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Authors: Cheng-Qiang Wang, Yu Zhang, and chao feng

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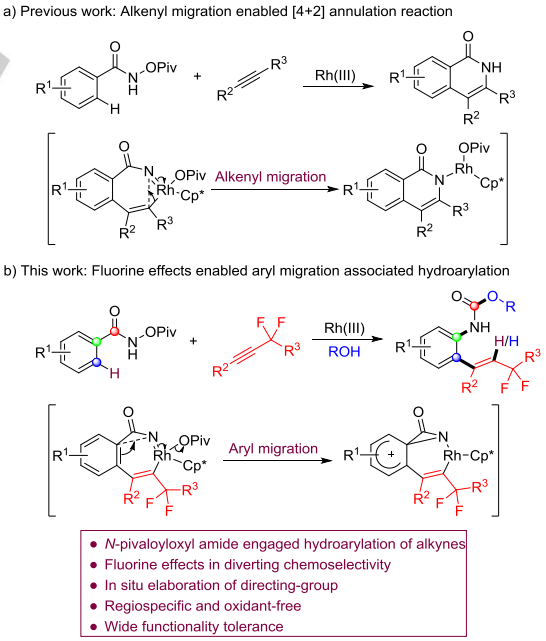
Fluorine Effects on Guiding Group Migration via Rh(V) Nitrenoid Intermediate

Cheng-Qiang Wang, Yu Zhang and Chao Feng*

Abstract: An unprecedented Rh(III)-catalyzed hydroarylation of α,α-difluoromethylene alkynes with *N*-pivaloxyl aroylamides through sequential C−H activation and aryl migration was detailed herein. A large array of α,α-difluoromethylene alkynes and *N*-pivaloxyl aroylamides were well amenable to this transformation, providing a novel synthetic protocol for the construction of difluorinated 2-alkenylaniline derivatives in high yields and excellent regioselectivity. Notably, the unique fluorine effects were uncovered to underlie the thus unconventional reaction manifold.

Fluorine-containing organic compounds constitute a rich resource for discovering lead candidates that possess unique physiochemical and biological properties.[1] Consequently, the development of new synthetic methods for the introduction of fluorinated fragments into organic molecules is gaining increasing attention from the synthetic community,[2] however, the inconsistent reactivity profile of fluorinated reagents with that of the non-fluorinated congeners should not be underappreciated.[3] The fluoroalkylation reaction, which allows a direct incorporation of fluorine-containing alkyl fragments, proves to be a fertile domain for the expedient construction of organofluorine molecules.[4] Continuing efforts in this direction have eventually led to a plethora of direct C−H bond fluoroalkylations.[5] Notwithstanding the advance obtained, the majority of efforts have been paid to the fluoroalkylation of arene derivatives with little attention being drew to the development of novel synthetic strategies that entail easy access to alkenyl fluoroalkane architectures.[6]

As an important class of structural motifs that found widespread use in synthetic chemistry, *ortho*-alkenylated aniline derivatives and their preparation have attracted considerable attention from organic chemists.[7] The well-known Suzuki, Mizoroki-Heck couplings, Fujiwara-Moritani reaction, directing group assisted dehydrogenation coupling and hydroarylation of alkyne represent the main current strategies.[8-11] While synthetically enabling, prominent limitations with respect to these protocols still remain, such as the requirement of substrates pre-functionalization, stoichiometric amount of external oxidants and/or harsh reaction conditions. Therefore, the development of novel and efficient synthetic protocols which allow the straightforward access to these structural motifs is still highly desirable. Herein, we would like to report the first example of fluorine effects induced skeleton rearrangement associated hydroarylation of internal alkynes, a scenario that not only nicely fulfills those synthetic demands but more importantly elicits an unprecedented reactivity divergence engendered by the fluorine substituent. It is worth noting that previous reports have revealed *N*-pivaloyloxyl amides as the privileged substrates for C−H activations,[12] which engage alkynes in [4+2] annulation reactions via alkenyl group migration and protonation almost without exception (Scheme 1a).[13] Experimental endeavors substantiate that the introduction of fluorine atoms adjacent to the alkyne group has engendered dual roles in such transformation: i) inducing the polarization of alkyne functionality, which in turn guarantee the otherwise nontrivial regioselective migratory insertion in the case of unconjugated alkyne substrates; ii) the induction effect of fluorine substituents detracts from the migratory aptitude of alkenyl moiety in the key Rh(V) nitrenoid intermediate,[14] thus favoring the competing aryl group migration. Of note, the unique fluorine effects being explicitly capitalized upon underpin the feasibility of this fundamentally novel synthetic transformation (Scheme 1b). It is also worth mentioning that despite the boom of chelation assisted C−H bond functionalizations,[15] reactions that integrate the ensuing elaboration of otherwise inert directing-groups via skeletal rearrangement or reorganization remain far less developed.[14c,16] Nevertheless, the accomplishment of such strategy would not only be of synthetic importance but bring forth new insight and far-reaching influence to the C−H activation chemistry.



