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Rhodium- and Iridium-Catalyzed (Enantioselective) Fluoroamidation of *gem*-Difluoroalkenes via Chelation Assistance

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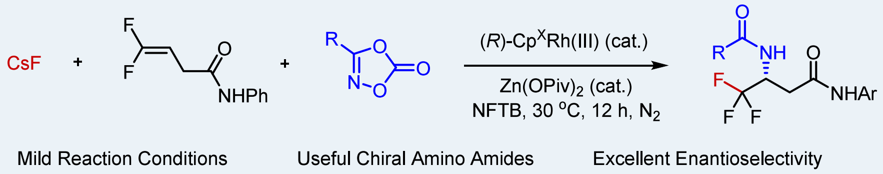


ABSTRACT: The incorporation of fluorine atoms into organics often significantly improved the lipophilicity and metabolic stability of pharmaceuticals. Herein, two classes of fluoroamidation reactions of *gem*-difluoroalkenes are described. Rhodium-catalyzed asymmetric 1,2-fluoroamidation of 4,4-difluoro-3-butenamide proceeded in excellent enantioselectivity to give a CF_3-containing diamide using CsF as a convenient fluoride source. On the other hand, the 1,4-fluoroamidation of *gem*-difluoro-1,3-dienes required iridium catalysis using AgF as a fluoride source under mild reaction conditions. In both cases, fluorometalation occurs as a key elementary step, with a metal−alkyl intermediate being stabilized by chelation or allyl formation as a driving force.

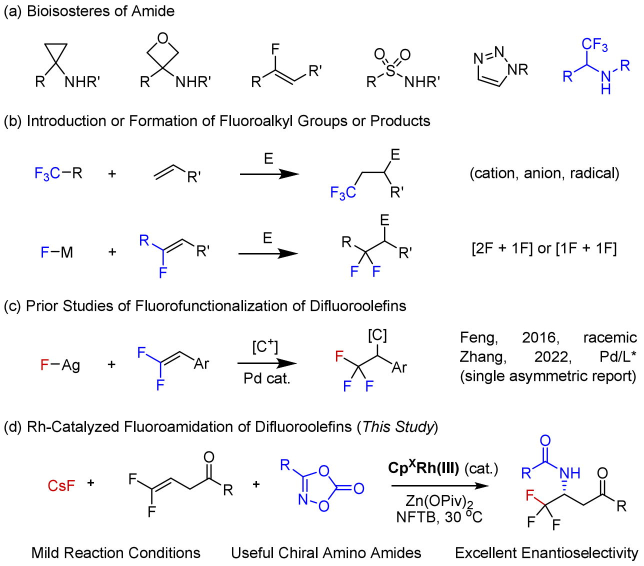
KEYWORDS: *rhodium, iridium, fluoroamidation, gem-difluoroalkene, chelation*

INTRODUCTION

It is widely recognized that introduction of fluorine atoms into organics can improve biological activities such as lipophilicity, membrane permittivity, and metabolic stability.[1] Indeed, a large number of pharmaceuticals are fluorine-containing.[2] Organofluorines can also act as bioisosteres of the ubiquitous amides that have found wide applications in drug design (Scheme 1a).[3] Therefore, increasing efforts have been directed to construction of complex organofluorines. Two categories of synthetic methods have been developed toward construction of fluoroorganics.[4] Many synthetic methods rely on a substrate with a preinstalled fluoroalkyl group, and transformations of this substrate or delivery of this group to the product results in formation of desired products.[5] In the case of introduction of a fluoroalkyl group, electrophilic,[6] nucleophilic,[7] and radical[8] fluoroalkylating reagents have been utilized (Scheme 1b). Nevertheless, these systems heavily rely on existing synthetic methods that can accommodate both reagents. However, loss of a fluorine atom may readily occur during these transformations.[9] On the other hand, there is increasing interest in utilizing a simple fluoride reagent that reacts with a fluorinated (or nonfluorinated) unsaturated reagent, generating a more fluorine-rich product (Scheme 1b).[10] This strategy is challenging given the low nucleophilicity of the fluoride and reversibility of fluoride addition in metal catalysis.[11]

