JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

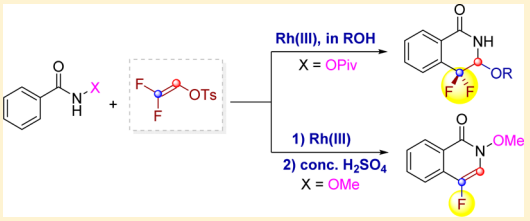
Experimental and Theoretical Studies on Rhodium-Catalyzed Coupling of Benzamides with 2,2-Difluorovinyl Tosylate: Diverse Synthesis of Fluorinated Heterocycles

Jia-Qiang Wu,[§,†] Shang-Shi Zhang,[§,†] Hui Gao,[§,†] Zisong Qi,[‡] Chu-Jun Zhou,[†] Wei-Wei Ji,[†] Yao Liu,[†] Yunyun Chen,[†] Qingjiang Li,[†] Xingwei Li,*[,‡] and Honggen Wang*[,†]

[†]School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China
[‡]Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China

Supporting Information

ABSTRACT: Fluorinated heterocycles play an important role in pharmaceutical and agrochemical industries. Herein, we report on the synthesis of four types of fluorinated heterocycles via rhodium(III)-catalyzed C—H activation of arenes/alkenes and versatile coupling with 2,2-difluorovinyl tosylate. With *N*-OMe benzamide being a directing group (DG), the reaction delivered a monofluorinated alkene with the retention of the tosylate functionality. Subsequent one-pot acid treatment allowed the efficient synthesis of 4-fluoroisoquinolin-1(2*H*)-ones and 5-fluoropyridin-2(1*H*)-ones. When *N*—OPiv benzamides were used, however, [4 + 2] cyclization occurred to provide *gem*-difluorinated dihydroisoquinolin-1(2*H*)-ones. Synthetic applications have been demonstrated and the ready availability of both the arene and the coupling partner highlighted the synthetic potentials of these protocols. Mechanistically, these two processes share a common process involving N—H deprotonation, C—H activation, and olefin insertion to form a 7-membered rhodacycle. Thereafter, different reaction pathways featuring *β*-F elimination and C—N bond formation are followed on the basis of density functional theory (DFT) studies. These two pathways are DG-dependent and led to the open chain and cyclization products, respectively. The mechanistic rationale was supported by detailed DFT studies. In particular, the origins of the intriguing selectivity in the competing *β*-F elimination versus C—N bond formation were elucidated. It was found that *β*-F elimination is a facile event and proceeds via a *syn*-coplanar transition state with a low energy barrier. The C—N bond formation proceeds via a facile migratory insertion of the Rh—C(alkyl) into the Rh(V) amido species. In both reactions, the migratory insertion of the alkene is turnover-limiting, which stays in good agreement with the experimental studies.



INTRODUCTION

The unique properties imparted by fluorine atom have rendered it a popular element in functional molecules.[1] The introduction of fluorine or fluorine-containing structural motifs into small molecules often brings about desirable properties in pharmaceuticals and agrochemicals.[2] By merging heterocyclic and fluoroorganic chemistry, ring-fluorinated heterocycles have found widespread applications, as evidenced by their occurrences in numerous bioactive compounds and drugs (Figure 1).[3] Thus, the assembly of fluorinated heterocycles has been a topic of ongoing interest.[4] However, formidable challenges remain, especially in the synthesis of fluorinated isoquinolinone and derivatives that are among the most intriguing structural motifs. Among the limited methods that have been reported, the majority of them suffer from the necessity of highly functionalized starting materials, lengthy synthetic operations, harsh reaction conditions, and/or overfluorinations.[3c−e,5] Therefore, new synthetic options featuring high efficiency and flexibility are still under great demand.

Transition metal-catalyzed C—H activation has emerged as an effective strategy for diverse C—C and C—X bond formation in an atom- and step-economical fashion,[6] especially in heterocycle synthesis.[7] Nevertheless, there is generally a lack of valuable functional groups in the resulting heterocyclic rings, which thus gave rise to rather limited structural diversity. Recently, Glorius[8] and Wang[9] independently reported the

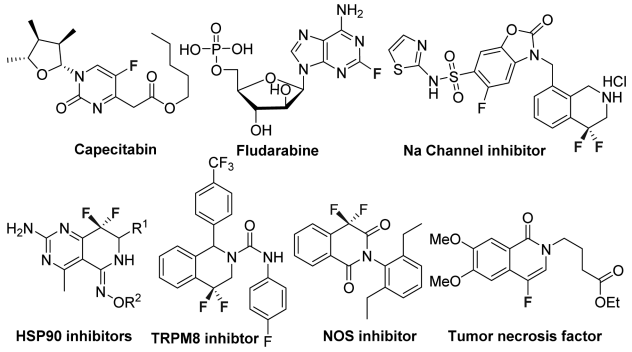


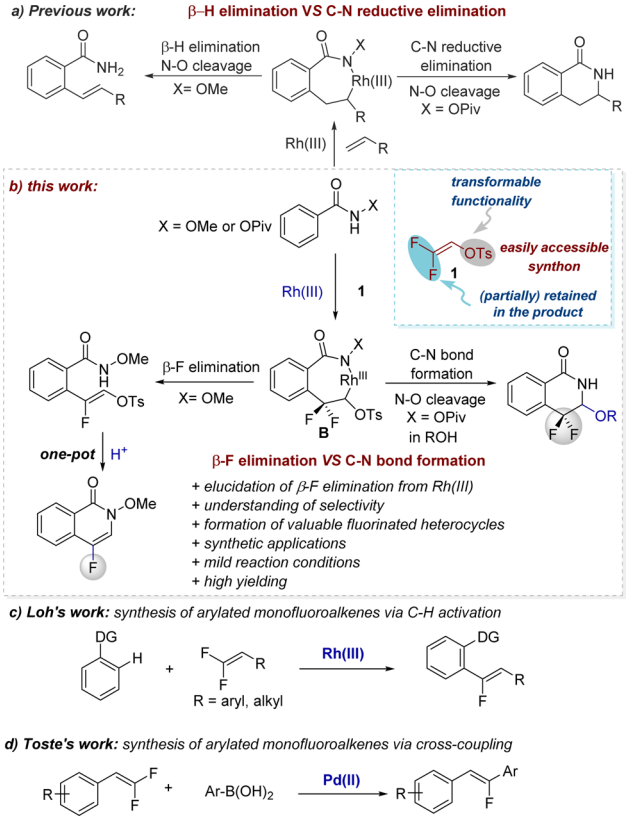
Figure 1. Representative Bioactive Compounds or Drugs Containing Fluorinated Heterocycles.

Received: January 4, 2017
Published: February 8, 2017

DOI: 10.1021/jacs.7b00118
J. Am. Chem. Soc. 2017, 139, 3537−3545

straightforward synthesis of boron- and phosphorus-functionalized heterocycles via arene C—H activation and coupling with the corresponding functionalized alkynes. We therefore envisioned a fluorinated building-block strategy for the synthesis of fluorinated heterocycles. Compared to the classical approaches, this strategy is expected to offer higher flexibility and simplicity. Our strategy is to use 2,2-difluorovinyl tosylate **1** as a readily available fluorinated synthon.[10] We reasoned that the 1,2-disposition of fluorine (pull) and oxygen (push) should sufficiently activate it to convey interesting reactivity such as cleavage of bond C—F bond via β-elimination (Scheme 1b).[10−12] Moreover, the tosylate group provides an easily transformable handle for further manipulations.[13]

Scheme 1. Related Work and Reaction Design



Although β-F elimination is well-known for early transition metals, the incorporation of this process into late transition metal catalysis is still underexplored.[14] In this regard, two elegant reports, among others, are disclosed recently. The group of Loh reported a Rh(III)-catalyzed C—H[15] olefination of arenes using gem-difluoroalkenes, with no cyclization (Scheme 1c)[14a] or with complete defluorination being involved.[14b] Of note, a hydrogen-bonding-assisted β-F elimination from Rh complex was proposed to explain the reactivity and selectivity.[14a] Toste developed a palladium-catalyzed coupling of difluoroalkenes with boronic acids for synthesis of monofluorostilbenes, in which a β-F elimination from the palladium complex was accounted for the C—F bond cleavage (Scheme 1d).[14c] Although well accepted, theoretical understanding of β-F elimination of late transition metal organometallic species is largely lacking.[16]

