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RESEARCH ARTICLE

# Rhodium-Catalyzed Enantioselective 1,4-Oxyamination of Conjugated *gem*-Difluorodienes via Coupling with Carboxylic Acids and Dioxazolones

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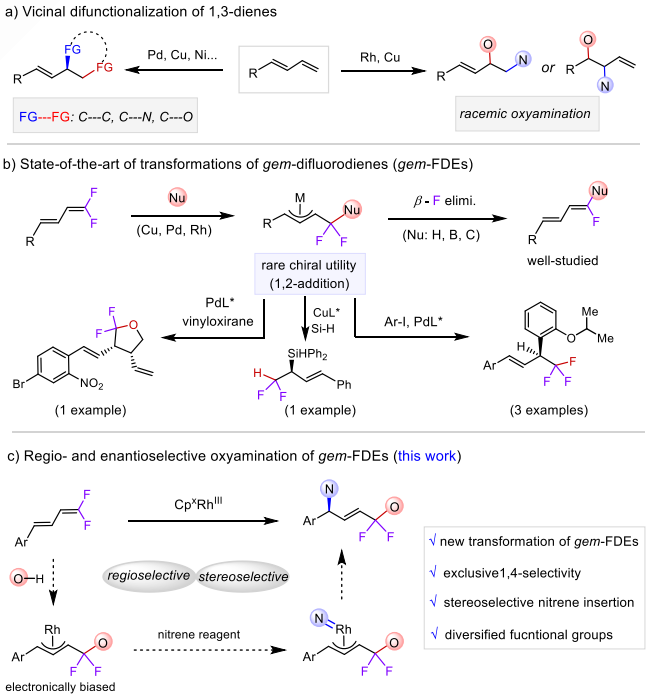
**Abstract:** The incorporation of fluorine atoms in organics improves their bioactivity and lipophilicity. Catalytic functionalization of *gem*-difluorodienes represents one of the most straightforward approaches to access fluorinated alkenes. In contrast to the regular 1,3-dienes that undergo diverse asymmetric di/hydrofunctionalizations, the regio- and enantioselective oxyamination of *gem*-difluorodienes remains untouched. Herein, we report asymmetric 1,4-oxyamination of *gem*-difluorodiene via chiral rhodium-catalyzed three-component coupling with readily available carboxylic acid and dioxazolone, affording *gem*-difluorinated 1,4-amino alcohol derivatives. Our asymmetric protocol exhibits high 1,4-regio- and enantioselectivity with utility in the late-stage modification of pharmaceuticals and natural products. Stoichiometric experiments provide evidences for the π-allylrhodium pathway. Related oxyamination was also realized when trifluoroethanol was used as an oxygen nucleophile.

## Introduction

Conjugated dienes are increasingly exploited as versatile building blocks toward transition metal-catalyzed asymmetric difunctionalization, allowing direct access to value-added unsaturated molecules.[1] Significant advances on catalytic enantioselective difunctionalization of conjugated dienes have been achieved using palladium,[2] nickel,[3] copper,[4] and other catalysts.[5] Such transformations have been typically initiated by regio- and enantioselective addition of organometallic or radical species to the diene or by oxidative cyclometallation with unsaturated chemical bonds.[6] In the former case, the resulting π-allyl intermediate undergoes enantioselective coupling with a functionalizing reagent to deliver a diverse scope of C-C, C-N, C-O, and N-N difunctionalized scaffolds as well as hydrofunctionalized compounds[7] (scheme 1a, left). Among the privileged scaffolds, enantioenriched amino alcohols generated by oxyamination of dienes have long been intriguing owing to their potential biological activities and ligand applications.[8] Although directing group-assisted[9] or oxygen- and nitrogen-tethered strategies[10] have been established in (two-component) couplings that circumvented the distinctive challenges in regio- and enantioselective difunctionalization of conjugated dienes, the modular and selective three-component *N*- and *O*-difunctionalization of conjugated dienes remains rare and challenging. Very recently, Rovis reported a Rh(III)-catalyzed three-component approach to achieve diastereoselective vicinal oxyamination of conjugated dienes, [11] while Wang developed a site-selective 1,2-amino oxygenation of 1,3-diene via copper-mediated *N*-centered radical addition (scheme 1a, right).[12] However, these systems are limited to racemic synthesis, and compared with the exhaustively explored asymmetric carbon-based functionalization of conjugated dienes, regio- and enantioselective installation of both *N*- and *O*-functional groups across conjugated dienes is less explored. This is ascribed to the hard Lewis base nature of oxygen nucleophiles that do not easily form an O-M or O-C bond.




