DOI: 10.1002/adsc.201900220
Advanced Synthesis & Catalysis

Cobalt(III)/Rhodium(III)-Catalyzed Regio- and Stereoselective Allylation of 8-Methylquinoline via sp^3 C–H Activation

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Manuscript received: February 16, 2019; Revised manuscript received: May 16, 2019;
Version of record online: July 12, 2019

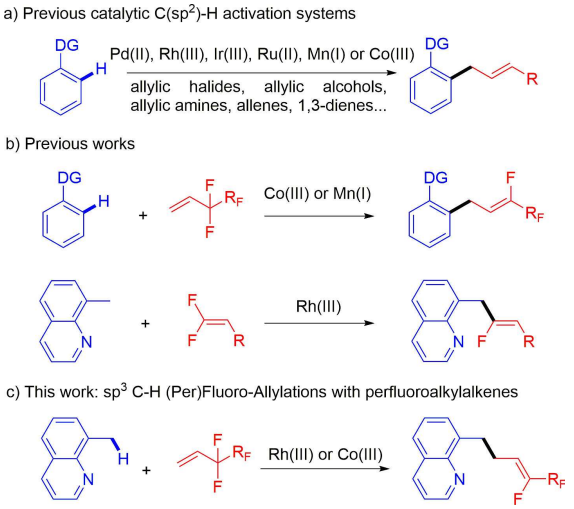
Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.201900220

Abstract: Regio- and stereoselective benzylic allylation of 8-methylquinolines with (per)fluoroalkyl olefins has been realized via benzylic C–H activation and subsequent C–F cleavage. Both cobalt(III) and rhodium(III) catalysts can effect this transformation in good to high efficiency. The Rh(III)-catalyzed system proceeded under moderate conditions with decent substrates scope, providing (*Z*)-alkenyl fluorides with good to excellent regio- and stereoselectivity.

Keywords: C–H activation; fluoroalkyl olefin; 8-methylquinoline; Cobalt(III); Rhodium(III)

Organofluorines represent a class of privileged structural motifs,[1] and the introduction of fluorine atoms into organics enables distinct enhancements of their polarity, solubility, lipophilicity, and metabolic stability. Its small size, high electronegativity, and high carbon-fluorine bond energy conduce to significant changes in physical, chemical, and biological properties. The size of a molecule does not change appreciably while the interactions with neighbouring groups may be profoundly affected. Thus, fluorine can alter the molecular conformation so as to enhance the selectivity and binding affinity to target protein. It also serves to block metabolically labile sites to increase the metabolic stability of drugs.[2,3] Therefore, the development of practical and efficient methodologies to introduce fluoroalkyl groups has received increasing attention.

On the other hand, allylation reactions have received significant attention as they provide direct access to various functionalized complex structures. In particular, introduction of branched fluorinated allyl groups may significantly improve the biological properties and applications of organics. Numerous methodologies have been developed for synthesis of allylated structures. Traditional routes such as Lewis acid-catalyzed,[4,5] Friedel-Crafts-type allylation,[6] Claisen rearrangement of allyl ethers, metal-catalyzed cross-coupling[7] have been extensively investigated. In addition, metal-catalyzed C–H activation/allylation of arenes represents a straightforward and atom-economical process. Thus, palladium,[8] ruthenium,[9] rhodium,[10] iridium,[11] and other metals have been widely applied as catalysts for allylation of C–H bonds using various allylating reagents including allyl halides, allylic alcohols, allylic amines, allenes, and 1,3-dienes via a C–H activation pathway (Scheme 1a).[8–14] Nevertheless, examples of introduction of branched fluorinated allyl groups are still limited. Recently, Loh, Wang, Li, and other groups developed monofluoroleflination of arenes via C(sp^2)–H activation using Ru (II),[15] Rh(III),[16] Co(III),[17] and Mn(I)[18] catalyst. Ackermann extended the allylation systems using earth abundant metals such as Co(III) and Mn(I). In addition, Ackermann also realized C(sp^2)–H allylation of arenes using perfluoroalkyl olefins.[19] However, direct allylation of sp^3 C–H bonds together with simultaneous introduction of fluoroalkyl groups remains rarely investigated. Recently, our group reported Rh(III)-catalyzed benzylic C–H α-fluoroalkenylation of 8-methylquinolines (Scheme 1b).[20] In continuation of

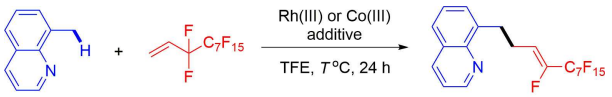


Scheme 1. Coupling of aromatic and perfluoroalkylalkene via C–H activation, DG = directing group.

our interest in C(sp^3)–H bond functionalization, we now reported cobalt(III) and rhodium(III)-catalyzed regio- and stereoselective allylation of 8-methylquinoline.