In 2016, Feng reported a seminal work on Pd-catalyzed fluoroallylation of *gem*-difluorostyrene using AgF as a fluorine source and allyl halide as the electrophilic reagent (Scheme 1c).[12] The electrophilic reagent has been extended to an aryl iodide by the same group.[13] Related radical fluoroallylation has

Scheme 1. Fluorofunctionalization of Olefins



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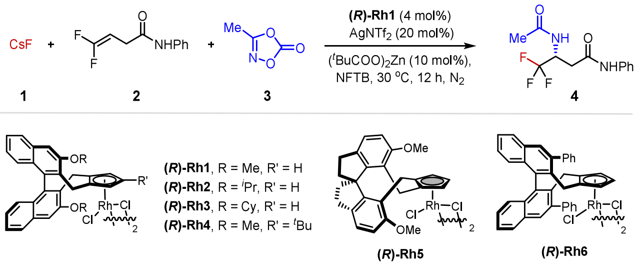
also been realized under electrochemical conditions.[14] Recently, the group of Zhang developed an enantioselective version of fluoroarylation based on judicious ligand design.[15] Despite the reports of this type of [2F + 1F][16] or [0F + 3F][17] strategies, existing methods and reaction patterns are rather limited. The electrophilic reagent is also limited to carbon-based ones, and there is only a single asymmetric report.[15] We rationalized that the formation of a CF_3-containing metal alkyl species is a crucial step, and such a metal alkyl should be efficiently trapped by an electrophilic reagent; otherwise, reversible β-F elimination may take place. We reasoned that a high valent metal such as Rh(III) may suffice owing to its high electrophilicity to activate the olefin toward nucleophilic attack of a fluoride. To stabilize the metal alkyl species, we resort to chelation assistance using an olefin bearing a chelating group. Meanwhile, to enhance the polarity of the metal−alkyl bond, a high-valent Rh(III) catalyst is employed to give a reactive Rh(III) alkyl that is intercepted by nitrene.[18] Despite the design, the hard−hard interaction in a stable Rh(III)-F bond may defy nucleophilic attack of the fluoride on the olefin. We now report rhodium-catalyzed enantioselective 1,2-fluoroamidation of *gem*-difluoroolefins, and the olefins have been extended to racemic *gem*-difluorodienes under iridium catalysis.

METHODS

We initiated our studies by optimization of the reaction conditions of the three-component fluoroamidation of 4,4-difluoro-3-butenamide with CsF being a fluoride source and methyldioxazolone[19] being an amidating reagent (Table 1). The optimal reaction conditions eventually consist of the Cramer type chiral Rh(III) cyclopentadienyl catalyst (***R***)-**Rh1**,[20] $AgNTf_2$ as a halide scavenger, and $Zn(OPiv)_2$ as an additive in nonafluoro-*tert*-butyl alcohol (NFTB) solvent. Under these conditions, the β-amino amide product was isolated in good yield and 94% ee (entry 1). Switching to other catalysts of this series such as (***R***)-**Rh2**−**Rh6** all gave inferior enantioselectivity and/or coupling efficiency (entries 2−6). The employment of other fluorinated alcohol solvents such as TFE and HFIP led to somewhat lower coupling efficiency.

In contrast, no desired product was detected when other common solvents were used. Evaluation of fluoride salts revealed CsF as the optimal one (entries 9−11), indicating the crucial role of the cation. The reaction was promoted by $Zn(OPiv)_2$, and its omission caused a slow reaction (entry 12). The $AgNTf_2$ additive ensured both efficiency and enantioselectivity, since shifting to other common silver salts provided a slightly lower yield (entries 14−16).

Table 1. Optimization Studies of the Asymmetric Fluoroamidation[a]



entry	variations from standard conditions	yield/%[b]	ee/%[c]
1	none	72[d]	94
2	(*R*)-**Rh2** as a chiral catalyst	53	67
3	(*R*)-**Rh3** as a chiral catalyst	68	78
4	(*R*)-**Rh4** as a chiral catalyst	72	89
5	(*R*)-**Rh5** as a chiral catalyst	23	−42
6	(*R*)-**Rh6** as a chiral catalyst	21	−12
7	TFE as a solvent	52	89
8	HFIP as a solvent	61	90
9	NaF as a F source	54	35
10	CuF_2 as a F source	71	27
11	ZnF_2 as a F source	64	28
12	no zinc additive	53	90
13	$Zn(OAc)_2$ instead of $Zn(OPiv)_2$	68	90
14	$AgSbF_6$ instead of $AgNTf_2$	70	88
15	$AgBF_4$ instead of $AgNTf_2$	76	87
16	AgOTf instead of $AgNTf_2$	69	90