**Scheme 1**. Catalytic selective functionalization of conjugated dienes.

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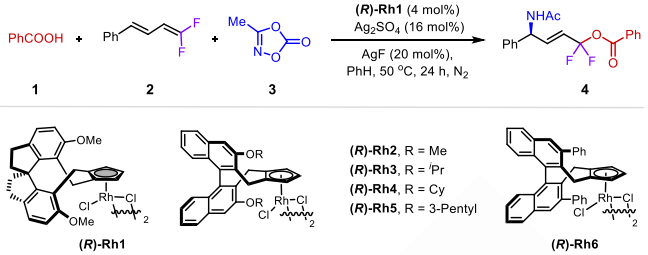
Our strategies then boil down to employment of more Lewis-acidic dienes and metal catalysts. In contrast to regular 1,3-dienes, the strong electron-withdrawing properties of two fluorine atoms in conjugated *gem*-difluorodienes (*gem*-FDEs) readily facilitate the addition of various nucleophiles to $CF_2$ carbon. [13] Besides the well-encountered successive β-fluorine elimination of the resultant *gem*-difluoro allyl species (scheme 1b, top), [14] subsequent enantioselective transformations of such species lag far behind when compared with the non-fluorinated counterpart. Up to now, highly limited asymmetric examples including fluoroarylation,[15] formal [3+2] cycloaddition,[16] and hydrosilylation[17] have been disclosed (Scheme 1b), but all these systems follow the 1,2-regioselectivity. Thus, enantioselective alternative 1,4-difunctioanlization of *gem*-FDEs has remained elusive. The significance of a *gem*-difluoro motif in biologically active compounds, along with the useful 1,4-amino alcohol tethered to a transformative olefin group, has called for development of new strategies for regio- and enantioselective oxyamination of *gem*-FDEs.[18] We anticipated that the *gem*-difluoroallyl rhodium species could be forged by nucleophilic addition of an *O*-nucleophile to *gem*-FDEs (scheme 1c). Whereafter, the biased allyl species undergoes regio- and stereospecific migratory insertion into a nitrene to eventually fulfil the task. Herein, we present the first asymmetric three-component 1,4-oxyamination of *gem*-FDEs for synthesis of chiral *gem*-difluorinated 1,4- amino alcohol derivatives.

## Results and Discussion

On the basis of our conceptual design, our initial studies were carried out by examining the enantioselective 1,4-oxyamination of (*E*)-(4,4-difluorobuta-1,3-dien-1-yl)benzene (**2**) using benzoic acid (**1**) and 3-methyl-1,4,2-dioxazol-5-one (**3**)[19] under rhodium catalysis (Table 1). The desired 1,4-oxyamination occurred in the presence of a spirocyclic **(*R*)-Rh1** catalyst/$Ag_2SO_4$,[20] with a catalytic amount of AgF as an additive in benzene, and the corresponding product **4** was isolated in high yield with high regio- and enantioselectivity regioselectivity (Table 1, entry 1). An inferior catalytic reactivity and enantioselectivity were found when a representative set of binaphthalene-based chiral rhodium(III) catalysts[21] were applied (entries 2-3, and 5-6), and a slightly higher enantioselectivity but a lower yield was obtained by using binaphthalene-based chiral catalyst bearing an OCy substitution (entry 4). Of note, the employment of binaphthalene-derived chiral catalysts all afforded the oppositely configured product due to the opposite spatial orientation of the chiral ligands. Screening of solvents revealed the superiority of benzene, and the reactions proceeded with higher efficiency in non-polar solvents compared with some polar ones such as TFE, MeOH, and acetone (entries 7-13). $AgNTf_2$ was identified as the optimal Cl scavenger, while other silver salts such as $AgSbF_6$, $AgBF_4$, and $AgPF_6$ were slightly inferior in terms of the yield and enantioselectivity (entries 14-18).