The coupling of 8-methylquinoline (**1a**) and a perfluoroalkyl olefin (**2a**) was chosen as the model reaction (Table 1). No desired reaction occurred when the reaction was catalyzed by [Cp*Co(CO)I_2] in TFE in the absence of any additive (Table 1, entry 1). The desired allylation product **3aa** started to be detected when $AgNTf_2$ was introduced (entry 2). Upon further introduction of $Ca(OH)_2$, the yield was improved to 12%. Interestingly, the use of $Zn(OAc)_2$ (0.5 equiv.) as an additive afforded the allylated product in 50% yield with a moderate *Z*/*E* ratio (7:1, entry 4), which likely accelerated the C–H activation process. Different calcium salts including CaO, $CaCO_3$, and $Ca(OAc)_2$ were then screened, and CaO was the best choice, where the calcium salt likely scavenges the HF coproduct and facilitates the anion change of the Rh(III)F or Co(III)F species to the active Rh(III)OAc or Co(III)OAc intermediates (entries 5–7). To our delight,

Table 1. Optimization Studies[a]



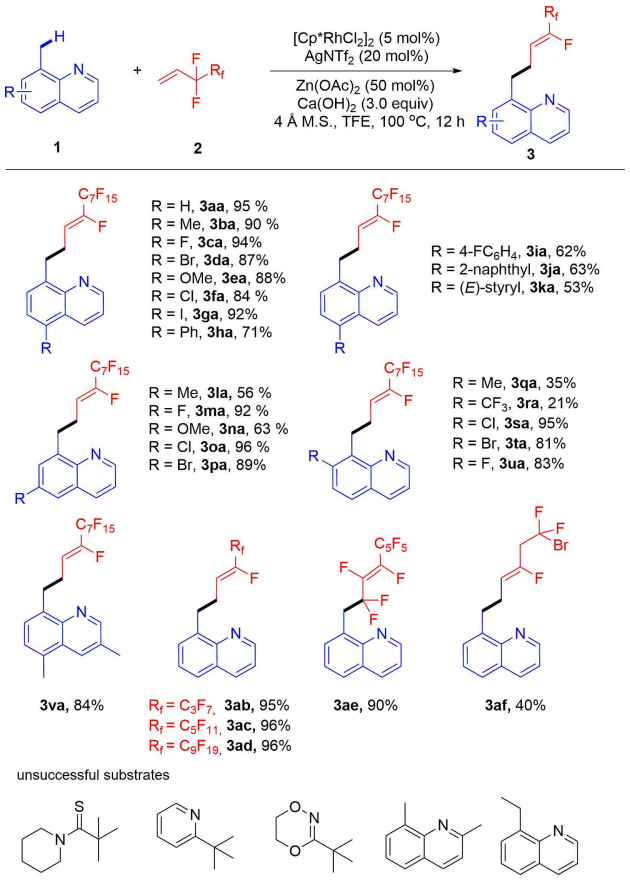
1a 2a 3aa

Entry	Cat.[b]	T (°C)	Solvent	Additive (equiv.)	Yield(%)[c]
1[d]	A	80	TFE	–	< 5
2	A	80	TFE	–	8
3	A	80	TFE	$Ca(OH)_2$ (3)	12
4	A	80	TFE	$Ca(OH)_2$ (3)/$Zn(OAc)_2$ (0.5)	50
5	A	80	TFE	CaO (3)/$Zn(OAc)_2$ (0.5)	70
6	A	80	TFE	$CaCO_3$ (3)/$Zn(OAc)_2$ (0.5)	trace
7	A	80	TFE	$Ca(OAc)_2$ (3)/$Zn(OAc)_2$ (0.5)	trace
8[e]	A	**80**	**TFE**	**CaO (3)/$Zn(OAc)_2$ (1.5)**	**86**
9	A	80	DCE	CaO (3)/$Zn(OAc)_2$ (1.5)	n.r.
10	A	80	dioxane	CaO (3)/$Zn(OAc)_2$ (1.5)	n.r.
11	A	80	PhMe	CaO (3)/$Zn(OAc)_2$ (1.5)	n.r.
12[f]	A	80	MTBE	CaO (3)/$Zn(OAc)_2$ (1.5)	30
13	A	80	*t*-AmOH	CaO (3)/$Zn(OAc)_2$ (1.5)	< 5
14	A	80	HFIP	CaO (3)/$Zn(OAc)_2$ (1.5)	< 5
15[g]	B	80	TFE	$Ca(OH)_2$ (3)/$Zn(OAc)_2$ (0.5)	93
16[h]	B	**100**	**TFE**	**$Ca(OH)_2$ (3)/$Zn(OAc)_2$ (0.5)**	**95**
17	A	80	TFE	$Ca(OA_C)_2$ (1)/$Zn(OAc)_2$ (1.5)	trace