[a] Conditions: **1** (0.15 mmol), **2** (0.1 mmol), **3** (0.2 mmol), Rh catalyst (4 mol %), Ag salt (20 mol %), additive (10 mol %), and solvent (0.6 mL), 30 °C, 12 h, N_2 atmosphere. [b] ^{19}F NMR yields by using fluorobenzene as an internal standard. [c] ee value determined by chiral HPLC. [d] Isolated yields.

After establishment of the optimal reaction conditions, we next went on to evaluate the scope of this coupling system (Scheme 2). The scope of the amide functionality in the difluoro-3-butenamide was explored using methyldioxazolone as an amidating reagent. A series of electron-donating and -withdrawing groups at the *para* or *meta* position of the phenyl ring were fully tolerated (**5**−**16**), and the amino amide products were isolated in generally excellent enantioselectivity. The *para* group was also extended to an alkyl derived from the chiral drug Zolmitriptan, and the product **11** was isolated in moderate yield and excellent diastereoselectivity. Lower enantioselectivity was realized for a 4-biphenyl-substituted and 4-phenylbutyl amide substrate (**21** and **22**). Compared to *para* substituents, the *meta* substituents had marginal influence on the enantioselectivity and reaction efficiency (**12**−**16**, 93−94% ee). A series of *ortho* substituents such as F, OMe, and Cl in the phenyl were also compatible (**17**−**19**). However, extension to bulkier *ortho* substituents resulted in lower enantioselectivity (**23** and **24**), and only racemic product was obtained when an *ortho* iodo substrate was employed (**24**). These negative selectivity data may provide insight into the chiral induction mode during the enantiodetermining step (see Scheme 5). A homologous 5,5-difluoro-3-pentenamide substrate was also attempted, but essentially no coupling was detected, indicating the important setting of the amide directing group. The scope of the dioxazolone reagent was next examined. The linear alkyl chain of the dioxazolone was extended to *n*-propyl, -butyl, and -heptyl groups, and the enantioselectivity of the corresponding product was well maintained (**25**−**27**). Several α- and β-branched alkyl groups were also compatible (**28** and **29**). A *cis* olefin group, terminal olefin group, terminal phenyl group, and chloro group all turned out to be compatible (**30**−**34**). Furthermore, a trifluoroethyl group also worked (**35**). In contrast, extension of the alkyl group in the amidating reagent to a phenyl-substituted dioxazolone reagent gave rather poor enantioselectivity and low coupling efficiency (**36**). Also, extension to an olefin with an extra methylene group failed to give any product, indicating the importance of the chelating ring size.

Having examined the scope of asymmetric 1,2-fluoroamidation via chelation assistance, we next sought to extend the olefin to *gem*-difluorodienes (*gem*-FDEs) as another class of olefin by resorting to an allyl intermediate as a driving force