**Table 1**. Optimization Studies.[a]




| Entry | Variations from standard conditions | Yield/%[b] | ee/%[c] |
|---|---|---|---|
| 1 | none | 80 | 88 |
| 2 | (*R*)-**Rh2** as a chiral catalyst | 63 | -71 |
| 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 | 78 | -80 |
| 6 | (*R*)-**Rh6** as a chiral catalyst | 53 | -77 |
| 7 | TFE as a solvent | 32 | 14 |
| 8 | MeOH as a solvent | - | - |
| 9 | acetone as a solvent | 54 | 35 |
| 10 | 1,4-dioxane as a solvent | 71 | 86 |
| 11 | toluene as a solvent | 64 | 88 |
| 12 | THF as a solvent | 68 | 67 |
| 13 | DCE as a solvent | 89 | 50 |
| 14 | $AgSbF_6$ instead of $Ag_2SO_4$ | 86 | 88 |
| 15 | $AgBF_4$ instead of $Ag_2SO_4$ | 80 | 91 |
| **16**[d] | **$AgNTf_2$ instead of $Ag_2SO_4$** | **83** | **92** |
| 17 | $AgPF_6$ instead of $Ag_2SO_4$ | 78 | 87 |
| 18 | $AgClO_4$ instead of $Ag_2SO_4$ | 63 | 87 |

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), **3** (0.2 mmol), Rh catalyst (4 mol%), Ag salt (16 mol%), additive (20 mol%), and solvent (1 mL), 50 °C, 24 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.

Having established the optimal oxyamination conditions, we started to examine the generality of this methodology. As given in Scheme 2, regardless of the electronic properties and substitution pattern of the benzene ring, a variety of benzoic acids were effective in this reaction, producing the corresponding chiral 1,4-oxyamianting products in 67−91% yields and 84−99% ee (**4**-**28**, Scheme 2). The absolute configuration of (*S*)-**12** has been secured by X-ray crystallographic analysis. It is worth noting that diversified aromatic carboxylic acids with synthetically useful functional groups, such as iodine, bromine, chlorine, ester, and even free hydroxyl groups, were also amenable to this three-component system (**6**-**8**, **13**-**15**, **17**, and **24**), which provides synthetic handles for further derivations. Complex biological active molecules bearing reactive hydroxyl and sulfonamide groups are well applicable to the reaction, including probenecid (**29**) and diflunisal (**30**). Moreover, 2-thienyl- and furanyl-carboxylic acids (**31** and **32**) were converted to desired products in 70% yield with 95% ee and 66% yield with 90% ee, respectively. Benzofuranyl carboxylic acid was also successfully converted to the 1,4-oxyaminated product in high yield and excellent enantioselectivity (**33**).