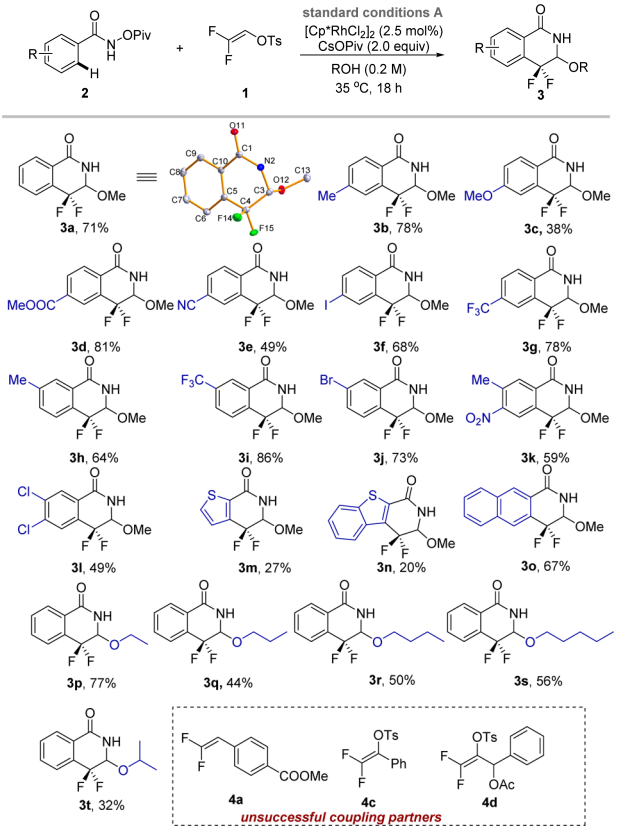
Previously, independent works from the groups of Glorius[17a] and Fagnou[17b] have demonstrated an intriguing directing group-controlled reactivity, namely selective C—N reductive elimination versus β-H elimination.[17c] Thus, under Rh(III) catalysis, the reaction of N—OPiv benzamides with olefins afforded a cyclization product, while the coupling reaction of N—OMe benzamides led to the formation of an open-chain olefin (Scheme 1a). In both cases, the N—O bond was cleaved and served as an internal oxidant.

We have observed an analogous scenario in this study by integrating C—H activation and fluorine chemistry. Herein, we disclose our observation that different directing groups (N—OMe and N—OPiv amides) could also dictate the selectivity of C—N formation versus β-F elimination. Thus, by using 2,2-difluorovinyl tosylate as a coupling partner, the reaction of N—OPiv benzamides gave annulated products dihydroisoquinolin-1(2*H*)-ones. Whereas for N—OMe benzamides, the monofluorine-retentive, tosylate functionalized olefin products were obtained via β-F elimination (Scheme 1b). Detailed mechanistic studies have been performed. In particular, the stereospecificity of the β-F elimination and the origin of directing group-controlled β-F elimination versus C—N bond formation pathways were elucidated by detailed computational studies.

RESULTS AND DISCUSSION

Synthesis of *Gem*-Difluorinated Dihydroisoquinolin-1(2*H*)-ones. *Method Development and Scope.* We first investigated the coupling of *N*-(pivaloyloxy)benzamide **2a** with 2,2-difluorovinyl tosylate **1** (Table 1). We were pleased to find that under the reaction conditions of $[Cp^*RhCl_2]_2$ (2.5 mol %)

Table 1. Synthesis of 4,4-Difluoro-3-alkoxy-3,4-dihydroisoquinolin-1(2*H*)-ones[a]



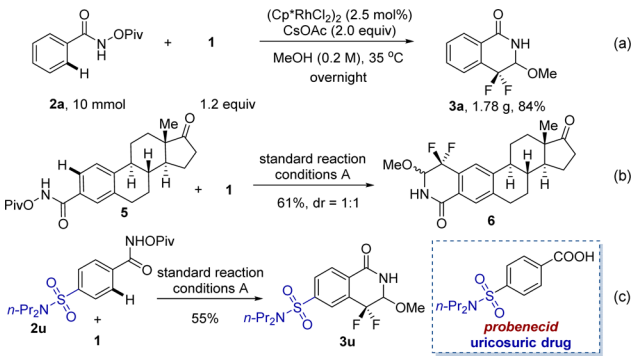
[a]Reaction conditions: **2** (0.5 mmol), 2,2-difluorovinyl tosylate **1** (0.6 mmol, 1.2 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), CsOPiv (2.0 equiv), in ROH (0.2 M), 35 °C, 18 h.

DOI: 10.1021/jacs.7b00118
J. Am. Chem. Soc. 2017, 139, 3537−3545

and CsOPiv (2.0 equiv) in MeOH at 35 °C, an annulated product dihydroisoquinolin-1(2*H*)-one (**3a**) bearing a *gem*-difluorides substituent at the C4 position was isolated in 71% yield. The structure of **3a** was unambiguously confirmed by X-ray crystallography.[18] The incorporated methoxy group α to the nitrogen atom, derived from the solvent MeOH, provides a good handle for further elaboration. The scope of this reaction was then explored. Gratifyingly, a variety of synthetically useful functional groups, such as methoxy (**3c**), ester (**3d**), cyano (**3e**), chloro (**3l**), bromo (**3j**), iodo (**3f**), trifluoromethyl (**3g**), and nitro (**3k**) were well tolerated, giving the corresponding products in 38−86% yields. Of note, good regioselectivities favoring activation of the less congested C—H bond were observed when *meta*-substituted substrates were applied (**3h**−**l**). Unfortunately, some electron-rich heteroaromatic substrates only gave lower yields (**3m** and **3n**). Switching the solvent to other primary or secondary alcohols led to the formation of the corresponding alkoxylated product (**3p**−**t**). In contrast, the coupling of Loh's *gem*-difluoroalkene **4a**[14a] gave no corresponding cyclization products, while the use of (*E*)-fluorovinyl tosylate or (*Z*)-fluorovinyl tosylate (**4b**) as coupling partner led only to the defluoroalkenylation products, indicating the unique reactivity of 2,2-difluorovinyl tosylate.[19] Unfortunately, the cyclization of a tetra-substituted 2,2-difluorovinyl tosylate (**4c** and **4d**) was also unsuccessful probably for steric reasons. The low yield of several cases is due to the competitive substrate decomposition via Lossen rearrangement.

Synthetic Applications and Product Elaborations. To further demonstrate the robustness and usefulness of the reaction, several experiments were conducted. A gram-scale reaction of **2a** furnished **3a** in 84% yield (1.78 g, Scheme 2a). In addition, the

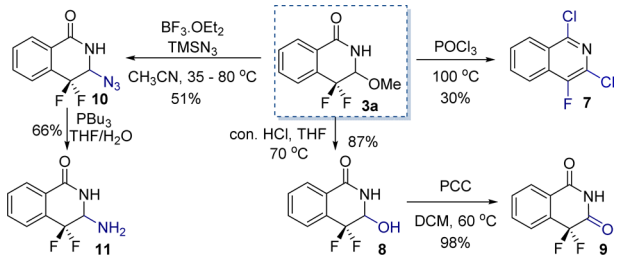
Scheme 2. Gram-Scale Preparation and Synthetic Applications



estrone-derived substrate **5** was also amenable to cyclization to give the corresponding product **6** in 61% yield with 1:1 diastereomeric ratio (Scheme 2b). Probenecid is a uricosuric drug.[20] To our delight, by following a simple directing group installation/cyclization sequence, the fluorinated probenecid analog **3u** was successfully accessed (Scheme 2c).