Scheme 1. The dichotomy of group migration in Rh(V) nitrenoid intermediate.

Initially, the model reaction between *N*-pivaloyloxyl benzamide **1a** and *gem*-difluoromethylene alkyne **2a** was tested. After extensive screening of reaction parameters, we found that **4aaa** could be generated in 92% isolated yield when using 2 mol%

[*] C.-Q. Wang, Y. Zhang, Prof. Dr. C. Feng
Institute of Advanced Synthesis (*IAS*), School of Chemistry and Molecular Engineering, Jiangsu National Synergetic Innovation Center for Advanced Materials (*SICAM*)
Nanjing Tech University
30 South Puzhu Road, Nanjing 211816, P. R. China
E-mail: iamcfeng@njtech.edu.cn

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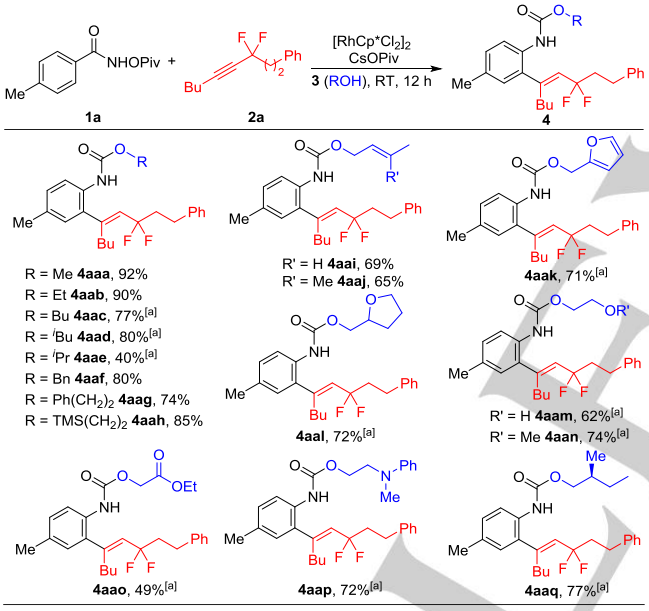
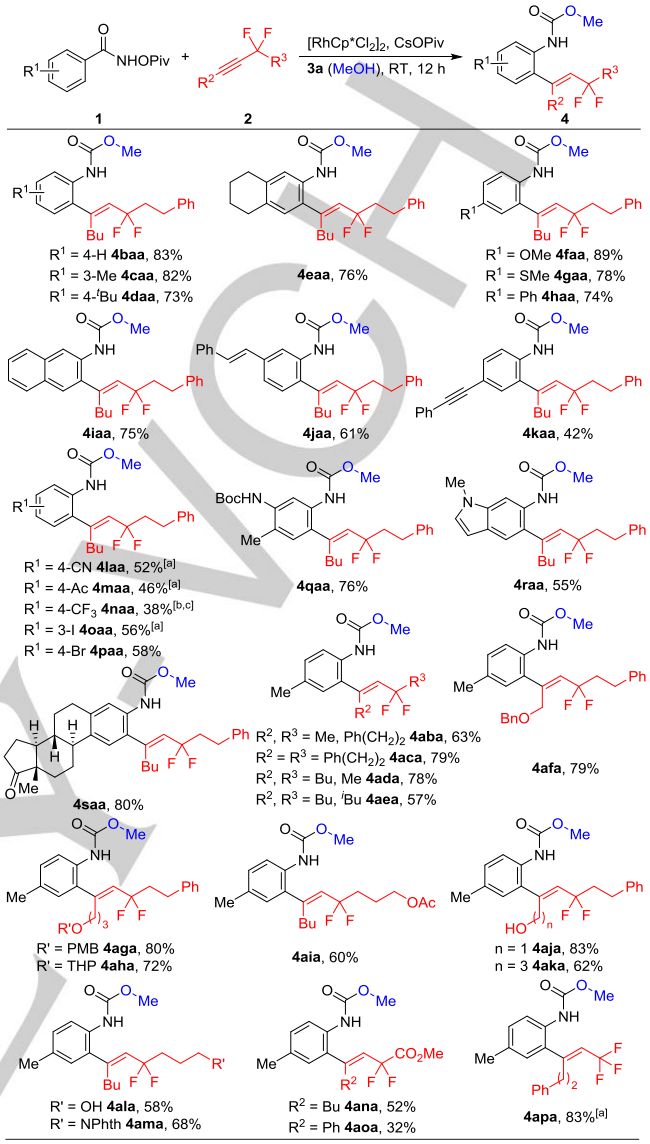
$[RhCp^*Cl_2]_2$ and 30 mol% CsOPiv as the catalyst system in 0.2 M MeOH (**3a**) at ambient temperature.[17] The structure of compound **4aaa** was confirmed by X-ray analysis.[18] With the optimal reaction conditions in hand, the substrate scope of alcohols was investigated. Most saturated aliphatic alcohols were able to be integrated into the desired products in good to high yields (**4aaa**-**4aah**), except ^{i}PrOH which afforded compound **4aae** merely in 40% yield even at elevated temperature probably because of the steric hindrance (Scheme 2). Besides, alcohols bearing alkenyl groups also proved to be good candidates for this conversion (**4aai**-**4aaj**), which indicates the high functional group compatibility of this procedure. To our delight, alcohols containing heterocycles, such as furan and tetrahydrofuran, were also amendable to this protocol, delivering **4aak** and **4aal** in 71% and 72% yield, respectively. Interestingly, product **4aam** as well as a trace amount of difunctionalization product were generated when ethane-1,2-diol was employed. Moreover, methoxyl, ester and tri-substituted amine were also well tolerated in this transformation (**4aan**-**4aap**). Of note, chiral 2-methylbutan-1-ol performed well to afford the desired product **4aaq** in 77% yield.



