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C−F Bond Cleavage Enabled Redox-Neutral [4+1] Annulation via C−H Bond Activation

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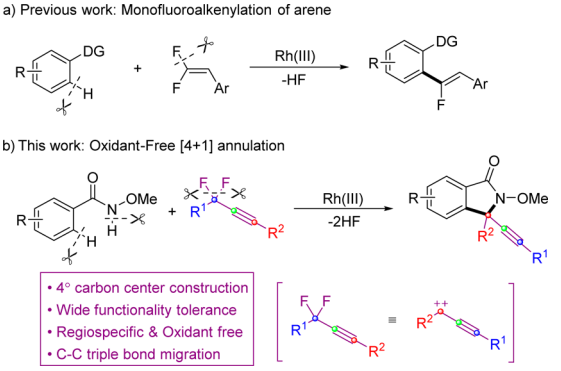
Supporting Information

ABSTRACT: Using α,α-difluoromethylene alkyne as a nontraditional one-carbon reaction partner, a synthetically novel method for the construction of isoindolin-1-one derivatives via Rh(III)-catalyzed [4+1] annulation reaction is reported. The 2-fold C−F bond cleavage not only enables the generation of desired product under an overall oxidant-free condition but also results in a net migration of carbon−carbon triple bond. In addition, the present reaction protocol exhibits a tolerance of a wide spectrum of functional groups due to the mild reaction conditions employed.

The *N*-heterocyclic compounds are widely present in naturally occurring compounds and find a broad application in pharmaceutical research and materials science.[1] For this reason, research investigations targeting their efficient construction represent a blossoming area in the synthetic organic chemistry.[2] Among the methods developed, transition-metal catalyzed intermolecular annulation in its own right constitutes a powerful and privileged strategy.[3] In this context, direct annulation via C−H bond activation has spurred great interest in the synthetic community as they enable a rapid construction of diverse 5 or 6-membered *N*-heterocyclic compounds from simple starting materials without resorting to substrate prefunctionalization, leading to a more environmentally benign and atom-economical process.[4] Within this field, [*n*+2] annulations using alkyne/alkene/allene as the two-carbon unit have been well documented; however, the regioselectivity issue with respect to π system insertion is often of concern especially in the case of sterically or electronically nonbiased reaction partners.[5] By contrast, [*n*+1] type annulations that integrate only one carbon atom essentially obviate such intrinsic issue. Nevertheless, the reaction pattern is comparatively underdeveloped because of the scarcity of readily available one-carbon reaction components.[6] In this regard, the exploration of novel one carbon partner in [*n*+1] annulation protocol is still highly desirable.

With our continuing effort in the realm of C−H bond functionalization and the pursuit of new synthetic methodology for the assembly of pharmaceutical relevant structural motifs,[7] we have quite recently developed an efficient protocol for monofluoroalkene synthesis via Rh(III)-catalyzed C−H/C−F bond activation (Scheme 1a).[8] By harnessing heterolytic C−F bond cleavage,[9] which allows a net removal of two electrons, a redox-neutral C−H bond functionalization was thus attained.[10] Keeping the merit of C−F bond cleavage in mind, a continuing struggle in this arena was pursued. Under this circumstance, it was found that *gem*-difluoromethylene alkyne could act as a one-carbon reaction component in an unprecedented Rh(III)-catalyzed [4+1] annulation with *N*-methoxyl aroyl amide, enabling a straightforward synthesis of multisubstituted isoindolin-1-one derivatives (Scheme 1b). Specifically, the whole transformation was characterized by the following points: (i) an oxidant-free process because of two consecutive C−F bonds cleavage; (ii) a regiospecific annulation with both C−C and C−N bonds formation occurred on the same distal sp hybridized carbon atom, which could be rationalized by electronic activation of alkyne group by *gem*-difluoromethylene functionality; (iii) a relocation of alkyne group throughout the reaction, which resembles a 2-fold S_N2' displacement of fluorine atoms.[9i,11] In addition, the introduction of an alkyne motif would provide a great opportunity for the further synthetic elaboration. It is also of synthetic importance, the unprecedented integration of C−H bond activation, C−F bond cleavage and C−C triple bond

