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RESEARCH ARTICLE

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Rhodium(III)-Catalyzed Enantio- and Diastereoselective C–H Cyclopropylation of *N*-Phenoxylsulfonamides: Combined Experimental and Computational Studies

Guangfan Zheng,[†][b] Zhi Zhou,[†][a] Guoxun Zhu,[†][a] Shuailei Zhai,[b] Huiying Xu,[a] Xujing Duan,[b] Wei Yi*[a] and Xingwei Li*[b]

Abstract: Cyclopropane ring is a prominent structural motif in a number of bioactive molecules, natural products, and pharmaceutical drugs. From a perspective of atom-/step-economy, enantio- and diastereoselective construction of cyclopropanes via C–H activation of arenes and coupling with readily available cyclopropenes is highly appealing but remains very challenging. In this article, by virtue of a dual directing-group-assisted C–H activation strategy, Rh(III)-catalyzed mild and redox-neutral C–H activation and cyclopropylation of *N*-phenoxylsulfonamides have been realized in a highly enantioselective, diastereoselective, and regioselective fashion with cyclopropenyl secondary alcohols as a cyclopropylating reagent. Synthetic and biological applications have been demonstrated, which manifested potentials of the developed protocol. Integrated experimental and computational mechanistic studies revealed that the reaction proceeds via a Rh(V) nitrenoid intermediate, and Noyori-type outer sphere concerted proton-hydride transfer from the secondary alcohol to the Rh=N bond conduces to the observed *trans* selectivity.

Introduction

Cyclopropanes are key structural motifs found in a broad range of bioactive compounds and natural products.[1] They are also of great importance as synthetic intermediates and building blocks.[2,3] In particular, there is an increasing trend in applying cyclopropyl rings in drug discovery owing to their prominent pharmacological properties such as (1) reducing off-target effects, (2) increasing metabolic stability, and (3) improving brain permeability.[4,5] Thus, an overall improvement of the pharmacological property can be well expected with introduction of proper cyclopropyl ring. Especially, the 1,1-dimethylcyclopropane motif as a privileged structural unit has frequently appeared in FDA-approved drugs, such as boceprevir and cilastatin (Figure 1).[4c] Therefore, the development of efficient synthetic methods for rapid construction of highly valuable cyclopropane core represents an important research objective. Consequently, notable synthetic progress has been made,[6-10] including classical metal-catalyzed decomposition of diazoalkanes,[6] Simmons-Smith type cyclopropanations,[7] Michael addition-initiated ring closure,[8] and enzymatic synthesis.[9]

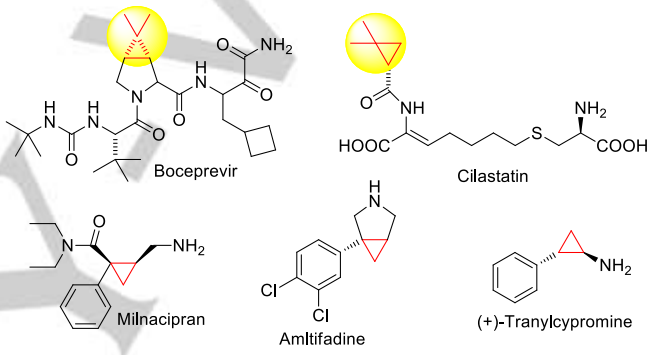

Figure 1. The representative examples for FDA-approved drugs bearing a cyclopropane motif.