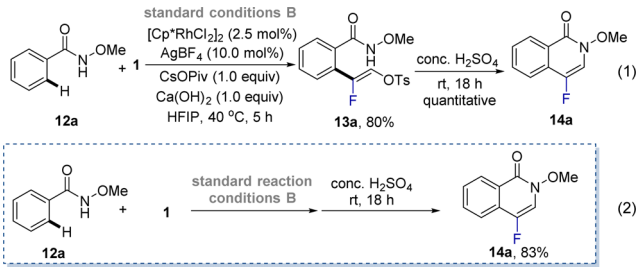
Elaboration of the product has been achieved by taking advantage of lability of the methoxy group (Scheme 3). Thus, treatment of **3a** with $POCl_3$ at 100 °C delivered a dichlorinated 4-fluoroisoquinoline **7** in 30% yield. In addition, the hemiaminal ether functionality in **3a** was easily hydrolyzed to give hemiaminal **8**. Further oxidation of **8** furnished 4,4-difluoroisoquinoline-1,3(2*H*,4*H*)-dione **9** in quantitative yield, which is the core structural motif of an NOS inhibitor depicted in Figure 1.[3f] Furthermore, exchange of methoxy with azido was

Scheme 3. Elaboration of 3a



accomplished by treating **3a** with boron trifluoride and azidotrimethylsilane.[21] The Staudinger reduction of azide with PBu_3 gave aminal **11** in good yield.

Synthesis of 4-Fluoroisoquinolin-1(2*H*)-ones and 5-Fluoropyridin-2(1*H*)-ones. *Method Development and Scope.* Interestingly, when the amide was switched to *N*-methoxybenzamide **12a**, an open chain monofluoroalkene **13a** started to be generated (eq 1). The geometry of the alkene



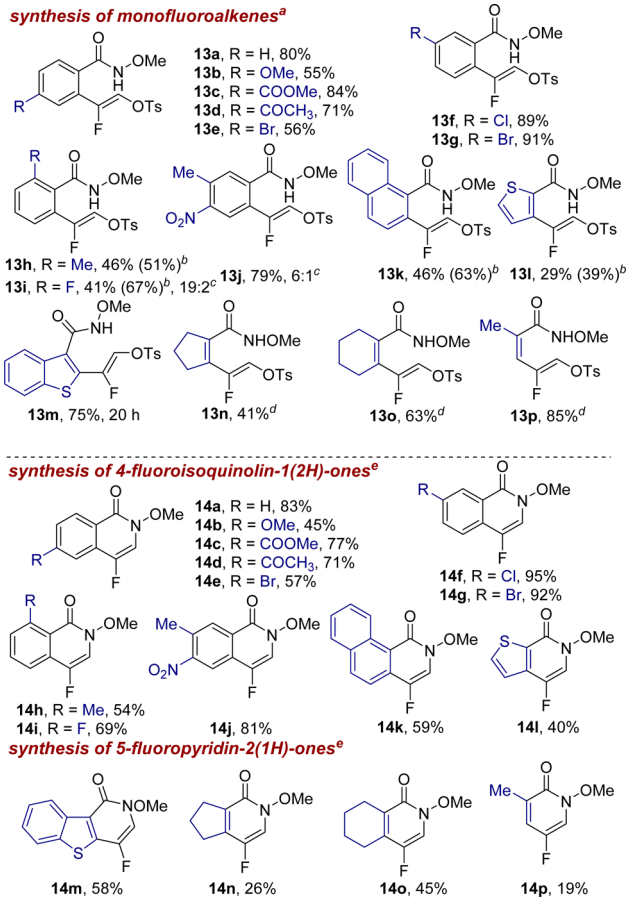
was determined to be *Z* according to NOE analyses. An extensive examination of the reaction parameters revealed that a high isolated yield of 80% was obtained under the reaction conditions of $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgBF_4$ (10.0 mol %), CsOPiv (1.0 equiv) and $Ca(OH)_2$ (1.0 equiv) at 40 °C. The use of $Ca(OH)_2$ as an additive is beneficial presumably due to its ability to scavenge the HF coproduct via the formation of CaF_2. We realized that the presence of a tosylate in the product might offer a good handle for an intramolecular cyclization. Indeed, treatment of **13a** with conc. H_2SO_4 at room temperature furnished 4-fluoroisoquinolin-1(2*H*)-one[22] **14a** in quantitative yield. To further enhance the efficiency of the cyclization, a telescoping synthesis of **14a** without the isolation of intermediate **13a** was realized with a good yield of 83% (eq 2).

The generality for both synthesis of monofluoroalkene **13** and 4-fluoroisoquinolin-1(2*H*)-one **14** were then investigated. As shown in Table 2, differently substituted *N*-methoxybenzamides, regardless of the electronic property and the position of the substituents, underwent smooth reaction to give the monofluoroalkenes in moderate to excellent yields. Various meta-substituents were allowed and the functionalization occurred at the less hindered position (**13f**, **13g**, **13j**). It is noteworthy that *ortho*-substituents were also tolerated in this reaction, albeit with lower yield (**13h**, **13i**). Naphthalene-(**13k**), thiophene-(**13l**), and benzothiophene-derived (**13m**) substrates were also compatible with the reaction conditions. Interestingly, the minor *E* isomeric products started to be detected when **12i** and **12j** were applied. The functionalization of alkenyl C—H bonds was also attempted. It was found that by elevating the temperature to 60 °C, moderate yields of the corresponding products could be obtained (**13n**−**p**).

Gratifyingly, all the substrates examined in the monofluoroalkenation reactions could be amenable to the telescoping

DOI: 10.1021/jacs.7b00118
J. Am. Chem. Soc. 2017, 139, 3537−3545

Table 2. Synthesis of Monofluoroalkenes, 4-Fluoroisoquinolin-1(2*H*)-ones, and 5-Fluoropyridin-2(1*H*)-ones



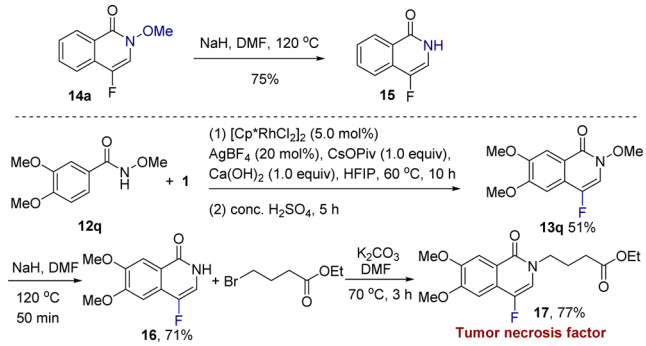
[a]Standard conditions B: $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgBF_4$ (10 mol %), CsOPiv (1.0 equiv), $Ca(OH)_2$ (1.0 equiv), HFIP, 40 °C, 5–24 h. [b]^1H NMR yield. [c]The ratio of *Z*/*E* isomers, the major *Z* isomer is shown. [d]At 60 °C. [e]Standard conditions B, then conc. H_2SO_4, rt, 3–18 h.

synthesis of 4-fluoroisoquinolin-1(2*H*)-one **14**. Therefore, a wide variety of functionalized 4-fluoroisoquinolin-1(2*H*)-ones and 5-fluoropyridin-2(1*H*)-ones[23] were assembled in a simple and straightforward manner. In certain cases, the isolated yields for the telescoping synthesis are higher than the monofluoroalkenation. This is due to the relatively poor solubility of the arylated monofluoroalkenes in common organic solvents which defied efficient isolation.

