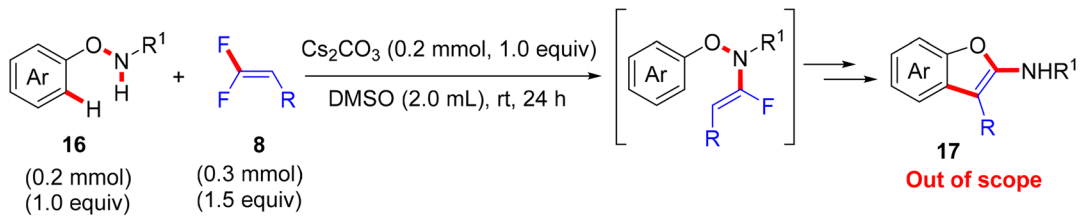
Scheme 11 Metal-free KHMDS-mediated direct C(sp^2)–H α-fluoroalkenylation of benzothiazole (**4**) with **10a**.

affect the *gem*-difluoroalkenes through the formation of the alkynylated products.

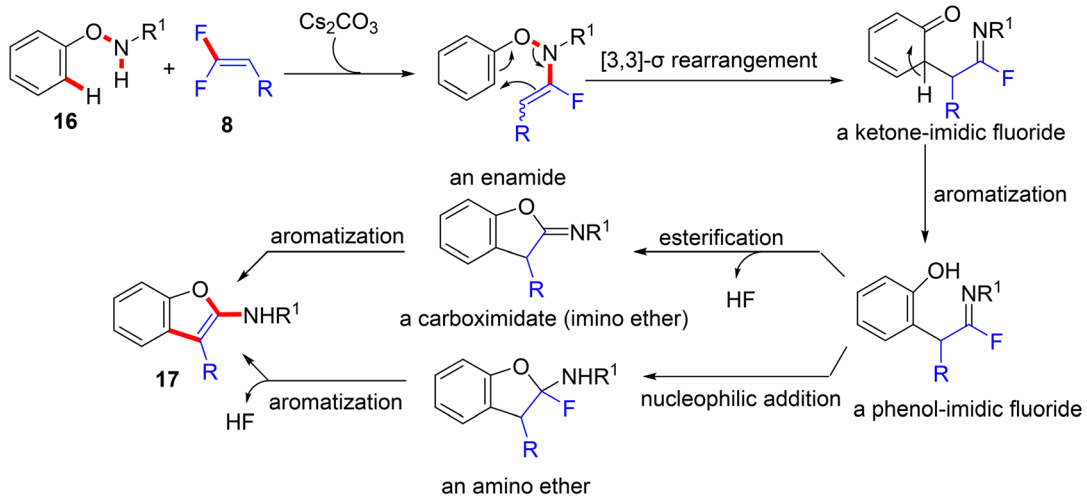
In a similar synthetic vein, Cao's lab (2015) also reported a metal-free, base-mediated direct C(sp^2)–H α-fluoroalkenylation of non-containing NH-azoles (**1** and **4**) with tetrasubstituted symmetrical and unsymmetrical *gem*-difluoroalkenes **10a** to generate the corresponding fluoroalkenylated azoles **13–15**.[54] As in the prior study,[52] the reaction was achieved *via* the S_NV mechanism,[53] which included base-assisted formation of nucleophilic sp^2 carbanion of azoles (transition state) and subsequent addition–elimination steps with electrophilic **10a** to furnish the desired products. After several investigations,



Scheme 12 Metal-free NaH-mediated direct C(sp^2)–H α-fluoroalkenylation of benzoxazole (**4**) with **10a**.



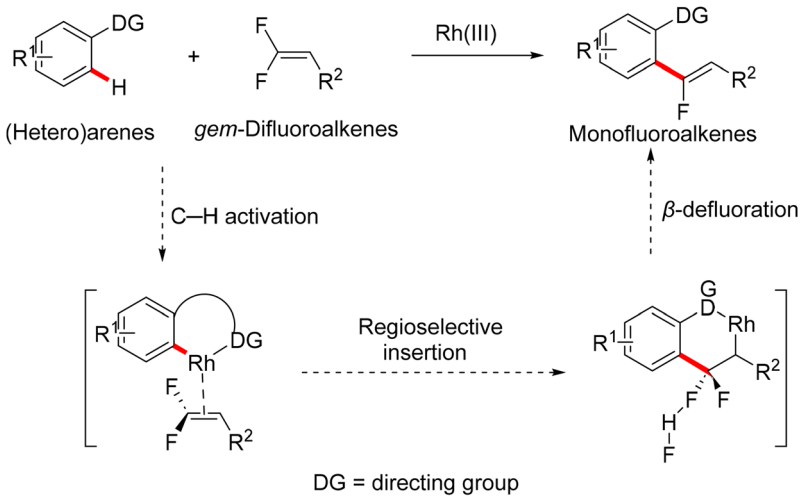
Scheme 13 Metal-free Cs_2CO_3-mediated direct synthesis of 2-aminobenzofurans **17** *via* N–H α-fluoroalkenylation of *N*-phenoxy secondary amides **16** with **8**.



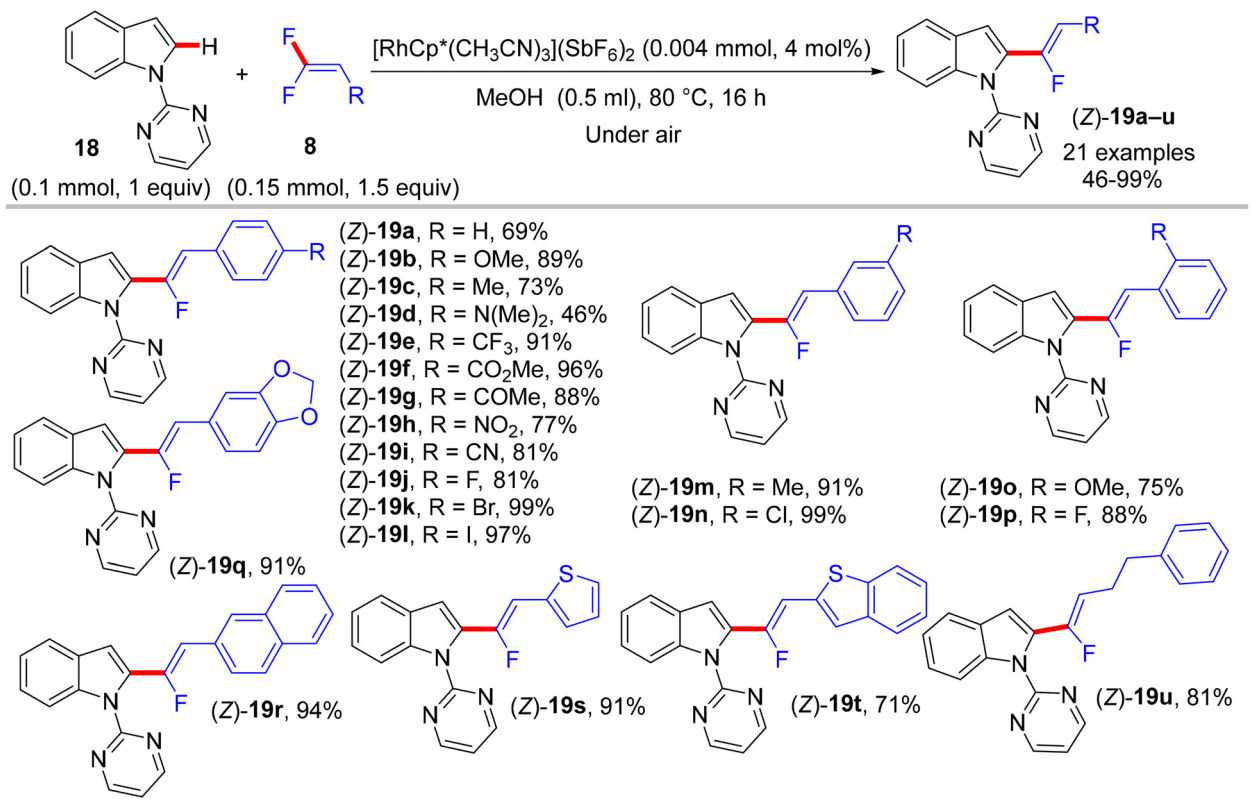
Scheme 14 Proposed mechanism of Cs_2CO_3-mediated direct synthesis of 2-aminobenzofurans **17** *via* N–H α-fluoroalkenylation of *N*-phenoxy secondary amides **16** with **8**.

the optimum conditions were established as follows: dry dimethyl sulfoxide (DMSO) as a solvent and non-nucleophilic bases such as potassium bis(trimethylsilyl)amide (KHMDS) or NaH were the best choices at ambient temperature (Schemes 10–12).[54]

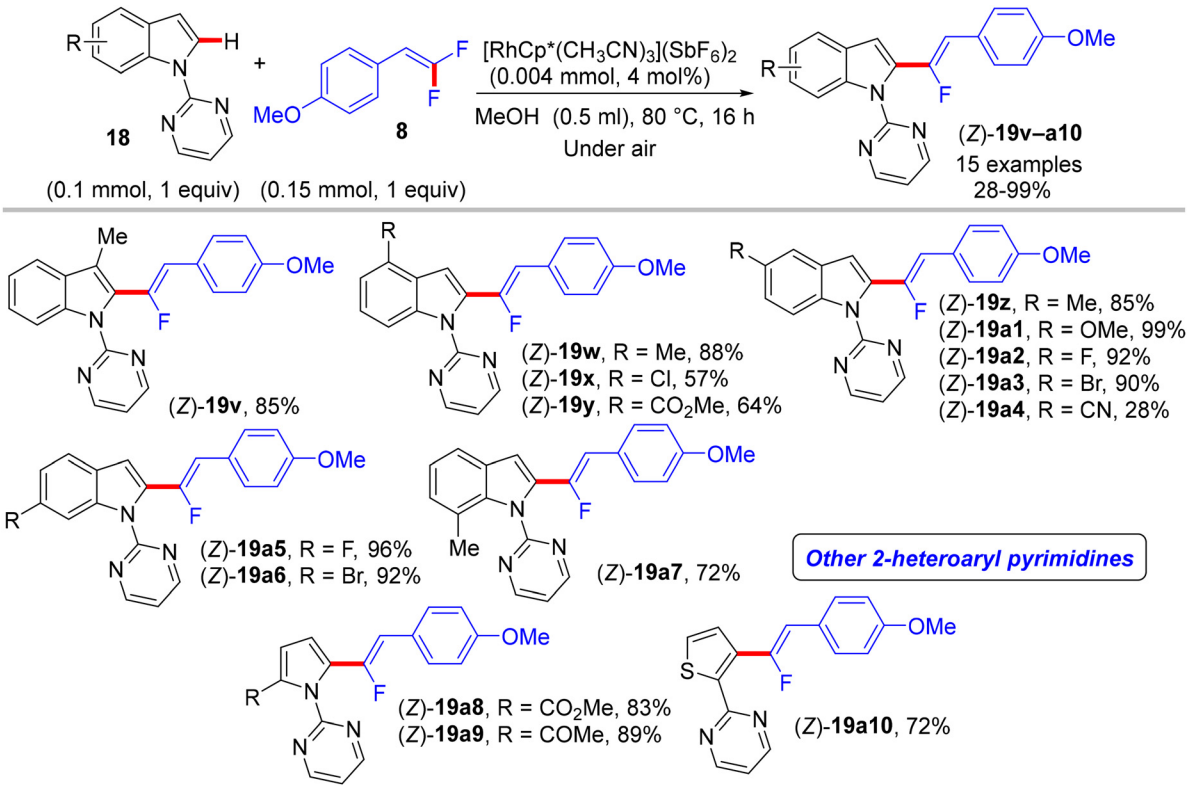
In comparison with the above metal-based studies,[26,28] the substrate scope in this study is limited as a drawback owing to the absence of a metal catalyst that assisted the cleavage of C–H bonds in heteroarenes. For instance, trisubstituted *gem*-difluoroalkenes **8** were unsuitable (though the reason was not mentioned, but they might form alkynylated side products), and tetrasubstituted counterparts **10a** bearing strong EWG such as CF_3 or EDG such as CH_3 were unfavorable, resulting in a low conversion. Regarding azole partners, the presence of



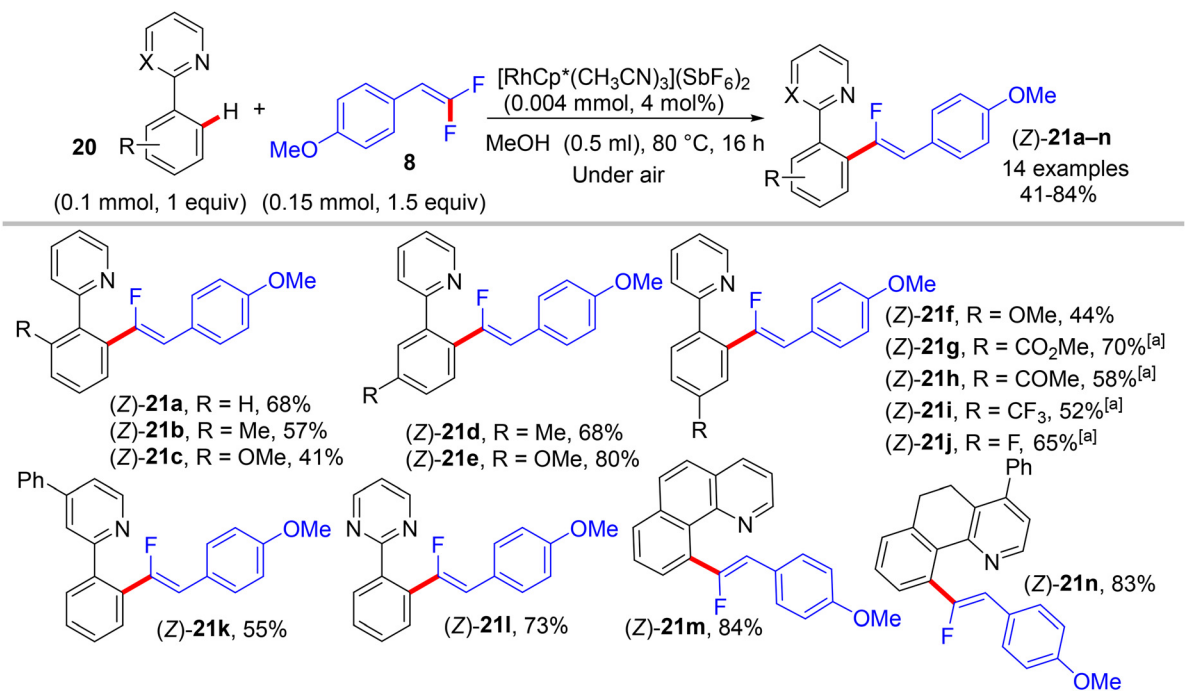
Scheme 15 Chelation-assisted direct C(sp^2)–H α-fluoroalkenylation of (hetero)arenes using Rh(III)-based catalysis.



Scheme 16 Scope of **8** in Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **18**.



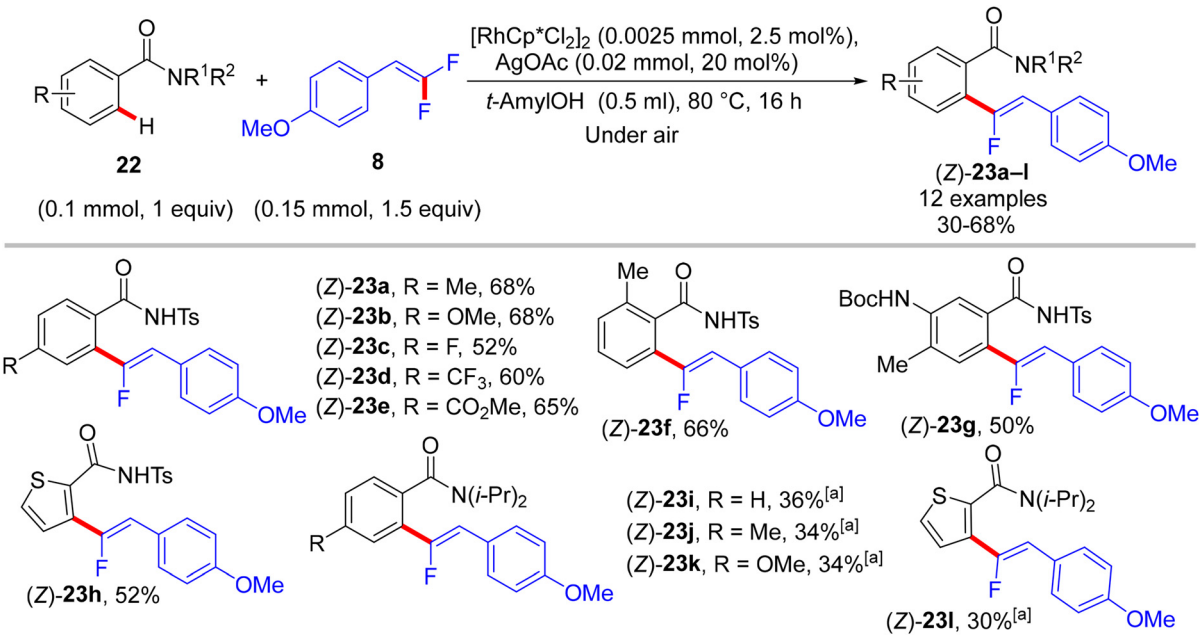
Scheme 17 Scope of **18** in Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation by **8**.



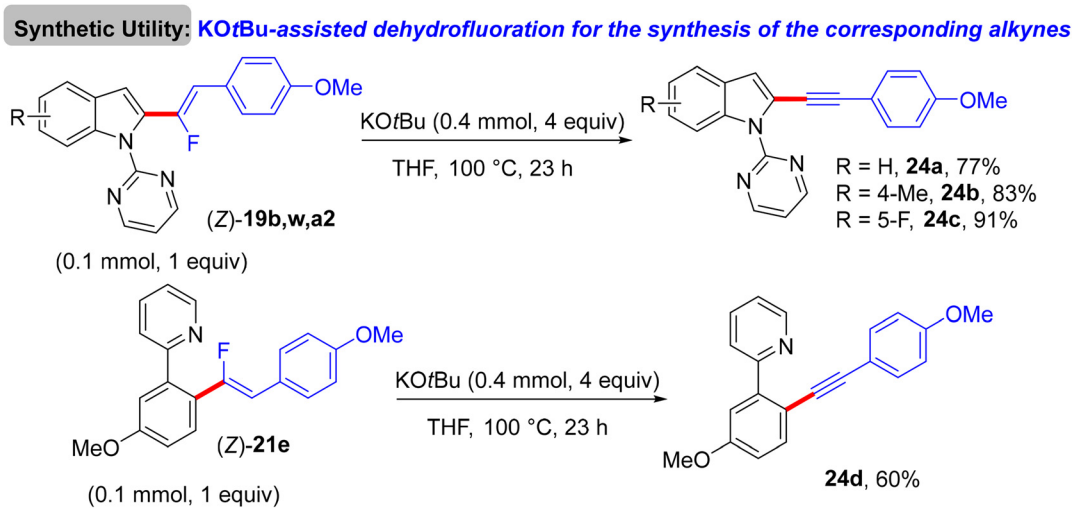
Scheme 18 Scope of 2-arylpyridines **20** in Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation by **8**. [a] Use trifluoroethanol (TFE) as reaction solvent instead of MeOH.

the benzene ring as a substituent such as 2-phenyl-1,3,4-oxadiazole (**1**) or fused as in benzothiazole and benzoxazole (**4**) was essential for driving the reaction smoothly, limiting the azole scope in this reaction.

According to the Yi *et al.* study (2021), when *N*-phenoxy secondary amides **16** are employed instead of azoles under metal-free conditions, Cs_2CO_3-assisted domino N–H fluoroalkenylation-[3,3]-sigmatropic rearrangement ensures, which is used to directly access a variety of 2-aminobenzofurans (**17**, out of scope). The amide-NH fluoroalkenylation was suggested to occur transiently, and the trial with *t*-amide resulted in no reaction, proving the importance of the N–H bond in this annulation. After that, several cleavages of multiple bonds were performed to deliver the final products (Scheme 13).[55] The assumed mechanism is illustrated in Scheme 14. Cs_2CO_3 promoted the nucleophilic substitution reaction of *N*-phenoxy secondary amides **16** with **8** to yield the corresponding enamide intermediate. After that, the [3,3]-σ rearrangement afforded a ketone-imidic fluoride that converted to the phenolic analog through aromatization. The latter may be transformed either to the imino ether (carboximidate) or the amino ether *via* the esterification process or nucleophilic addition.



Scheme 19 Scope of benzamides **22** in Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation by **8**. [a] Use $[RhCp^*(MeCN)_3](SbF_6)_2$ (0.004 mmol) as catalyst, 1,2-dichloroethane (DCE) as reaction solvent.

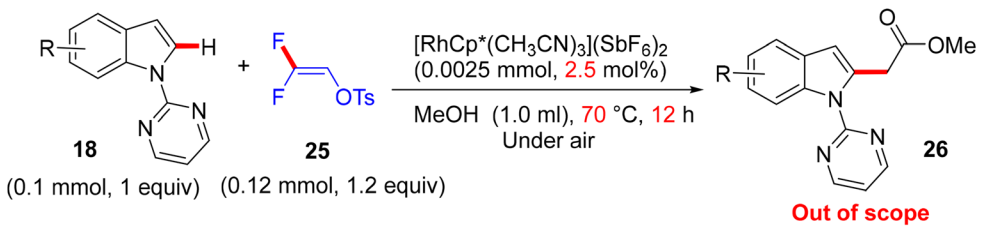


Scheme 20 KO*t*Bu-assisted dehydrofluoration of **19b**, **w**, **a2**, and **21e** for the synthesis of the corresponding alkynes **24a–d**, respectively.

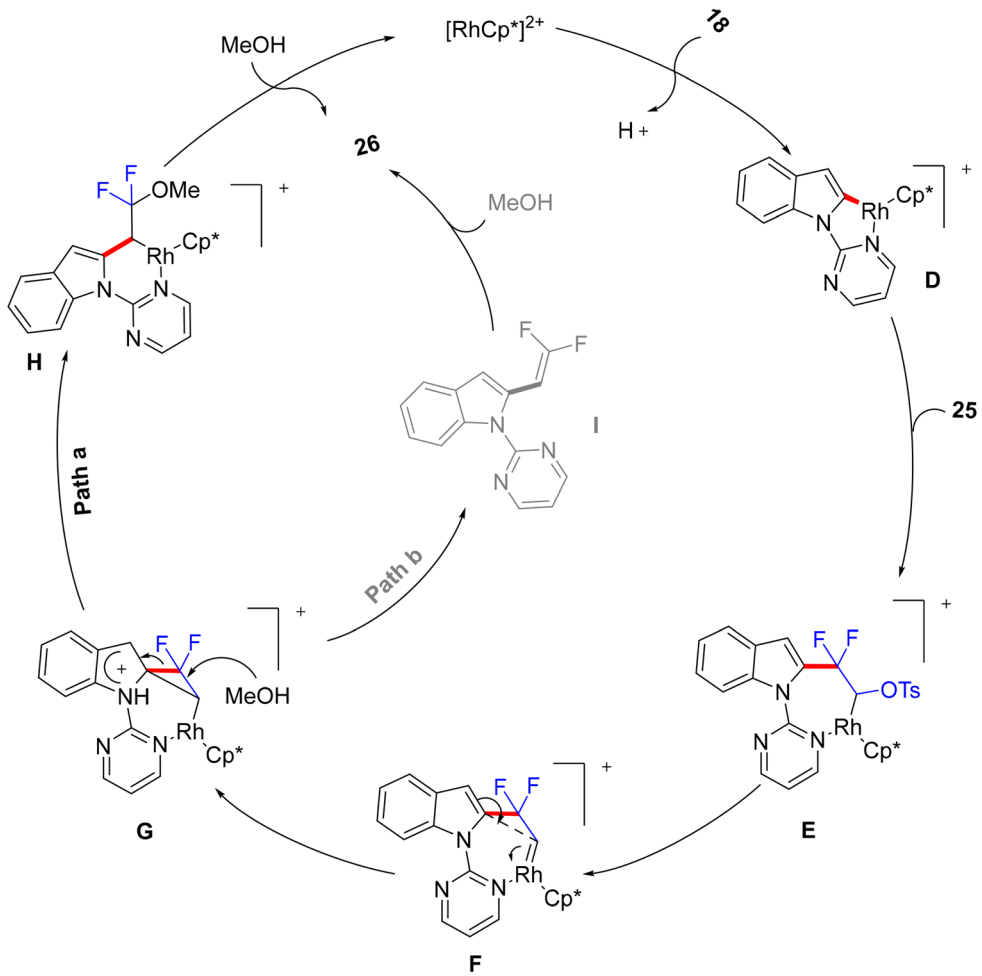
Finally, the aromatization delivered the 2-aminobenzofuran product **17**. It is worth noting that the use of Cs_2CO_3 did not deliver the alkynylated side products.