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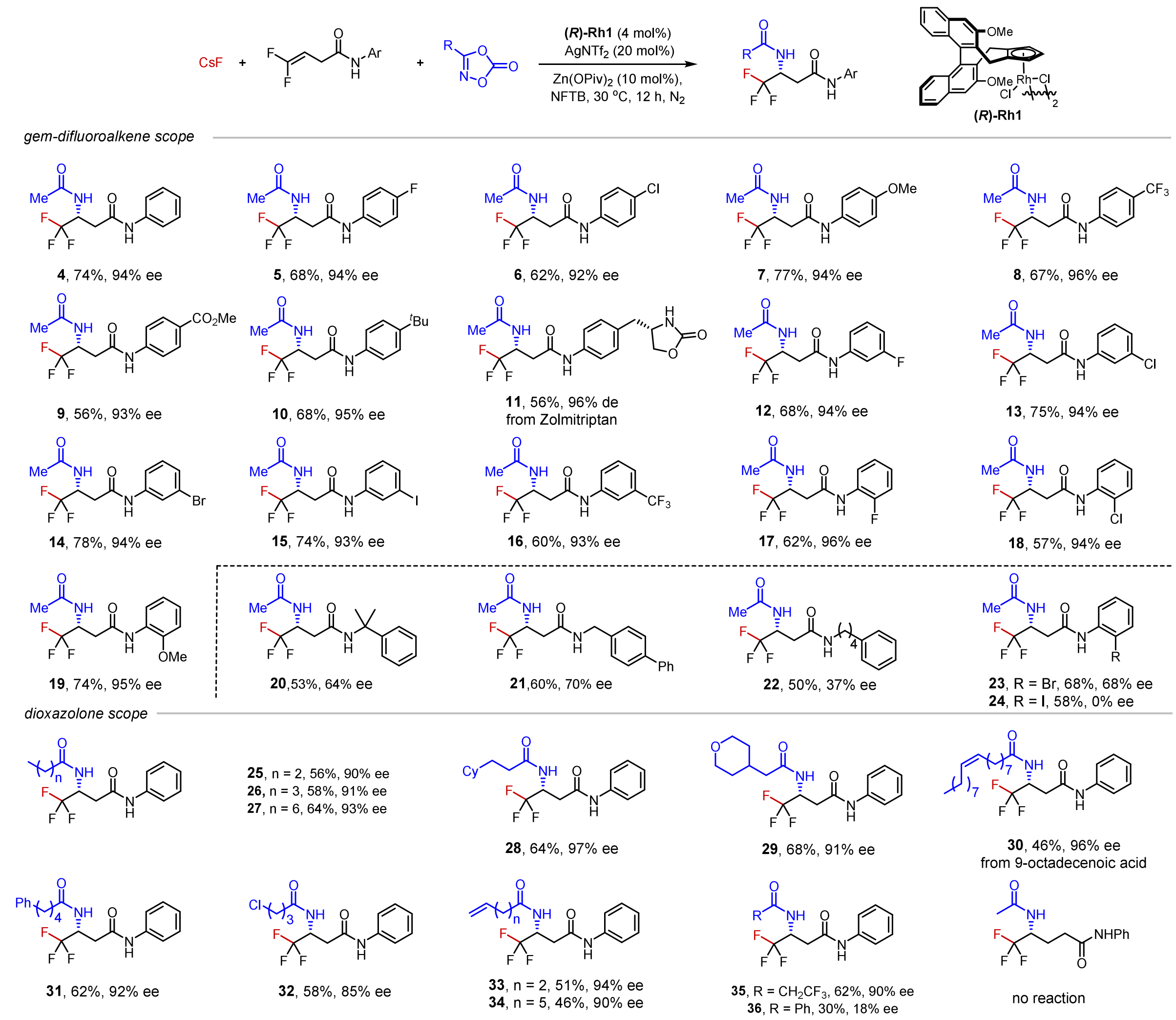
Scheme 2. Rh(III)-Catalyzed Asymmetric 1,2-Fluoramidation of *gem*-Difluoroalkenes[a]