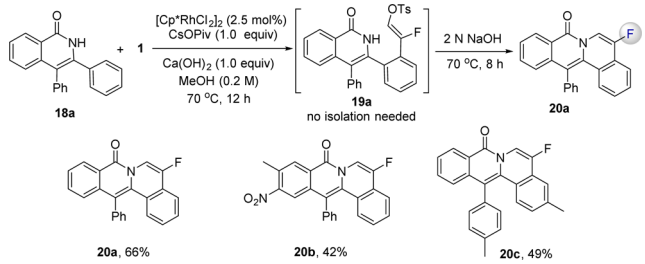
Synthetic Applications and Product Elaboration. The N—O bond in the product **14** could be easily cleaved upon treatment with NaH in DMF,[24] thereby providing a handle for further decoration at the nitrogen atom (Scheme 4). Delightfully, our protocol is well suited for the synthesis of compound **17**, a tumor necrosis factor (Figure 1).[3e] Thus, the C—H functionalization and a subsequent cyclization of **12q** furnished the fluorinated isoquinolinone **13q** in 51% yield. The N—O bond cleavage occurred smoothly to go give compound **16**, which was alkylated to readily provide the final target product **17**.

Synthesis of 5-Fluoro-8*H*-isoquinolino[3,2-*a*]-isoquinolin-8-one. Analogously, by using a similar strategy for the construction of 4-fluoroisoquinolin-1(2*H*)-ones, the reaction of isoquinolones and **1** furnished the monofluoroalkene **19**, which was then converted to the cyclized product 5-fluoro-8*H*-isoquinolino[3,2-*a*]isoquinolin-8-one **20**

Scheme 4. N—O Bond Cleavage and Synthetic Application



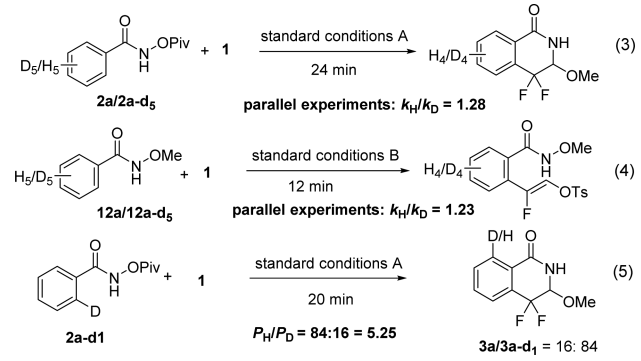
Scheme 5. Synthesis of 5-Fluoro-8H-isoquinolino-[3,2-*a*]isoquinolin-8-ones



in moderate to good efficiency upon treatment with aq NaOH (Scheme 5).

Mechanistic Studies. Mechanistic studies using a combined experimental and computational approach were conducted to delineate the reaction mechanism, specifically on: (1) which step is turnover limiting? (2) what is the origin of the observed regioselectivity for the migratory insertion of 2,2-difluorovinyl tosylate? (3) what is the origin of selectivity of C—N bond formation versus *β*-F elimination? and (4) how is the fluorine atom eliminated and why is the *Z*-alkene formed preferentially over the *E* one?

Kinetic Studies. To probe whether C—H activation is turnover-limiting, kinetic isotope effect studies were conducted. On the basis of initial rate kinetics, KIE values of 1.28 (eq 3) and 1.23 (eq 4) were obtained for the cyclization and mono-



fluoroalkenation reactions, respectively. In addition, the measurement of the intramolecular KIE provided a P_H/P_D value of 5.25 for the cyclization reaction (eq 5). These results indicate that C—H cleavage is not likely turnover-limiting.[25]

Kinetic experiments by the method of initial rates on the reaction of N—OPiv benzamide **2a** and **1** provided additional insight into the reaction mechanism. This cyclization reaction was found to be first order with respect to the catalyst and

DOI: 10.1021/jacs.7b00118
J. Am. Chem. Soc. 2017, 139, 3537–3545

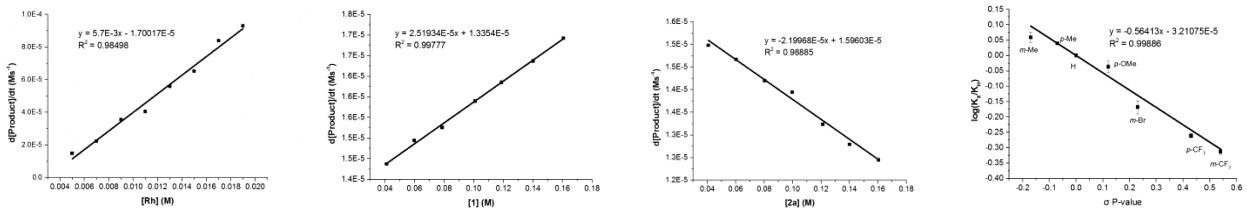
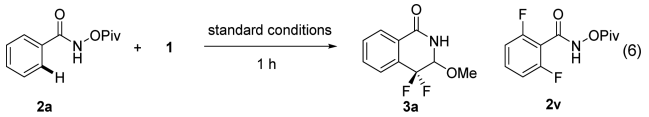


Figure 2. Kinetic profile for the cyclization reactions. From left to right: (a) Plot of initial rate versus catalyst. (b) Plot of initial rates versus **1**. (c) Plot of yield versus time with different [**2a**]. (d) Hammett Plot with differently substituted **2a**.

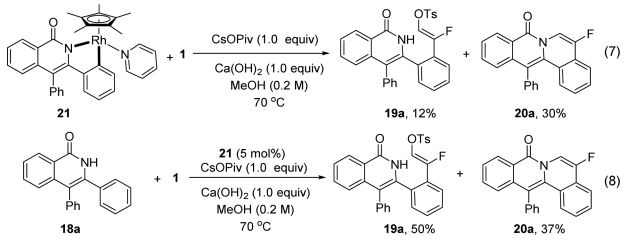
2,2-difluorovinyl tosylate **1**, indicating that both the catalyst and **1** are likely involved in the turnover-limiting step (Figure 2a and 2b). Interestingly, however, an inverse first order was observed for substrate **2a** (Figure 2c). This result might suggest a dual role of **2a** working as a substrate as well as an inhibiting ligand in the catalytic cycle. Its inhibitory effect was further evidenced by the decreased reaction efficiency when a non-productive amide **2v** was added to the reaction (eq 6).



w/o **2v**: 52% yield
with **2v**: (1.0 equiv): 12% yield

The Hammett experiments gave a negative value of $\rho = -0.56$, indicating that buildup of positive charge in the transition state (Figure 2d). In addition, no product inhibition was found.[26]

Identification of Reaction Intermediate. We attempted but failed to isolate the rhodycycle species from the interactions of the Rh(III) catalysts and the N—OPiv or N—OMe benzamides. However, the corresponding isoquinolinone-based metallacycle **21** was obtained following Wang's procedure.[27] The activity of this complex was then examined. In stioichiometric reaction, the reaction of complex **21** with **1** delivered 12% yield of the alkenylation product **19a**, along with 30% yield of cyclized **20a** (eq 7). The use of complex **21** as a catalyst delivered the open chain and the cyclized products as well, albeit with a different ratio.



These results indicated that complex **21** is either a reaction intermediate or a direct precursor (eq 8).

COMPUTATIONAL STUDIES

To further cast light on details of the mechanism, theoretical calculations were performed at the density functional theory level (B3LYP and M11L).[28] The proposed mechanism was broken into 4 key steps: N—H deprotonation, C—H activation, migratory insertion, and C—N bond formation (or β-F elimination).