Cyclopropenes[11] represent versatile and reactive electrophilic cyclopropylating reagents owing to the ring strain (approximately 54 kcal/mol). Metal-catalyzed *cis*-selective carbofunctionalization of cyclopropenes has been realized via insertion of main group organometallics, terminated by an electrophile (Scheme 1a).[12] On the other hand, enantioselective hydrofunctionalization[13] (such as hydroamination, hydroboration, hydrostannylation and hydroacylation) of cyclopropenes have also been extensively studied under various metal-catalyzed conditions. Arenes represent abundant carbonucleophiles (Scheme 1b). From the perspective of atom/step-economy, metal-catalyzed C–H activation of arenes offers a highly desirable strategy for direct construction of cyclopropanes using readily available cyclopropenes.[14] Despite the conceptual simplicity, successful examples are rather rare (Scheme 1c). The main obstacle resides in the high activity but low compatibility of cyclopropenes associated with the ring strain, which generally conduces to ring-opening reactions in C–H activation chemistry[15] instead of cyclopropylation reactions. Thus, although various couplings of arenes and cyclopropenes have been realized by Wang, Glorius, and Rovis under Rh(III) catalysis, the majority of such functionalization falls into ring-scission couplings.[16,17] In 2017, by using a designed Rh(III) catalyst, Rovis reported the first redox-neutral *cis*-diastereoselective (2.3:1 to >20:1 dr) synthesis of cyclopropa[*c*]dihydroisoquinolones (Scheme 1c), where the cyclopropene acted as a special olefin in this [4+2] annulation.[14b] Given the rarity of C–H cyclopropylation systems and the improvable diastereoselectivity of orphaned example, it is highly desirable to develop efficient synthesis of cyclopropanes in both excellent

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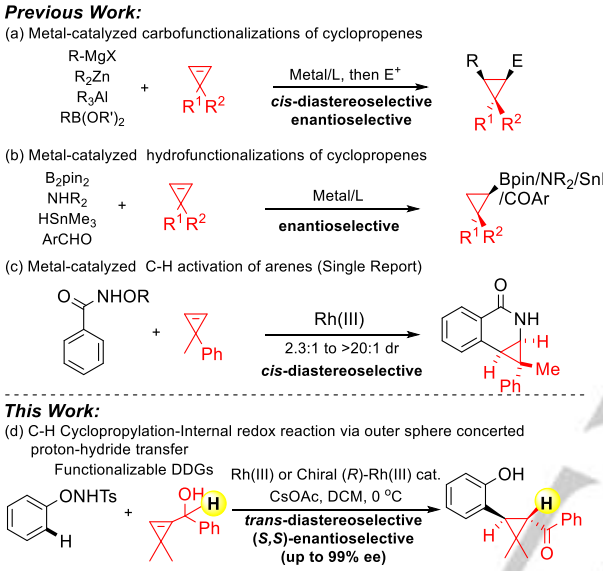
diastereoselectivity and enantioselecvitiy, especially with the embedment of synthetically useful functionalities. We now report the first Rh(III)-catalyzed redox-neutral C–H cyclopropylation of arenes with cyclopropenyl alcohols for straightforward synthesis of functionalized *trans*-cyclopropanes in a specific diastereoselective and enantiostereoselective fashion (Scheme 1d). Further experimental and computational studies revealed that the O–NHTs and OH dual-directing-group (DDG)-assisted Noyori-type outersphere concerted proton-hydride transfer to a Rh(V) nitrenoid conduces to this exclusive regioselective, *trans*-diastereoselective, and excellent (*S,S*)-enantioselective cyclopropanation. We also demonstrated synthetic and biological applications in the rapid derivation of natural products and as promising antitumor agents.

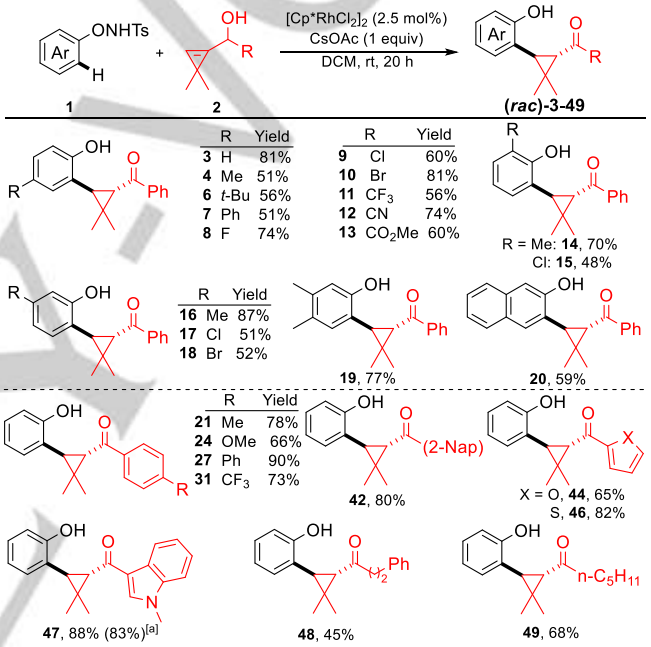


Scheme 1. Metal-catalyzed cyclopropylation of nucleophiles.