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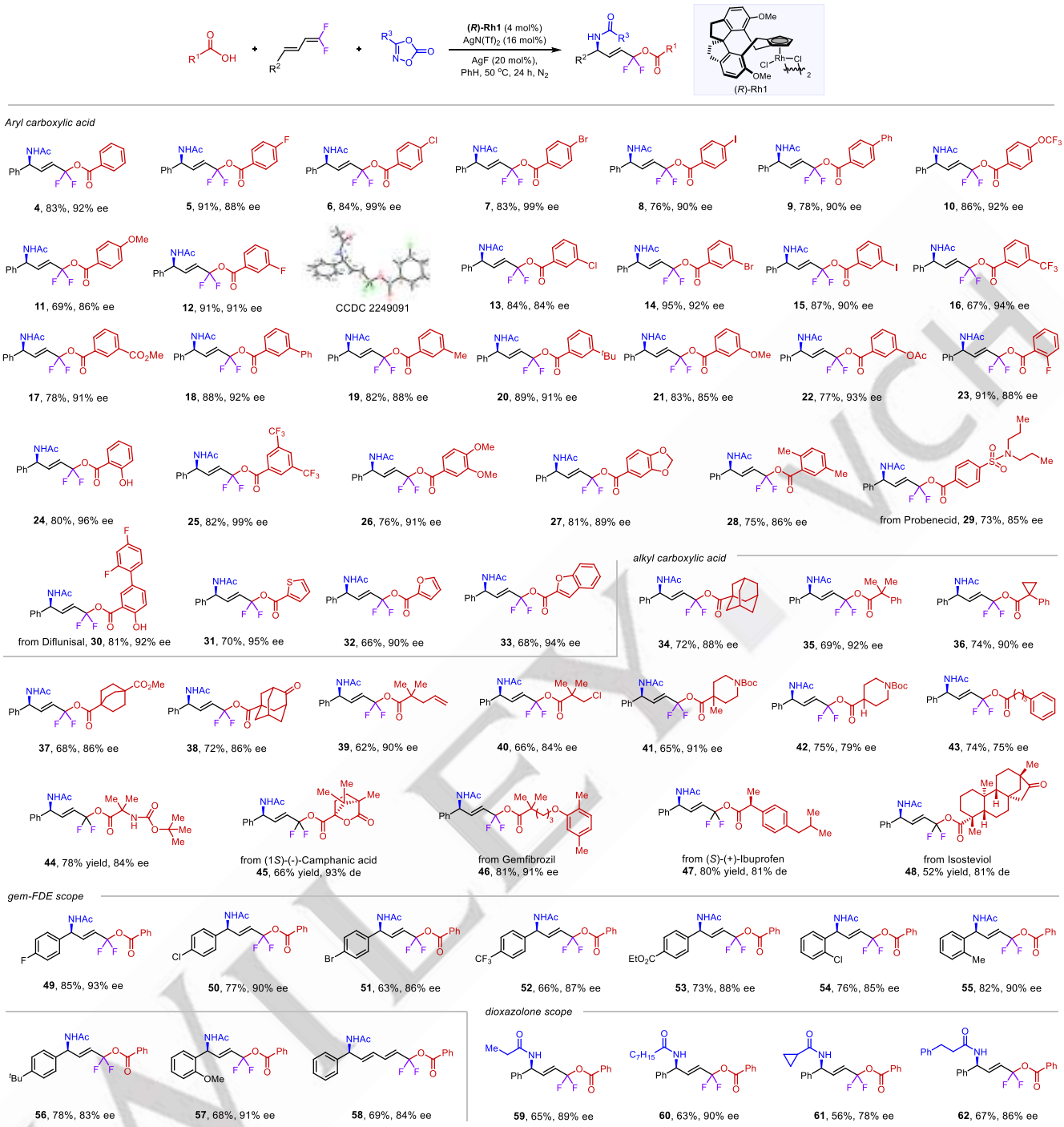


**Scheme 2.** Scope of carboxylic acid. Reaction conditions: carboxylic acid (0.2 mmol), *gem*-FDEs (0.1 mmol), dioxazolone (0.2 mmol), **(*R*)-Rh1** (4 mol%), $AgNTf_2$ (16 mol%), AgF (20 mol%), and benzene (1 mL), 50 °C, 24 h, $N_2$ atmosphere; Isolated yields.