Scheme 2. Reaction scope of alcohols. Unless otherwise noted, the reactions were carried out at room temperature (28 °C) using **1a** (0.1 mmol), **2a** (0.12 mmol), $[Cp^*RhCl_2]_2$ (0.002 mmol), CsOPiv (0.03 mmol) in **3** (ROH) (0.5 mL) for 12 h and the isolated products were listed. [a] Reaction temperature was 80 °C.

The reaction generality of *N*-pivaloyloxyl amides and *α,α*-difluoromethylene alkynes were subsequently examined (Scheme 3). It was found that a broad range of *N*-pivaloyloxyl amides bearing electron-releasing groups at *meta*- or *para*-position were well tolerated, and the corresponding products were isolated in modest to excellent yields (**4baa**-**4haa**). Amides equipped with alkene or alkyne moieties also turned out to be proper candidates, giving products **4jaa** and **4kaa** in moderate yields. Electron-deficient *N*-pivaloyloxyl amides (**1l**-**1p**) afforded the desired products in slightly diminished yields. Surprisingly,



Scheme 3. Reaction scope of *N*-pivaloyloxyl amides and alkynes. Unless otherwise noted, the reactions were carried out at room temperature using **1** (0.1 mmol), **2** (0.12 mmol), $[Cp^*RhCl_2]_2$ (0.002 mmol), CsOPiv (0.03 mmol) in **3a** (MeOH) (0.5 mL) for 12 h and the isolated products were listed. [a] Reaction temperature was 80 °C. [b] Reaction temperature was 50 °C. [c] [4+2] annulation product was formed in 33% yield.

when **1n** containing a *p*-CF_3 group was employed, the reaction resulted in the generation of the desired product **4naa** in 38% yield and [4+2] annulation product **5na** in 33% yield.[17,19] In addition, when *meta*-substituted substrates were employed, reactions occurred selectively at less hindered site (**4caa**, **4eaa**, **4iaa**, **4jaa**, **4oaa**, **4qaa**-**4saa**). As expected, Br and I were well tolerated, enabling further elaboration through conventional cross-coupling reactions. Furthermore, potentially bioactive indole derivative was also compatible and afforded **4raa** in 55% yield. What particularly worth mentioning was that estrone-derived substrate **1s** worked nicely and provided **4saa** in 80% yield, indicating the applicability of this protocol to the late-stage modification of complex molecules. With respect to the alkyne