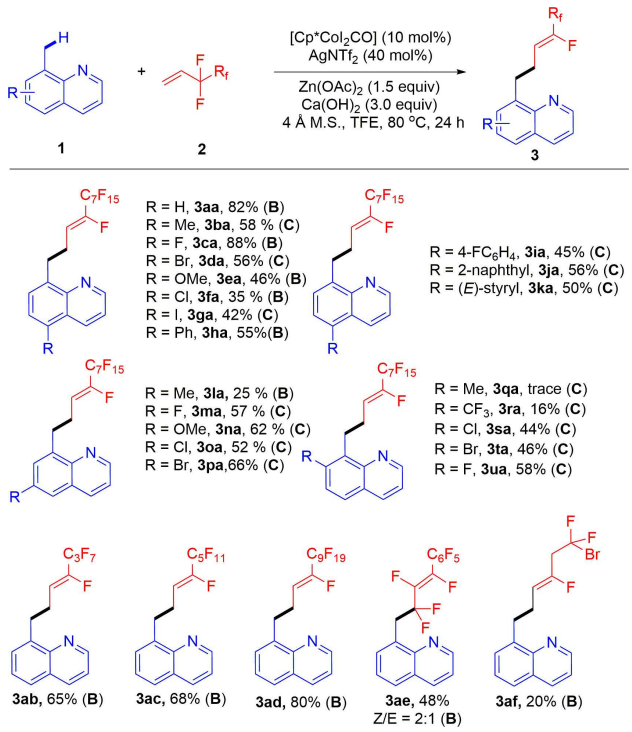
[a] Reaction conditions: 8-methylquinoline **1a** (0.2 mmol), perfluoroalkylalkene **2a** (0.3 mmol), catalyst, silver salt, and an additive in TFE (2.0 mL) under Ar for 24 h. The ratio of Z/E in parenthesis was determined by ^{1}H NMR spectroscopy (Z/E = 7:1 unless otherwise mentioned). TFE = 2,2,2-trifluoroethanol, *t*-AmOH = *tert*-Amyl alcohol, HFIP=Hexafluoroisopropanol.
[b] Catalyst **A** = [Cp*Co(CO)I_2] (10 mol%)/$AgNTf_2$ (20 mol%), Catalyst **B** = [Cp*$RhCl_2$]$_2$ (5 mol%)/$AgNTf_2$ (20 mol%).
[c] Isolated yield after chromatography.
[d] silver-free.
[e] $AgNTf_2$ (40 mol%), *Z*/*E* = 7:1.
[f] *Z*/*E* = 1:1.
[g] *Z*/*E* > 20:1.
[h] 12 h, *Z*/*E* > 20:1.

increasing the amount of $Zn(OAc)_2$ improved the yield of **3aa** to 86% yield (entry 8). Solvent screening verified that TFE was optimal due to the high polarity and ionizing ability compared to HFIP and ^{t}AmOH. Both the reaction efficiency and the Z/E selectivity were low in other solvents (entries 9–14). Furthermore, switching the catalyst from [Cp*Co(CO)I_2] to [Cp*RhCl_2]$_2$ led to nearly quantitative isolation of the product with excellent stereoselectivity (Z/E > 20/1, entry16). Trace of the product was obtained when one equiv. of CaO was used under Co(III) catalysis (entry 17).