In addition to aryl carboxylic acids, aliphatic carboxylic acids were also examined, and various functionalized alkyl carboxylic acids were all converted into the corresponding 1,4-amino alcohol derivatives in good yields and high enantioselectivities (**34**-**41**), including substrates containing adamantane (**34**), cyclopropane (**36**), bicyclo[2.2.2]octane (**37**), adamantanone (**38**), olefin (**39**), alkyl chloride (**40**), and alkylamine (**41**). Secondary and primary alkyl carboxylic acids also underwent smooth oxyamination, albeit with attenuated enantioselectivity possibly due to reduced steric effect (**42-43**). Several naturally occurring products or drugs including α-amino acid (**44**), camphanic acid (**45**), gemfibrozil (**46**), ibuprofen (**47**), and isosteviol (**48**) also reacted to afford the corresponding products in 81-93% ee or de.

Next, we evaluated the scope of 1,3-dienes. Enantioenriched *gem*-difluorinated 1,4-amino alcohol derivatives containing halogenated aryl groups (**49-51, 54**), electron-withdrawing (**52** and **53**) and -donating (**55-57**) groups were produced in 63-85% yields with 83-93% ee. We were pleased to find that the reaction was extendable to 1,3,5-triene, affording the corresponding chiral *gem*-difluorinated 1,6-amino alcohol derivative containing an internal 1,3-diene fragment (**58**). A series of dioxazolones readily prepared from alkyl carboxylic acids were applicable to this 1,4-

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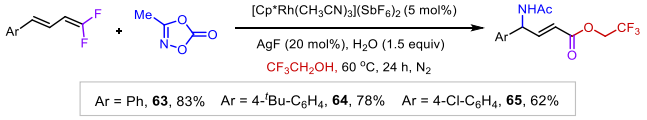
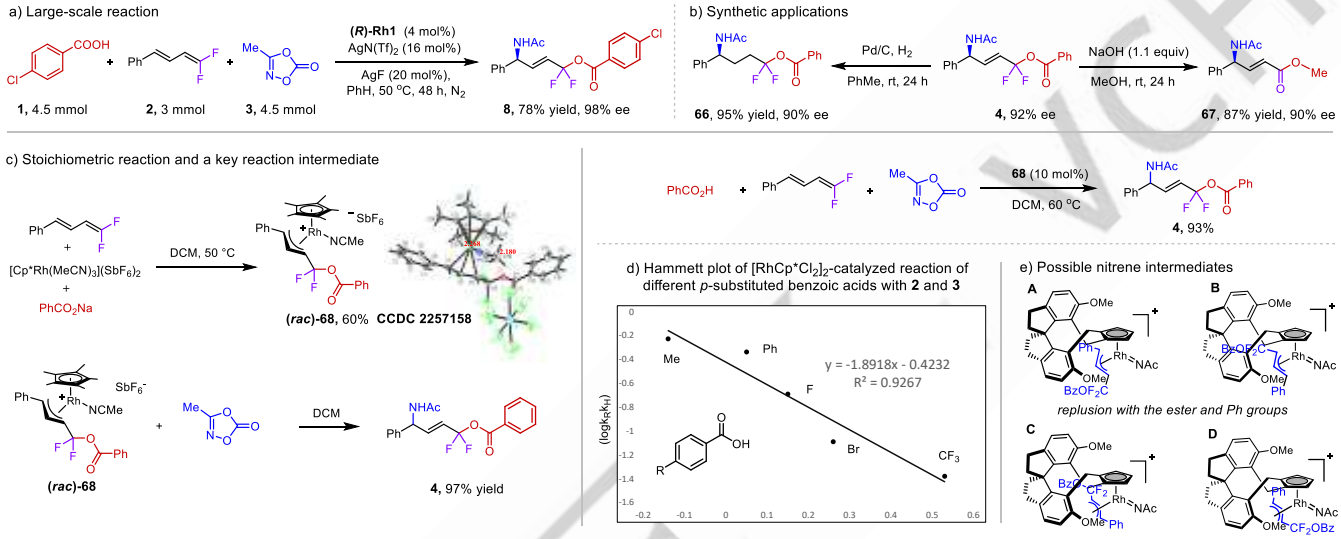
oxyamination system, suggesting that less steric hindered dioxazolones are beneficial to the high enantioselectivity (**59**-**62**). At the current stage, aryl-substituted dioxazolones failed to undergo any oxyamination.