3.2. C–H α-Fluoroalkenylation using Rh(III)Cp*

In 2015, Loh and his co-workers pioneering study described a base- and oxidant-free (redox neutral), highly efficient, and chelation-assisted direct C(sp^2)–H α-fluoroalkenylation of (hetero)arenes using Rh(III)Cp*-based catalysis for the first time. As a hypothesis postulated by the authors, chelation-assisted C(sp^2)–H activation of (hetero)arenes *via* five-membered rhodacycle formation was followed by C–F activation of *gem*-difluoroalkenes through H-bond interaction with the *in situ* generated HF, and hence β-F elimination delivered the final products (Scheme 15). Starting with highly polarized and easily accessible **8** and readily available (hetero)arenes-containing N-based DG (**18**, **20**, and **22**), the transformation proceeds smoothly with a regio- and stereoselective manner, wide-scope, and broad functionality tolerance, affording the corresponding (*Z*)-(hetero)arylated monofluoroalkenes (**19a–a7**, **21a–n**, and **23a–l**) in fair to quantitative yields (Schemes 16–19).[29]



Scheme 21 Rh(III)-catalyzed direct C(sp^2)–H alkylation of **18** with **25**.

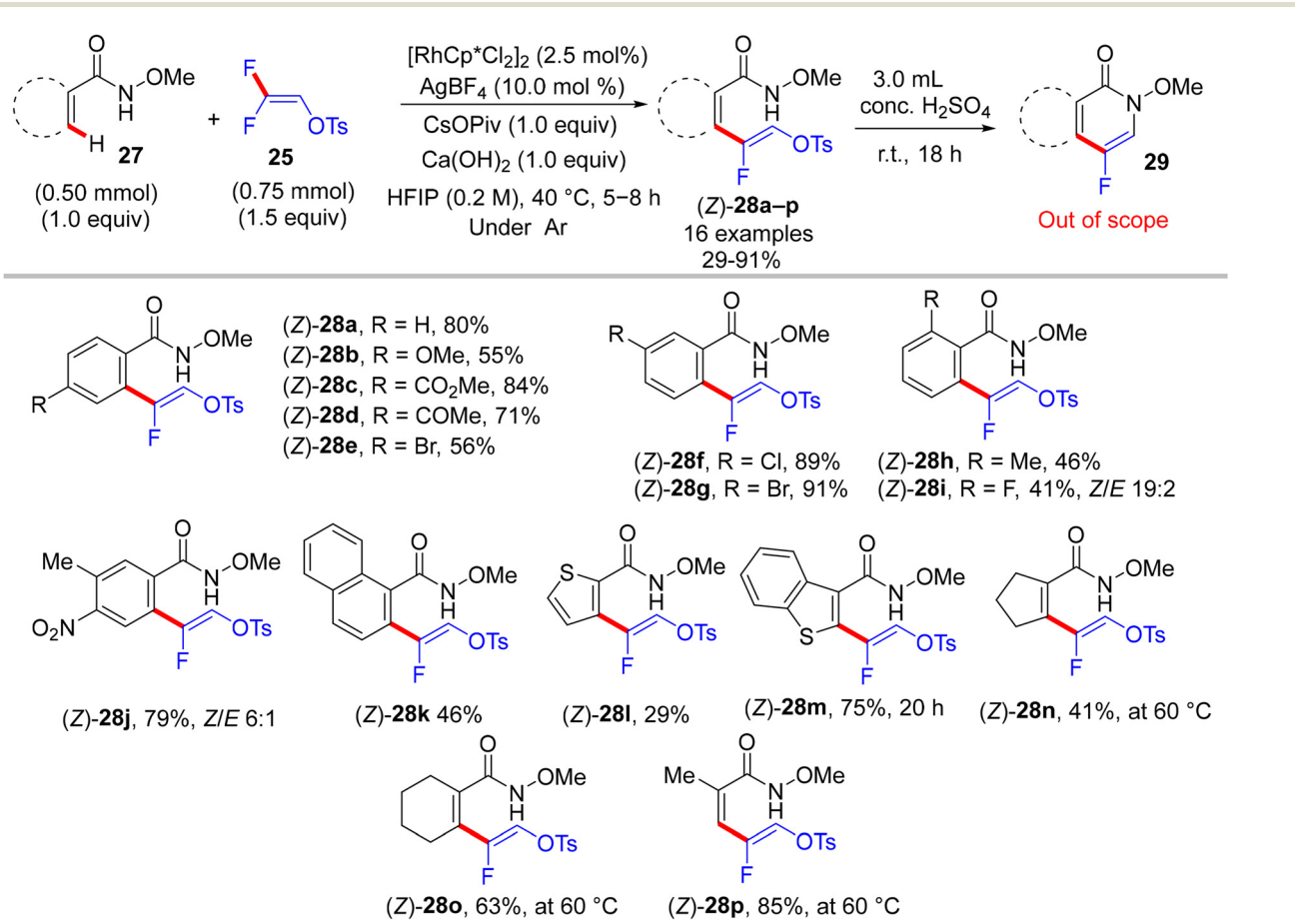


Scheme 22 Proposed catalytic cycle of Rh(III)-catalyzed C(sp^2)–H alkylation of **18**.

The preliminary investigation was commenced with 1-(2,2-difluorovinyl)-4-methoxybenzene (**8**) and 1-(pyrimidin-2-yl)-1*H*-indole (**18**) starting materials, and the best isolated yield (89%) of the expected monofluoroalkene **19a** was achieved under these optimal conditions: cationic $[RhCp^*(CH_3CN)_3](SbF_6)_2$ as the catalyst and methanol (MeOH) as solvent, and at 80 °C for 16 h under air. The substrate scope with EWG or EDG substituents was extended, including 1-pyrimidin-2-yl indoles **18**, 2-arylpyridines **20**, and benzamides **22**, as well as a variety of **8**. Regarding benzamides **22**, Ts-amide derivatives were tested with slight modification [$[RhCp^*Cl_2]_2$ (2.5 mol%), AgOAc (20 mol%) as catalytic system, solvent was *tert*-amyl alcohol (*t*-AmylOH)] and proved to be more effective (**23a–h**, moderate yields) than *N*,*N*-diisopropylbenzamides (**23i–l**, low yields), which was attributed to their low conversion in this transformation (Scheme 19).[29] As a limitation of this simple protocol, chelation-directing groups such as imine, anilide, and ketone proved unsuitable as coupling partners. Preparation of the corresponding alkynes **24a–d** as a synthetic utility for this approach was accomplished *via* the KO*t*Bu-assisted dehydrofluoration process in THF at 100 °C for 23 h (Scheme 20),[29] even though the counterpart base, LiO*t*Bu, did not promote this type of process in the (*E*)-*gem*-bromofluoroalkene **2** Cu(I)-based protocol as mentioned above.[28]

Surprisingly, when Loh and co-workers used trisubstituted *gem*-difluorovinyl tosylate **25** instead of **8** as a coupling partner with **18** under approximately the same conditions, C(sp^2)–H alkylation products **26** (out of scope) were generated rather than monofluoroalkenes (Scheme 21).[56] The other heteroarenes (**20** and **22**) in the prior study were unsuccessful substrates.[29] In this transformation, the tosyl difluorinated enol ether functioned as an valuable substitute for an acetate building block.[17,23]

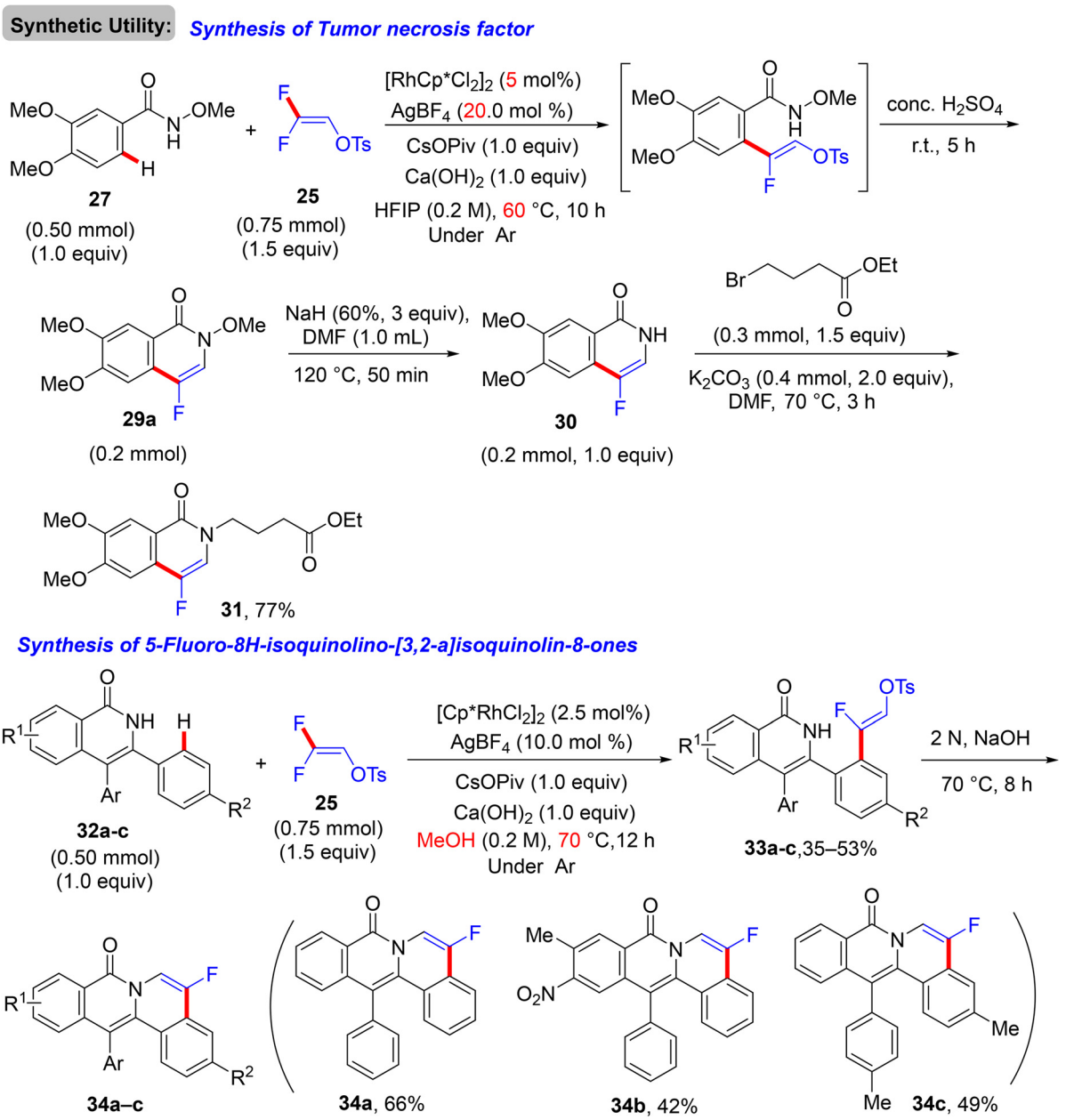
The authors conducted some control experiments to postulate a mechanism (Scheme 22) that was not further theoretically and experimentally consolidated so far. Firstly, pyrimidinyl DG-promoted C(sp^2)–H activation of **18** by Rh(III)Cp* catalyst to produce the five-membered rhodacycle complex **D**. Next, the addition of C(sp^2)–Rh to the double bond of **25** produced the seven-membered rhodacycle intermediate **E**. Subsequently, **E** underwent a tosylate α-elimination to install the Rh(V)-carbenoid intermediate **F**.[57] Then, an intramolecular migration of the indolyl core delivered a strained difluorocyclopropane transition state **G**, which produced a six-membered rhodacycle intermediate **H** by the nucleophilic attack of MeOH. Later, the alcoholysis of **H** produced the final product **26** and regenerated the catalyst (Path a). In another possible pathway (which still cannot be ruled out at



Scheme 23 Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **27** with **25**.

this stage), a nucleophilic attack of MeOH on **G** might generate an indolyl *gem*-difluoroalkene intermediate **I** that might further convert to **26** (Path b).

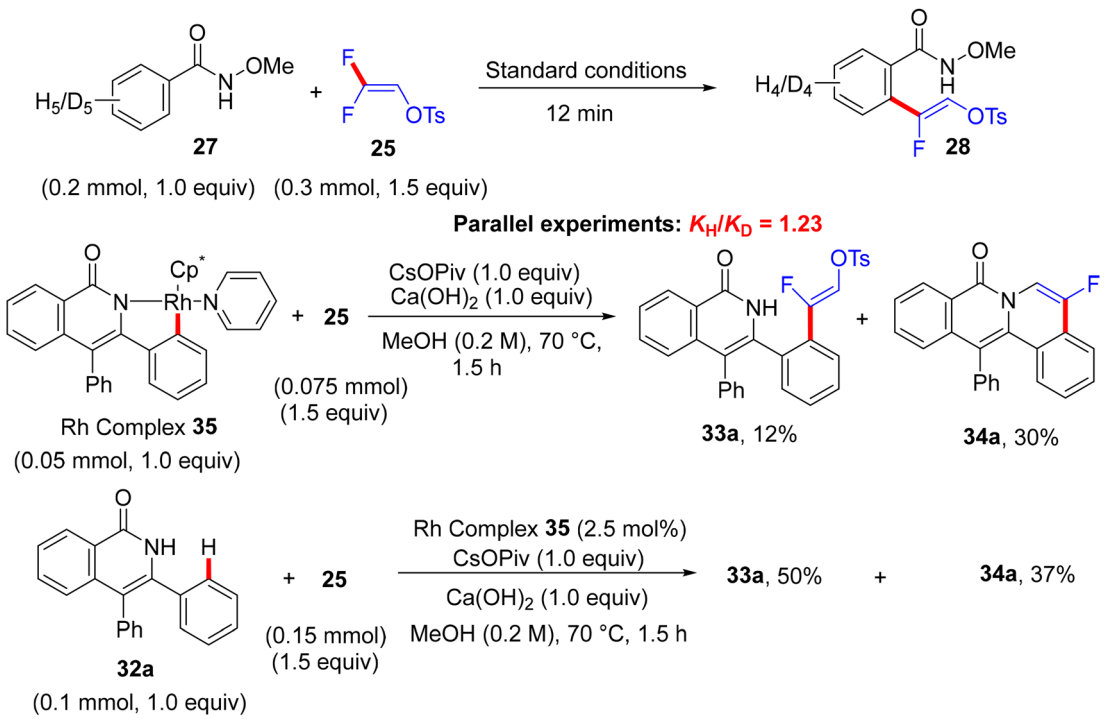
Two years later (2017), Honggen Wang, Xingwei Li *et al.* described pioneering experimental and supporting theoretical investigations for the direct C(sp^2)–H α-fluoroalkenylation of *N*-OMe secondary amides **27** *via* the doubly bridged dimer $[RhCp^*Cl_2]_2$ catalyst, using **25** synthon as a versatile coupling partner. After extensive trials of the reaction parameters under inert atmosphere, optimum conditions to produce the expected (*Z*)-monofluoroalkenes **28** were obtained as follows: $[RhCp^*Cl_2]_2$ (2.5 mol%), $AgBF_4$ (10.0 mol%), CsOPiv (1.0 equiv.), and $Ca(OH)_2$ (0.2 M 1.0 equiv., as HF scavenger) in hexafluoroisopropanol (HFIP) at 40 °C for 4–8 h. After that, these conditions showed wide *N*-OMe amide substrate scope and compatibility of functional groups. As a good leaving group, the tosylate unit proved to be a good handle for an intramolecular cyclization upon treatment with concentrated aqueous H_2SO_4 at ambient temperature to generate the corresponding 4-fluoroisoquinolin-1(2*H*)-ones **29** that were also obtained *via* a one-pot reaction, skipping the isolation of acyclic monofluoroalkenes (Scheme 23).[30] As a synthetic application for this strategy, a tumor necrosis factor **31** was obtained in 77% yield *via* multi-step chemical synthesis, including the *N*-OMe bond cleavage of fluorinated isoquinolinone **29a** by NaH/DMF, followed by the alkylation of the NH



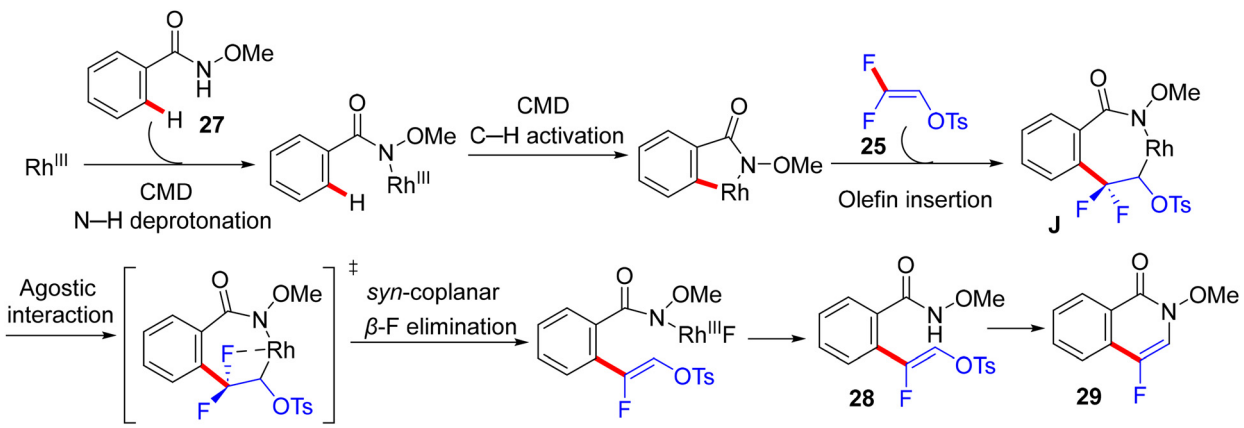
Scheme 24 Synthesis of the tumor necrosis factor **31** and 5-fluoro-8*H*-isoquinolino[3,2-*a*]isoquinolin-8-ones (**34a–c**).

product (**30**, 1.0 equiv.) with 4-bromobutyrate (1.5 equiv.) in the presence of K_2CO_3 (2.0 equiv.). As an analogy, this approach was also extended to include isoquinolone substrates **32a–c**, and the monofluoroalkenes **33a–c** were isolated in 35–53% yields and afforded the corresponding cyclized 5-fluoro-8*H*-isoquinolino[3,2-*a*]isoquinolin-8-ones (**34a–c**) upon treatment with 2N NaOH solution (Scheme 24).[30]

From the mechanistic viewpoint, the authors conducted some experimental work combined with computational studies. KIE studies showed that C–H dissociation is not likely the turnover-limiting step. Attempts to isolate the rhodacycle intermediate from the reaction between the Rh(III) catalyst and *N*-OMe benzamide failed, but were successful with the isoquinolinone derivative *via* Wang's protocol.[58] The stoichiometric transformation of Rh complex **35** with **25** delivered the alkenylation product **33a** in 12% quantitative ^{1}H NMR yield, while the catalytic pathway furnished the same product with 50% quantitative ^{1}H NMR yield (Scheme 25). Regarding the theoretical calculations executed at the density functional theory (DFT) level (B3LYP and M11L),[59] the formation of a seven-membered rhodacycle intermediate **J** was achieved after three steps, including N–H deprotonation, C–H activation, and olefin insertion (Scheme 26). Both N–H deprotonation and C–H activation proceeded through a concerted metalation-



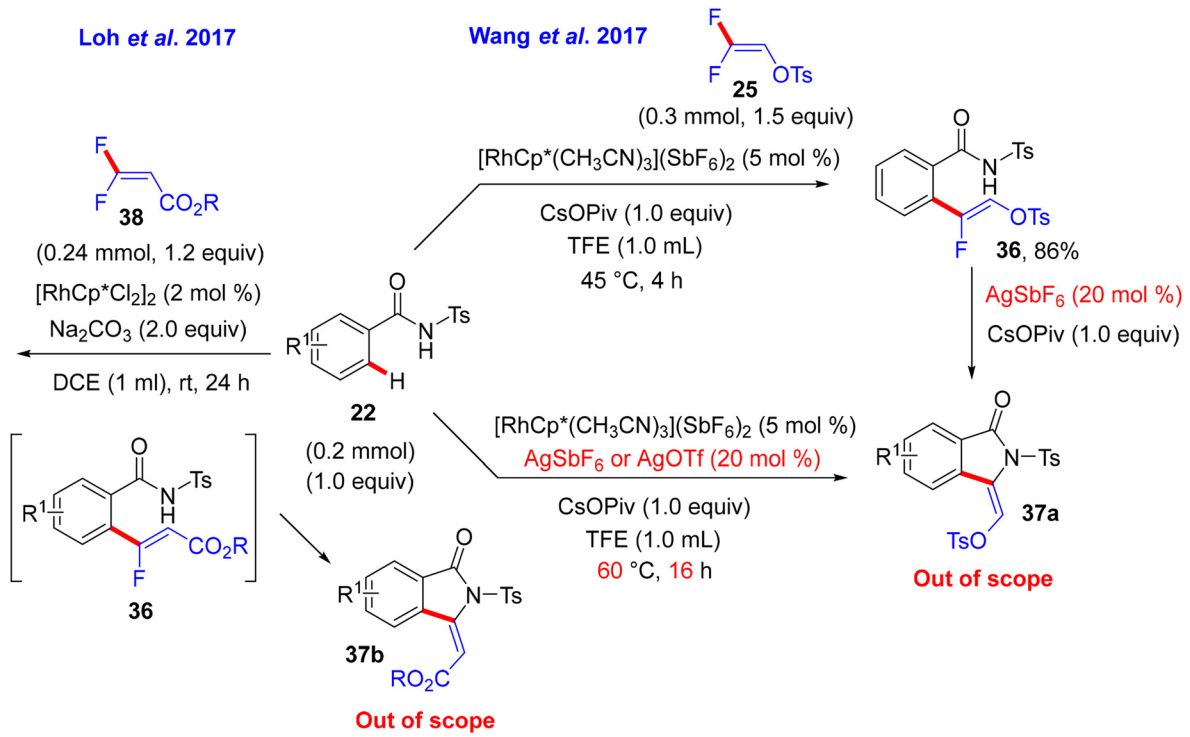
Scheme 25 Control experiments in Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **27** with **25**.



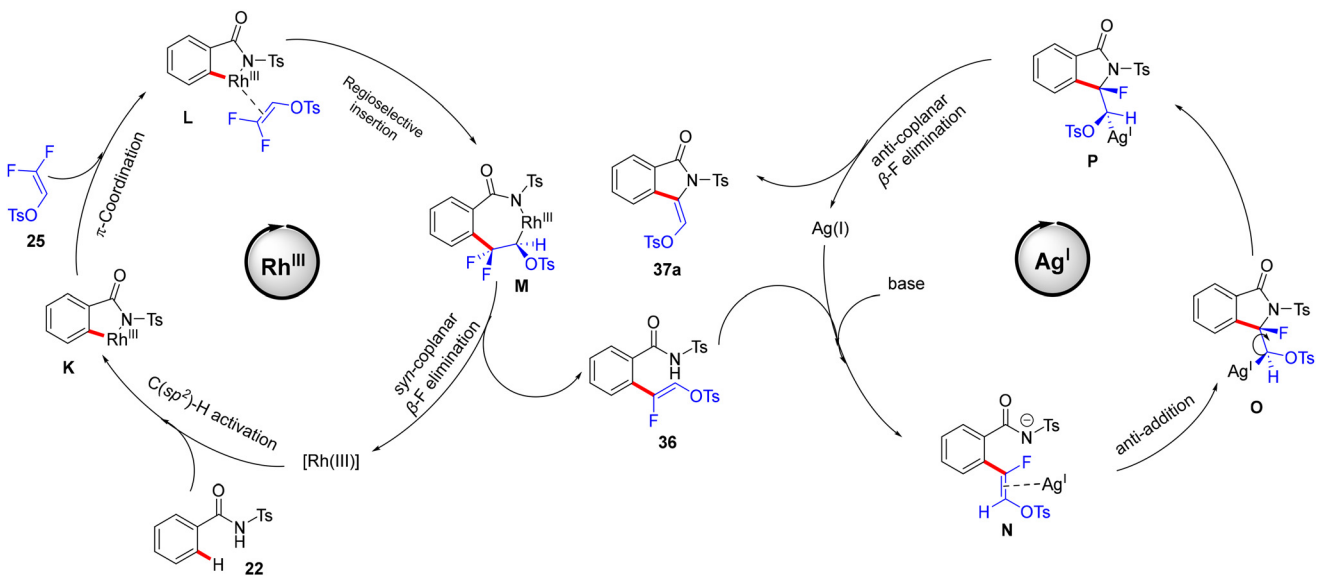
Scheme 26 Summary of mechanistic proposal of Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **27** with **25**.

deprotonation (CMD) pathway.[60] Next, the olefin insertion occurred *via* a transition state that has the highest activation barrier. Natural Bond Orbital (NBO) analysis[61] supported the regioselectivity in the migratory insertion of **25** *via* the β-carbon, which is highly positively charged owing to the strong inductive effect(I) of F atoms.