Scheme 1. C−F Bond Cleavage Enabled Redox-Neutral C−H Bond Functionalization



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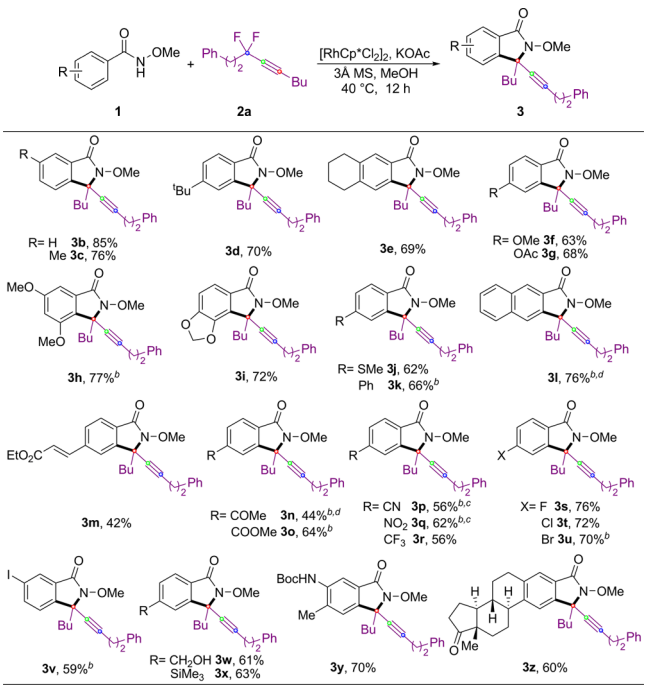
migration provides a conceptually novel strategy for the access of isoindolin-1-one derivatives.[12]

Our study was commenced by examining the model reaction between *N*-methoxyl benzamide **1a** and *gem*-difluoromethylene alkyne **2a** using Rh(III) as the catalyst (see Supporting Information for detail, Table S1). To our delight, the desired product **3a** was formed in 33% yield when the reaction was carried out with $[RhCp^*Cl_2]_2$, NaOAc as catalyst and additive in methanol at 60 °C for 12 h (Table S1, entry 1). Notably, a marked increase of reaction efficiency was observed when molecular sieve was added, among which 3 Å series was superior (Table S1, entries 2−4). For basic additives, KOAc turned out to be optimal (Table S1, entries 2, 5−6). Interestingly, when the reaction temperature was decreased to 40 °C, product **3a** was isolated in 82% yield (Table S1, entry 7). It is also noteworthy that using AcOH instead of KOAc also led to the formation of **3a** in 70% yield (Table S1, entry 8). Furthermore, control experiments indicted that the annulation hardly proceeded in the absence of either $[RhCp^*Cl_2]_2$ or KOAc (Table S1, entries 9 and 10). Intriguingly, the use of a stoichiometric amount of KOAc was found to have a severe impediment to the reaction outcome, implying that the in situ generated HF may play a vital role in the C−F bond cleavage step, presumably via hydrogen bond activation, which is consistent with our previous work.[8]

Having obtained the optimal reaction conditions, we next investigated the generality of this transformation with respect to the *N*-methoxyl benzamide derivatives, and the results are summarized in Table 1. It is delightful to find that both electron-donating and electron-withdrawing substituents were well accommodated, delivering the desired products in moderate to high yields. *N*-Methoxyl benzamide **1b** was converted into product **3b** in 85% yield, comparable to that of **1a**. Substrates containing methyl, *tert*-butyl or fused cycloalkyl groups all readily underwent the annulation (**3c**−**3e**). Methoxyl, acetyloxyl functionalities were compatible to the reaction conditions, furnishing the products in 63−77% yields (**3f**−**3h**). In the case of methlenedioxyl substituted *N*-methoxyl benzamide **1i**, the sterically more hindered C−H bond was selectively cleaved in contrast to other *meta*-substituted substrates wherein sterically more accessible cites are preferred (**3c**, **3e**, **3l**, **3v**, **3y** and **3z**). Notably, methylthio group which is susceptible to oxidative reaction conditions was well tolerated thanks to the oxidant-free reaction conditions employed, giving rise to the product **3j** in 62% yield. Biphenyl and naphthyl derived amides also worked well, providing products **3k**, **3l** in good yields. Interestingly, amide with alkenyl substituent also proved to be the viable substrate and when **1m** was employed, product **3m** was isolated in synthetically useful yield, with the alkene residue remaining intact. The nice compatibility of this reaction was further demonstrated by the fact that acetyl, ester, cyano, nitro, trifluoromethyl and silyl groups were all well tolerated, although slightly tuning of the reaction conditions was occasionally required (**3m**−**3r**, **3x**). In addition, halogen atoms were all well tolerated, which provide the opportunity for further derivatizations (**3s**−**3v**). It is also worth mentioning that when substrates possessing additional potential chelation functionalities such as alcohol, carbamate were employed, the annulations occurred selectively on the *ortho*-position of the amide directing group (**3w**, **3y**). Moreover, estrone-derived substrate was amenable to this transformation and furnished product **3z** in 60% yield, indicating the potentiality of the present protocol for the late-stage functionalization of complex molecules.