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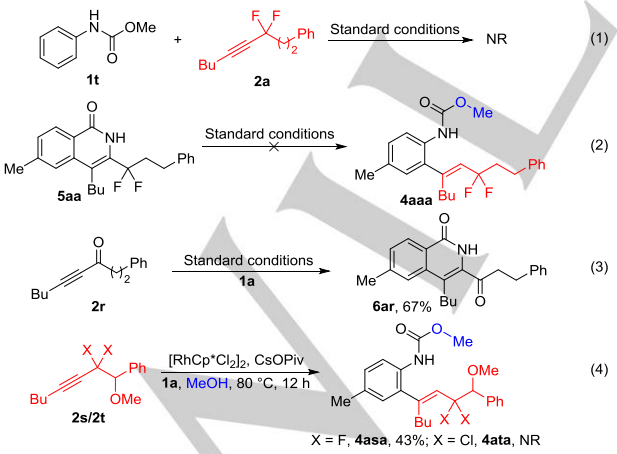
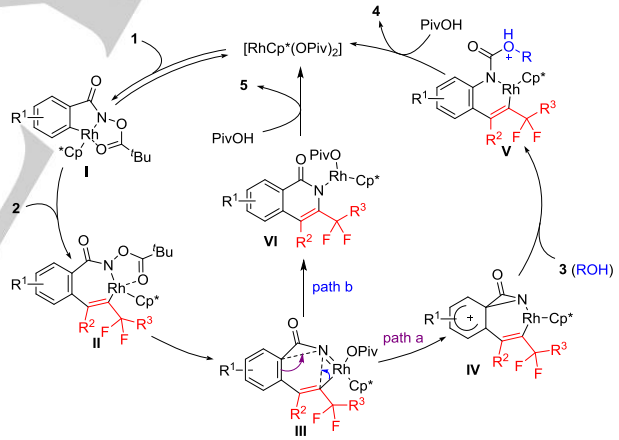
reaction partner, most of the *gem*-difluoroalkyne derivatives listed in Scheme 3 engaged in such transformation smoothly and a wide variety of functionalities including alkyl, ether, ester, acetal, hydroxyl, phthalimidyl all proved to be nicely accommodate, which corroborates the generality of this transformation. It also needs to point out that aryl alkyne was also amenable to this reaction, albeit with somewhat diminished reaction efficiency as the formation of product **4aoa**. Whereas reaction between *α,α,α*-trifluoromethylene alkyne **2p** and amide **1a** afforded the desired product **4apa** in 83% yield, no reaction occurred by using mono-fluorine substituted alkyne **2q** as reaction partner.[17]

To gain deep insight into the reaction mechanism, a series of control experiments were carried out (Scheme 4). Competing experiment between amide **1b** and pentadeuterated counterpart **1b-*d*$_5$** led to a KIE value of 4.2, indicating that C−H bond cleavage would be involved as the rate-determining step. The incorporation of 75% deuterium at the vinylic position of product **4aaa-*d*$_4$** was observed when the model reaction was conducted with CD_3OD as reaction solvent, implicating the involvement of a protodemetallation step at the vinylic carbon atom. [17] In order to distinguish whether the Lossen-rearrangement occurs before or after the C−H bond activation step, methyl phenylcarbamate **1t** was subjected to the standard reaction conditions with **2a**, which, however, resulted in only starting materials recovery (eq. 1). In addition, no rearrangement of **1a** occurred in the absence of **2a**.[17] It was also found that the conventional [4+2] annulation product, such as **5aa**, could not be transformed into the desired hydroarylation product under standard conditions, which firmly precludes its intermediacy in the catalytic cycle (eq. 2). To further probe the role of fluorine effects in this intriguing transformation, an extra couple of experiments were examined. The reference reaction between amide **1a** and alkynone **2r** afforded only the normal [4+2] annulation product **6ar**, with no hydroarylation product being observed (eq. 3). The contrasting outcomes of chloro- and fluoro-based alkyne substrates engaged reactions further substantiated involvement of fluorine effects in this reaction (eq. 4).