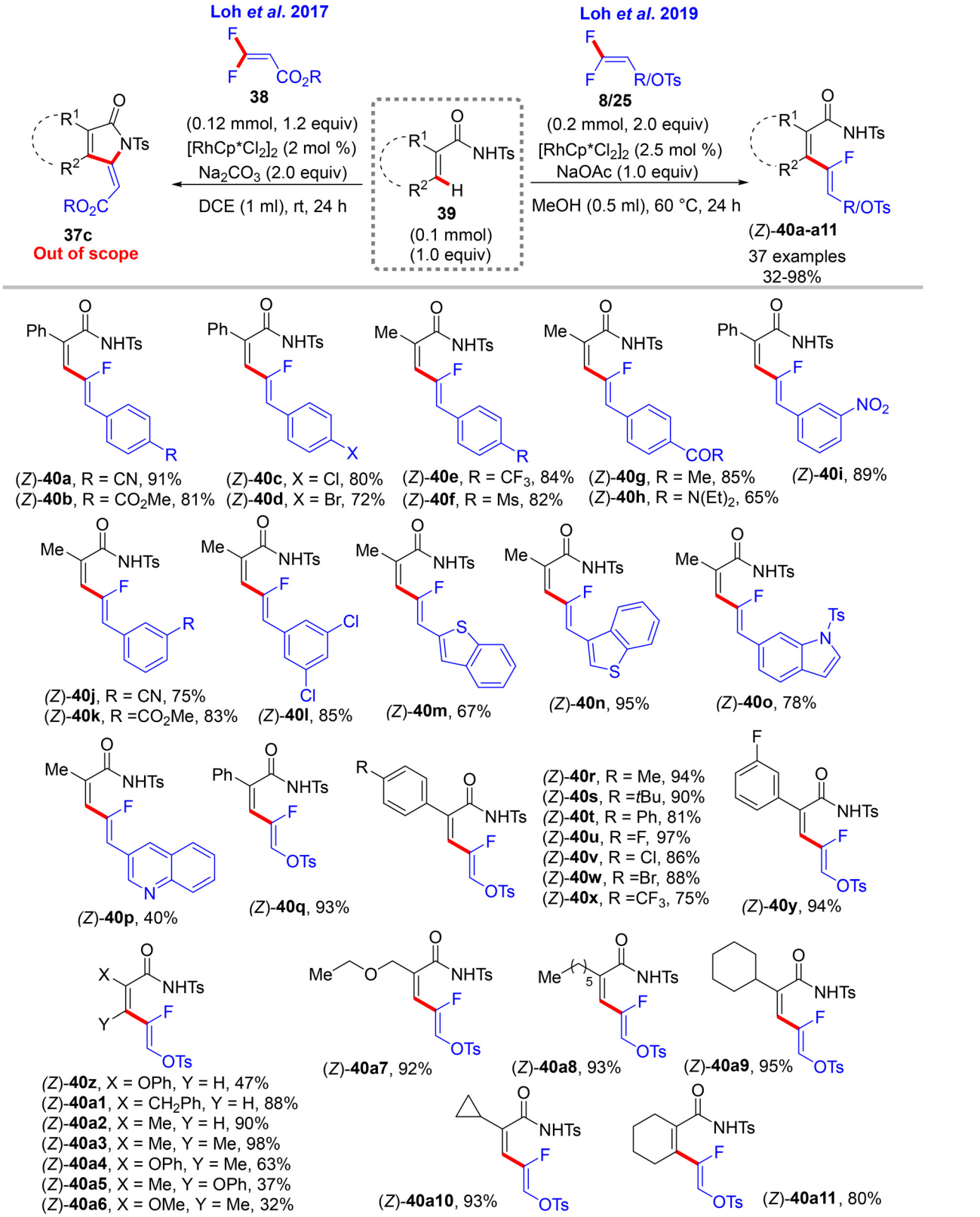
Hence, the computational work points to the establishment of an "agostic" interaction between the C–F bond and Rh center, followed by a *syn*-coplanar β-F elimination *via* a transition state with an activation Gibbs energy of $\Delta G^{\ddagger}$ ~7 kcal mol^{-1} and subsequently the formation of (*Z*)-monofluoroalkenes **28** as observed experimentally. While the *anti*-coplanar H-bonding-assisted β-F elimination that was suggested by the prior study[29] of Loh was accomplished *via* a transition state with an activation barrier of $\Delta G^{\ddagger}$ = 19 kcal mol^{-1}, by 12 kcal mol^{-1}, a higher energy barrier than that of the *cis*-coplanar



Scheme 27 Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **22** with **25** and **38**.



Scheme 28 Proposed mechanism of a bimetallic Rh(III)/Ag(I) relay catalytic system on **22** with **25**.

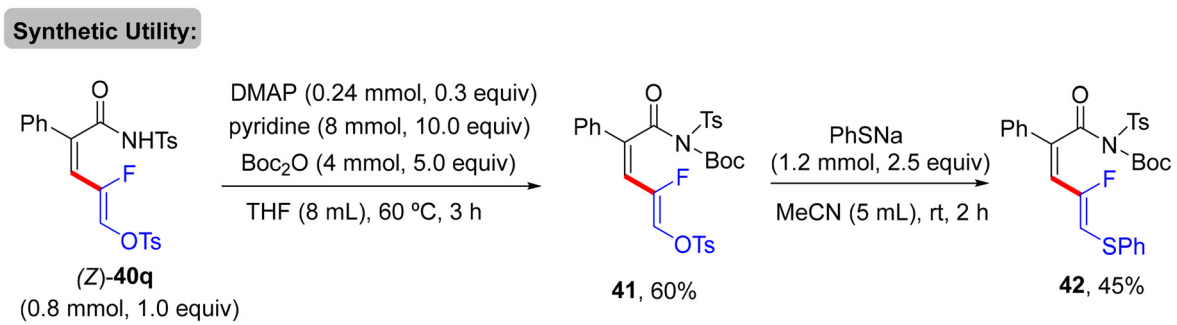


Scheme 29 Scope investigation in Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of acrylamides **39** with **8** to create 2-fluoro-1,3-dienes **40a–a11**.

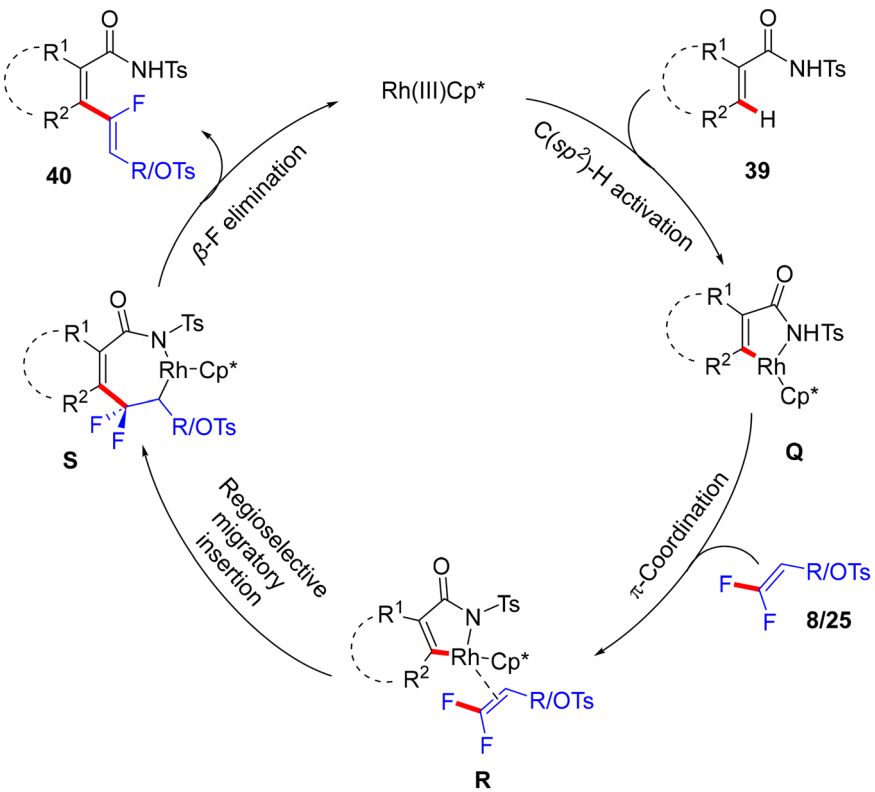
one, thus giving support to the proposal of a dominant *syn*-coplanar route for this type of transformation. Overall, the migratory olefin insertion carries the highest activation barrier ($\Delta G^{\ddagger}$ = 26 kcal mol^{-1}) and is the rate-determining step in agreement with experimental results. The authors summarized the mechanistic proposal as displayed in Scheme 26.

After that, in May 2017, Wang and co-researchers used the same starting materials, but *N*-tosylbenzamide (**22**) instead of the prior one *N*-methoxybenzamide (**27**), to install the corresponding (*Z*)-monofluoroalkene **36** *via* a redox-neutral Rh(III)-based catalysis approach. Their study aimed to obtain the well-known bioactive 3-alkylidene isoindolinone **37a** (out of scope), and this was achieved by applying a bimetallic Rh(III)/Ag(I) relay catalytic system. The Rh(III) catalyst catalyzed direct C(sp^2)–H α-fluoroalkenylation, whereas the Ag(I) salt ($AgSbF_6$ or AgOTf) activated the subsequent cyclization process (Scheme 27).[31] In addition, Loh's group in the same year conducted a similar reaction under very mild conditions: [4 + 1] annulation of **22** and *gem*-difluoroacrylate **38** at room temperature using the $[RhCp^*Cl_2]_2/Na_2CO_3$ catalytic system without Ag salts to obtain **37b**, which contains CO_2R instead of the OTs group. The reaction proceeds *via* a monofluoroalkene intermediate, followed by a cyclization step to afford the annulation product (Scheme 27).[32]

Wang's group proposed a reaction mechanism according to the previous studies[30] and the transformation outcomes. In the Rh cycle, the amide DG-assisted Rh(III) species catalyzes the C(sp^2)–H activation to afford the five-membered rhodacycle



Scheme 30 Synthesis of thioether **42**.

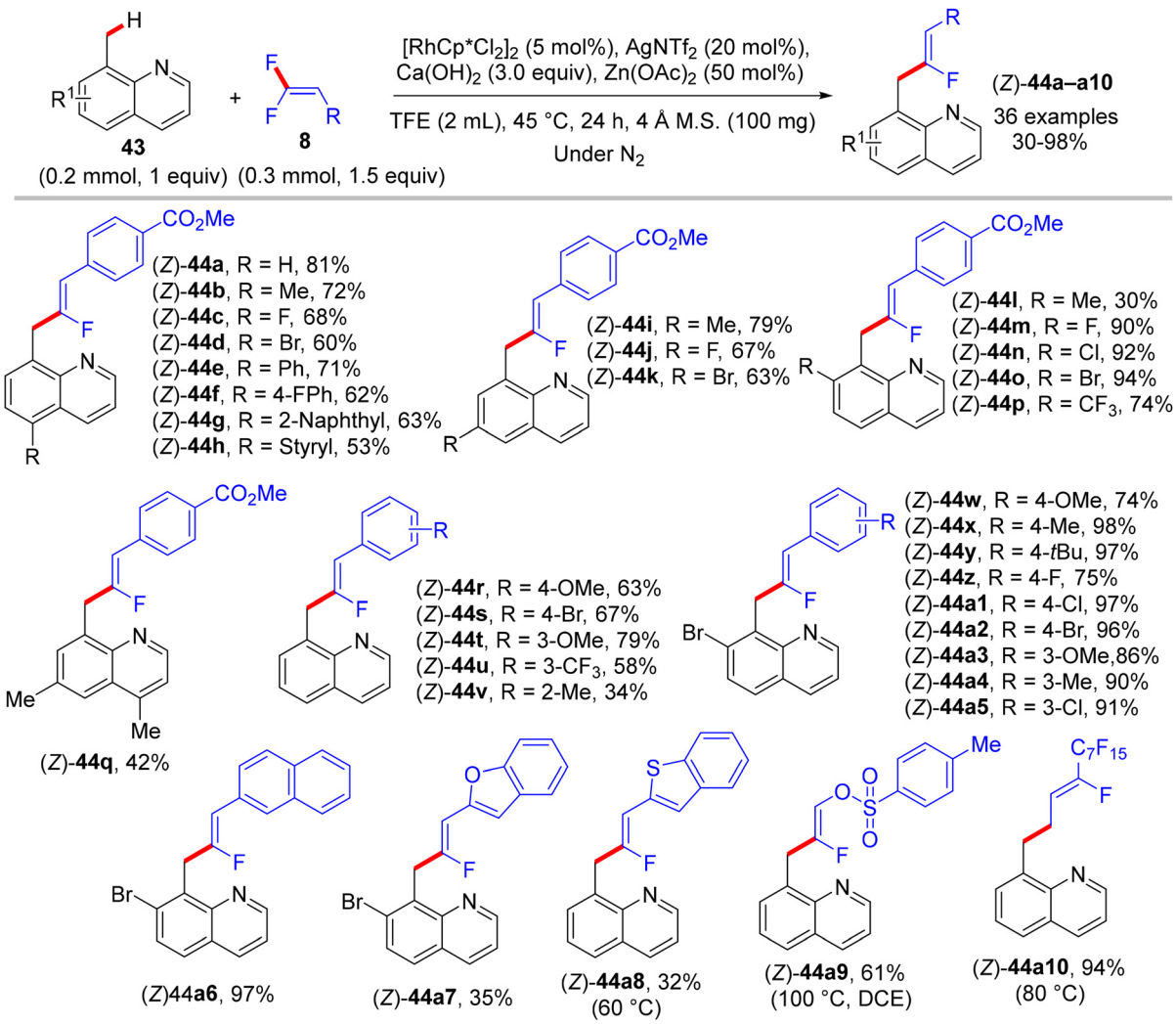


Scheme 31 Proposed catalytic cycle of Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **39** with **8/25**.

complex **K**. The π-coordination of alkene **25** generates **L**, followed by a regioselective migratory alkene insertion to create the seven-membered rhodacycle intermediate **M**. According to the abovementioned study,[30] a *syn*-coplanar β-F elimination provides the expected (*Z*)-monofluoroalkene **36** with good stereoselectivity. Hence, while the N–H group is deprotonated by a base, the Ag(I) salt acts as a π acid, which activates the olefin to produce the **N** intermediate. Next, the *anti*-addition to the activated double bond results in a 5-*exo* cyclization to yield **O** and then **P**. Finally, an anti-coplanar β-F elimination affords the cyclized (*Z*)-stereospecific 3-alkylidene isoindolidone product **37a** (Scheme 28).

Still with Ts-secondary amide substrates, Loh's research group also introduced acrylamides **39** for C(sp^2)–H α-fluoroalkenylation with different *gem*-difluoroalkenes (**8**, **25**, and **38**). Under the aforementioned conditions in Scheme 23,[32] such as Ts-benzamides, **39** with **38** form [4 + 1] cyclization product **37c** *via* Rh(III)-catalyzed alkenyl C(sp^2)–H activation and a two-fold C(sp^2)–F cleavage strategy. With **8** and **25**, slight modifications in the mild conditions lead to the formation of (1*Z*,3*Z*)-2-fluoro-1,3-dienes as (*Z*)-monofluoroalkenes **40a–a11** in poor to excellent yields (32–98%) with complete stereoselectivity (Scheme 29).[33]

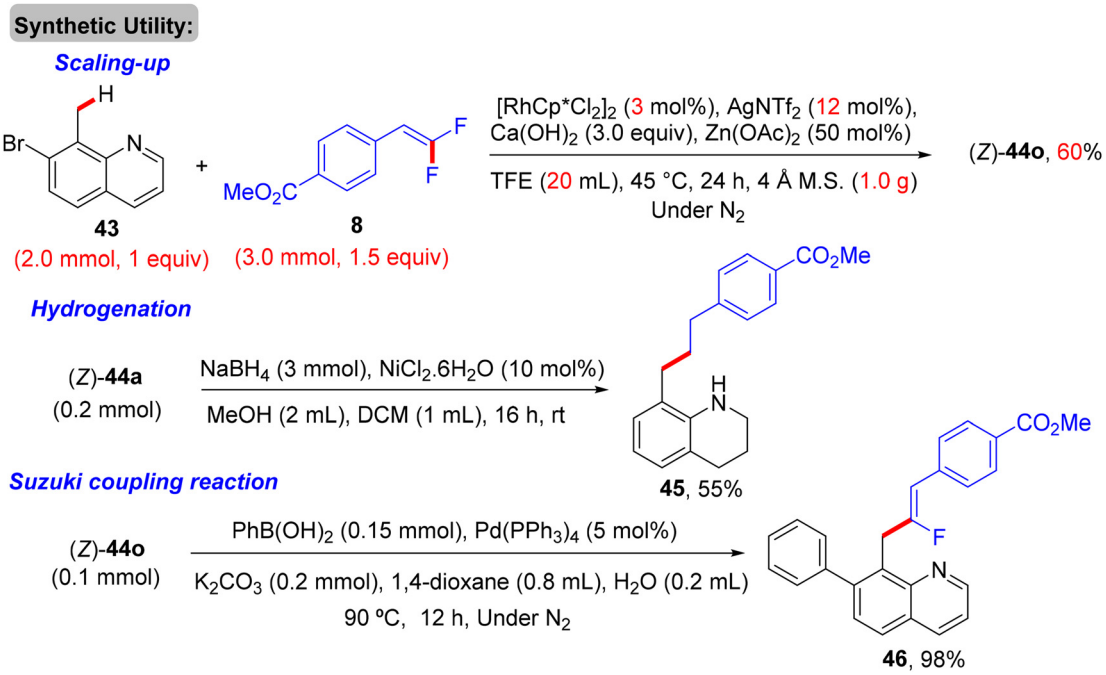
As a synthetic extension of this protocol, the OTs group was replaced by the SPh unit to form the corresponding thioether **42** in 45% isolated yield. Initially, base-promoted NH group protection of **40q** by di-*t*-butyl dicarbonate (Boc_2O) generated **41** in 60% yield. Thereafter, treatment of **41** with sodium benzenethiolate at room temperature furnished **42** (Scheme 30).[33] Mechanistically, the authors experimentally confirmed that *gem*-difluoroalkenes are essential for this transformation, where the analogues containing heavier halides (*gem*-dibromo-, *gem*-dichloro-, and *gem*-bromofluoroalkenes **2**) were unsuitable, though the specific reason was not mentioned. The plausible mechanism matched those proposed in previous reports.[30,31] Namely (Scheme 28), *N*-tosylamide-assisted C(sp^2)–H activation by Rh(III) to form rhodacycle intermediate **Q**, which was followed by π-coordination to afford **R**.



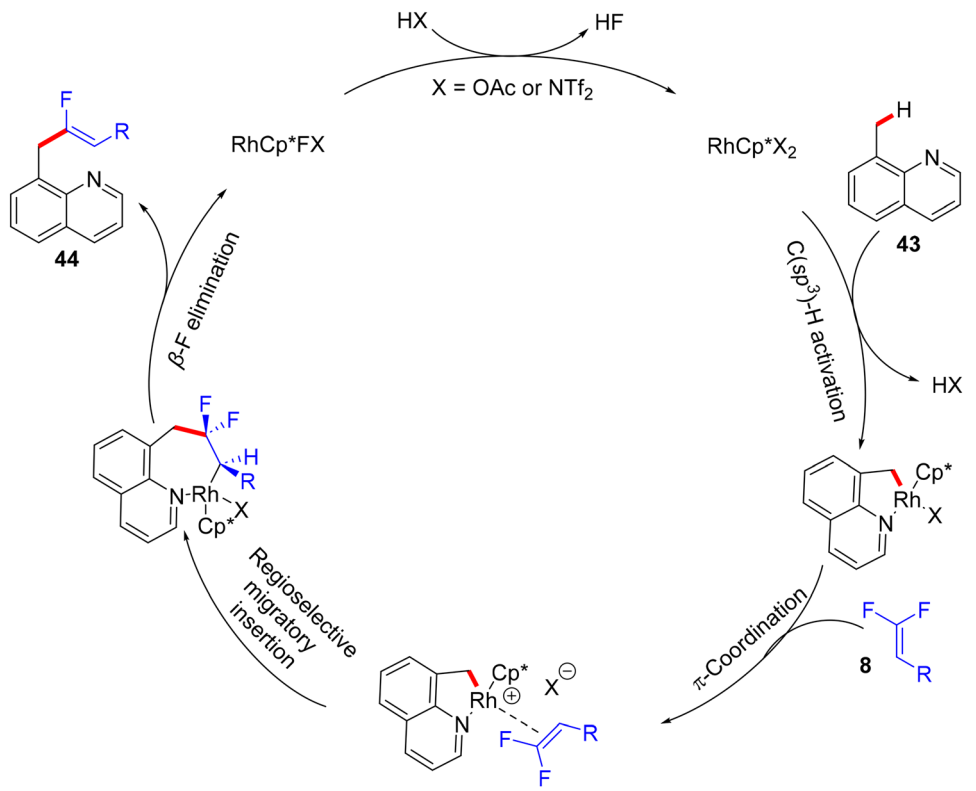
Scheme 32 Scope investigation in Rh(III)-catalyzed direct C(sp^3)–H α-fluoroalkenylation of **43** with **8**.

Subsequent olefin insertion forms the **S** species, which undergoes a *syn*-coplanar β-F elimination to deliver **40** as a (*Z*)-isomer (Scheme 31).

Thereafter, Xingwei Li, Fen Wang, and their co-workers reported the first benzylic α-fluoroalkenylation also by Rh(III) Cp*-based catalysis. This seldom direct C(sp^3)–H activation



Scheme 33 Synthetic applications of Rh(III)-catalyzed direct C(sp^3)–H α-fluoroalkenylation of **43** to access **45** and **46**.