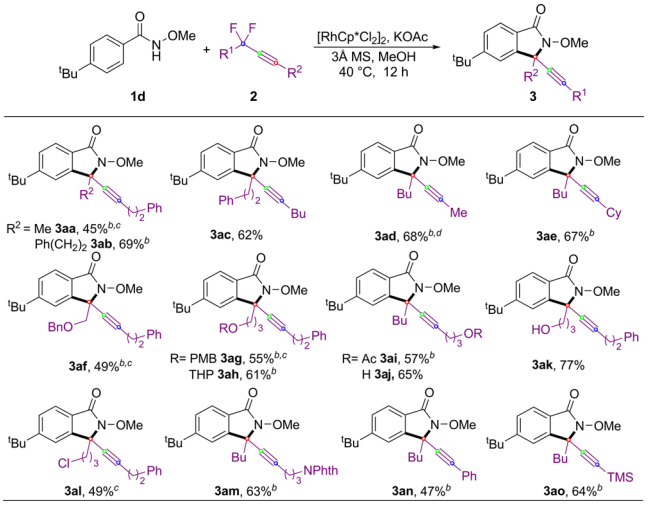
As depicted in Table 2, the reaction scope with respect to *α*,*α*-difluoromethlene alkyne was further examined with amide **1d** as the model reaction partner. Alkyne substrates with different primary alkyl substituents engaged in this reaction uneventfully and provided the desired products in moderate to good yields (**3aa**−**3ad**). Substrate **2f**, which bears a cyclohexyl group on the *gem*-difluoromethylene carbon atom, reacted smoothly to afford

Table 1. Scope of *N*-Methoxyl Benzamide Derivatives[a]



[a]All experiments were performed with **1** (0.1 mmol), **2a** (0.12 mmol), $[RhCp^*Cl_2]_2$ (0.002 mmol), KOAc (0.03 mmol), 3 Å molecular sieve (100 mg) in MeOH (0.5 mL) at 40 °C for 12 h. [b]Reactions were carried out at 80 °C. [c]Reaction time 24 h. [d]PivOH was used instead of KOAc.

Table 2. Scope of *α*,*α*-Difluoromethlene Alkynes[a]



[a]All experiments were performed with **1d** (0.1 mmol), **2** (0.12 mmol), $[RhCp^*Cl_2]_2$ (0.002 mmol), KOAc (0.03 mmol), 3 Å molecular sieve (100 mg) in MeOH (0.5 mL) at 40 °C for 12 h. [b]Reactions were carried out at 80 °C. [c]PivOH was used instead of KOAc. [d]Without the addition of 3 Å molecular sieve.

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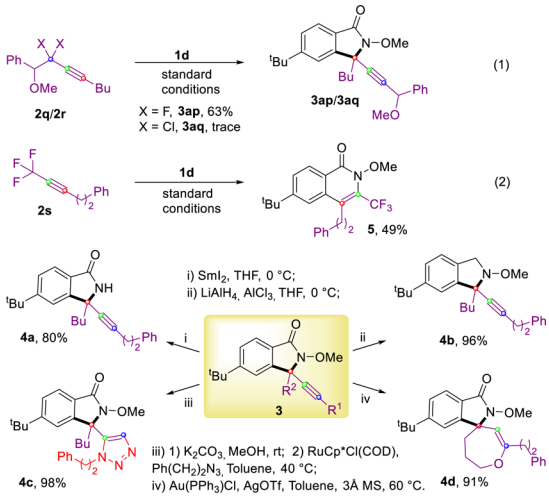
3ae in 67% yield. The smooth annulations with alkyne substrates containing Bn, PMB, THP as well as Ac-protected hydroxyl group also bore out the mildness of reaction conditions (**3af**–**3ai**). It is noteworthy that free hydroxyl containing substrates **2k** and **2l** participated in this annulation nicely without any deleterious effects on the reaction efficiency. Isoindolin-1-one product **3al** with a chlorine substituent on the alkyl chain was also readily obtained when pivalic acid was used as the additive. Alkyne **2n** bearing a phthaloyl protected amino group was also examined, which gave rise to the product **3am** in 63% yield. Notably, the R^1 of **2** was not restricted to alkyl substituents. Specifically, phenylethynyl incorporated product **3an** was obtained in 47% yield, whereas silyl-derived α,α-difluoromethlene alkyne **2p** uneventfully participated in this reaction and produced **3ao** in 64% yield. Additionally, the practicality of this reaction was further proved by a gram-scale reaction, which provided the desired product in comparable yield as small-scale reaction (see Supporting Information for detail).