**Scheme 3.** Defluorinative coupling of *gem*-FDEs. Reaction conditions: *gem*-FDEs (0.1 mmol), dioxazolone (0.2 mmol), Rh catalyst (5 mol%), $H_2O$ (1.5 equiv), AgF (20 mol%), and $CF_3CH_2OH$ (1 mL), 60 °C, 24 h, $N_2$ atmosphere; Isolated yields.

At the stage of optimization of the reaction conditions, it was found that 2,2,2-trifluoroethyl (*E*)-4-aminobut-2-enoate was obtained as the major product for the coupling of diene **2** and dioxazolone **3** when 2,2,2-trifluoroethnol was used as a solvent in the presence of water (Scheme 3). This product is likely generated from an oxyamination-hydrolysis pathway. Thus, (*E*)-4-aminobut-2-enoates were isolated in good yields under these modified reaction conditions (**63**-**65**, Scheme 3), which offered a new strategy to yield a range of racemic γ-amino α, β-unsaturated carboxylic acid esters.[22] The asymmetric version of this reaction, however, failed after extensive attempts.




**Scheme 4.** Synthetic applications and mechanistic studies.

The utility of this methodology was briefly demonstrated through product transformations (Scheme 4). The reaction could be performed on a gram-scale (scheme 4a), affording the enantioenriched product in 78% yield with 98% ee. Stereospecific transformation of the *gem*-difluorinated allyl skeletons is of great challenge, as the defluorination often occurs. Hydrogenation of **4** in the presence of Pd/C delivered product **66** in 95% yield, while treatment of **4** with NaOH-MeOH gave chiral γ-amino α,β-unsaturated carboxylic ester **67** in 87% yield via a defluorinative transesterification process (scheme 4b). In both reactions, only negligible erosion of enantiopurity was observed.

To further explore the mechanistic details, a stoichiometric reaction was performed using the diene, a cationic Rh(III) complex, and sodium benzoate, from which a *gem*-difluoroallyl rhodium(III) compound **68** was isolated and was fully characterized, including by X-ray crystallography (CCDC 2257158). Meanwhile, while we failed to isolate the analogous Rh(III) allyl complex bearing a chiral Cp ligand by using the **(*R*)-Rh1** complex, HRMS signal corresponding to an analogous complex **69** was detected (see Supporting Information). The $\eta^3$-allyl rhodium[23] complex **68** proved to be an active catalyst for the three-component oxyamination (Scheme 4c), disclosing the intermediacy of the *gem*-fluoroallylrhodium species **68**. In addition, stoichiometric coupling of **68** with dioxazolone **3** also afforded (*rac*)-**4** in excellent yield (Scheme 4c). In the crystal structure of the allyl moiety of complex **68**, the length of the Rh-CH($CF_2$) bond (2.180 Å) is significantly shorter than that of the Rh-CH(Ph) bond (2.268 Å).[24] This indicates drastically biased electronic effects of these two allyl substituents, and the strong electron-withdrawing $CF_2OBz$ group renders the allyl site a better π-acid, which leaves the Rh-CH(Ph) site more reactive toward migratory insertion into the nitrene, accounting for the observed 1,4-selectivity. The Hammett plot of log($k_R/k_H$) against substituent constant $\sigma_p$ for the racemic reaction of a series of *para*-substituted benzoic acids with diene **2** and dioxazolone **3** gave a straight line with decent correlation (scheme 4d). The rather large negative slope ($\rho$ = -1.9) suggests accumulation of positive charge in the transition state, which is consistent with the external attack of the carboxylate on the ligated *gem*-FDEs (oxyrhodation) where a more electron-rich carboxylate exhibits higher reactivity.