Scheme 4. Mechanistic studies.

Based on the experimental results, a plausible mechanism was proposed in Scheme 5. Initially, the coordination of amide **1** with active Rh(III) catalyst would trigger *ortho* C−H bond cleavage to form the five-membered rhodacycle **I**. Subsequently, the Rh−C bond of cyclic complex undergoes regioselective insertion into the alkyne **2**, delivering the seven-membered rhodacycle **II**, wherein the regioselectivity profile hinges upon the inherent polarity of *α,α*-difluoromethylene alkyne **2**. Then, the migration of OPiv from N to Rh through a five-membered ring transition state yields the Rh(V) nitrenoid intermediate **III**.[20] At this juncture, two competing reaction pathways could be envisioned: i) the conventional avenue delivers the [4+2] annulation product **5** via intermediated **VI** which arises from alkenyl group migration (path b); ii) the dearomative *ipso*-attack of arene group affords cationic intermediate **IV**, which is labile to alcohol nucleophilic addition induced rearomatization through C−C bond cleavage to afford six-membered rhodacycle **V**. The ensuing protodemetalation of **V** allows the formation of product **4** accompanied by the regeneration of active Rh(III) catalyst (path a). The overwhelming production of aryl migration product **4** is attributed to the inherent property of fluorine substituent which results in the attenuation of the magnitude of alkenyl group migration, considering from both its electronic and steric effects. Furthermore, the electronic effect of the substituent on the aryl of amide substrate closely correlating to the reaction efficiency is also in nice accordance with the proposed reaction mechanism.



Scheme 5. Proposed reaction mechanism.

In summary, by taking advantage of Rh(III)-catalyzed C−H activation of *N*-pivaloyloxyl aroylamides, a straightforward and efficient protocol for the synthesis of difluorinated 2-alkenylaniline derivatives was developed. The fluorine substituents in alkyne substrates were revealed to be essential for diverting the reaction sequence from conventional avenue, thus securing the aforementioned Lossen-rearrangement associated hydroarylation process. Moreover, this reaction proceeds under mild and oxidant-free reaction conditions with a wide spectrum of functionalities being well accommodated. Additionally, the intriguing role of fluorine effects in this transformation provides a

good example showing the contrasting reactivity profiles between fluorinated and non-fluorinated substrates.

Acknowledgements

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Keywords: C-H bond activation• rhodium • hydroarylation • fluorine effects • Lossen-rearrangement

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[17] See Supporting Information for details.

[18] CCDC 1565938 (**4aaa**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[19] The formation of both hydroarylation and conventional [4+2] annulation products was ascribed to the attenuated aryl migration aptitude due to the presence of electron-withdrawing substituents, therefore resulting in the comparability of both alkenyl and aryl migration.

[20] This process is in stark contrast to our previous work, wherein the use of *N*-methoxyl amide solely led to [4+1] annulation products, thus indicating the vital role of the OPiv in preventing β-F elimination of intermediate **II** by the chelation of ester group, see: C.-Q. Wang, L. Ye, C. Feng, T.-P. Loh, *J. Am. Chem. Soc*. **2017**, *139*, 1762-1765.

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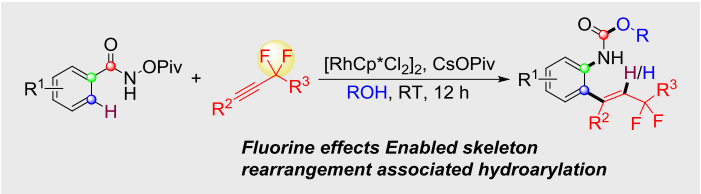

Fluorine effects Enabled skeleton rearrangement associated hydroarylation

C.-Q. Wang, Y. Zhang, C. Feng*

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Fluorine Effects on Guiding Group Migration via Rh(V) Nitrenoid Intermediate

By taking advantage of Rh(III)-catalyzed hydroarylation of α,α-difluoromethylene alkynes with *N*-pivaloyloxyl aroylamides, a straightforward and efficient protocol for the regiospecific synthesis of difluorinated 2-alkenylaniline derivatives was developed. The fluorine substituents in alkyne substrates were revealed to play an essential role in diverting the reaction sequence from conventional avenue, thus securing the nontraditional Lossen-rearrangement associated hydroarylation process.