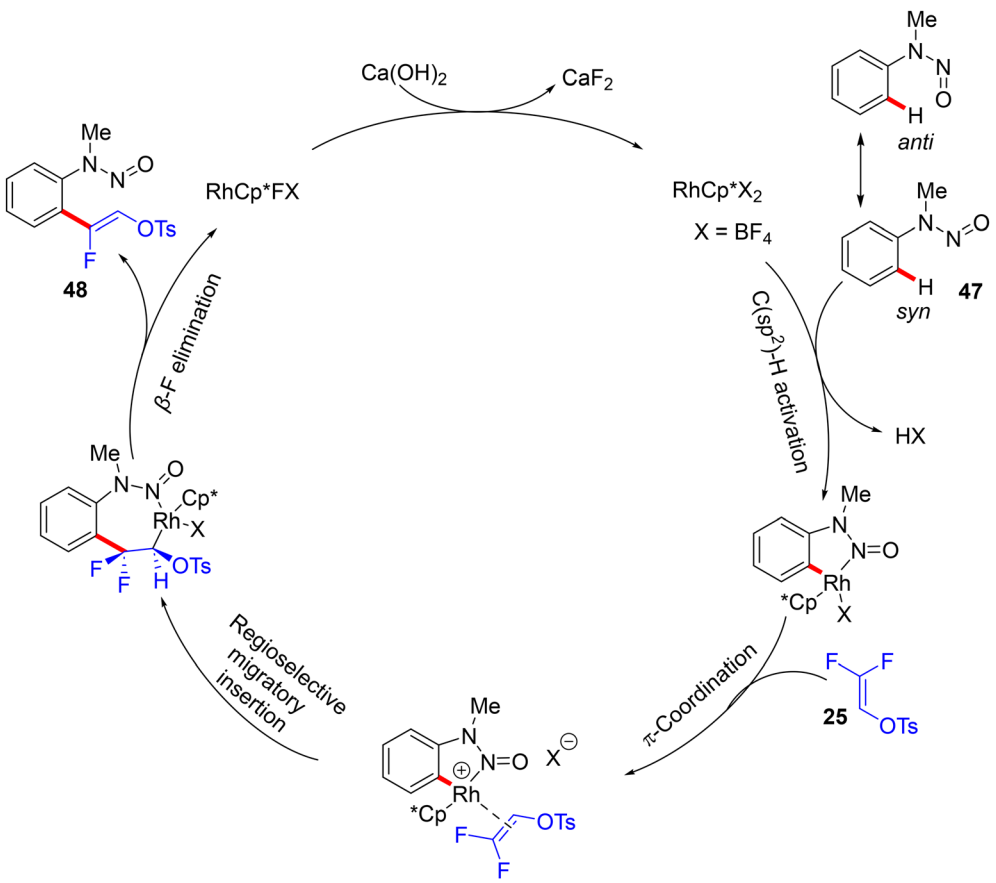
Scheme 34 Proposed catalytic cycle of Rh(III)-catalyzed direct C(sp^3)–H α-fluoroalkenylation of **43**.

was conducted between 8-methylquinolines **43** and **8** *via* regio- and stereoselective route to produce the corresponding (*Z*)-monofluoroalkenes **44a–a10** in poor to excellent yields (30–98%) under mild and redox-neutral circumstances (Scheme 32).[34] To achieve this transformation type, the best effective conditions were $[RhCp^*Cl_2]_2$ (5 mol%), $AgNTf_2$ (20 mol%), $Ca(OH)_2$ (3.0 equiv.), and $Zn(OAc)_2$ (50 mol%) in TFE (2 mL) at 45 °C for 24 h using 100 mg of 4 Å molecular sieves. Regarding the reaction scope, coupling between **43** and **25** or perfluoroalkyl alkene partners was successful and exhibited the desired products in 61% (**44a9**, 100 °C, DCE) and 94% (**44a10**, 80 °C) isolated yields, respectively (Scheme 32). As a scope limitation, 2-methylquinoline and 8-ethylquinoline were found to be unsuitable substrates for this transformation. Furthermore, the authors demonstrated some synthetic applications, such as a scaling up (2.0 mmol) of the **44o** (60%) derivative and catalytic hydrogenation ($NaBH_4/NiCl_2{\cdot}6H_2O$) of **44a** to produce the corresponding 1,2,3,4-tetrahydroquinoline derivative **45** (55%). Moreover, the Pd-catalyzed Suzuki–Miyaura coupling reaction of organohalide **44o** as a late-stage functionalization (LSF) to install the biphenyl product **46** in excellent yield (98%) (Scheme 33).[34] Scheme 34 shows the catalytic cycle that was proposed according to the previous studies.[30,31]

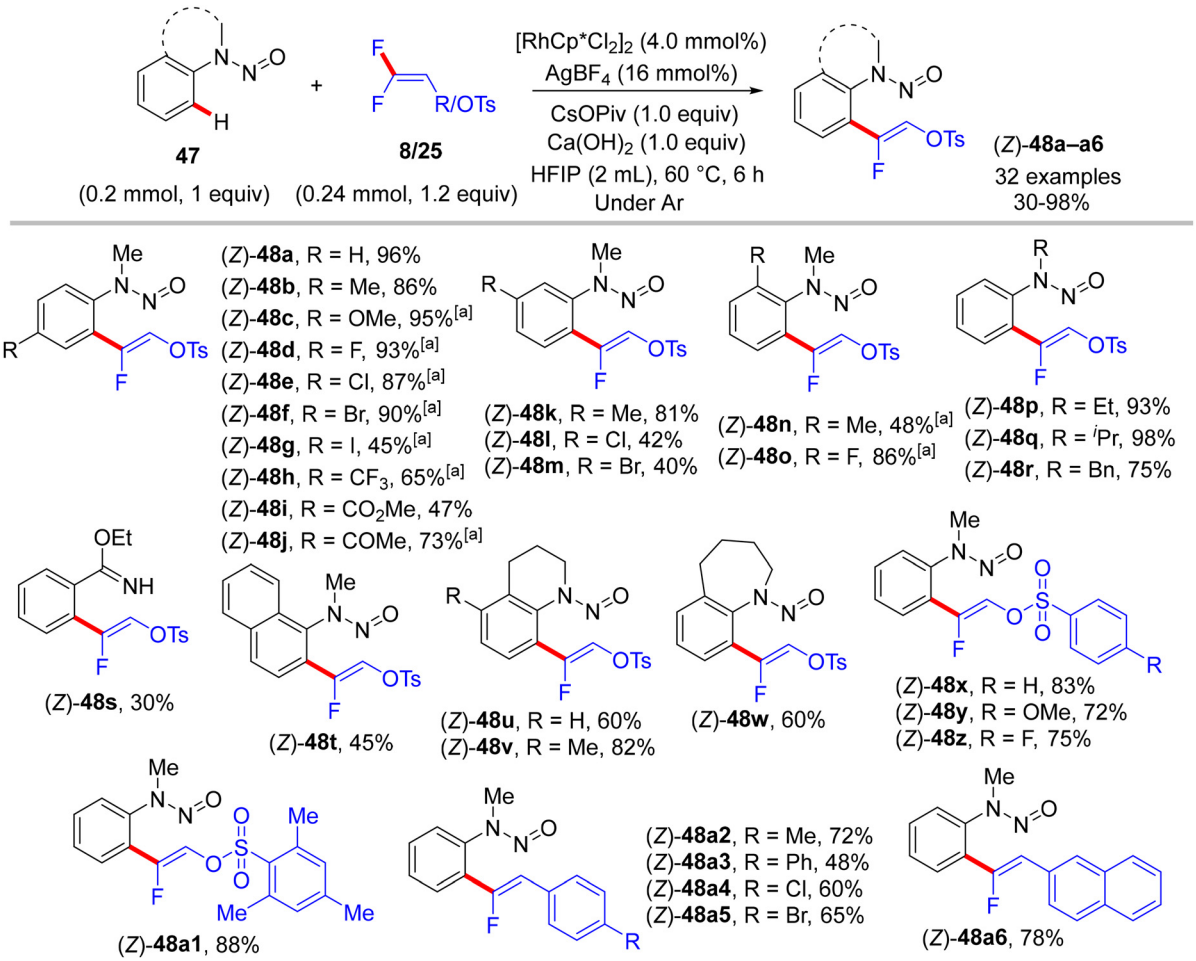
Furthermore, the research work of the Xingwei Li group (2018) described the first catalytic synthesis of (*Z*)-monofluoroalkenes **48a–a6** from the nitrogenous-directed *N*-nitrosoaniline substrates **47** and **8**/**25**. This transformation is accomplished under mild and redox-neutral conditions *via* the aforementioned steps, including chelation-assisted rhodacycle formation, alkene regioselective insertion, and *syn*-coplanar β-F elimination (Scheme 35). Optimal conditions were identified as follows: $[RhCp^*Cl_2]_2$ (4.0 mol%), $AgBF_4$ (16.0 mol%), CsOPiv (1.0 equiv.), $Ca(OH)_2$ (1.0 equiv.), HFIP (2 mL) at 60 °C for 6 h under argon. The scope of both reactants was screened (Scheme 36).[35]

The synthetic usefulness of the final product (**48**) was investigated. As a removal directing group (^{R}DG) type,[62] the *N*-nitroso unit was reductively removed using either pathways, that is, Zn (2 equiv.)/NH_4Cl (2 equiv.) in a mixed solvent of MeOH : H_2O (3 : 1) at 45 °C or $NiCl_2{\cdot}6\ H_2O$ (2 equiv.)/$NaBH_4$ (6 equiv.) at room temperature in THF, producing the corresponding *N*-methylaniline derivative **49** in 68 and 75%, respectively. Next, treatment of **49** with 2N NaOH (6 equiv.) in MeOH at 70 °C provided *N*-methylisatin (**50**) in a 70% isolated yield. Further, the versatile pseudohalide tosylate group (OTs) of **49** could be coupled with phenylboronic acid *via* the Suzuki–Miyaura reaction to produce the cross-coupled product **51** in 78% isolated yield (Scheme 37).[35]

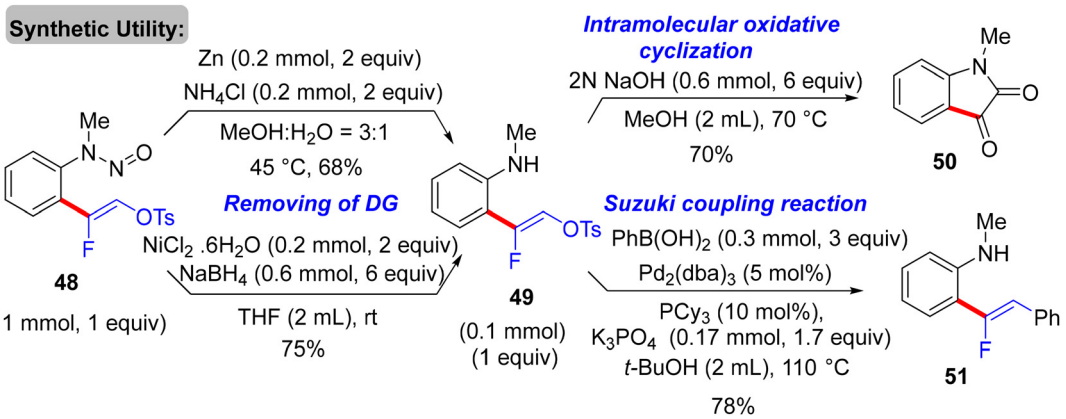
In 2020, five years after Loh's study,[29] Peng's lab used the same cationic Rh catalyst $[RhCp^*(MeCN)_3](SbF_6)_2$ to catalyze



Scheme 35 Proposed catalytic cycle of Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **47**.



Scheme 36 Scope investigation in Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **47** with **8/25**. [a] CsOAc (1.0 equiv.) was used instead of CsOPiv.

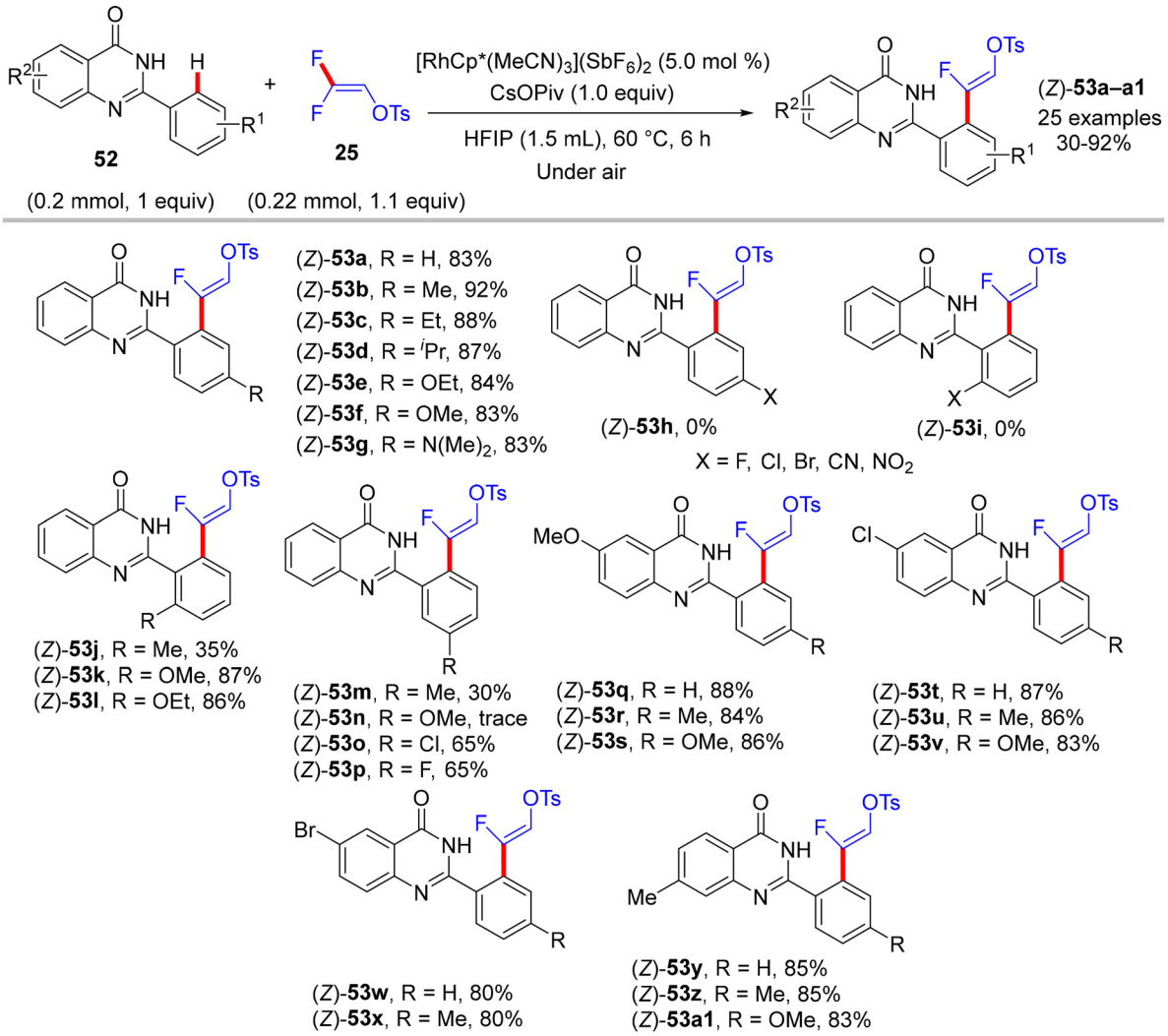


Scheme 37 Synthetic applications of Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **47** to synthesize **49–51**.

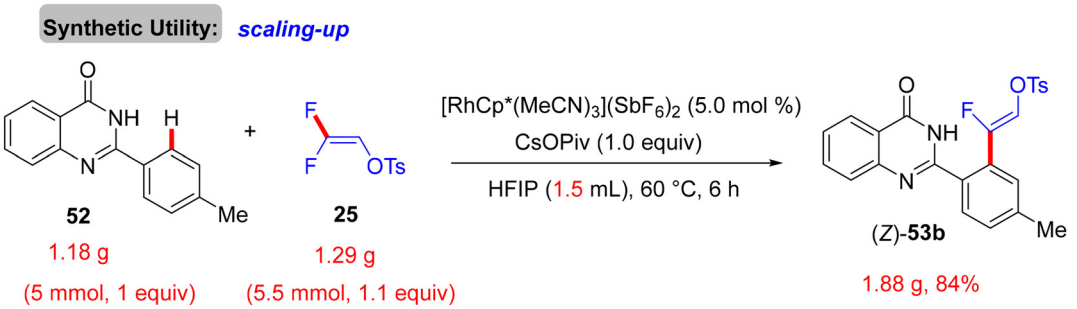
the direct C(sp^2)–H α-fluoroalkenylation of 2-arylquinazolinones **52** using **25** synthon. 2-Arylquinazolinone contains an amide-imine unit that served as a permanent DG (^{P}DG) to assist C(sp^2)–H activation *via* rhodacycle key intermediate formation. Following Honggen Wang's study findings,[30] which confirmed the *syn*-coplanar β-F elimination pathway other than *anti*-coplanar H-bonding-assisted β-F elimination (Loh's study[29]) and the impact of the oxygenated bases, Peng and co-workers used CsOPiv, and optimal conditions were obtained after the initial investigation as follows:

$[RhCp^*(MeCN)_3](SbF_6)_2$ (5.0 mol%), CsOPiv (1.0 equiv.), HFIP (1.5 mL), at 60 °C for 6 h under atmospheric oxygen.[36]

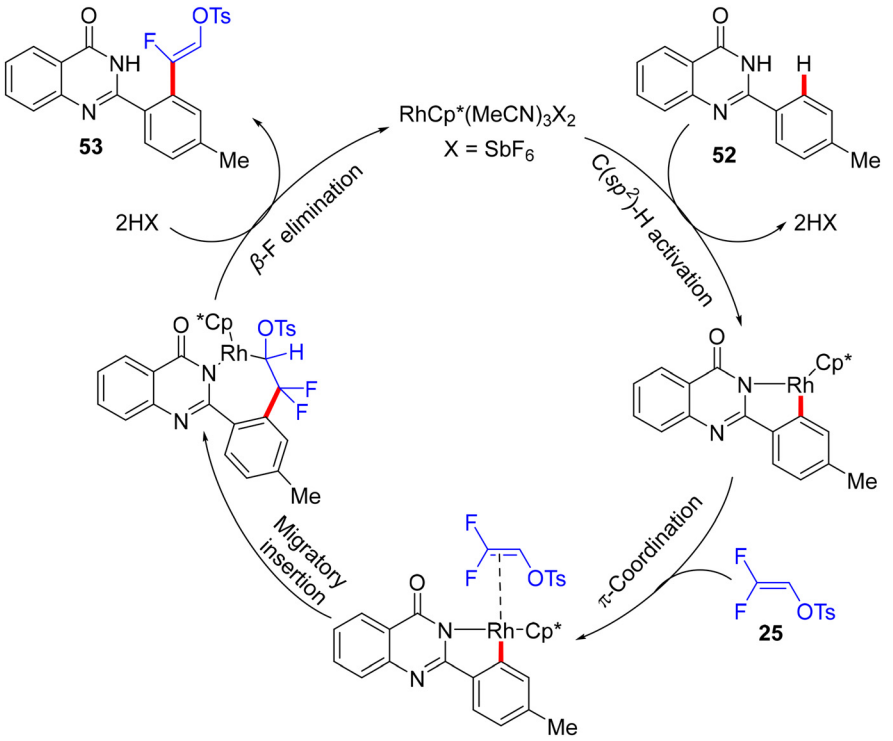
Scheme 38 displays the synthesis of (*Z*)-**53a–a1**, the generality, and substrate scope of this protocol. When the R^1 group at the *para* or *ortho* positions of the 2-aryl group is EDG, the (*Z*)-monofluoroalkenes are generated in good to excellent yields (83–92%). When the R^1 group is an EWG at the same positions, no reaction occurs, but the *reverse* is correct with the *meta* position (**53m–p**). Surprisingly, whatever the electronic feature of the R^2 group of the quinazolinone ring, that is either EDG or EWG, the desired monofluoroalkenes (**53q–a1**) are iso-



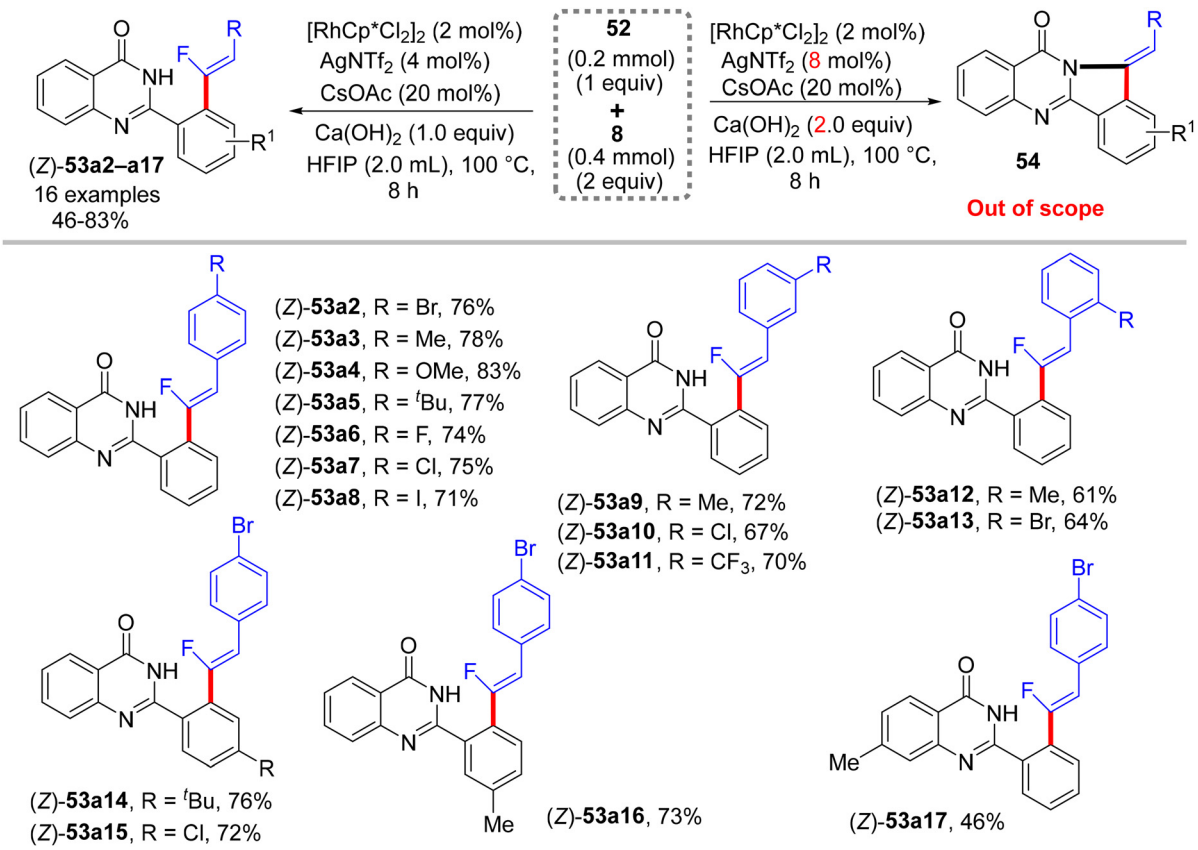
Scheme 38 Scope investigation in Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **52** with **25**.



Scheme 39 Gram-scale synthesis of (*Z*)-**53b**.



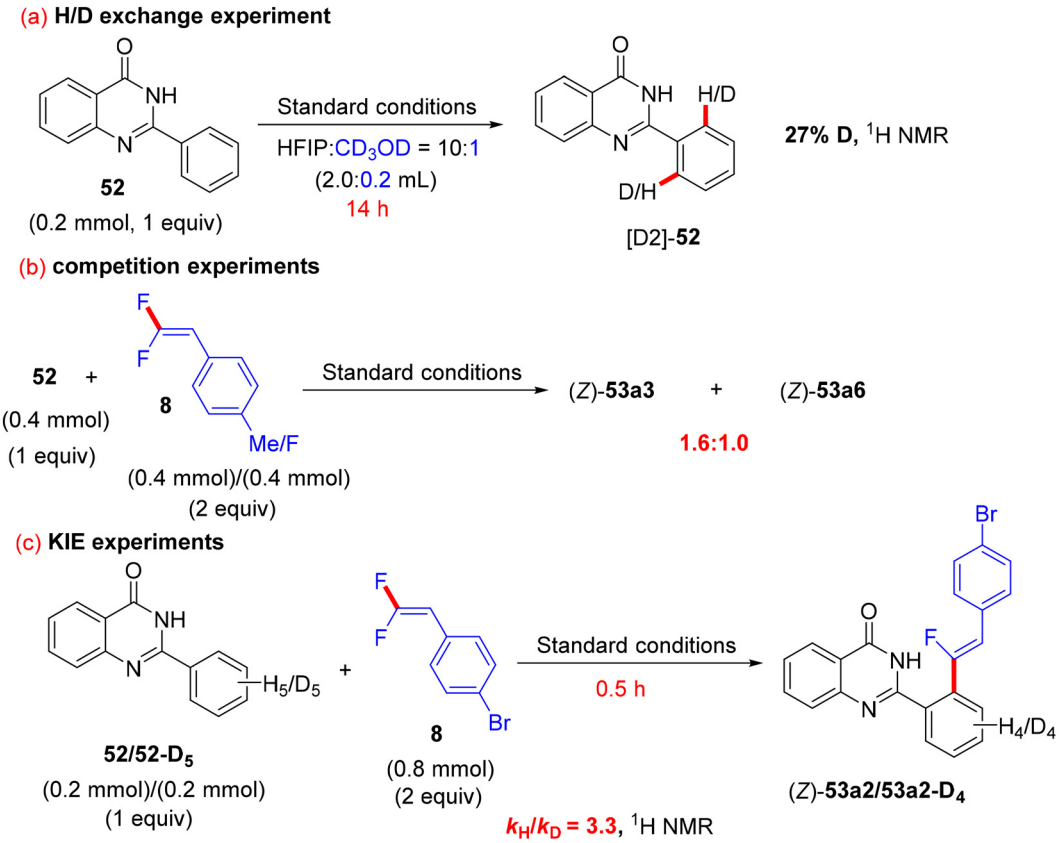
Scheme 40 Proposed catalytic cycle of Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **52**.