N—H Deprotonation, C—H Activation, and Alkene Insertion. Figure 3 shows the computational results for the formation of a seven-membered rhodacycle. The OPiv-ligated complex Cp*Rh(OPiv)$_2$ was selected as the starting point. With N—OPiv benzamide **2a** being a substrate, it was found that both of the N—H and C—H activation occur via a concerted metalation-deprotonation (CMD)[29] mechanism with pivalate acting as intramolecular base, through transition states **TS-1** ($\Delta G^{\ddagger}$ = 11.6 kcal/mol) and **TS-2** ($\Delta G^{\ddagger}$ = 20.3 kcal/mol), respectively. Thereafter, a regioselective alkene insertion proceeds via **TS-3** ($\Delta G^{\ddagger}$ = 25.7 kcal/mol), which has a higher activation barrier than the first two steps. The observed inverse reaction order on substrate **2a** could be explained by the competing formation of an

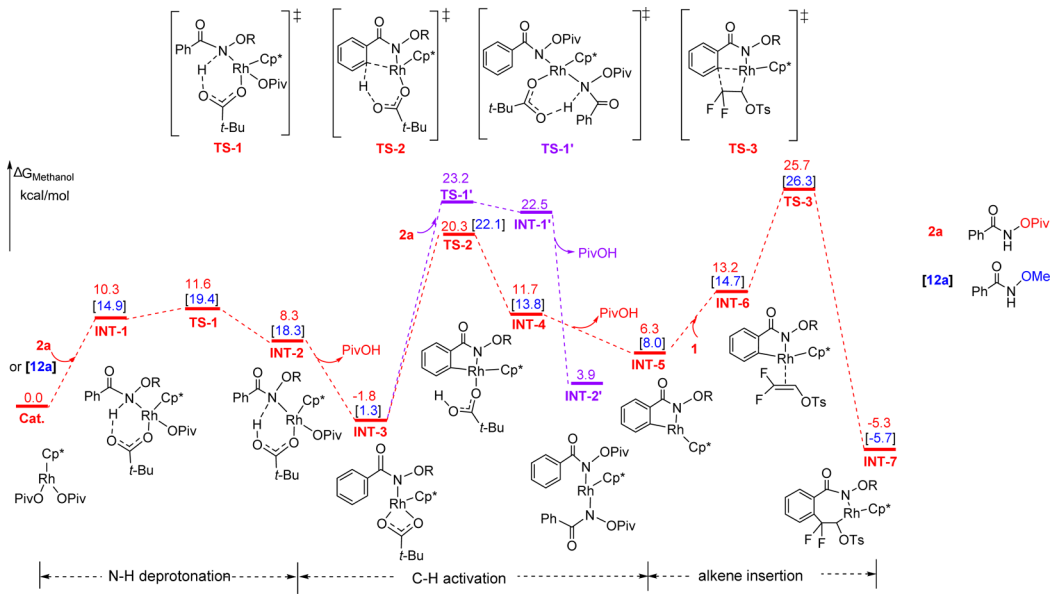


Figure 3. Computed pathways for N—H deprotonation, C—H activation, and alkene insertion. The values in square brackets correspond to the energies for compound **12a**.

DOI: 10.1021/jacs.7b00118
J. Am. Chem. Soc. 2017, 139, 3537–3545

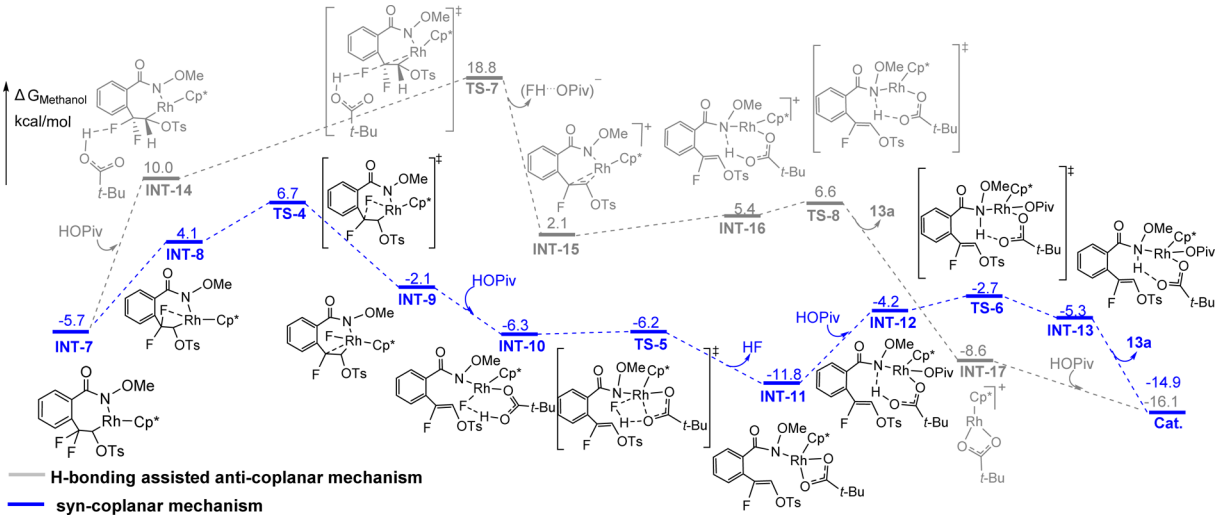


Figure 4. Two computed pathways for β-F elimination.

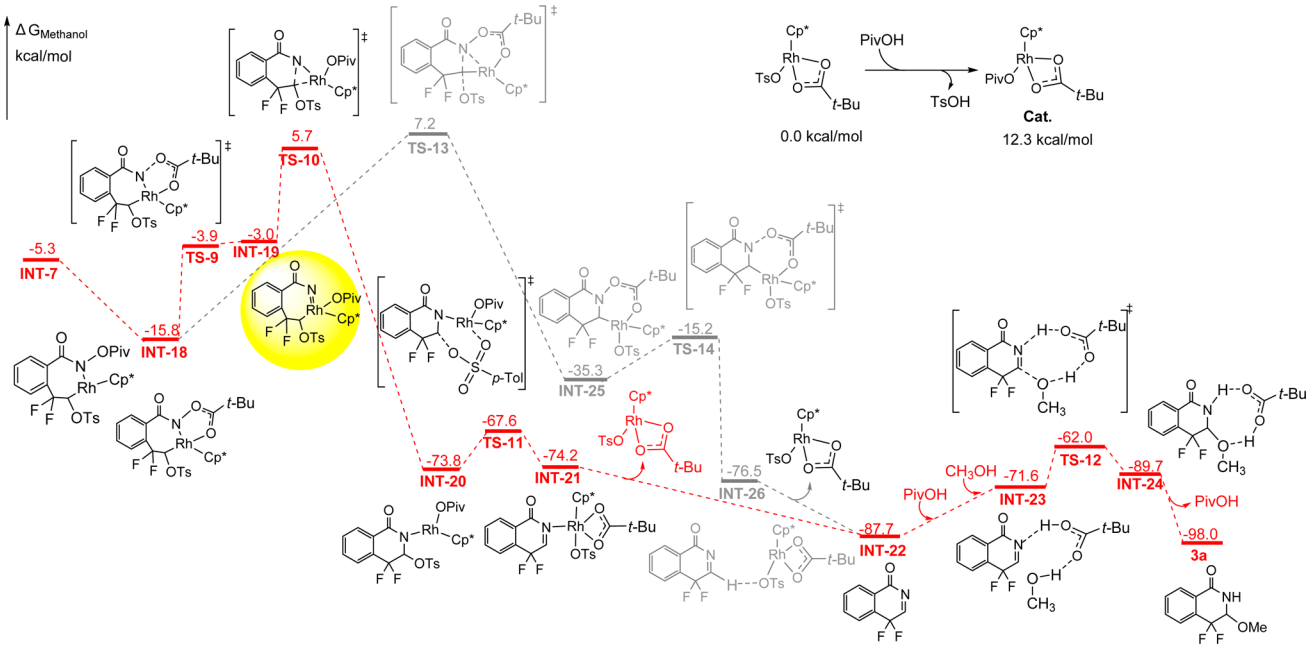


Figure 5. Computed mechanism for C—N bond formation.

off-loop diamidate intermediate **INT-2′**. The *N*-OMe substrate reacts through a similar reaction mechanism with a similar energy profile (values in the square brackets). The computational results suggest that C—H activation is not the turnover limiting step for both amide substrates, consistent with the observed small experimental KIE values.

***β*-F Elimination.** On the basis of literature precedents,[14a,16] two possible pathways have been taken into account for the cleavage of the C—F bond in complex **INT-7**, namely, the syn-coplanar β-F elimination and H-bonding-assisted β-F elimination.