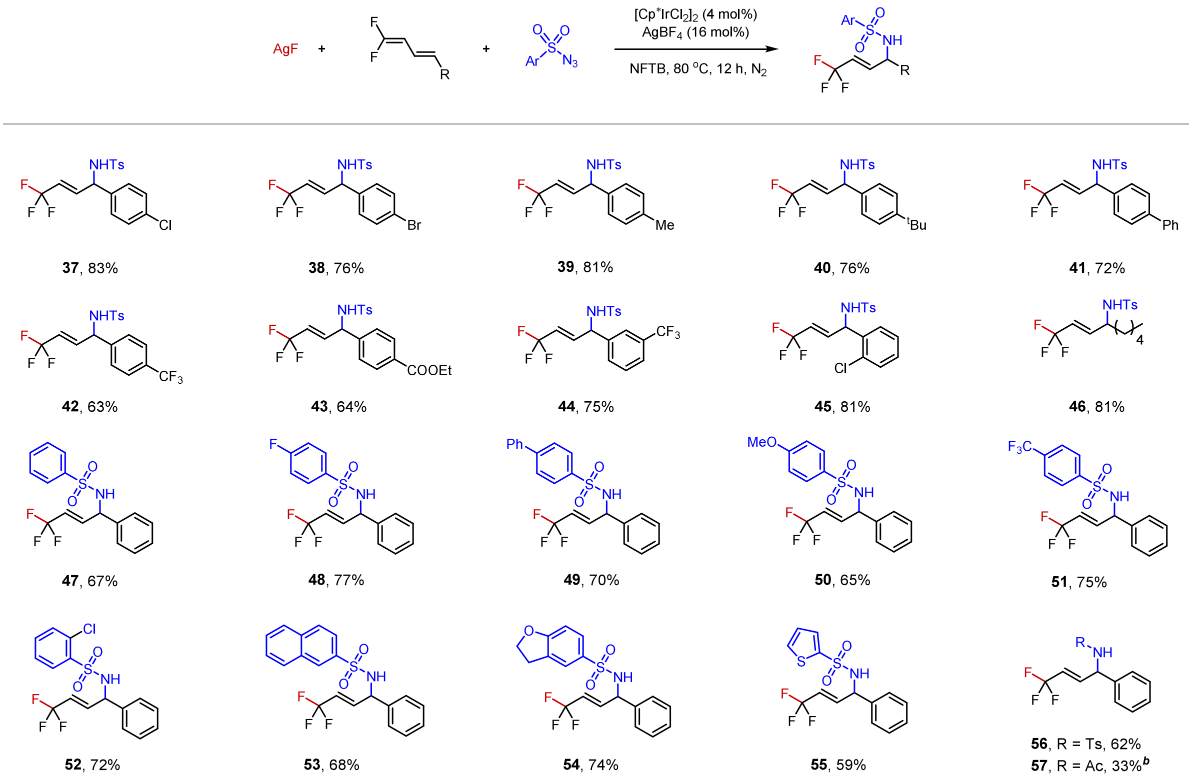


[a] Conditions: CsF (0.15 mmol), *gem*-difluoroalkene (0.1 mmol), dioxazolone (0.2 mmol), **(*R*)-Rh1** (4 mol %), $AgNTf_2$ (20 mol %), Zn $(OPiv)_2$ (10 mol %), and NFTB (0.6 mL), 30 °C, 12 h under N_2 atmosphere, isolated yield. The enantioselectivity was determined by chiral HPLC.

(Scheme 3).[21] Poor reactivity was observed after extensive studies using various rhodium catalysts. To our delight, switching to the $[IrCp^*Cl_2]_2$ catalyst enabled the 1,4-fluoroamidation reaction when sulfonyl azide was selected as an amidating reagent. The observed 1,4-selectivity was possibly due to the steric effect of the CF_3 group that orients the amidation to the distal allyl position. Under similar reaction conditions using NFTB as a solvent and AgF as the fluorinating reagent, the scope of this racemic coupling reaction was next examined. The aryl group in the *gem*-FDE was extended to those bearing different alkyl, halo, and electron-withdrawing groups at the *para* and *meta* positions (**37**−**44**). The presence of an *ortho* halo group was also tolerated (product **45**). The terminal substituent of the *gem*-FDE was not limited to an aryl, and a long aliphatic chain was compatible (**46**, 81%). Examination of the scope of the sulfonyl group in the amidating reagent also verified the compatibility of a large scope of aryl groups. Thus, the inclusion of alkyl, aryl, halo, methoxy, CF_3, and heteroaryl groups was demonstrated with isolation of the corresponding products in good to high efficiency (**47**−**56**). In contrast, low catalytic activity was observed when various rhodium(III) catalysts were attempted (**57**). In this coupling system, based on our related mechanistic studies of oxyamidation of exactly the same diene,[21a] we speculate that a similar mechanism of fluorometalation is followed.