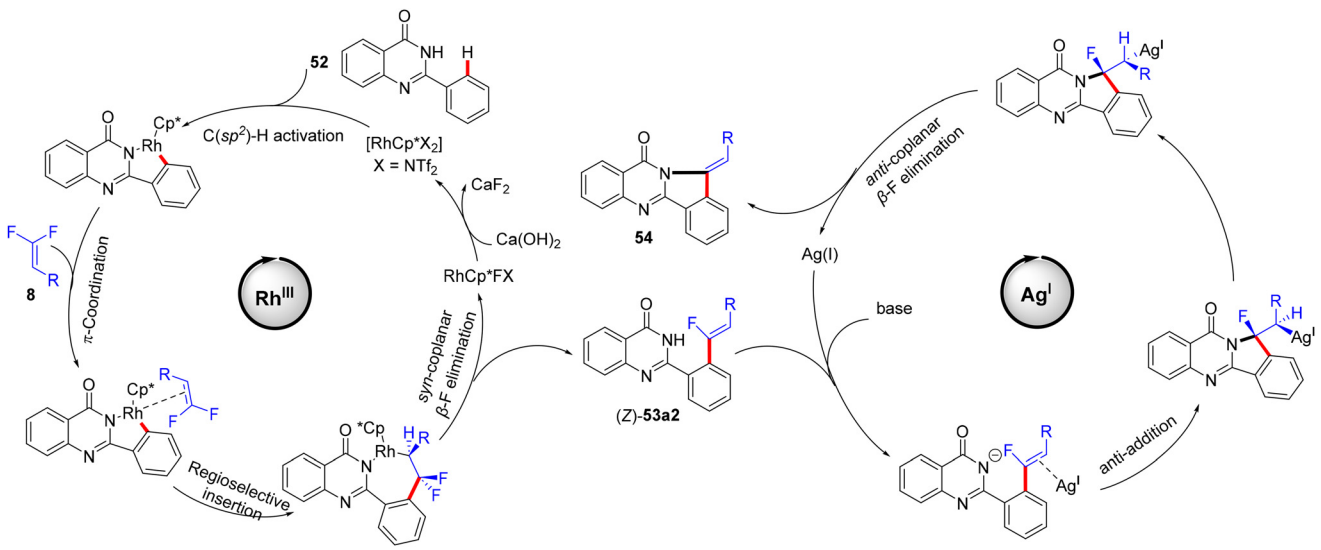
Scheme 41 Scope investigation in Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **52** with **8**.

lated in high yields (80–88%). Of note, no cyclization products are obtained owing to the absence of either Ag salts (removal of AgF)[31] or acidic (H^+)/basic (OH^-) conditions (removal of TsOH),[30] as indicated above. Moreover, the authors succeeded in achieving the gram-scale synthesis of (*Z*)-**53b** (Scheme 39). As shown in Scheme 40, according to the findings of the previous studies,[30–35] the catalytic cycle of this transformation was established.

Recently (2023), Ji and co-workers employed the same prior substrate **52** for the direct C(sp^2)–H α-fluoroalkenylation with **8**



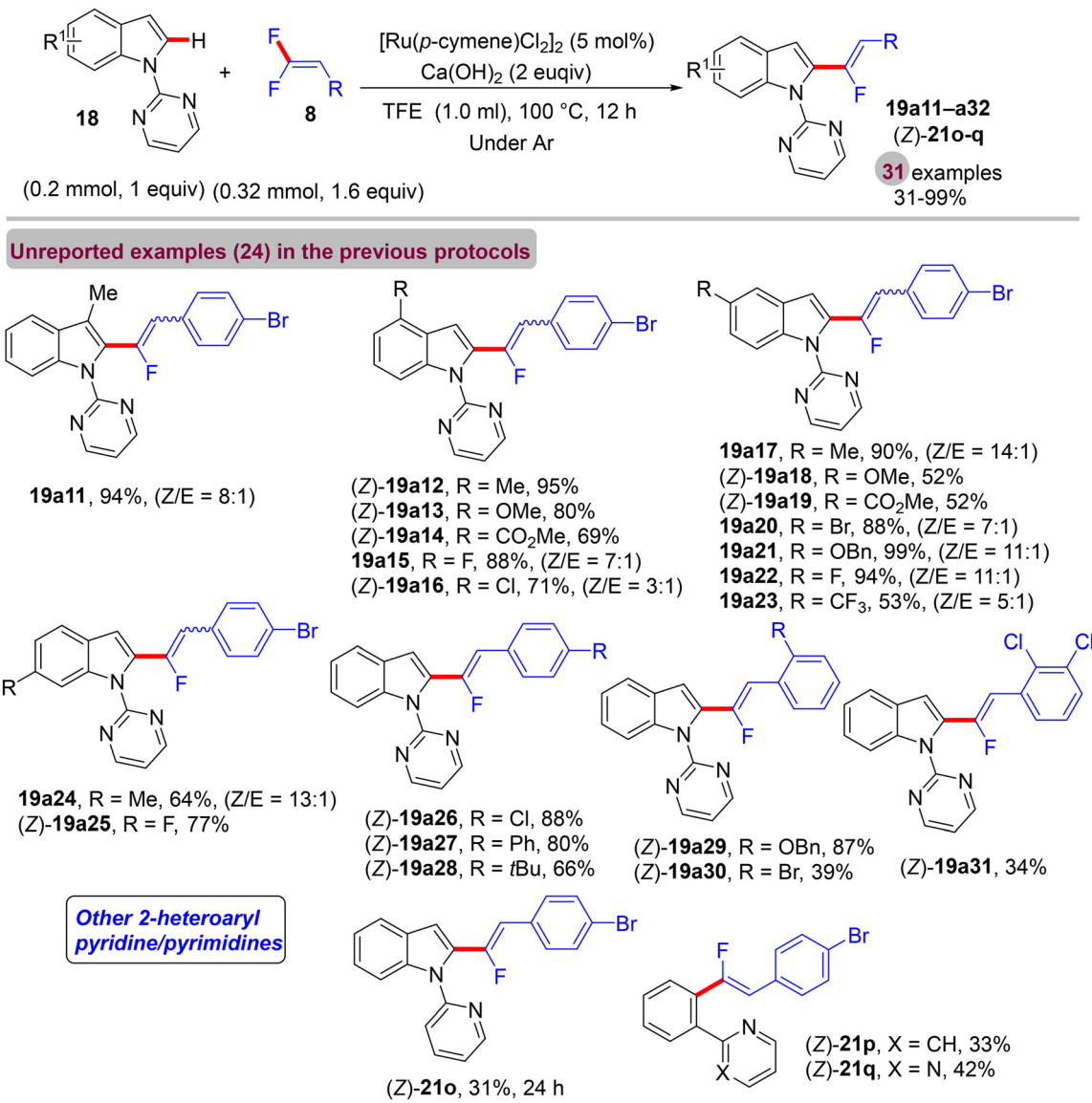
Scheme 42 Control mechanistic experiments of Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **52** with **8**.



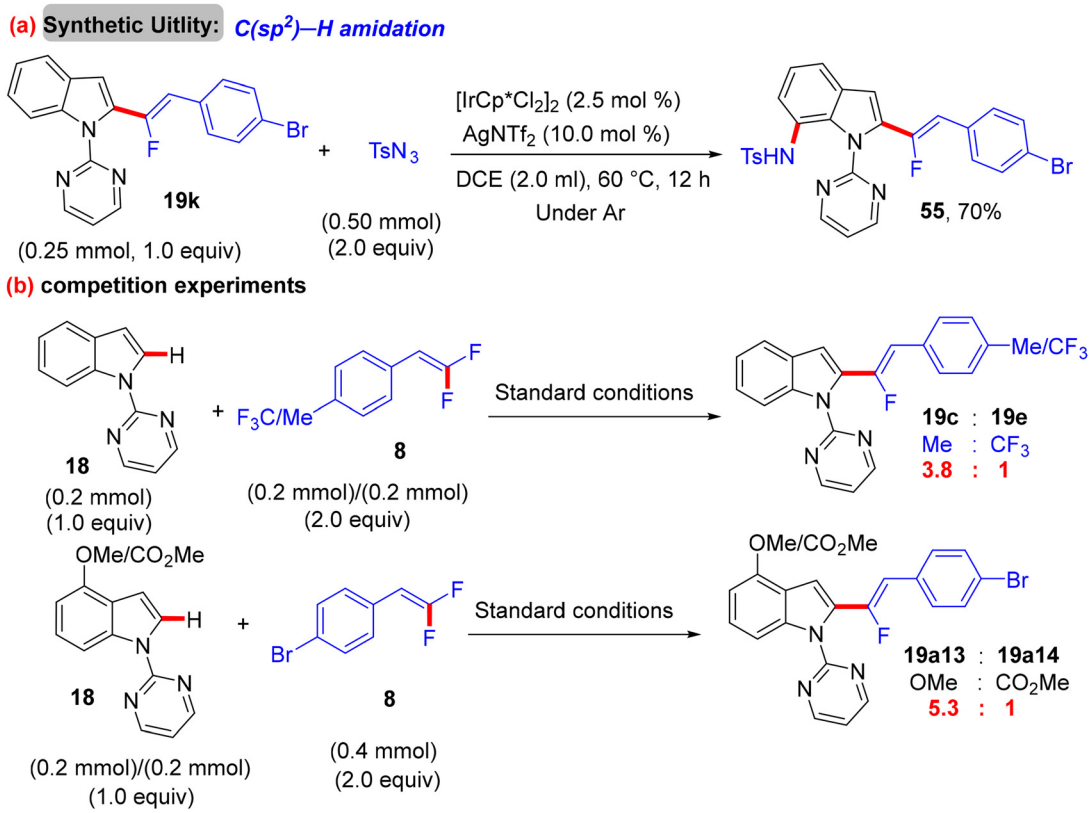
Scheme 43 Proposed catalytic cycle of Rh(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **52** with **8**.

by $[RhCp^*Cl_2]_2$ catalyst.[37] Like in the previous occurrences, this stereoselective transformation was also aided by ^{P}DG (amide-imine) and afforded the desired (*Z*)-monofluoroalkenes (**53a2–ax**) in fair to very good, isolated yields (46–83%), especially with EDGs of *para*- and *meta*-trisubstituted *gem*-difluoroalkenes (**8**), as well as featuring good functional group compatibility. After several optimization trials, the optimum conditions were settled as follows: $[RhCp^*Cl_2]_2$ (2 mol%), $Ca(OH)_2$ (1.0 equiv.), CsOAc (20 mol%), and $AgNTf_2$ (4 mol%) in HFIP (2.0 mL) at 100 °C for 8 h (Scheme 41). Doubling the amount of $Ca(OH)_2$ (2.0 equiv.) and $AgNTf_2$ (8 mol%) led to domino (tandem) C(sp^2)–H and N–H activation (two-fold C–F cleavage/[4 + 1] cyclization[31]) that furnished the corresponding isoindolo[1,2-*b*]quinazolin-10(12*H*)-ones **54**, which is beyond the scope of this review. It is worthy of note that this catalytic procedure (C(sp^2)–H activation) is similar to the prior one (C(sp^3)–H activation),[34] with the replacement of $Zn(OAc)_2$ by CsOAc.

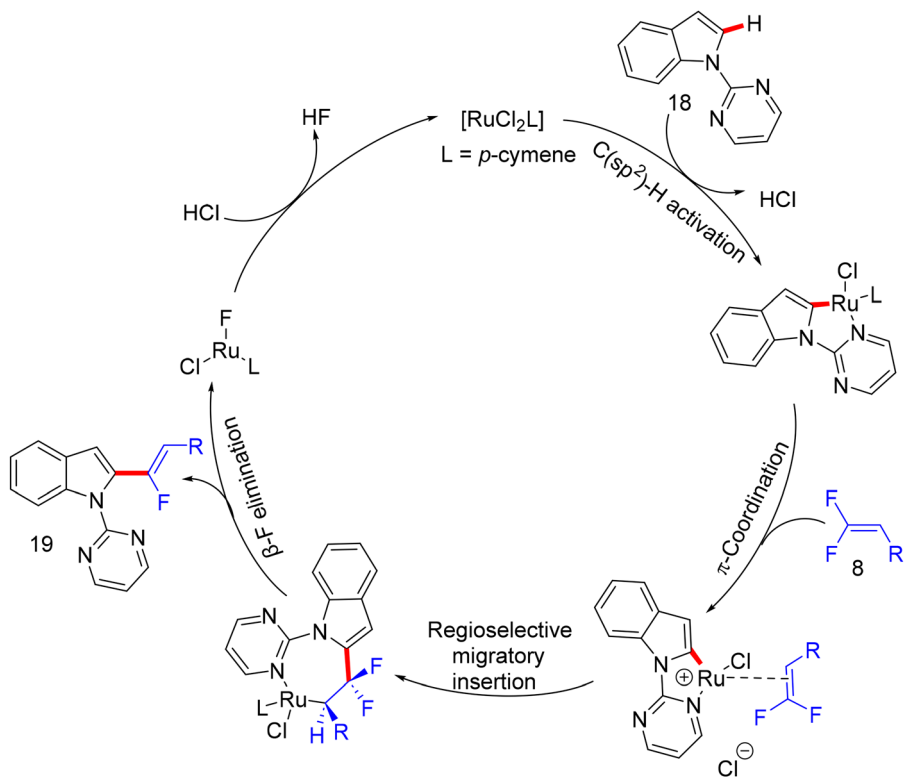
The authors conducted some control mechanistic experiments. An H/D exchange by CD_3OD was observed at the two *ortho*-positions ([D2]-**52**, 27% D) of **52**, demonstrating that the C(sp^2)–H activation was reversible. Like the previous studies, the competition experiments proved that **8** with EDGs were more efficient than their EWG counterparts (1.6 : 1.0). The KIE (k_H/k_D, ^{1}H NMR) value equals 3.3, indicating that the C(sp^2)–H cleavage might participate in the rate-determining step (Scheme 42).[37] Besides these observations and the literature findings,[30] a catalytic cycle similar to the above-mentioned one in Wang's study[31] was proposed and is depicted in Scheme 43.



Scheme 44 Scope investigation in Ru(II)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **18** with **8**.



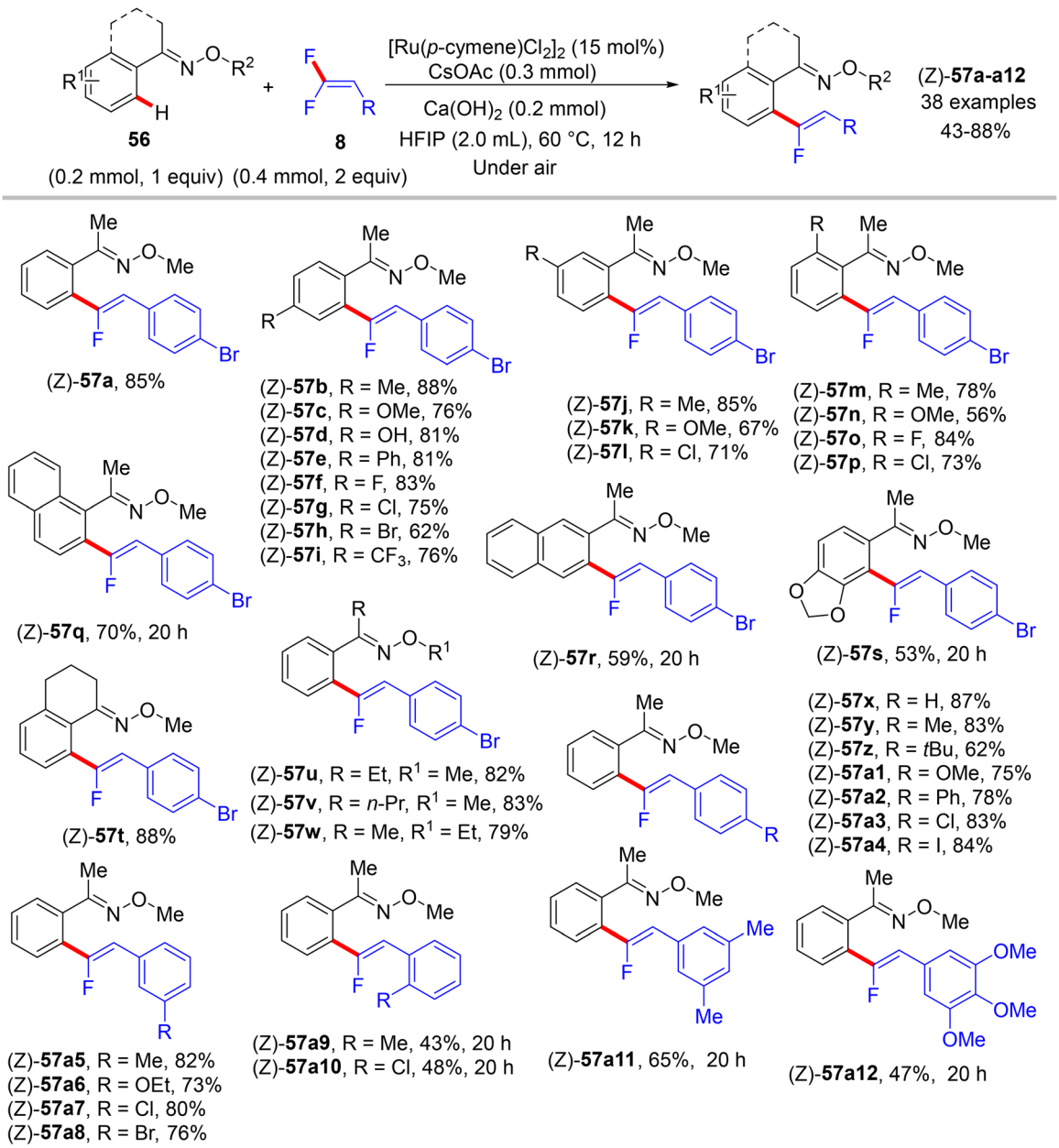
Scheme 45 Synthetic application and competition experiments of Ru(II)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **18** with **8**.



Scheme 46 Proposed catalytic cycle of Ru(II)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **18** with **8**.

3.3. C–H α-Fluoroalkenylation using Ru(II)

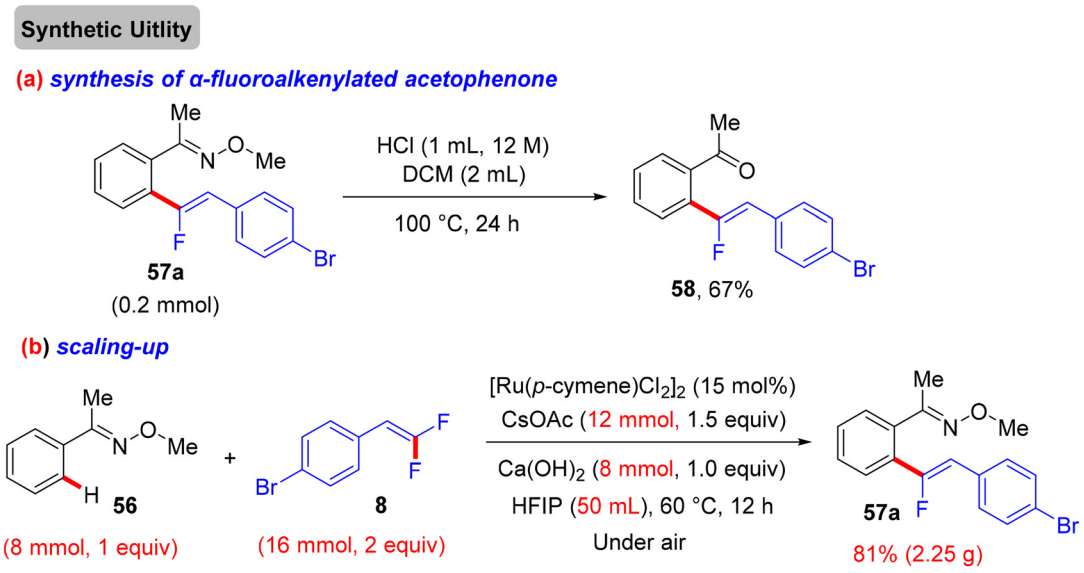
After Loh's study in 2015 on α-fluoroalkenylation of *N*-pyrimidinylindoles **18** by Rh(III)Cp* catalyst,[29] Li's group conducted the same work with a "Ru(II) catalysis" for the first time ever.[38] With the $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%)/$AgSbF_6$ (10 mol%)/$Ca(OH)_2$ (2 equiv.) catalytic system, the desired product was not obtained, and after several trials, the optimum Ag-free conditions were demonstrated as follows: $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), $Ca(OH)_2$ (2 equiv.), TFE (1 mL), stirring under argon at 100 °C for 12 h. To examine the applicability of this Ru(II) protocol, the scopes of **18** and olefinic reagent **8** were investigated, and the expected products (**19a11–a32** and **21o–q**) were isolated with good to excellent regio- and stereoselectivity (Scheme 44). Overall, the yield and the stereoselectivity (*Z*/*E* ratio) are lower than those in Loh's procedure,[29] demonstrating the high efficiency of Rh(III)Cp* catalysis. As a synthetic application, compound **19k** was subjected to LSF by treatment with sulfonyl azide (TsN_3) in the presence of the $[IrCp^*Cl_2]_2$ (2.5 mol%)/$AgNTf_2$ (10.0 mol%) catalytic system to furnish the corresponding $C(sp^2)$–H amidation product **55** (70% isolated yield, Scheme 45a). As in previous studies, competition experiments indicated that electron-rich substrates (**18** and **8**) are preferred and most effective (Scheme 45b). Moreover, the mechanistic pathway was proposed based on the aforemen-



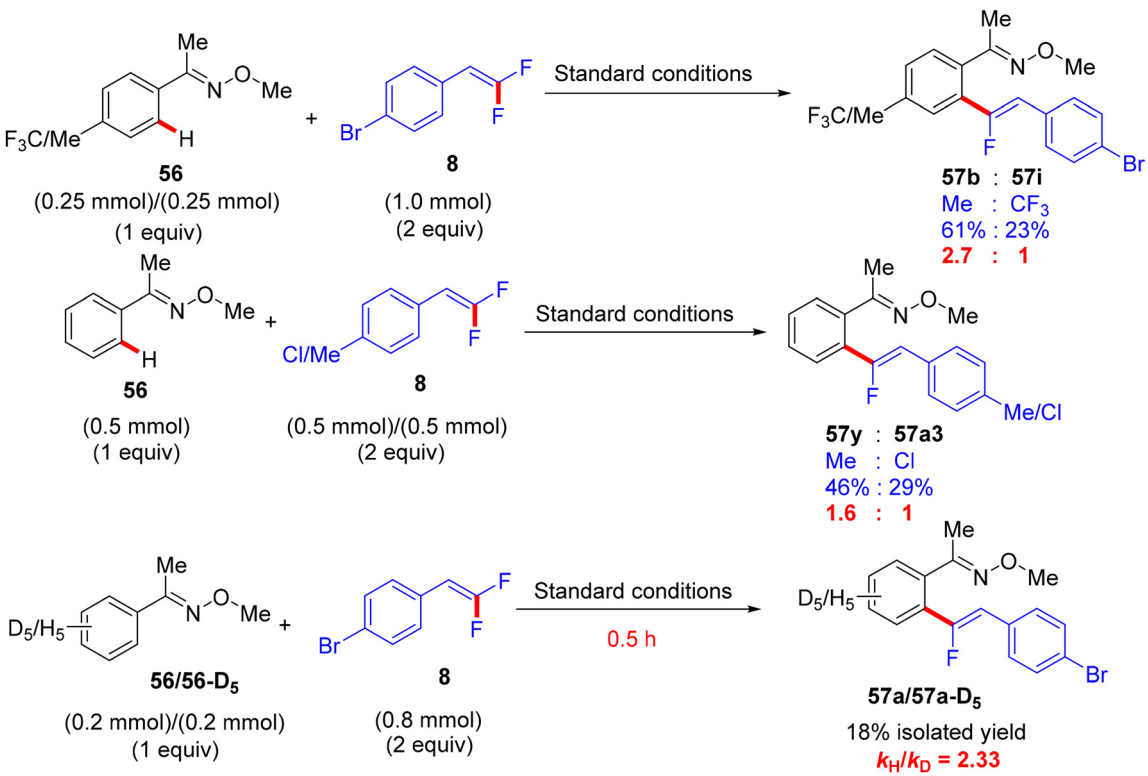
Scheme 47 Scope investigation in Ru(II)-catalyzed direct $C(sp^2)$–H α-fluoroalkenylation of **56** with **8**.

tioned outcomes,[30] and the Ru(II) mode is similar to the Rh (III) one (Scheme 46).