To shed more light on the role of *gem*-difluorine group on this reaction and reveal the synthetic potential of thus obtained structural motifs, several control experiments and synthetic elaborations were attempted, and the results are shown in Scheme 2. As outlined in eq 1, although the reaction between **1d**

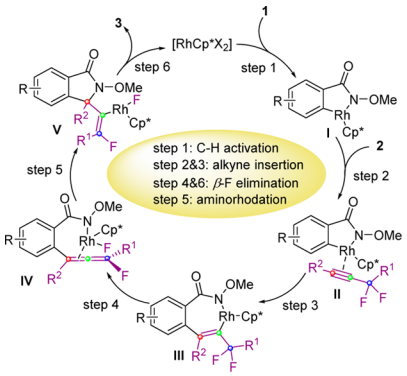
Scheme 2. Control Experiments and Synthetic Elaborations



and α,α-difluoromethlene alkyne substrate **2q** worked effeciently to deliver product **3ap** in 63% yield, only trace of desired product could be detected in the case of *gem*-dichlorine congener **2r**. In addition, essentially no desired products were observed when either monofluorine or ketal counterparts were used in place of α,α-difluoromethlene alkyne, thus implicating the key role of the *gem*-difluorine group on this transformation (see Supporting Information for details). Interestingly, when α,α,α-trifluoromethyl alkyne **2s** was reacted with amide **1d**, no desired [4+1] but the traditional [4+2] annulation product **5** was obtained, for which the exact reason was unclear at the present stage (eq 2). Furthermore, the isoindolin-1-one derivatives obtained using this method are also well suited for further synthetic elaborations because of their enriched functionalities. For example, isoindolin-1-one **3d** was amenable to SmI_2-mediated demethoxylation to afford **4a** in moderated yield, whereas isoindoline **4b** could be obtained in 96% yield with $LiAlH_4/AlCl_3$ reductive system. The embed alkynyl substituent is also primed for further synthetic derivatization. For example, triazole **4c** could be generated in quantitative yield from **3ao** via desilylation/Ru-catalyzed azide alkyne cycloaddition, whereas for **3ak**, Au-catalyzed intramolecular cyclization enabled the formation of spirocyclic product **4d** in 91% yield.

Although it is too arbitrary to draw a whole picture with respect to the reaction mechanism based upon the present experimental results, a simplified reaction pathway shown in Scheme 3 was tentatively proposed for the interpretation of

Scheme 3. Proposed Reaction Mechanism



outcomes of this novel transformation. At first, chelation assisted C–H bond cleavage of benzamide **1** occurs to afford the corresponding five-membered rhodacycle **I**. Subsequently, a regioselectively migratory insertion, owing to the polarization of alkynyl motif by the adjacent gem-difluorine substituent, via intermediate **II** would occur to deliver the seven-membered rhodacycle **III**. With the assistance of acid the following cleavage of one of these two C–F bonds happens to selectively afford allene **IV**,[13] which further undergoes intramolecular aminorhodation of the proximal double bond of allene tether to generate alkenyl rhodium intermediate **V**.[13c,14] At this stage, the following second β-F-elimination would enable the generation of desired product **3** through a migratory reconstruction of C–C triple bond accompanied by the catalyst regeneration.[15] It is worth noting, that it is the 2-fold C–F bonds heterolytic cleavage, which on one hand removes electrons from reaction composite and on the other hand allows the relocation of C–C triple bond, that a redox-neutral [4+1] annulation with skeleton rearrangement comes true.

In conclusion, we have reported a conceptually novel protocol of C–H bond activation engaged defluorinative [4+1] annulation, which allows the expedient construction of isoindolin-1-one derivatives. The polarization of alkyne substrate by neighboring *gem*-difluoromethylene group is deemed to be the key fact that guarantee a regioselective insertion of π-system. Notably, this reaction is featured by C–C triple bond relocation and oxidant-free functionalization of C–H/N–H bonds thanks to the consecutive 2-fold β-F eliminations. Furthermore, this method provides a redox-neutral, regio-specific and atom-economical pathway for the assembly of structurally defined alkynyl-substituted isoindolin-1-ones, which are not easily accessible using the known methods. Last but not the least, this catalytic process represents a rare example of utilizing sp carbon atom of alkyne as a one carbon reaction partner in the transition-metal-catalyzed [n+1] annulation. We hope this methodology could find a broad application in pharmaceutical research and organic synthetic chemistry and further study to elucidate the detailed reaction mechanism is ongoing in our lab.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental details (PDF)

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Notes

The authors declare no competing financial interest.

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