We first computed the feasibility of *syn*-coplanar β-F elimination. To this end, complex **INT-7** is first isomerized to a less stable intermediate **INT-8**, in which an agostic interaction of the C—F bond with metal center is observed (Figure 4, blue lines). β-F elimination then occurs via a cis-coplanar transition state **TS-4** ($\Delta G^{\ddagger}$ = 6.7 kcal/mol), leading to a fluoride intermediate **INT-9**. The Rh—F bond is cleaved with the aid of a coordinated PivOH (via **TS-5**) with a low energy barrier. Likewise, the release of the final product (cleavage of the Rh—N) follows a similar mechanism. With this model, the elimination of the *cis*-F atom forming the *E* type product requires higher activation energy of 9.6 kcal/mol.[26] Thus, this mechanism scenario is consistent with our observation that *Z*-monofluoroalkene is formed preferentially.

Of note, Loh and co-workers have proposed an H-bonding-assisted β-F elimination mechanism in their monofluoroalkene synthesis, on the basis of the observation that the addition of exogenous bases was detrimental to reaction.[14a] In our reaction, however, the use of CsOPiv and $Ca(OH)_2$ as bases was found to be beneficial, which thus suggests such H-bonding is less likely involved for C—F cleavage. Indeed, our computation results showed that the anticoplanar H-bonding assisted β-F elimination (via **TS-7**) is accompanied by a free energy of 18.8 kcal/mol, 12.1 kcal/mol higher than that of the syn-coplanar one (Figure 4, gray lines). Therefore, the syn-coplanar mechanism is likely operative in our reaction.

C—N Bond Formation. The use of N—OPiv benzamides led to the cyclization reaction. Thus, the origin of C—N bond formation over β-F elimination was explored, and the results were shown in Figure 5. Initially, the coordination of the pendent carbonyl oxygen to the Rh center leads to complex **INT-18**, setting a stage for an intramolecular oxidation of Rh(III) (red lines). Subsequently, the migration of OPiv from N to Rh occurs via a 5-membered ring transition state

DOI: 10.1021/jacs.7b00118
J. Am. Chem. Soc. 2017, 139, 3537−3545

(**TS-9**) with an activation barrier of 11.9 kcal/mol, yielding a Rh(V) nitrenoid intermediate **INT-19**.[30] The Rh—N bond (1.86 Å) in **INT-19** is dramatically shortened compared to that in **INT-18** (2.09 Å). The high-valent Rh(V) species **INT-19** then undergoes nitrenoid insertion to produce **INT-20**. This process proceeds via **TS-10** with a free energy of only 5.7 kcal/mol and the process is extremely exergonic by 73.8 kcal/mol. Thereafter, a formal β-oxygen elimination via transition state **TS-11** lead to an imine intermediate **INT-22**. The attack of MeOH solvent with the assistance of PivOH furnishes the final product **3a**.

The intermediacy of a high-valent Rh(V) nitrenoid species was proved by a Natural Bond Orbital (NBO) analysis.[31] From intermediate **INT-18** to **TS-9** and further to intermediate **INT-19**, diminished NBO charge of 0.262, 0.386, and 0.417, respectively, was found on the metal. Furthermore, the electron binding energy[32] of the Rh 4s electron for intermediate **INT-18**, **TS-9**, and intermediate **INT-19** is calculated to be 87.6, 88.3, and 88.6 eV, respectively. These results are in good agreement with the proposal that a Rh(V) oxidation state is likely involved.

Another mechanistic possibility featuring direct C—N bond-reductive elimination from the Rh(III) intermediate is also examined. As shown in Figure 5 (gray lines), our attempt to locate a transition state for the direct C—N reductive elimination from **INT-18** lead to an intramolecular migration of the tosylate, forming another Rh(III) complex **INT-25**. Thereafter, a formal β-oxygen elimination could deliver the same imine intermediate **INT-22**. In the entire process, the oxidation state of rhodium stays unchanged. Energetically, this pathway is associated with a higher activation energy than the Rh(V) pathway. Therefore, the Rh(V) pathway is more likely.

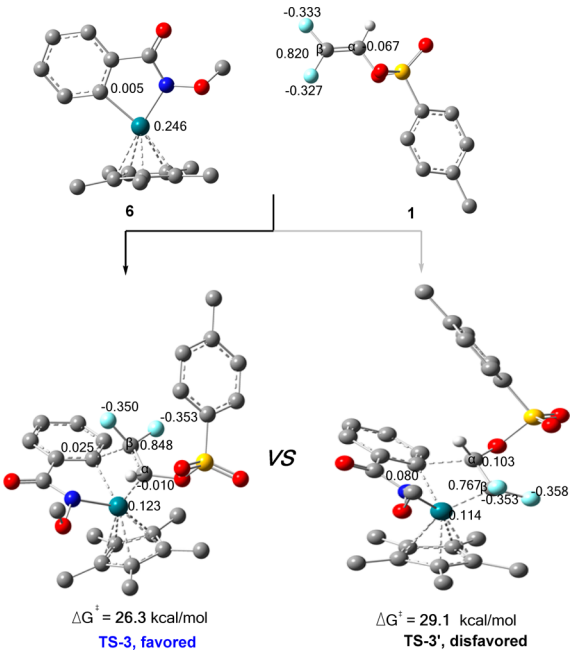


Figure 6. Natural Bond Orbital (NBO) analysis to account for the regioselectivity.

The energy profile for the β-F elimination from intermediate **INT-7** was also conducted.[26] In this case, β-F elimination occurs via a syn-coplanar transition state ($\Delta G^{\ddagger}$ = 6.6 kcal/mol) is accompanied by a relatively higher kinetic barrier. However, thermodynamically, this process was found to be far less exergonic than the C—N bond formation process. Taken together, the theoretical calculation demonstrated the cyclization product should be selectively formed, which goes well with the experimental observations.

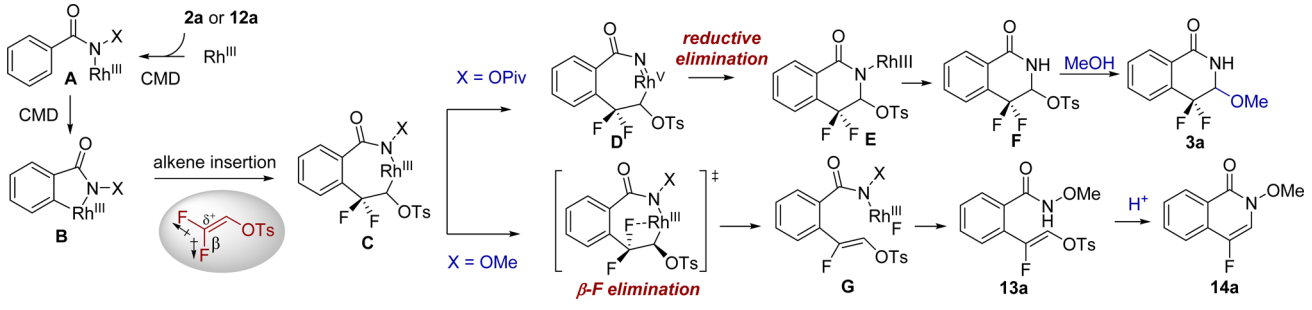
Selectivity for Migratory Insertion. The regioselectivity in migratory insertion of 2,2-difluorovinyl tosylate is worth noting. Natural Bond Orbital (NBO) analysis revealed that the β-carbon in free 2,2-difluorovinyl tosylate is highly positively charged (0.820) due to the strong inductive effect of fluorine atoms (Figure 6).[33] However, in complex **INT-5**, the Rh—C carbon atom (0.005) is found to be relatively more negatively charged compared to the metal center (0.246). Therefore, the carbon center is expected to be prone to attack the β-carbon of **1**. Consistently, calculations showed that a higher kinetic barrier is required for the inverse regioselective insertion (29.1 kcal/mol vs 26.3 kcal/mol). These results are also in line with our Hammett plot experiments that electron-rich substrates react faster.