In 2020, an article also from Ji's lab illustrates the usage of the same prior Ru(II) catalyst for direct C(sp^2)–H α-fluoroalkenylation of arene-containing oxime ethers **56** (as a removal *ortho*-directing group, ^{R}DG) with **8** to exhibit the expected monofluoroalkenes **57** and subsequent α-fluoroalkenylated acetophenones **58** after removing the oximyl ether DG.[39] Additionally, this approach proceeds *via* C(sp^2)–H functionalization and alkenyl C(sp^2)–F cleavage in a (*Z*)-stereoselective manner with good functional group tolerance. The authors attempted to use $[RhCp^*Cl_2]_2$ and $Pd(OAc)_2$



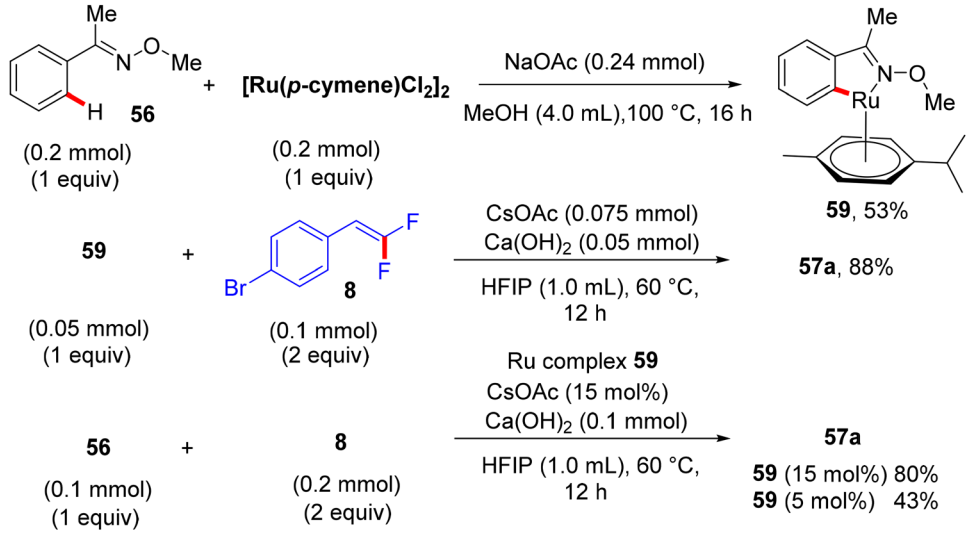
Scheme 48 Chemical synthesis of acetophenone derivative **58** and gram-scale formation of **57a**.



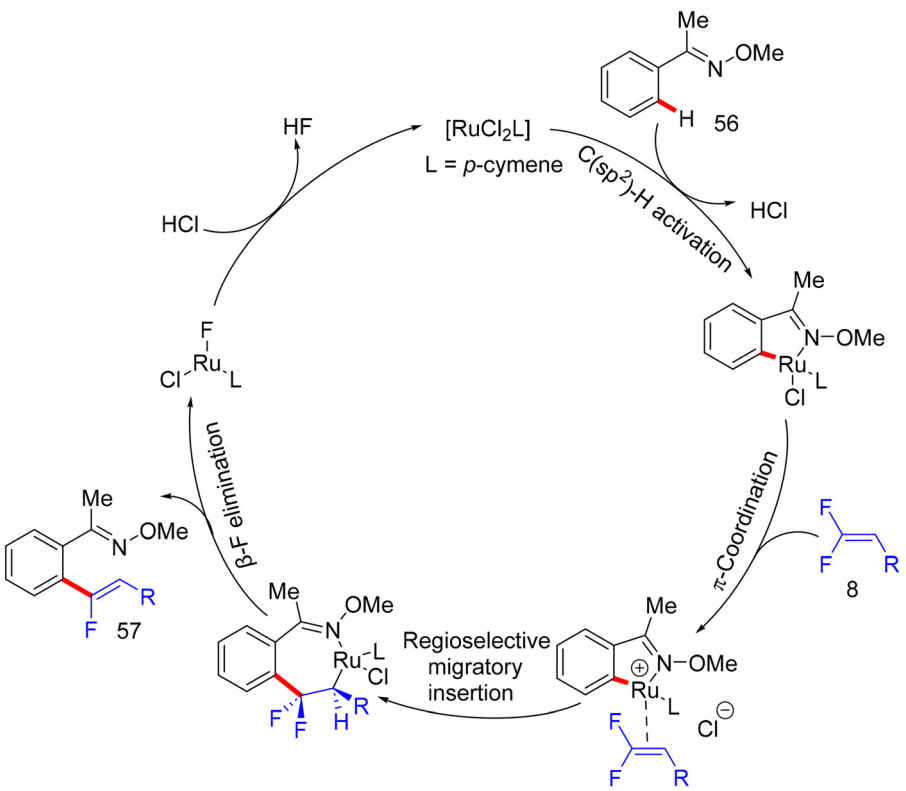
Scheme 49 Competition experiments of Ru(II)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **56** with **8**.

as catalysts, respectively, but the expected product did not form. Next, they used the diamagnetic dimer [Ru(*p*-cymene)Cl_2]$_2$, and after several tests, they reached the optimal conditions as follows: catalyst (15 mol%), $Ca(OH)_2$ (0.2 mmol), and CsOAc (0.3 mmol) in HFIP (2.0 mL) at 60 °C for 12 h. Under these conditions, the substrate scopes of **56** and **8** were investigated (Scheme 47). Like the previous protocols, *para*- and *meta*-substituted substrates are more favorable than their *ortho* counterparts, proving the importance of the substituent steric effect. Changes in the alkyl group of the oximyl ether are also tolerated in this transformation, and their products were isolated in good yields (**57t–w**, 79–88%).

Synthetic applications of this protocol were demonstrated by the authors, where acetophenone derivative **58** was obtained



Scheme 50 Synthesis and α-fluoroalkenylation of intermediate Ru complex **59**.

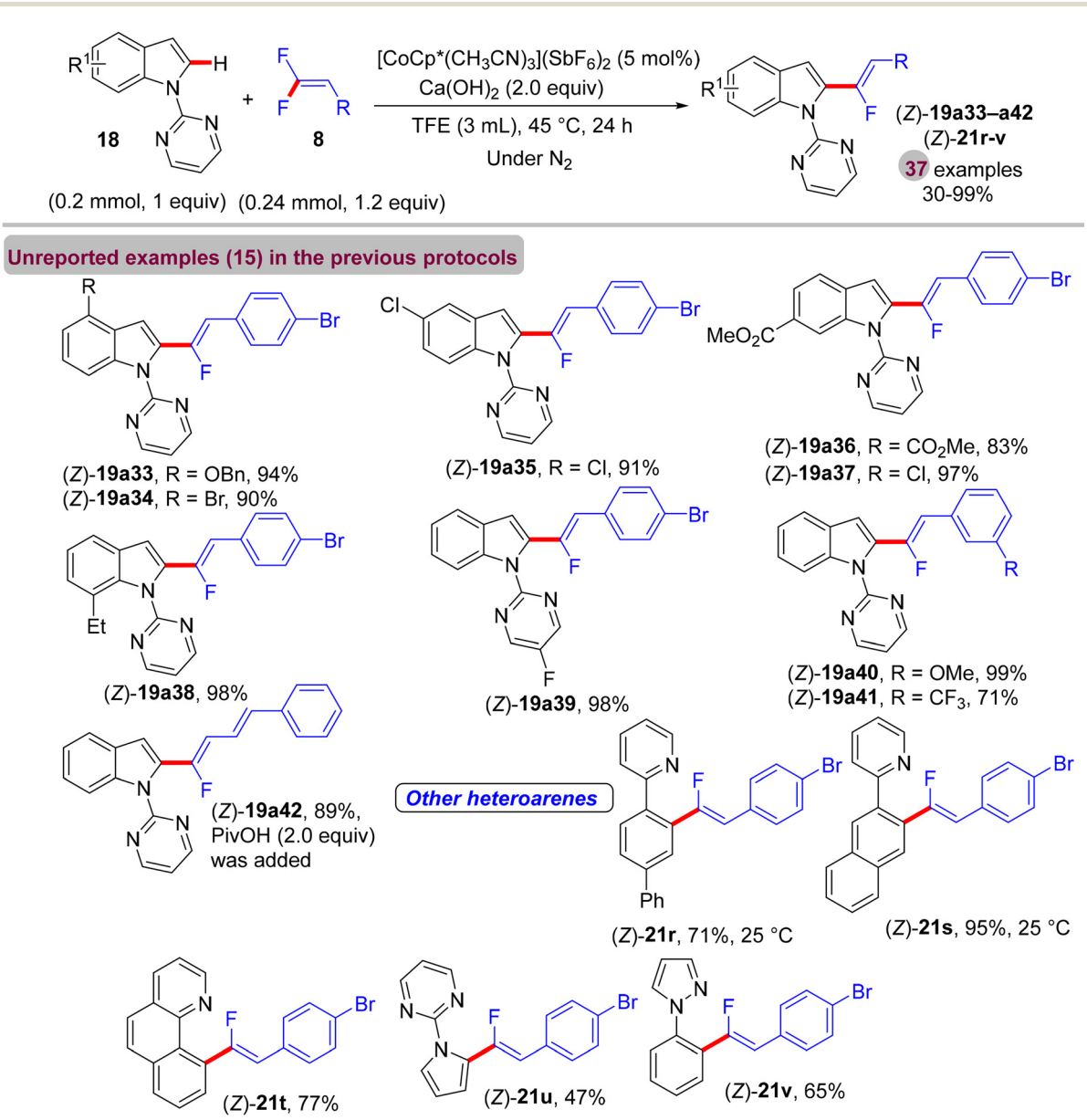


Scheme 51 Proposed catalytic cycle of Ru(II)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **56**.

in 67% isolated yield *via* the removal of the DG by acidic hydrolysis with HCl (12 M) in DCM at 100 °C. In addition, gram-scale synthesis of **57a** was achieved, as illustrated in Scheme 48. Most importantly, several control experiments were performed to support the proposed mechanism (Scheme 49). Firstly, the intermolecular kinetic competition experiments of electronically biased **56** and **8** indicated that the EDG on both reactants facilitated the transformation. Secondly, KIE experiments of **56** and **56-D$_5$** with two equivalents of **8** afforded **57a**/**57a-D$_5$** with a k_H/k_D value of 2.33 (^{1}H NMR), suggesting that the activation of the C(sp^2)–H bond could be rate-determining. Finally, the isolation of cyclometallated Ru complex **59** (Scheme 50) and its successful usage in stoichiometric and catalytic reactions confirm its active role in the catalytic cycle (Scheme 51), which is similar to the previous one.[38]

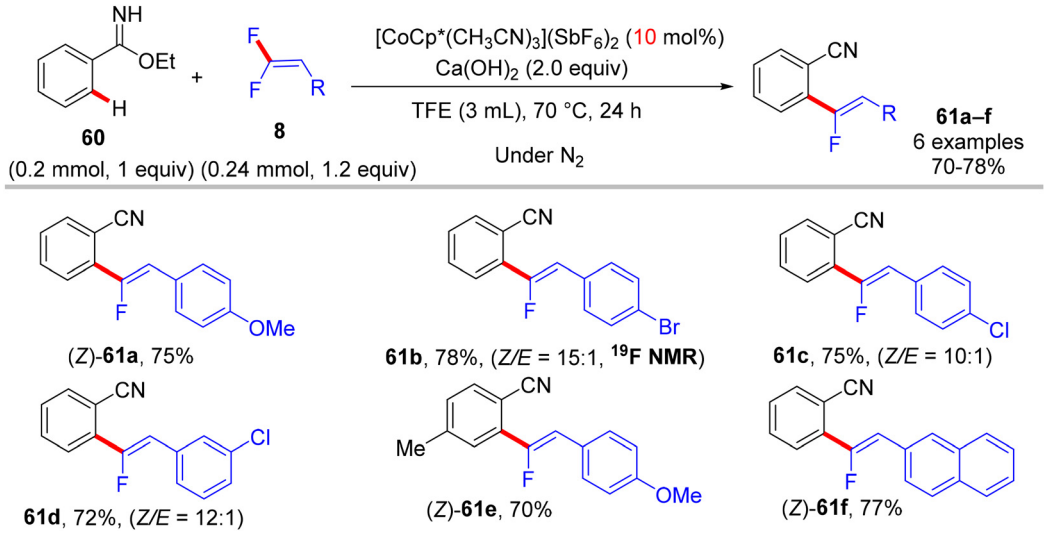
3.4. C–H α-Fluoroalkenylation using Co(III)Cp*

Before their work on the direct C(sp$^{2/3}$)–H α-fluoroalkenylation of heteroarenes by Rh(III)Cp* and Ru(II) catalysts in 2017 and 2018,[30,34,35,38] in 2016 the Li research group[40] tried to use Co(III)Cp*-based catalysis for conducting the same reaction as a low-cost alternative to Loh's procedure with Rh(III) in 2015.[29] In their preliminary investigation, they used 10 mol% of [CoCp*(CO)I$_2$][63,64] and 20 mol% of AgNTf in TFE solvent (1.5 mL) at 80 °C in the presence of an additive, mostly Ca salts. The desired monofluoroalkenes were obtained in 61–95% isolated yield, but with poor stereoselectivity (*Z*/*E* ratio = 1.6–3.7/1, ^{19}F NMR). Among the employed HF scavenger Ca salts, Ca(OH)$_2$ was the best choice and was mostly used after that in similar studies as shown above. Moreover, they

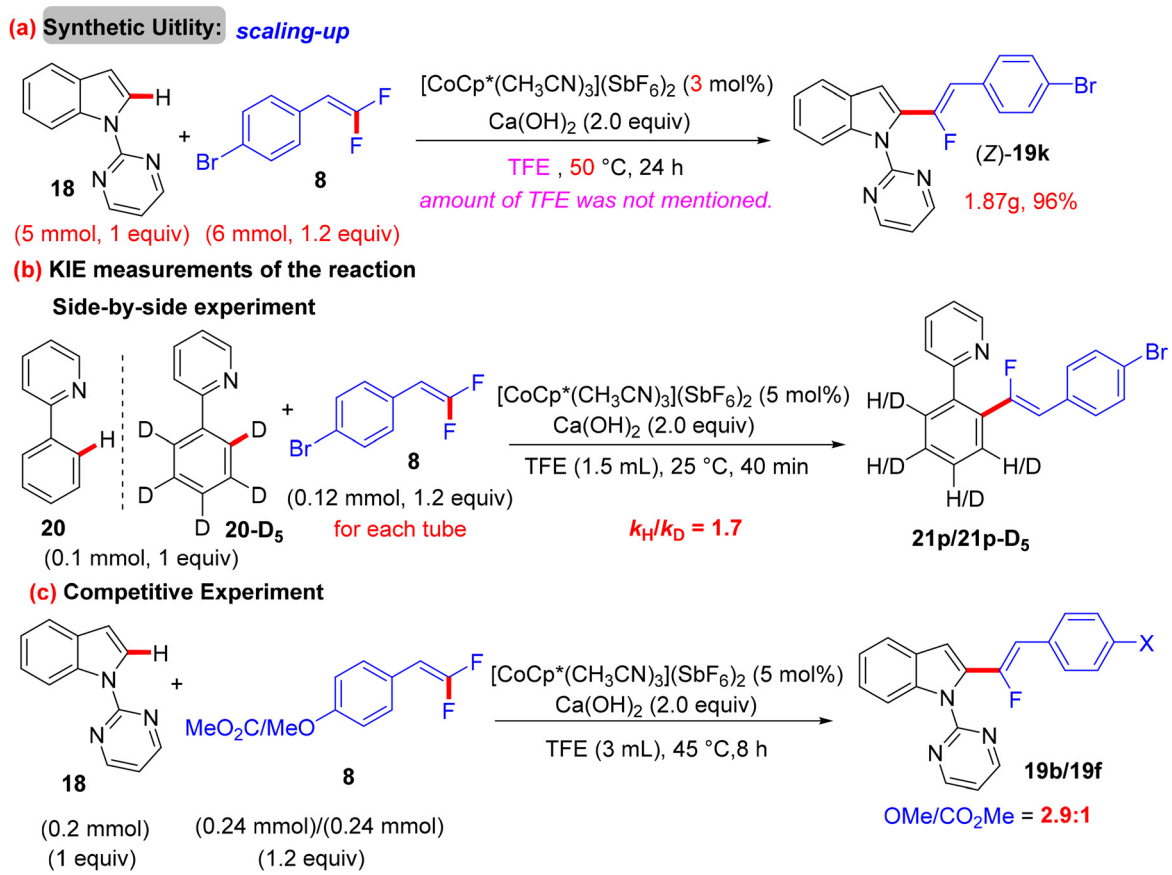


Scheme 52 Scope investigation in Co(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **18**/**21** by **8**.

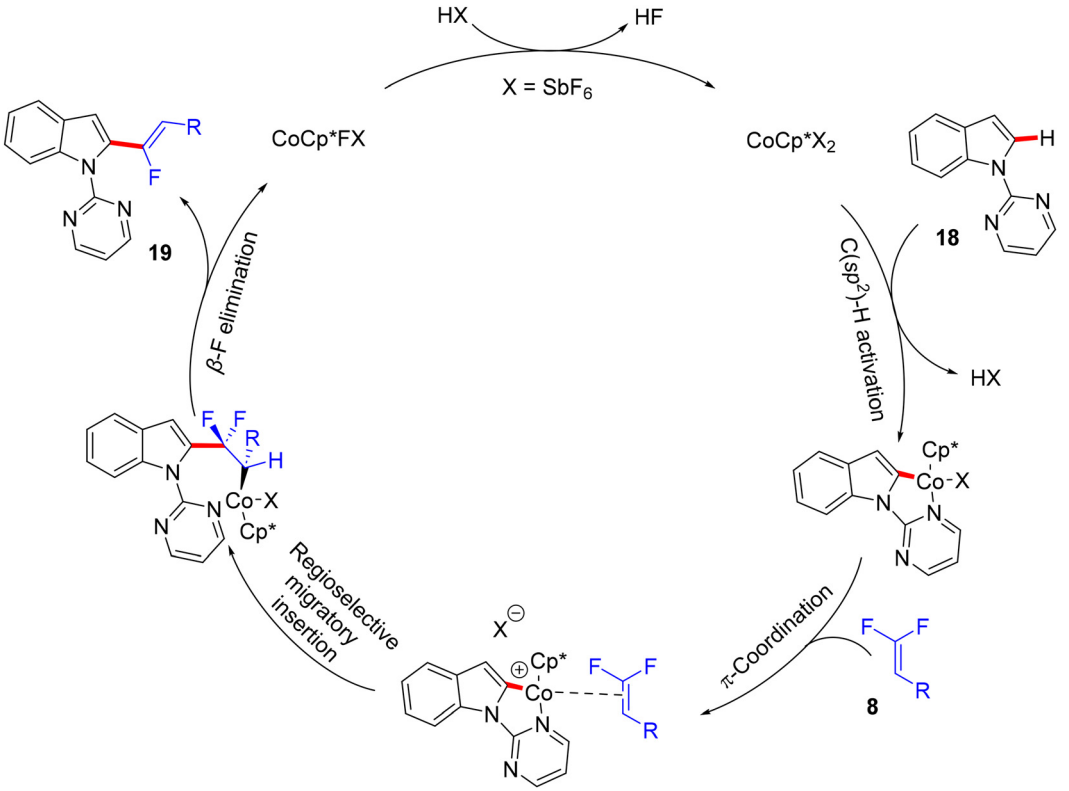
switched to the cobalt analogue of $[RhCp^*(CH_3CN)_3](SbF_6)_2$, which was utilized in Loh's study.[29] The optimal conditions were settled as follows: $[CoCp^*(CH_3CN)_3](SbF_6)_2$ (5 mol%) and $Ca(OH)_2$ (2.0 equiv.) in TFE (3 mL) at 45 °C for 24 h, improving the isolated yields and enhancing the stereoselectivity (Z/E > 20/1). As in Loh's protocol,[29] **18** was chosen as a model sub-



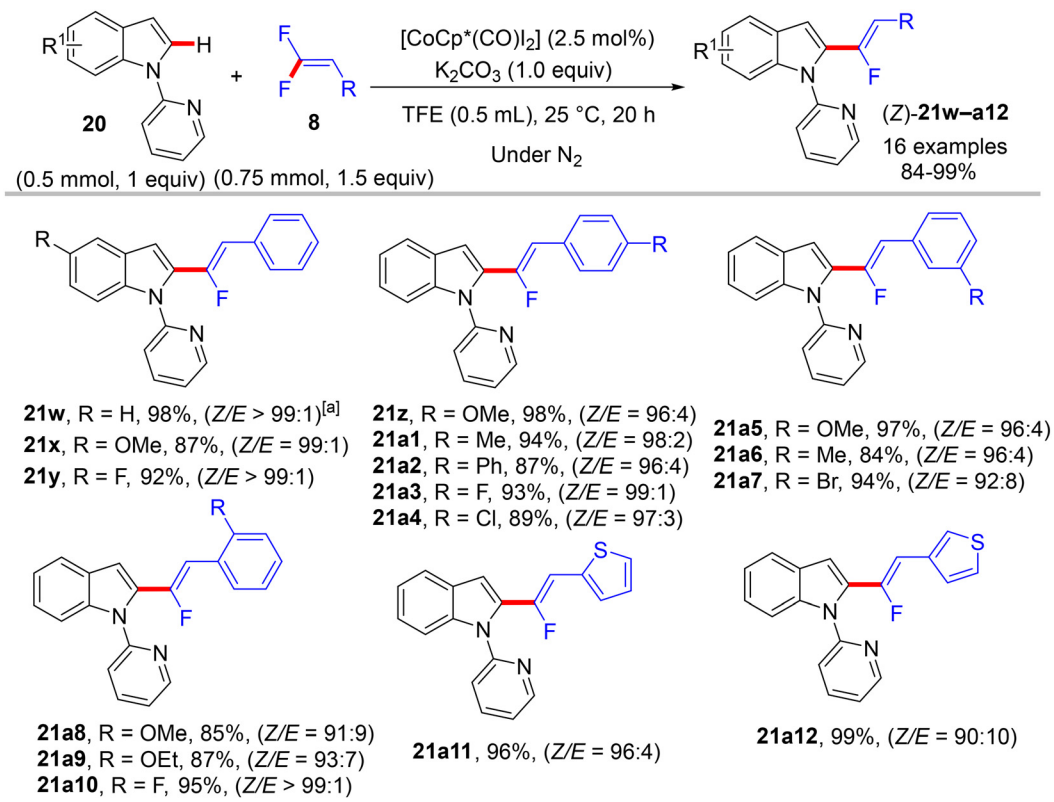
Scheme 53 Scope of **60** in Co(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation with **8**.



Scheme 54 Gram-scale synthesis of **19k**, KIE, and competitive experiments of Co(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **18/20** with **8**.



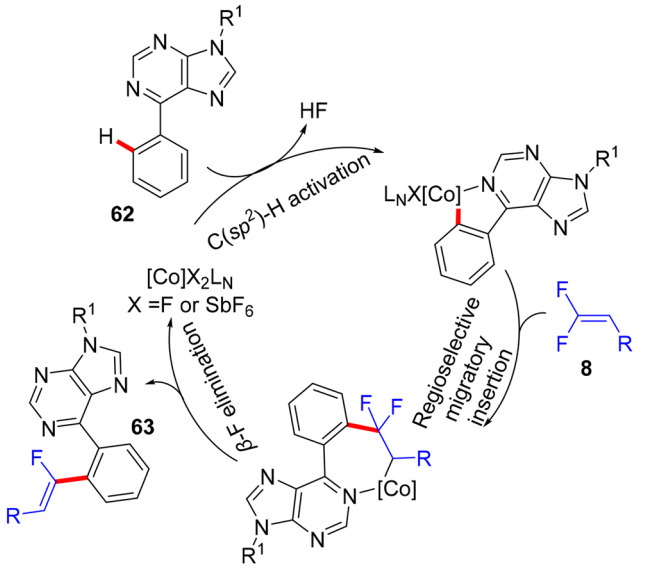
Scheme 55 Proposed catalytic cycle of Co(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **18**.