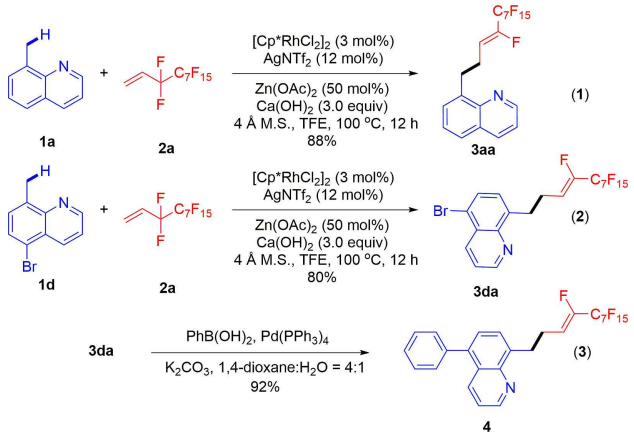
We next investigated the scope and limitation of this transformation using [Cp*RhCl_2]$_2$ as the catalyst. The applicability of various 8-methylquinolines (**1a**–**1u**) in the coupling with (per)fluoalkyl olefins was examined (Scheme 2). A variety of halogen groups (F, Cl, Br, and I) at the 5-position were tolerated, affording the desired products in 84–94% yields (**3ca**–**3da**, **3fa**–**3ga**). In addition, 8-methylquinolines bearing electron-donating groups (Me and OMe) were also effective substrates (**3ba**, **3ea**). Substrates bearing phenyl, 4-FC_6H_4, 2-naphthyl, and (*E*)-styryl groups coupled to give the corresponding products in good to excellent yields (**3ha**–**3ka**). Various substitutes at of the 6- and 7- positions were also compatible (**3la**–**3pa**, **3sa**–**3ua**). The reaction seems sensitive to steric hindrance at the 7-position in that introduction of a 7-Me and 7-CF_3 group significantly lowered the yield (**3qa**, **3ra**). To our delight, multisubstituted substrate also reacted smoothly in the reaction system, afforded the product (**3va**) in 84% yield. Unfortunately, sp^3 C–H substrates such as 2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione, 2-(*tert*-butyl)pyridine, 3-(tert-butyl)-1,4,2-dioxazine, 2-methylquinoline, and 7-ethylquinoline failed to exhibit reactivity under the standard reaction conditions. Next, the generality of the fluoroalkyl olefins was examined. Olefins bearing fluoroalkyl groups of different chain lengths underwent smoothly coupling with **1a** in high efficiency (**3ab**–**3ad**). In addition,



Scheme 2. Scope of Rh(III)-Catalyzed System. [a]Reaction conditions A: **1** (0.2 mmol), **2** (0.3 mmol), [Cp*RhCl_2]$_2$/$AgNTf_2$ (5 mol%/20 mol%), $Zn(OAc)_2$ (0.5 equiv.), $Ca(OH)_2$ (3.0 equiv.), and 4 Å M.S. (100 mg) in TFE (2.0 mL) at 100 °C for 12 h in a sealed tube under Ar. [b]Isolated yield. [c]The ratio of Z/E in parenthesis was determined by ^{1}H NMR spectroscopy (Z/E > 20:1 unless otherwise mentioned).



Scheme 3. Scope of Co(III)-Catalyzed System. [a]Reaction conditions B: **1** (0.2 mmol), **2** (0.3 mmol), [Cp*Co(CO)I_2]/$AgNTf_2$ (10 mol%/40 mol%), $Zn(OAc)_2$ (1.5 equiv.), CaO (3.0 equiv.), and 4 Å M.S. (100 mg) in TFE (2.0 mL) at 80 °C for 24 h in a sealed tube under Ar. Reaction conditions C: **1** (0.2 mmol), **2** (0.3 mmol), [Cp*Co(CO)I_2]/$AgNTf_2$ (10 mol%/40 mol%), Zn$(OAc)_2$ (1.5 equiv.), $Ca(OH)_2$ (3.0 equiv.), $Fe(OTf)_2$ (0.5 equiv.), and 4 Å M.S. (100 mg) in TFE (2.0 mL) at 80 °C for 24 h in a sealed tube under Ar. [b]Isolated yield. [c]The ratio of Z/E in parenthesis was determined by ^{1}H NMR spectroscopy (Z/E = 7:1 unless otherwise mentioned).