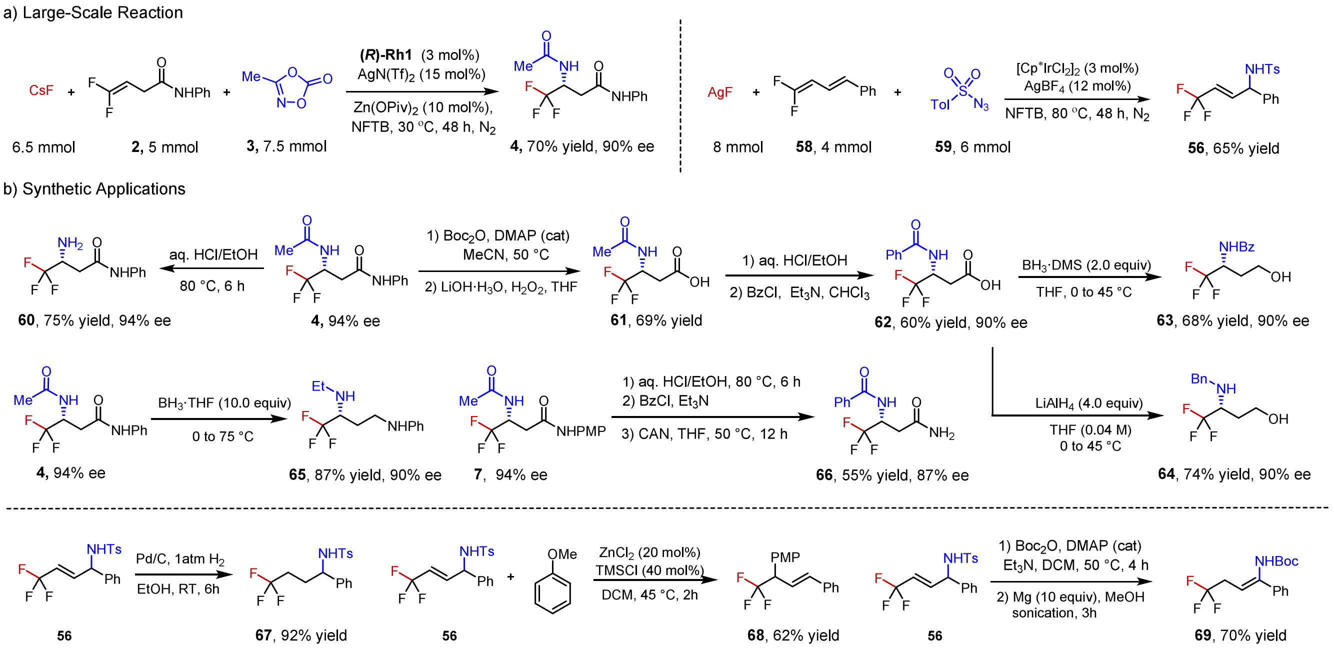
Synthetic applications of selected products were next conducted (Scheme 4). A gram-scale synthesis of product **4** was conducted (5 mmol scale), with no loss of enantioselectivity and efficiency under a slightly lower catalyst loading (Scheme 4a). Meanwhile, fluoramination of *gem*-difluorodienes (*gem*-FDEs) can also be achieved in the gram range. Selective hydrolytic cleavage of the acyl group in the amide moiety of **4** gave an unprotected *β* amino aimde **60** (Scheme 4b). The protic NH-phenyl amide moiety was hydrolyzed to give the amino carboxylic acid **61**. Treatment of **4** with BH_3 afforded the exhaustive reduction product 1,3-diamine **65**. The acyl protecting group in **61** was smoothly converted to a N-Bz group via deprotection−protection (**62**), and this transformation compensates the inapplicability of the phenyl-dioxazolone in the scope study. Both the carboxylic acid group and the amide group or the carboxylic acid group alone in **62** were selectively reduced under different reaction conditions, affording chiral 3-amino alcohols **63** and **64**. In

Scheme 3. Ir(III)-Catalyzed 1,4-Fluoramination of *gem*-FDEs[a]



[a]Conditions: (a) AgF (0.2 mmol), *gem*-FDEs (0.1 mmol), arylsulfonyl azide (0.2 mmol), $[Cp^*IrCl_2]_2$ (4 mol %), $AgBF_4$ (16 mol %) and NFTB (1.0 mL), 80 °C, 12 h, N_2 atmosphere, isolated yield; (b) AgF (0.2 mmol), *gem*-FDEs (0.1 mmol), dioxazolone (0.2 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgBF_4$ (16 mol %), and DCM (1.0 mL), 80 °C, 12 h, N_2 atmosphere, isolated yield.