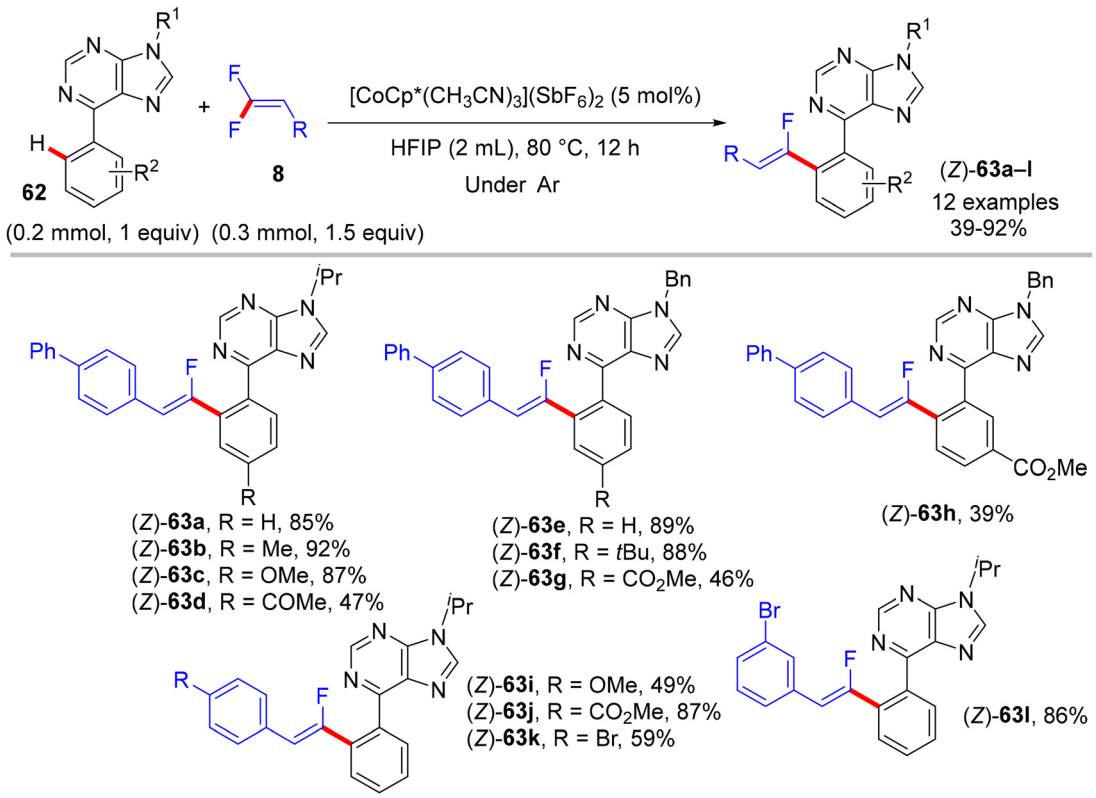
Scheme 56 Scope investigation in Co(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of *N*-pyridinylindoles (**20**) with **8**.

strate, and the study was also extended to other nitrogenous-directed substrates. The scope of **18** and **8** to access the corresponding (*Z*)-monofluoroalkenes (**19a33–a42**) was investigated (Scheme 52). The scope of the other heteroarenes (**20** afforded **21r–v**) that are assisted by pyridine, pyrimidine, or pyrazole is also demonstrated. Under the conditions of this procedure, substrate-based ethyl benzimidates **60**[65] afforded the corresponding benzonitrile monofluoroalkenes **61a–f** in good yields (Scheme 53), demonstrating the carboximidate unit as a transformable transient directing group (^{T}DG).[62,66] As shown in Scheme 54, the authors achieved the gram-scale synthesis of **19k** and the KIE experiment (k_H/k_D = 1.7 ^{1}H NMR, **20**/**20-D$_5$** gave **21p**/**21p-D$_5$**), which indicated the C–H activation step is not the rate-determining step in agreement with their aforementioned experimental and theoretical studies on *gem*-difluorovinyl tosylate (**25**) and *N*-OMe benzamides **27**.[30] The Co(III)Cp* catalytic cycle is also similar to the previous Rh(III) Cp* and Ru(II) ones (Scheme 55).

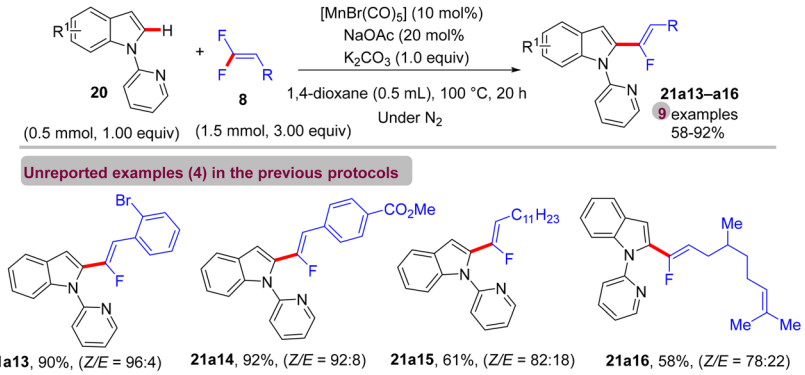
One year later, Ackermann *et al.* reported the first sustainable room-temperature direct C(sp^2)–H α-fluoroalkenylation of *N*-pyridinylindoles **20** (as 2-heteroaryl pyridines) by **8**, employing a low catalyst loading of [CoCp*(CO)I$_2$] and mild base (K_2CO_3). Optimization studies of this silver-free transformation generated the optimum conditions as follows: [Co(III)] (2.5 mol%), K_2CO_3 (1.0 equiv.), and TFE solvent (0.5 mL) at 25 °C for 20 h under nitrogen atmosphere to afford the expected monofluoroalkenes **21w–a12** in high to excellent yields (Scheme 56) with a *Z*/*E* ratio between 90 : 10 and 99 : 1. The stereoselectivity findings were confirmed by computational studies that indicated the (*Z*)-



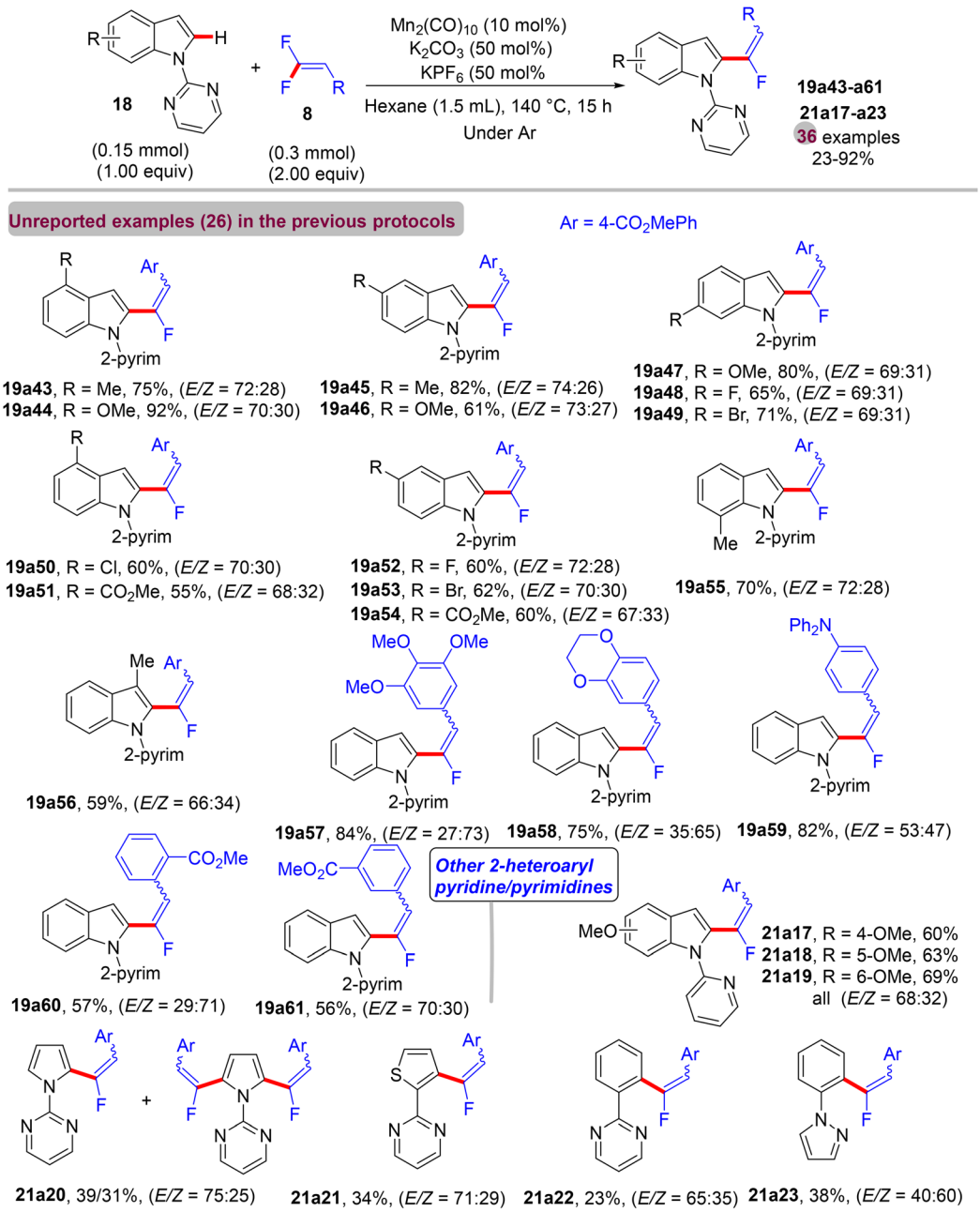
Scheme 58 Proposed catalytic cycle of Co(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **62**.



Scheme 57 Scope investigation in Co(III)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **62** with **8**.



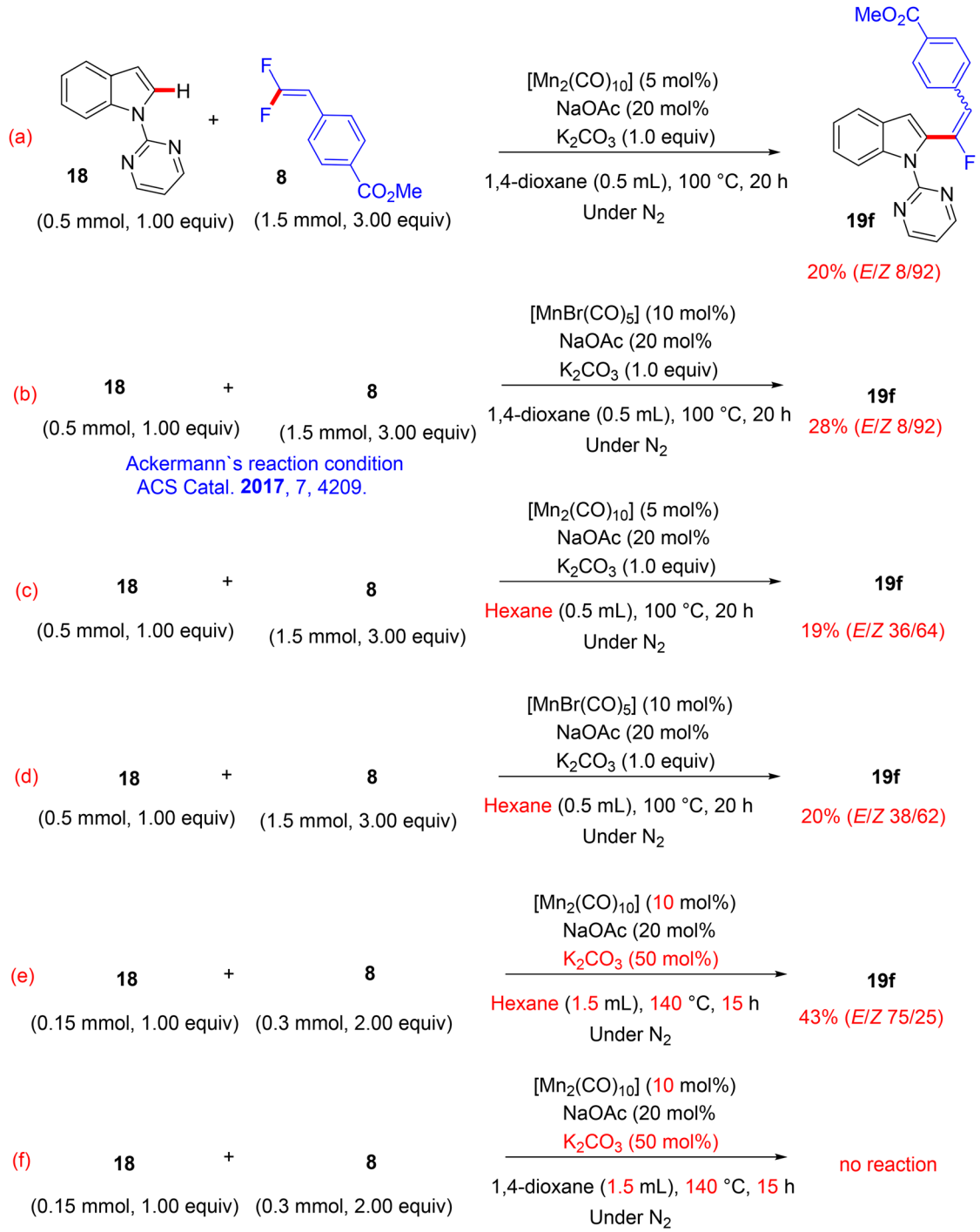
Scheme 59 Scope investigation in Mn(I)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **20** with **8**.



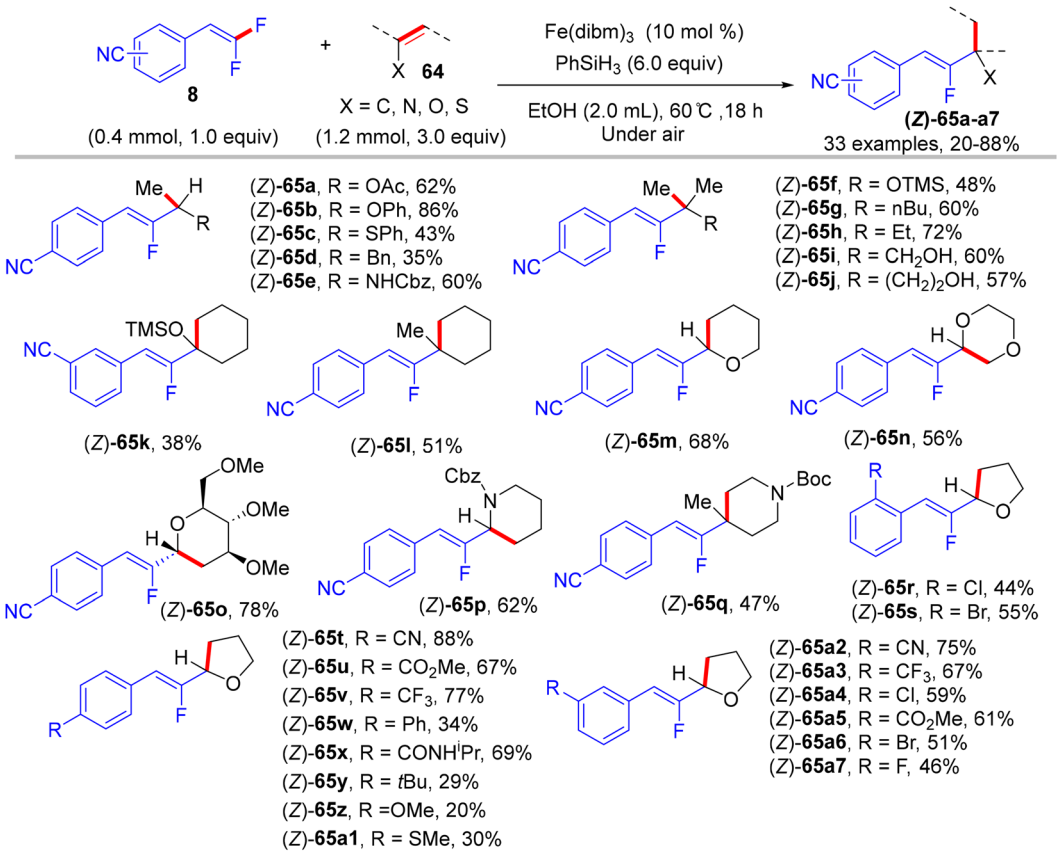
Scheme 60 Scope investigation in Mn(0)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **18/20** with **8**.

selective route is energetically favored owing to steric repulsion in the *E* counterpart.[41]

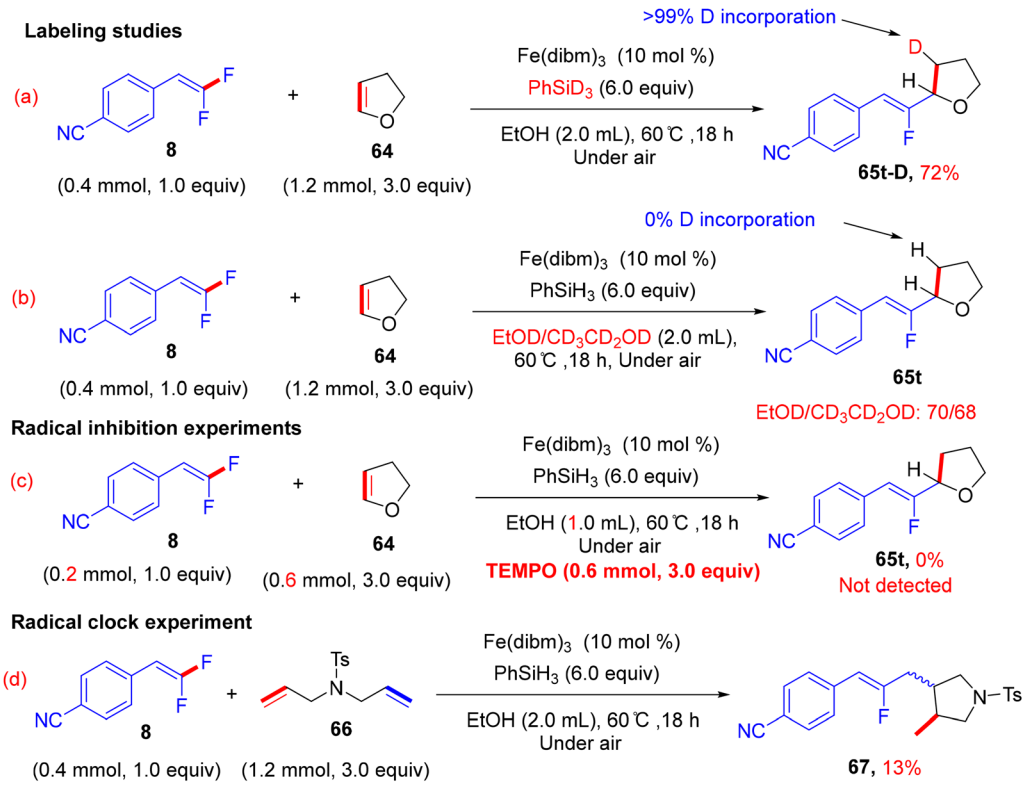
In 2018, fluoroalkenylation this time came from Hokkaido University, Japan, where the Matsunaga research group[42] used the same Co(III) catalyst as the Xingwei Li study,[40] but *via* Loh's methodology,[29] base- and additive-free. They performed direct C(sp^2)–H α-fluoroalkenylation of bioactive[67] and versatile substrate-containing ^{P}DG[62] 6-arylpurines **62** using **8** in a high (*Z*)-stereoselective manner. The optimization stage was conducted on the model *N*-isopropyl-6-phenylpurine **62** with **8**, and the result showed that the single-component $[CoCp^*(CH_3CN)_3](SbF_6)_2$ (5 mol%, 95%) was better than the $CoCp^*(CO)I_2$ (5 mol%)/$AgSbF_6$ (10 mol%, 81%) catalytic system in the optimal alcoholic solvent HFIP (0.5 mL) at 80 °C. Scheme 57 shows the obtained products **63a–l** in moderate to good yields, and Scheme 58 displays the catalytic cycle.



Scheme 61 Study of the *E*/*Z* selectivity of **19f** in Mn(0)-catalyzed direct C(sp^2)–H α-fluoroalkenylation of **18** with **8**.



Scheme 62 Scope investigation in Fe(III)-catalyzed direct alkenyl C(sp^2)–H α-hydrofluoroalkenylation of olefins (**64**) with **8**.



Scheme 63 Mechanistic studies of Fe(III)-catalyzed direct alkenyl C(sp^2)–H α-hydrofluoroalkenylation of **64**.

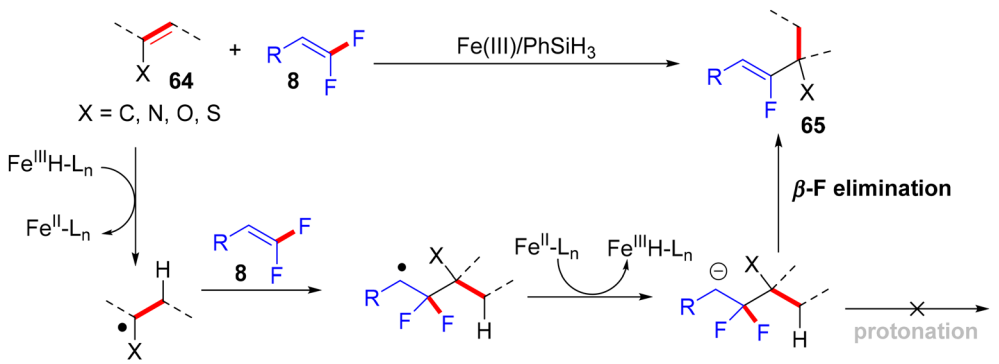
3.5. C–H α-Fluoroalkenylation using Mn(0/I)

In May 2017, Ackermann *et al.* published a study that mimicked the previous one,[41] but with a manganese(I)-based catalyst.[43] Mn(I)-Catalyzed direct C(sp^2)–H α-fluoroalkenylation of **20** by **8** to afford the corresponding monofluoroalkenes **21a13–a16** under these optimum conditions: [$MnBr(CO)_5$] (10 mol%), NaOAc (20 mol%, an additive), K_2CO_3 (1.0 equiv.) and 1,4-dioxane solvent (0.5 mL) at 100 °C for 20 h. The desired products were installed in moderate to high yields (Scheme 59) with a *Z*/*E* ratio between 78 : 22 and 96 : 4, proving the robustness of the Co(III) protocol[41] in contrast with this one.