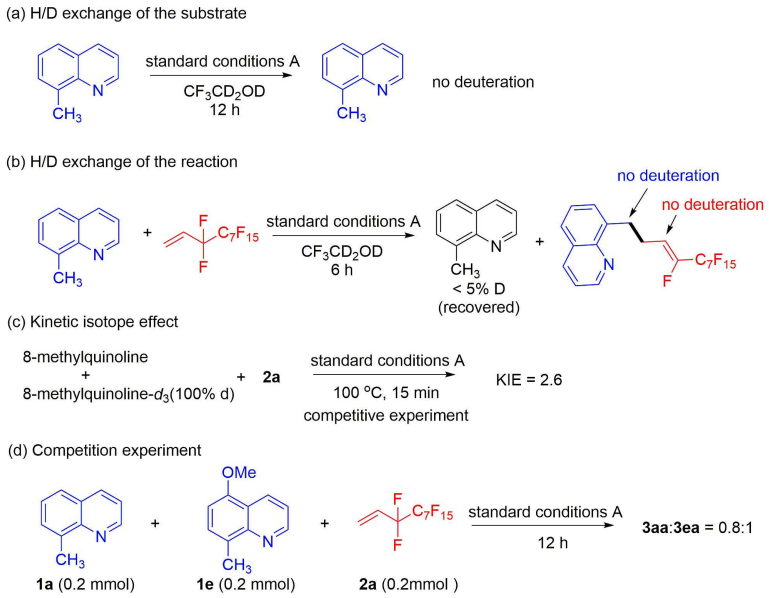
Scheme 4. Derivatization Reactions.

1,2,3,4,5-pentafluoro-6-(perfluoroallyl)benzene and 4-bromo-3,3,4,4-tetrafluorobut-1-ene were also applicable substrates, lead to formation of **3 ae** and **3 af** in 90% and 40% yield, respectively.

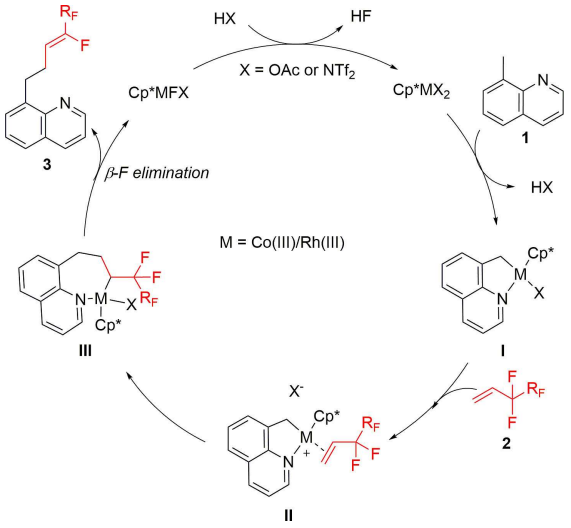
The versatility of Co(III) catalysis has been reflected in both C–H activation and C–F cleavage (Table 1, entry 8). Thus, the scope of Co(III)-catalyzed system was then examined. 8-Methylquinolines bearing both electron-donating and -withdrawing groups at different positions all underwent smooth coupling with olefin **2 a** to afford the desired products in moderate to good yield (**3 aa**–**3 pa**). 8-Methylquinolines bearing a relatively small 7-substituent reacted in moderate efficiency (**3 ra**–**3 ua**). However, introduction of a 7-methyl groups inhibited the reaction (**3 qa**), indicating the sensitivity to steric and electronic perturbation. The reaction also tolerated a similar scope of fluoroalkylated olefins. In general, the Co(III) catalyzed system is less efficient and less stereo-selective than the Rh (III)-catalyzed system (Scheme 3).

The scalability of this transformation was demonstrated in Rh(III)-catalyzed gram-scale (2 mmol) synthesis under a lower catalyst loading (eq 1–2, Scheme 4). Thus, both products **3 aa** and **3 da** were accessed in high yields (88% and 80%). Derivatization of **3 da** in Suzuki coupling was also examined. Coupling with phenylboronic acid in the presence of $Pd(PPh_3)_4$ afforded a biaryl product **4** in 92% yield (eq 3).