Mechanistic Proposal. On the basis of the above studies, our mechanistic summary is depicted in Scheme 6. Initially, the ligand exchange with bezamide **2a** or **12a** via a CMD-like deprotonation yields complex A. Likewise, another CMD type *ortho* C—H activation of benzamide gives the rhodacycle B, which then undergoes migratory insertion into 2,2-difluorovinyl tosylate **1** to delivers intermediate **C**. The observed regioselectivity can be rationalized by the decreased electron density at the β-carbon center induced by the strong inductive effect of the two fluorine atoms.[33] Thereafter, there are two distinct reaction pathways depending on the nature of directing group. For *N*-(pivaloyloxy)benzamide (X = OPiv), a facile intramolecular oxidation of the Rh(III) yields a Rh(V) nitrenoid intermediate **D**. Upon migratory insertion into the nitrenoid, compound **F** is generated. An exchange of OTs with solvent-derived methoxy gives the dihydroisoquinolone product **3a**. While for the *N*-methoxybenzamide substrate, the corresponding intermediate **C** undergoes a selective β-fluorine elimination via a *syn*-coplanar transition state to regain the double bond. Ligand exchanges of **G** with PivOH releases the arylated monofluoroalkene **13a**, which is susceptible to an acid-promoted cyclization to give 4-fluoroisoquinolin-1(2*H*)-one **14a**. Overall, the alkene insertion step carries the highest activation barrier for both reactions, which is in good agreement with our observed experimental kinetic data.

CONCLUSIONS

In summary, by taking advantage of the unique reactivity of 2,2-difluorovinyl tosylate, we have accomplished facile synthesis of 4,4-difluoro-3,4-dihydroisoquinolin-1(2*H*)-ones, 4-fluoroisoquinolin-1(2*H*)-ones, and 5-fluoropyridin-2(1*H*)-ones by using Rh(III)-catalyzed C—H activation as the key strategy. The reactions proceeded under mild and redox-neutral reaction conditions.

Scheme 6. Summary of Mechanistic Proposal



DOI: 10.1021/jacs.7b00118
J. Am. Chem. Soc. 2017, 139, 3537–3545

The robustness of the protocols were fully investigated and found to be quite decent.

Mechanistic studies using a combined experimental and computational approach were conducted to interpret the reaction mechanism, specifically on the scenario of directing group-governed distinct reactivity, namely C—N formation and the β-F elimination. Of note, the β-F elimination was found to occur via a *syn*-coplanar transition state with a very low activation barrier. Given the importance of fluorinated heterocycles in functional molecules, we expect that these methods may find important applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b00118.

Detailed experimental procedures and characterization of all reported compounds (PDF)
CCDC data (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*xwli@dicp.ac.cn
*wanghg3@mail.sysu.edu.cn

ORCID

Xingwei Li: 0000-0002-1153-1558
Honggen Wang: 0000-0002-9648-6759

Author Contributions

§These authors contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the support of this work by the Key Project of Chinese National Programs for Fundamental Research and Development (2016YFA0602900), "1000-Youth Talents Plan", a Start-up Grant from Sun Yat-sen University and National Natural Science Foundation of China (Nos. 81402794, 21472250, 21525208, and 21472186).

■ REFERENCES

(1) *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Kirsch, P., Ed.; Wiley-VCH: Weinheim, 2004.

(2) (a) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; John Wiley & Sons, Ltd.; Chichester, UK, 2009. (b) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.

(3) (a) Lu, J.; Huang, G.; Li, H.-P.; Feng, K.-Y.; Chen, L.; Zheng, M.-Y.; Cai, Y.-D. *PLoS One* **2014**, *9*, 27878. (b) Majolino, I.; Davoli, M.; Carnevalli, E.; Locasciulli, A.; Bartolomeo, P. D.; Scimè, R.; Corradini, P.; Selleri, C.; Narni, F.; Musso, M.; Bregni, M.; Olivieri, A.; Fabritiis, P. D.; Pogliani, L.; Arbelaez, J. E. D.; Ruscio, C.; Bacigalupo, A. *Leuk. Lymphoma* **2007**, *48*, 759. (c) Liu, Q.; Wu, Y.; Chen, P.; Liu, G. *Org. Lett.* **2013**, *15*, 6210. (d) Piron, K.; Kenis, S.; Verniest, G.; Surmont, R.; Thuring, J. W.; Holte, P. t.; Deroose, F.; Kimpe, N. D. *Tetrahedron* **2012**, *68*, 6941. (e) Chao, Q.; Deng, L.; Shih, H.; Leoni, L. M.; Genini, D.; Carson, D. A.; Cottam, H. B. *J. Med. Chem.* **1999**, *42*, 3860. (f) Norman, M. H.; Bo, Y. Y.; Gore, V. K.; Horne, D.; Kaller, M.; Ma, V. V.; Monenschein, H.; Nguyen, T.; Nishimura, N.; Tamayo, N. WO 2009073203 (A1), 2009. (g) Komoda, M.; Kakuta, H.; Takahashi, H.; Fujimoto, Y.; Kadoya, S.; Katob, F.; Hashimotoa, Y. *Bioorg. Med. Chem.* **2001**, *9*, 121.

(4) (a) Petrov, V. A. In *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*; John Wiley & Sons: Hoboken, 2009. (b) Serguchev, Y. A.; Ponomarenko, M. V.; Ignat'ev, N. V. *J. Fluorine Chem.* **2016**, *185*, 1. (c) Nosova, E. V.; Lipunova, G. N.; Charushin, V. N.; Chupakhin, O. N. *J. Fluorine Chem.* **2010**, *131*, 1267. (d) Zhu, S.; Wang, Y.; Peng, W.; Song, L.; Jin, G. *Curr. Org. Chem.* **2002**, *6*, 1057.

(5) For selected examples, see: (a) Pan, Y.; Tumelty, D.; Holmes, C. P. *J. Org. Chem.* **2005**, *70*, 4897. (b) Arimitsu, S.; Fernández, B.; del Pozo, C.; Fustero, S.; Hammond, G. B. *J. Org. Chem.* **2008**, *73*, 2656. (c) Price, D. A.; James, K.; Osborne, S.; Harbottle, G. W. *Tetrahedron Lett.* **2007**, *48*, 7371. (d) Brooke, G. M.; Eggleston, I. M.; Hale, F. A. *J. Fluorine Chem.* **1988**, *38*, 421. (e) Kobayashi, Y.; Kumadaki, I.; Yamashita, T. *Heterocycles* **1982**, *17*, 429.

(6) For representative reviews, see: (a) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900. (b) Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040. (c) Jiao, J.; Murakami, K.; Itami, K. *ACS Catal.* **2016**, *6*, 610. (d) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (e) Campbell, A. N.; Stahl, S. S. *Acc. Chem. Res.* **2012**, *45*, 851. (f) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (g) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588. (h) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (i) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (j) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362. (k) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (l) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (m) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (n) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (o) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (p) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (q) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (r) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173.

(7) For reviews, see: (a) Shaikh, T. M.; Hong, F.-E. *J. Organomet. Chem.* **2016**, *801*, 139. (b) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (c) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084. (d) Zhu, C.; Wang, R.; Falck, J. R. *Chem. - Asian J.* **2012**, *7*, 1502. (e) Ferraccioli, R. *Curr. Org. Synth.* **2012**, *9*, 96. (f) Thansandote, P.; Lautens, M. *Chem. - Eur. J.* **2009**, *15*, 5874. (g) Mei, T.-S.; Kou, L.; Ma, S.; Engle, K. M.; Yu, J.-Q. *Synthesis* **2012**, *44*, 1778. (h) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624.

(8) Wang, H.; Grohmann, C.; Nimphius, C.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 19592.

(9) Li, B.; Yang, J.; Xu, H.; Song, H.; Wang, B. *J. Org. Chem.* **2015**, *80*, 12397.

(10) 2,2-Difluorovinyl tosylate could be easily prepared from the elimination reaction of 2,2,2-trifluoroethyl tosylate with butyllithium: Gøgsig, T. M.; Søbjerg, L. S.; Lindhardt, A. T.; Jensen, K. L.; Skrydstrup, T. *J. Org. Chem.* **2008**, *73*, 3404.