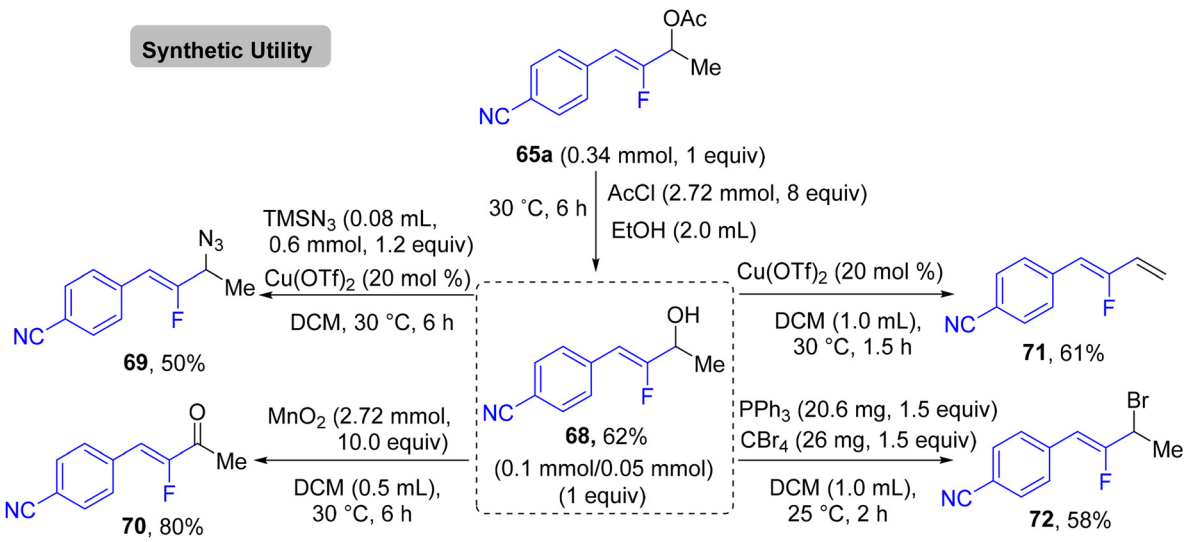
In contrast to the previous documented approaches that always showed the monofluoroalkenes in thermodynamically stable (*Z*)-stereoselectivity, in July 2017, a paper from Loh's lab described a redox-neutral direct C(sp^2)–H α-fluoroalkenylation protocol to access mostly the *E* counterpart as the major products using an Mn(0)-based catalyst.[44] The scope of **18**/**20** and **8** (Scheme 60) was investigated under the following optimal conditions: $Mn_2(CO)_{10}$ (10 mol%), K_2CO_3 base (50 mol%), and KPF_6 additive (50 mol%) in hexane (1.5 mL) at 140 °C for 15 h. When this transformation was performed by the prior Ackermann's method[43] with either [$MnBr(CO)_5$] (10 mol%) or [$Mn_2(CO)_{10}$] (5 mol%), the (*Z*)-isomer was always the major product (92%) (Scheme 61a and b). Under the same conditions, albeit with hexane instead of 1,4-dioxane, the (*E*)-isomer percentage increased to 36–38% (Scheme 61c and d). Additionally, applying Ackermann's protocol,[43] albeit with a Mn(0) catalyst and a catalytic amount of K_2CO_3 (50 mol%) at 140 °C for 15 h (mix between Mn protocols) in hexane provided the desired product with 43% isolated yield and an *E*/*Z* ratio of 75/25, while the reaction carried out in 1,4-dioxane gave no product (Scheme 61e and f), proving the key role of the solvent for the unusual *E*/*Z* selectivity in Loh's protocol.[44]

3.6. C–H α-Fluoroalkenylation using Fe(III)

In 2018, Wang *et al.*'s paper documented the synthesis of alkylated monofluoroalkenes *via* a hydrofluoroalkenylation reaction, which was enabled by the Fe(III)/$PhSiH_3$ catalytic system.[45] This approach was a combination of the Fe(III)/$PhSiH_3$-catalyzed hydrogen atom transfer (HAT) with the



Scheme 64 Proposed mechanistic pathway of Fe(III)-catalyzed direct alkenyl C(sp^2)–H α-hydrofluoroalkenylation of **64**.



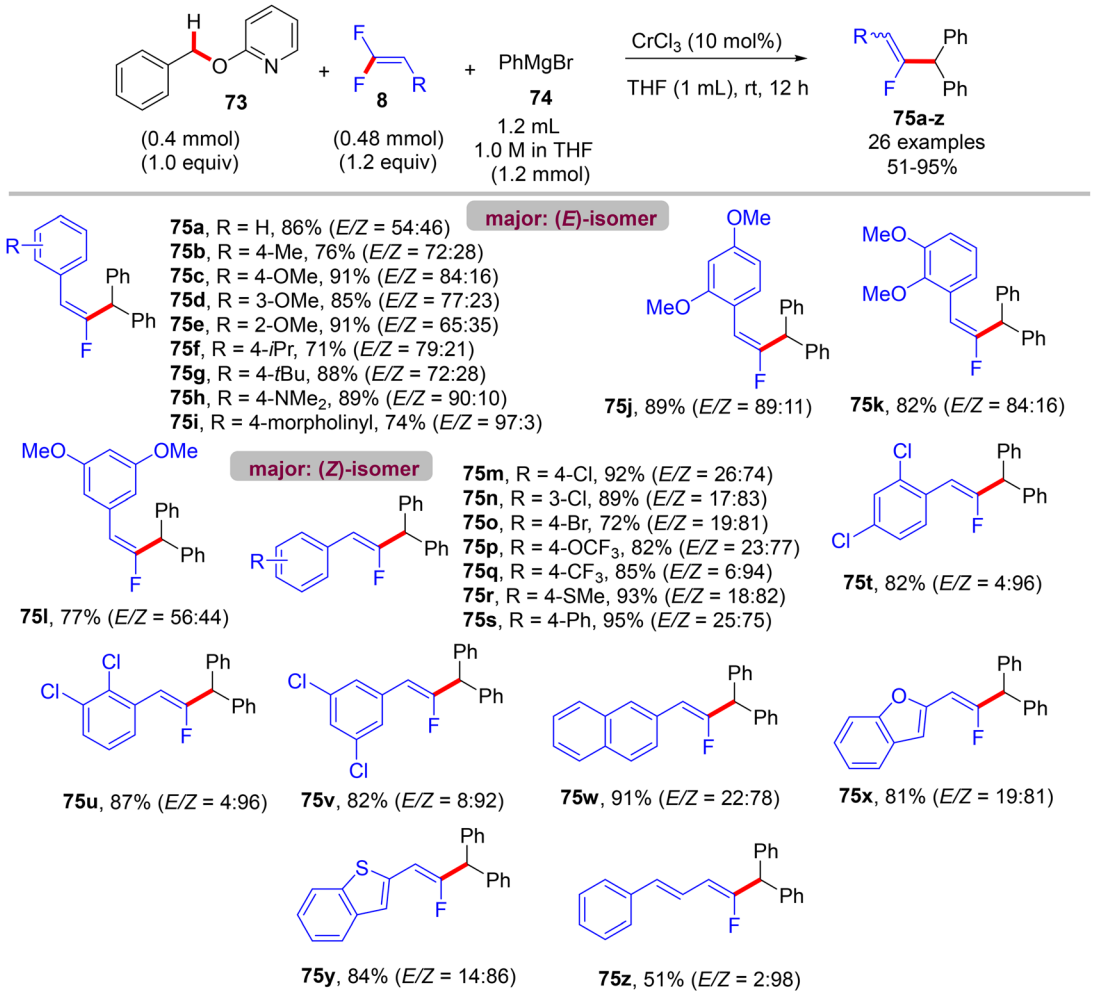
Scheme 65 Synthetic applications of α-hydrofluoroalkenylation product **65a** to synthesize **68**–**72**.

defluorinative cross-coupling strategy of various alkenes with **8**. The authors hypothesized that the reaction proceeds through a free radical-based process with excellent (*Z*)-selectivity under air- and water-tolerant reaction conditions. Vinyl acetate and 4-cyano-*gem*-difluoroalkene **8** were employed for the model reaction, and the optimal conditions were obtained as follows: $Fe(dibm)_3$ (10 mol%, dibm = diisobutyrylmethane) as a catalyst, and $PhSiH_3$ (6.0 equiv.) as a hydrogen source in EtOH (2.0 mL) at 60 °C for 18 h under atmospheric conditions. Under the optimized conditions, a variety of alkenes, including vinyl ester, aryl vinyl ether, silyl enol ethers, endocyclic enol ethers, enecarbamates, vinyl thioether, and 1,1-disubstituted olefins, were efficiently tolerated and furnished the corresponding products (*Z*)-**65a–a7** in 20–88% isolated yields (Scheme 62).[45]

In addition, the authors performed some control experiments to gain more mechanistic insights into this transformation type, where they used $PhSiD_3$ instead of $PhSiH_3$, a deuterated adduct **65t-D** was obtained (Scheme 63a),[45] and when EtOH was changed to the deuterated analogues (EtOD or CD_3CD_2OD), the deuterium was not detected (Scheme 63b),[45] suggesting that $PhSiH_3$ is the sole source of hydrogen. Regarding the free radical as a hypothetical pathway, the reaction was completely inhibited when (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) was utilized as a radical scavenger (Scheme 63c).[45] Moreover, when *N*,*N*-diallyl-4-methylbenzenesulfonamide **66** was employed as a coupling partner, the corresponding cyclized monofluoroalkene **67** was formed (Scheme 63d).[45] All these observations supported the depicted mechanism in Scheme 64,[45] which illustrates two main stages, including HAT and β-F elimination rather than protonation by solvent, as reported in the literature.[68–71] As a synthetic utility of this protocol, compound **65a** was converted to the corresponding 2-fluoroallylic alcohol **68** *via* the acidic hydrolysis of the acetyl group. Next, LSF of the OH group afforded some useful, structurally diverse fluorine-containing molecules (**69–72**) (Scheme 65).[45]

3.7. C–H α-Fluoroalkenylation using Cr(III)

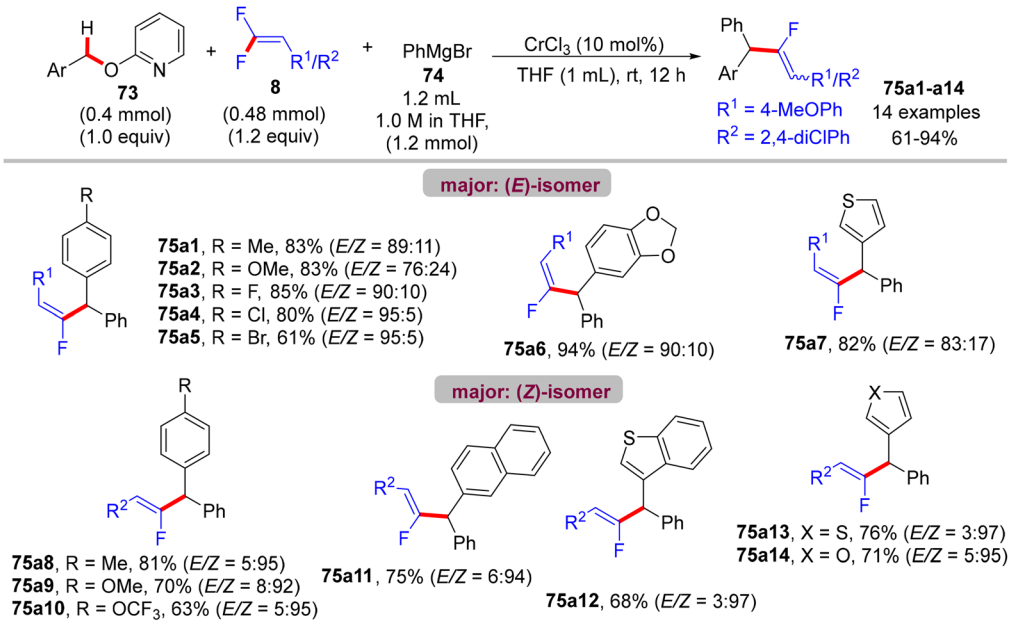
Recently (2023), Zeng *et al.* reported the first synthesis of diarylmethylated monofluoroalkenes **75a–ax** in good yields using $CrCl_3$ as catalyst at room temperature.[46] This catalytic



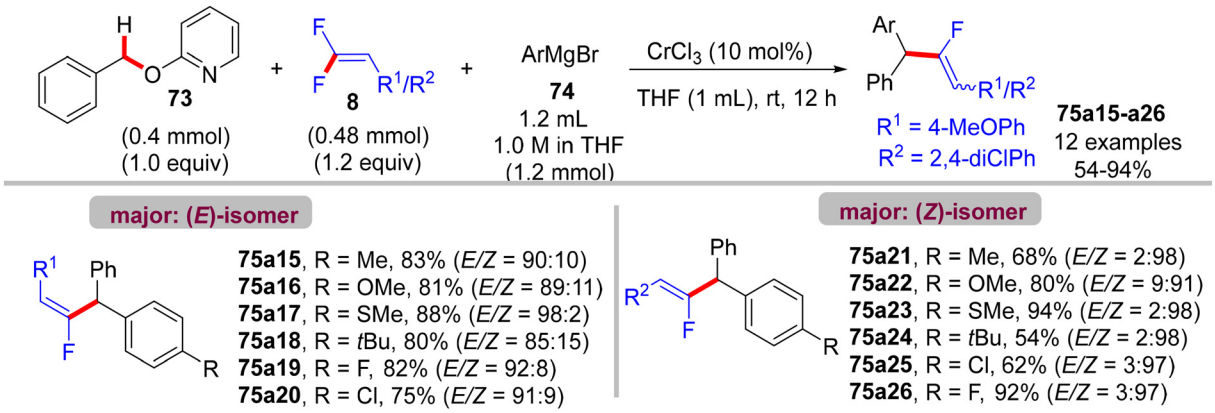
Scheme 66 Substrate scope of **8** in Cr(III)-catalyzed direct $C(sp^3)$–H/C–O α-fluoroalkenylation reaction.

transformation was conducted *via* a step-economy three-component defluorinative cross-coupling of **8** with benzyl 2-pyridinyl ethers **73** and aryl Grignard reagents **74** in good to excellent chemo- and stereoselectivities. The reaction proceeded *via* the merging of C–F and C(sp^3)–H/C–O activation. The authors tested several alternative metal salts ($CrCl_2$, $Cr(acac)_3$, $CoCl_2$, $NiCl_2$, and $FeCl_2$), but $CrCl_3$ proved the most effective, and optimal conditions were settled as follows: **8** (0.48 mmol), **73** (0.4 mmol), **74** (1.2 mmol), $CrCl_3$ (0.04 mmol, 10 mol%), and THF (1 mL) at room temperature for 12 h. Schemes 66–68 show the substrate scope of the three-component reactants. The ratio of *E*/*Z* stereoselectivity was determined by GC analysis. Obviously, the stereoselectivity of **75a–a26** depends predominantly on the electronic profile of the substituents on the aromatic ring of the fluorinated synthons **8**, where the EDGs afforded thermodynamically unfavorable (*E*)-isomer as a major one, and *vice versa*. Though the reason for (*E*)-isomer selectivity is not mentioned and, at present, is not clear yet.

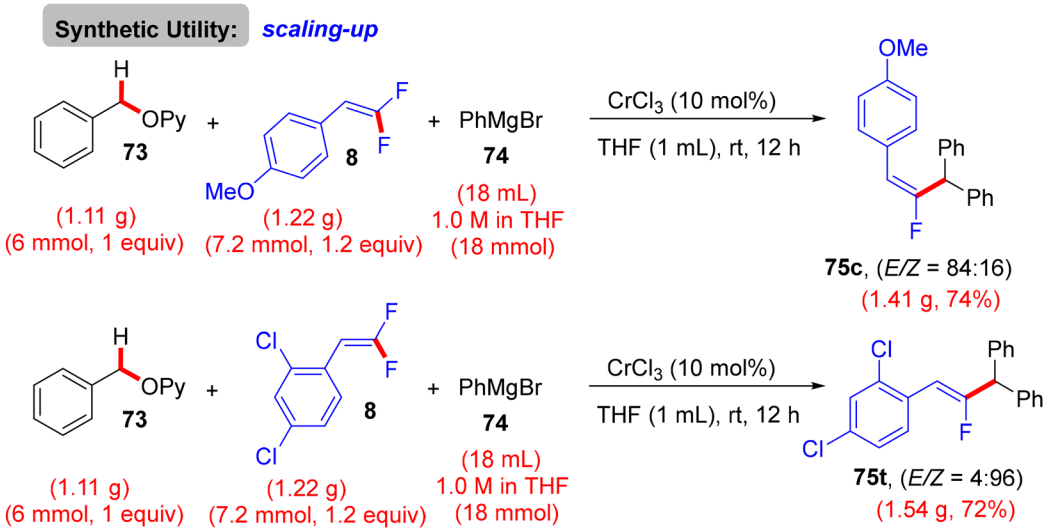
The gram-scale synthesis of **75c** and **75t** is depicted in Scheme 69.[46] The authors also exhibited a plausible mechanism, which needed further experimental and theoretical studies. Initially, Grignard reagent **74** reduced the pre-catalyst $CrCl_3$ to produce an active low-valent Cr (L_nCr), probably by reductive elimination. Benzylic C–O activation produced the intermediate **T**. Next, deprotonation by **74** afforded the bimetalated complex **U**, which was followed by transmetallation with **74** to yield **V**. Removing $MgBr_2$ by breaking the four-membered ring afforded the C–C coupling intermediate **W**. π-Coordination of olefin **8** with **W** yielded **X**, followed by migratory insertion to install **Y**. Finally, β-F elimination of **Y** exhibited the desired three-component coupling product **75** (Scheme 70).[46]



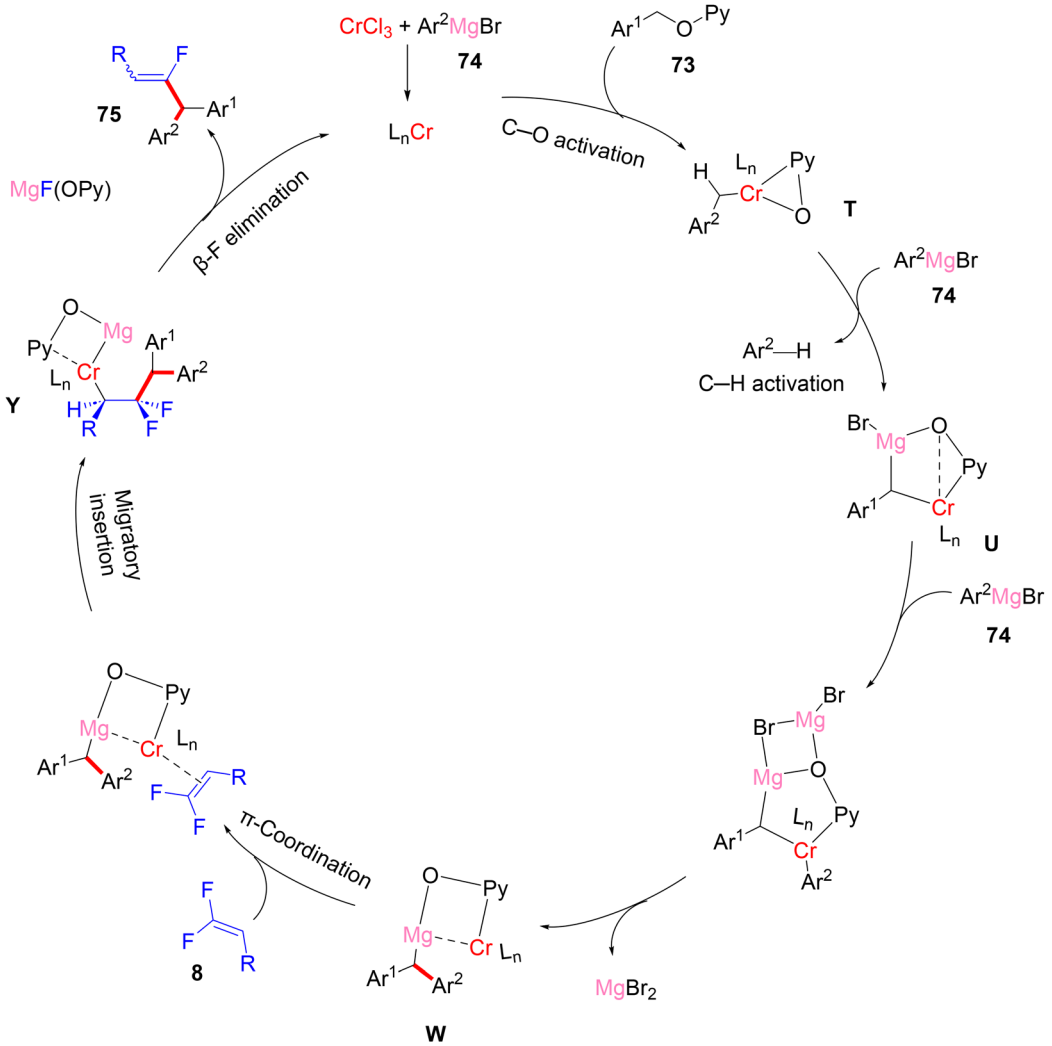
Scheme 67 Substrate scope of **73** in Cr(III)-catalyzed direct C(sp^3)–H/C–O α-fluoroalkenylation reaction.



Scheme 68 Substrate scope of **74** in Cr(III)-catalyzed direct C(sp^3)–H/C–O α-fluoroalkenylation reaction.



Scheme 69 Gram-scale synthesis of **75c** and **75t**.



Scheme 70 Proposed catalytic cycle of Cr(III)-catalyzed direct C(sp^3)–H/C–O α-fluoroalkenylation of three-component system (**73**, **74**, and **8**).

4. Conclusions and outlook

In the current review, we highlighted the progress of TM-catalyzed direct C–H α-fluoroolefination using easily accessible and commercially available *gem*-(bromo/di)fluoroolefins as fluorinated synthons. As seen throughout the reported procedures, several monofluoroalkenes are directly obtained in atom- and step-economically scalable pathways with high stereoselectivity and functional group tolerance. Importantly, some of the generated monofluoroalkenes are subjected to LSF to access distinct polyfunctionalized compounds. As a result, these approaches are suitable and applicable for the stereoselective synthesis of highly functionalized alkenes. Consequently, they can serve as a promising alternative to traditional cross-coupling transformations, the Wittig reaction or olefin metathesis. Nonetheless, numerous obstacles persist. Despite the achieved mild conditions and the use of earth-abundant TM-based protocols, such as those reported by Ackermann, Loh, and Li, the development of milder, somewhat "greener", and low catalyst loading approaches remains imperious. As shown above, expensive Rh-based catalysts are widely used, so expanding the applicability of cost-effective first-row TM (3d) catalysts as a surrogate pathway is highly desirable. Until now, heterogenous catalysis has not been examined in the α-fluoroalkenylation reaction. The limitation of the substrate scope is another challenge that needs to be addressed by innovative procedures to expand their applicability for the synthesis of highly complex molecules. Further experimental and theoretical mechanistic investigations, such as the isolation of stable metallocyclic intermediates and the probing of the proposed individual mechanistically relevant alkene-insertion step and following eliminations, are recommended to gain more insights and achieve a better understanding of kinetics. Furthermore, only one study by Wang and Li[30] reported the synthesis of cyclic monofluoroalkenes **29** and **34**; thus, accessing these compounds is also desirable and needs more attention. In comparison with **8** or **25**, *gem*-difluoroacrylate **38** as a fluorinated synthon was employed once in Loh's study.[32] Therefore, it and **2** (*gem*-bromofluoroalkenes) need more examination in the direct α-fluoroalkenylation reaction. Worthy of note, all the reported α-fluoroalkenylation protocols are C(sp^2)–H functionalization, except for the two examples of C(sp^3)–H activation documented by Li[34] and Zeng,[46] proving the extension of this research area, is a topic of great interest. Microwave-assisted α-fluoroalkenylation is considered in none of the surveyed reports, and it is suggested that more investigation on the use of this technique might prove valuable.

Last but not least, the possible intervention of incidental soluble metal nanoparticles[72] stemming from the decomposition of the metal complexes[73–76] in any of the reported catalytic procedures, which are all characterized by their use of complex mixtures of reagents, was not investigated or at least mentioned, if not ruled out, to the best of our knowledge. Similarly, most of the studies lack an assessment of the role of the additives and "basic promotors"[77] of the catalysis, which might be a must for further improvements away from the "trial and error" approach. This is an issue that clearly takes on a rather central relevance if one envisages the scaling to industrial levels of any of the reactions described here. The chemical speciation of the metal-containing species after the catalysis and the clear establishment of the fate of the catalyst after the catalytic event[78] are particularly desirable if one seeks the responsible development of promising industrial processes that include rational waste management. The development of new catalysts under the banner of sustainability and environmental acceptability[79] requires further efforts to establish the fate of the TM-catalysts after their task has been completed.

Finally, while great progress has been made, the development of the direct C–H α-fluoroolefination method seems within reach, and explorations of its chemistry might open new avenues for the synthesis of high-value organic compounds.

Abbreviations

CMD	Concerted metalation-deprotonation
DCE	1,2-Dichloroethane
DFT	Density functional theory
DG	Directing group
dibm	Diisobutyrylmethane
DMSO	Dimethyl sulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane
equiv	Equivalents
ERG/EDG	Electron-releasing (donating) group
EWG	Electron-withdrawing group
HAT	Hydrogen atom transfer
HFIP	Hexafluoroisopropanol
I	Inductive effect
KHMDS	Potassium bis(trimethylsilyl)amide
KIE	Kinetic isotope effect
LCD	Liquid crystal displays
LSF	Late-stage functionalization
MeOH	Methanol
NBO	Natural bond orbital
OTs	Tosylate group
^{P}DG	Permanent directing group
phen	1,10-Phenanthroline
^{R}DG	Removal directing group
S_NV	Vinylic nucleophilic substitution
^{T}DG	Transient directing group
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFE	Trifluoroethanol
Ts	Tosyl group

Author contributions

The manuscript was written through the contributions of all authors. All authors have given their approval to the final version of the manuscript.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

The authors declare no competing financial interests.

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