We conducted several experiments to explore mechanism of this coupling system (Scheme 5). To probe the Rh-catalyzed C–H activation process, H/D exchange of 8-methylquinoline (**1 a**) with CF_3CD_2OD was conducted in the absence and presence of the olefin coupling partner **2 a**. ^1H NMR analysis of the recovered substrate and the coupled product revealed essentially no H/D exchange either in the recovered starting material or the product (Schemes 5a, 5b). These results suggested irreversibility of the C–H activation. Then, the kinetic isotope effect (KIE) of this coupling reaction was measured. Intermolecular competition between **1 a** and **1 a**-d_3 gave a value of $k_H/k_D = 2.6$, suggesting that cleavage of the methyl C–H bond is likely involved in the turnover-limiting step (Scheme 5c). In addition, a competition reaction has been carried out using two electronically differentiated 8-methylquinolines (**1 a**, **1 e**) with **1 b** to afford a mixture of **3 aa** and **3 ea** in a ratio of 0.8:1, which revealed that the electron-rich 8-methylquinoline is kinetically more reactive.



Scheme 5. Mechanistic Studies.



Scheme 6. Proposed Catalytic Cycle.

On the basis of priror literature precedents, a plausible catalytic cycle is proposed in Scheme 6.[17–20] Starting from a MCp^*X_2 catalyst (M=Rh(III) or Co (III), X=OAc or NTf_2) catalyst, a five-membered metallacyclic intermediate **I** is produced via C(sp^3)–H bond activation of 8-Methylquinolines, together with formation of HX. Olefin coordination then affords the intermediate **II**. Subsequent M–C(alkyl) migratory insertion into the C=C bond generates a seven-membered metalacyclic intermediate **III**. Subsequent selective β-F elimination via a *syn*-coplanar[3a,17] transition state delivers the product **3** together with regeneration of a M(III) fluoride. The *Z* olefin was obtained as the major product probably due to minimized steric hindrance between the alkyl and R_f. Anion exchange with HX then regenerates the active M(III) catalyst for the next cycle.

In summary, we have developed rhodium(III) and cobalt(III)-catalyzed fluorallylation of 8-methylquinolines and (per)fluoroalkyl olefins. The reaction seems more reactive and selective under Rh(III)-catalyzed conditions. This catalytic system produced a series of *sp*3 C–H allylated products in good regio and seteroselectivity under mild and redox-neutral conditions. Future studies will be directed to metal-catalyzed coupling of *sp*3 C–H bonds with other unsaturated coupling partners.

Experimental Section

General Procedure for the Synthesis of Compound 3.

Conditions A: 8-methylquinoline **1** (0.2 mmol), (per)fluoroalkyl olefin **2** (0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgNTf_2$ (20 mol %), $Zn(OAc)_2$ (0.5 equiv.) $Ca(OH)_2$ (3.0 equiv.), 4 Å M.S. (100 mg) in TFE (2.0 mL) at 100 °C for 12 h in a sealed tube under Ar. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to afford the desired product. The ratio of *Z*/*E* in parenthesis was determined by ^{1}H NMR spectroscopy (*Z*/*E* > 20:1 unless otherwise mentioned).

Conditions B: 8-methylquinoline **1** (0.2 mmol), (per)fluoroalkyl olefin **2** (0.3 mmol), $[Cp^*Co(CO)I_2]/AgNTf_2$ (10 mol%/40 mol %), $Zn(OAc)_2$ (1.5 equiv.), CaO (3.0 equiv.), and 4 Å M.S. (100 mg) in TFE (2.0 mL) at 80 °C for 24 h in a sealed tube under Ar. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to afford the desired product. The ratio of *Z*/*E* in parenthesis was determined by ^{1}H NMR spectroscopy (*Z*/*E* = 7:1 unless otherwise mentioned).

Conditions C: 8-methylquinoline **1** (0.2 mmol), (per)fluoroalkyl olefin **2** (0.3 mmol), $[Cp^*Co(CO)I_2]/AgNTf_2$ (10 mol%/40 mol %), $Zn(OAc)_2$ (1.5 equiv.), $Ca(OH)_2$ (3.0 equiv.), $Fe(OTf)_2$ (0.5 equiv.), and 4 Å M.S. (100 mg) was heated in TFE (2.0 mL) at 80 °C for 24 h in a sealed tube under Ar. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to afford the desired product. The ratio of *Z*/*E* in parenthesis was determined by ^{1}H NMR spectroscopy (*Z*/*E* = 7:1 unless otherwise mentioned).

Acknowledgements

The NSFC (Nos. U1804283 and 21525208) and research fund from the Henan Normal University (5101034011009) are gratefully acknowledged.

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