(11) For a review on the reactivity of fluorinated enol ethers, see: Decostanzi, M.; Campagne, J.-M.; Leclerc, E. *Org. Biomol. Chem.* **2015**, *13*, 7351.

(12) For the use of 2,2-difluorovinyl tosylate in synthesis, see: (a) Fujiwara, M.; Ichikawa, J.; Okauchi, T.; Minami, T. *Tetrahedron Lett.* **1999**, *40*, 7261. (b) Ichikawa, J.; Fujiwara, M.; Nawata, H.; Okauchi, T.; Minami, T. *Tetrahedron Lett.* **1996**, *37*, 8799. (c) Fang, X.; Wu, Y.-M.; Deng, J.; Wang, S.-W. *J. Fluorine Chem.* **2004**, *125*, 1481. (d) Fang, X.; Wu, Y.-M.; Deng, J.; Wang, S.-W. *Tetrahedron* **2004**, *60*, 5487. (e) Zhang, B.; Zhang, X. *Chem. Commun.* **2016**, *52*, 1238. (f) McAlpine, I.; Tran-Dube, M.; Wang, F.; Scales, S.; Matthews, J.; Collins, M. R.; Nair, S. K.; Bian, J.; Alsina, L. M.; Sun, J.; Zhong, J.; Warmus, J. S.; O'Neill, B. T. *J. Org. Chem.* **2015**, *80*, 7266.

(13) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619. (b) Ackermann, L.; Fenner, S. *Chem. Commun.* **2011**, *47*, 430. (c) Choy, P. Y.; Luk, K. C.; Wu, Y.; So, C. M.; Wang, L.-L.; Kwong, F. Y. *J. Org. Chem.* **2015**, *80*, 1457.

(14) (a) Tian, P.; Feng, C.; Loh, T.-P. *Nat. Commun.* **2015**, *6*, 7472. (b) Liu, H.; Song, S.; Wang, C.-Q.; Feng, C.; Loh, T.-P. *ChemSusChem*

DOI: 10.1021/jacs.7b00118
J. Am. Chem. Soc. 2017, 139, 3537−3545

2017, *10*, 58. (c) Thornbury, R. T.; Toste, F. D. *Angew. Chem., Int. Ed.* **2016**, *55*, 11629. (d) Ichitsuka, T.; Fujita, T.; Arita, T.; Ichikawa, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 7564. (e) Ichitsuka, T.; Fujita, T.; Ichikawa, J. *ACS Catal.* **2015**, *5*, 5947. (f) Hu, M.; He, Z.; Gao, B.; Li, L.; Ni, C.; Hu, J. *J. Am. Chem. Soc.* **2013**, *135*, 17302. (g) Zhang, Z.; Zhou, Q.; Yu, W.; Li, T.; Wu, G.; Zhang, Y.; Wang, J. *Org. Lett.* **2015**, *17*, 2474. (h) Kikushima, K.; Sakaguchi, H.; Saijo, H.; Ohashi, M.; Ogoshi, S. *Chem. Lett.* **2015**, *44*, 1019. (i) Ichikawa, J.; Nadano, R.; Ito, N. *Chem. Commun.* **2006**, 4425. (j) Miura, T.; Ito, Y.; Murakami, M. *Chem. Lett.* **2008**, *37*, 1006. (k) Kong, L.; Zhou, X.; Li, X. *Org. Lett.* **2016**, *18*, 6320.

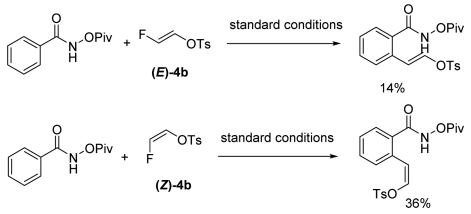
(15) For reviews on Rh(III)-catalyzed C−H activations, see: (a) Satoh, T.; Miura, M. *Chem. - Eur. J.* **2010**, *16*, 11212. (b) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (c) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (d) Patureau, F. W.; Wencel-Delord, J.; Glorius, F. *Aldrichimica Acta* **2012**, *45*, 38.

(16) Zhao, H.; Ariafard, A.; Lin, Z. *Organometallics* **2006**, *25*, 812.

(17) (a) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350. (b) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (c) Xu, L.; Zhu, Q.; Huang, G.; Cheng, B.; Xia, Y. *J. Org. Chem.* **2012**, *77*, 3017.

(18) CCDC 1482520 (**3a**) contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(19) The use of (*E*)-fluorovinyl tosylate or (*Z*)-fluorovinyl tosylate (**4b**) as coupling partner led to the formation of defluoroalkenylation products with stereospecificity, along with significant level of substrate decomposition. The observed product and the stereospecificity suggest that β-F elimination exists and it is more facile than the corresponding C—N reductive elimination.



(20) Silverman, W.; Locovei, S.; Dahl, G. *Am. J. Physiol., Cell Physiol.* **2008**, *295*, 761.

(21) Knapp, S.; Zhao, D. *Org. Lett.* **2000**, *2*, 4037.

(22) Selected examples for the synthesis of isoquinolones and derivatives via C—H activation: (a) Yu, D.-G.; de Azambuja, F.; Gensch, T.; Daniliuc, C. G.; Glorius, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 9650. (b) Fukui, Y.; Liu, P.; Liu, Q.; He, Z.-T.; Wu, N.-Y.; Tian, P.; Lin, G.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 15607. (c) Xu, X.; Liu, Y.; Park, C.-M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9372. (d) Hyster, T. K.; Knörr, L.; Ward, T. R.; Rovis, T. *Science* **2012**, *338*, 500. (e) Ye, B.; Cramer, N. *Science* **2012**, *338*, 504. (f) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (g) Mochida, S.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2010**, *39*, 744. (h) Song, G.; Chen, D.; Pan, C.-L.; Crabtree, R. H.; Li, X. *J. Org. Chem.* **2010**, *75*, 7487. (i) Tang, Q.; Xia, D.; Jin, X.; Zhang, Q.; Sun, X.-Q.; Wang, C. *J. Am. Chem. Soc.* **2013**, *135*, 4628.

(23) (a) Su, Y.; Zhao, M.; Song, G.; Li, X. *Org. Lett.* **2010**, *12*, 5462. (b) Hyster, T. K.; Rovis, T. *Chem. Sci.* **2011**, *2*, 1606. (c) Yu, Y.; Huang, L.; Wu, W.; Jiang, H. *Org. Lett.* **2014**, *16*, 2146. (d) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Org. Lett.* **2011**, *13*, 3278. (e) Shi, L.; Yu, K.; Wang, B. *Chem. Commun.* **2015**, *51*, 17277.

(24) (a) Manna, S.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 7324. (b) Zhang, S.-S.; Wu, J.-Q.; Liu, X.; Wang, H. *ACS Catal.* **2015**, *5*, 210.

(25) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066.

(26) See SI for details.

(27) Wang, N.; Li, B.; Song, H.; Xu, S.; Wang, B. *Chem. - Eur. J.* **2013**, *19*, 358.

(28) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision C.01*, Gaussian, Inc., Wallingford CT, 2010.

(29) (a) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848. (b) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118.

(30) (a) Park, S. H.; Kwak, J.; Shin, K.; Ryu, K.; Park, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 2492. (b) Park, Y.; Heo, J.; Baik, M.-H.; Chang, S. *J. Am. Chem. Soc.* **2016**, *138*, 14020. (c) Yang, Y.-F.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **2016**, *138*, 6861. (d) Yu, S.; Liu, S.; Lan, Y.; Wan, B.; Li, X. *J. Am. Chem. Soc.* **2015**, *137*, 1623.

(31) Weinhold, F.; Landis, C. R. *Valency and Bonding: A Natural Bond Orbital Donor-Acceptor Perspective*; Cambridge UniversityPress: Cambridge, U.K., 2005.

(32) Powers, D. C.; Benitez, D.; Tkatchouk, E.; Goddard, W. A.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14092.

(33) Qian, C.-P.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 4602.

DOI: 10.1021/jacs.7b00118
J. Am. Chem. Soc. 2017, 139, 3537−3545