Our proposed mechanism of this coupling reaction is given in Scheme 5. Coordination of the *gem*-FDEs on the cationic rhodium center gives a diene intermediate **II**, which activates the *gem*-FDEs toward external nucleophilic attack by the carboxylic acid, affording a *gem*-difluoroallyl rhodium intermediate **III**. The internal insertion of a ligated carboxylate seems less likely at this stage due to the observed large negative slope of the Hammett plot (Scheme 4d). Coordination of dioxazolone and subsequent release of $CO_2$ lead to formation of the nitrenoid species **IV**. Regio and stereo-determining migratory insertion of the allyl group into the nitrene gives intermediate **V**, followed by protonolysis of the

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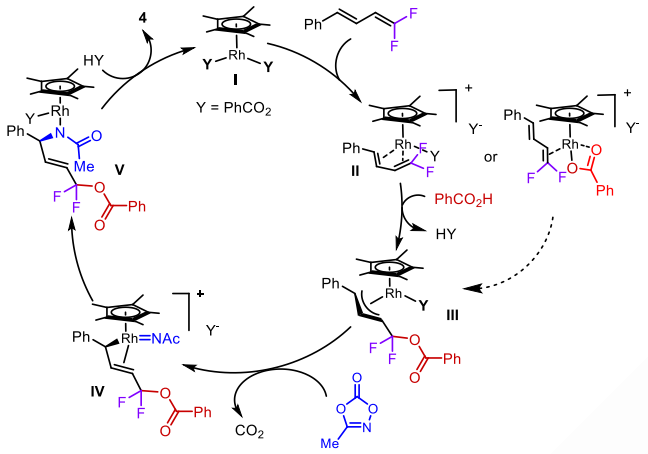
Rh-N bond to complete the catalytic cycle. The four possible orientations of the rhodium allyl nitrene intermediates (**A-D**) are given in Scheme 4e. It is proposed that the exo-orientated allyl intermediates **A** and **B** experience steric repulsions with the proximal chiral ligands. Consequently, they are energetically disfavored. In structure **D**, the steric repulsions between the more tightly bond, front-oriented $CHCF_2OBz$ group and the nitrene may exist during the insertion. Consequently, the insertion of intermediated **C,** in which the $CF_2OBz$ group resides in a less crowded chiral pocket, proceeds to give the (*S*)-**4** as the major enantiomeric product.




**Scheme 5.** Proposed mechanism of three-component reaction.

## Conclusion

In summary, we have realized rhodium-catalyzed asymmetric three-component oxyamination of *gem*-FDEs for the preparation of enantioenriched *gem*-difluorinated 4-amino allylic alcohol derivatives in 1,4-regioselectivity. This protocol features readily available substrates (dienes, carboxylic acids, and dioxazolones) affording novel *gem*-difluorinated scaffolds with good functional group compatibility. The isolation of a *gem*-difluoroallyl rhodium complex provided convincing evidence for the catalytic process. Given the significant interests of allyl intermediates, chiral amino alcohols, and introduction of *gem*-difluoro groups in the synthetic and medicinal communities, we anticipate that this asymmetric oxyamination system will provide a new avenue for the transformations of *gem*-FDEs as well as fabrication of *gem*-fluorinated molecules for research in chemistry and medicine.

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**Keywords:** *gem*-difluorodiene • oxyamination • rhodium catalysis • enantioselective • regioselective

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[24] Deposition Numbers 2249091 (for **12**) and 2257158 (for **68**) contain the supplementary crystallographic data for this paper.

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RESEARCH ARTICLE

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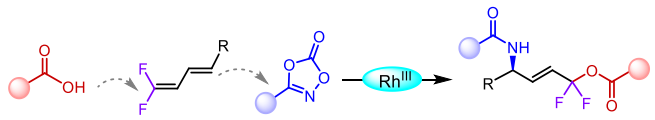


asymmetric oxyamination: high regio- and enantioselectivities

Oxyamination of *gem*-difluorodienes has been realized in excellent 1,4-regioselectivity and enantioselectivity to afford 1,4-amino alcohol derivatives. The reaction proceeded via rhodium(III) catalysis through an $\eta^3$-allyl intermediate.