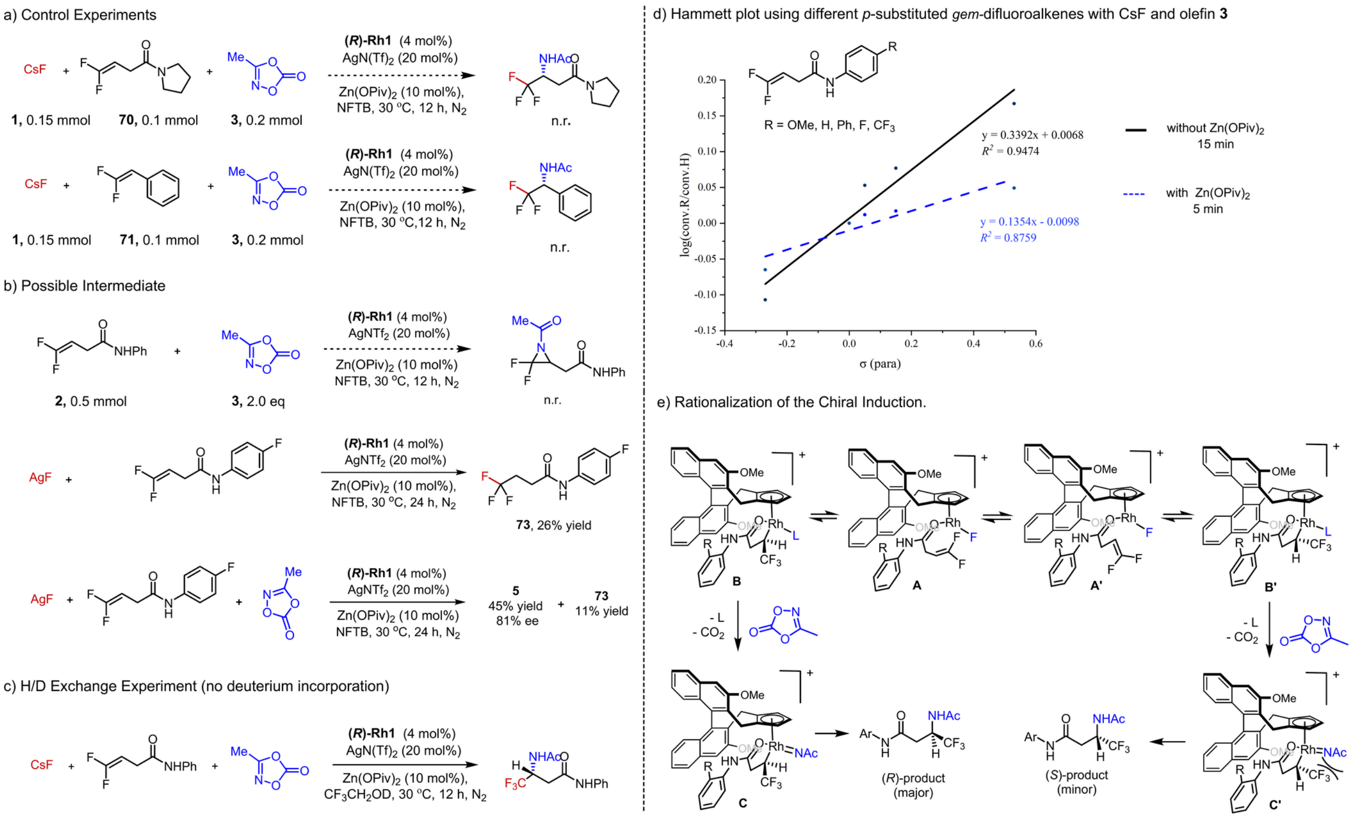
Scheme 4. Synthetic Applications of Representative Products



product **7**, the PMP group was oxidatively cleaved to give an unprotected amide **66** after simple transformations. Of note, the absolute configuration of (*S*)-**61** was confirmed by independent synthesis using a commercially available fluorine-containing amino acid (see the Supporting Information), and the structure of the rest of the products **4**–**36** was assigned by analogy. Brief transformations of product **56** were also performed, including olefin hydrogenation, deaminative arylation, and detosylation with double bond isomerization (**67**–**69**).

Mechanistic Studies. Several experiments were conducted to probe the mechanism of the asymmetric coupling system

Scheme 5. Mechanistic Studies and the Chiral Induction



(Scheme 5). No coupling occurred when a secondary 4,4-difluoro-3-butenamide was employed, suggesting that a protic amide group, upon facile deprotonation, offers a stronger chelating group to assist the fluoroamidation. On the other hand, subjection of *gem*-difluorostyrene to the optimal conditions also failed to give any desired product (Scheme 5a), again highlighting the necessity of a suitable directing group. While we failed to observed any aziridination intermediate of the alkene in the absence of CsF, it was found that when AgF, instead of CsF, was used as the fluoride source, a hydrofluorination product was observed in the absence or presence of dioxazolone (Scheme 5b). We also observed the hydrofluorination side product (typically ~10% yield) under the standard conditions when CsF, NaF, ZnF_2, or CuF_2 was used. These observations, together with the high electrophilicity[12] of difluoroolefins in general, suggests that the coupling system is likely initiated by fluororhodation of the olefin.

To probe the fate of a putative Rh(III) alkyl intermediate in this system, the coupling of olefin **2** and methyldioxazolone was conducted in TFE-*d* (Scheme 5c). The absence of H/D exchange at any alkyl position in the product may rule out reversible *β*-H elimination of this species, assuming rapid Rh(III)-H/D exchange with the protic solvent. To gain details of the turnover-limiting step, Hammett linear correlation has been conducted using a series of *N*-aryl amides in the coupling with methyldioxazolone when catalyzed by $[RhCp^*Cl_2]_2$ in the absence of any $Zn(OPiv)_2$ additive (Scheme 5d). The Hammett plot gave a rather small positive slope of $\rho = 0.34$. This suggests that fluororhodation of the olefin is probably turnover-limiting because a more acidic NH amide, with facile deprotonation, is transformed to a better directing group to assist the fluororhodation. In contrast, no appreciable electronic effect of the *N*-aryl group is expected if the nitrene insertion is turnover-limiting given the distal and unconjugated relation between this aryl and the migrating alkyl group. In the presence of a $Zn(OPiv)_2$ additive, a significantly higher reaction rate was evoked (also see Table 1), but a rather small positive slope with poor linear correlation was observed (Scheme 5c), which may indicate a shift of the turnover-limiting step due to ready deprotonation of the protic amide. In addition, the zinc salt is also a Lewis acid that may promote the fluororhodation.

On the basis of these studies, the chiral induction mode of this asymmetric coupling system was proposed (Scheme 5e). Fluororhodation of an coordinated olefin with an *s-cis* or *s-trans* geometry (**A** or **A′**) gives a chelation-stabilized cationic Rh(III) alkyl species **B** or **B′**, respectively. In each intermediate, the bulky CF_3 group is oriented frontward to minimize steric repulsions with the OMe moiety in the chiral Cp ligand. Following coordination and decarboxylation of the dioxazolone with **B**, the resulting nitrenoid intermediate **C** undergoes migratory insertion and protonolysis to eventually furnish the observed (*R*)-configured major product. With the reversibility of *β*-fluoride elimination, this C−N formation step is likely enantiodetermining. It follows that the CF_3 group is pointed toward the nitrene ligand in the nitrene intermediate **C′**, which causes increased steric repulsions during the migratory insertion and eventually leads to the minor enantiomeric product. In the case of an amide substrate bearing a bulky *N*-aryl group (*N*-aryl with a bulky *ortho* group), we rationalized that the bulky *N*-aryl and the CF_3 group in both intermediates **A** and **A′** are hardly sterically distinguishable, which accounts for the poor enantioselectivity observed for the product **24** (~0% ee).

CONCLUSION

In conclusion, we have developed two classes of three-component fluoroamidation reactions of *gem*-difluorolefins, which allow creation of both trifluoromethyl and amine groups in different spatial settings under operationally simple conditions. When catalyzed by a chiral Rh(III) catalyst, the 1,2-fluoroamidation of 4,4-difluoro-3-butenamide proceeded in excellent enantioselectivity to give a CF_3-containing diamide using CsF as a convenient fluoride source. Meanwhile, the iridium-catalyzed fluoroamidation of *gem*-difluorodienes proceeded efficiently in 1,4-selectivity using AgF as the fluoride source. In both cases, fluorometalation occurs as a key elementary step. Given the fcile incorporation of CF_3 and amino group for construction of amide isosteres, the products and the method in this work may find applications in future studies of asymmetric olefin functionalization.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.5c00001.

Detailed experimental procedures, characterization of new compounds, copies of ^1H, ^{13}C, ^{19}F NMR spectra, and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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