Results and Discussion

We reasoned that high diastereoselectivty of C–H cyclopropylation system calls for a rapid, irreversibly transformation in post-insertion reactions, ideally under mild conditions. This may be fulfilled in a putative cyclopropyl Rh(V) species[18] that is highly reactive toward reductive elimination and other elementary reactions. We thus chose reactive *N*-phenoxyacetamide and (3,3-dimethylcycloprop-1-en-1-yl)(phenyl)methanol (**2a**) as model substrates for racemic studies under typical Cp*Rh(III)-catalyzed reaction conditions (see the Supporting Information). The desired cyclopropylation-internal redox product **3** was obtained under rhodium-catalyzed simple conditions and was produced in exclusively *trans* selectivity as determined X-ray crystallography (CCDC 1907914).[19] Solvent screening indicated that CH_2Cl_2 was the optimal medium, and CsOAc was established as the optimal additive. Variation of the directing groups revealed that *N*-phenoxytosylamide (**1a**) outperformed others. By adjusting the substrate ratio, the optimized conditions were eventually identified (Scheme 2).

The scope of this racemic system was found to be quite broad (Scheme 2). Thus, *N*-phenoxytosylamides bearing various commonly encountered functional groups such as alkyl (**4** and **6**), phenyl (**7**), halogens (**8-10**), trifluoromethyl (**11**), cyano (**12**), and ester (**13**) were fully compatible, delivering the cyclopropanes in moderate to good yields, and the C–H bond cleavage occurred regioselectively at the less hindered site when *meta*-substituted substrates were used (**16-20**). Subsequently, a diverse array of cyclopropenyl alcohols was examined. It was found that aryl, naphthyl (**42**), furyl (**44**), thienyl (**46**), and indolyl (**47**) groups were well tolerated in the coupling with **1a**. Importantly, alkyl-substituted cyclopropenyl alcohols were also viable substrates (**48** and **49**). Finally, high-yielding synthesis of **47** on a 2.0 mmol scale further demonstrated the scalability. In all cases only the *trans* cyclopropane products were consistently detected.

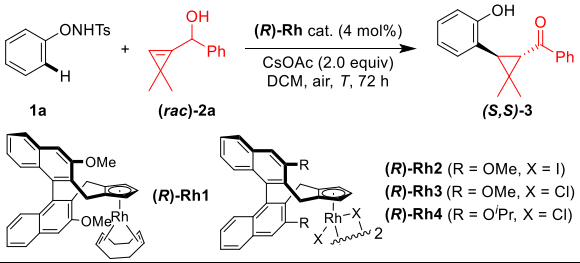


Scheme 2. Scope of racemic cyclopropylation. Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%) and CsOAc (1 equiv) in DCM (0.1 M) at room temperature for 20 h under air; isolated yields were reported. [a] Performed on a 2.0 mmol scale.

While asymmetric insertion of olefins into C–H bond has been increasingly employed using chiral Rh(III) catalysts,[20-23] including under internal redox-conditions,[21] the olefins have been limited to terminal,[21b-e,23] strained,[21d-e,22] and intramolecular olefins.[21a] We next screened the reaction parameters in the asymmetric C–H cyclopropylation[13a-c] of **1a** with *(rac)*-**2a** using a set of four chiral *(R)*-$RhCp^X$ catalysts (Table 1). Application of **Rh1** and $Cu(OAc)_2$ as an in situ generated Rh(III) catalyst afforded *(S,S)*-**3** in 93% ee albeit with less satisfactory yield (DCM, entry 1), and no improved yield was obtained in other common solvents (entries 2-5). Switching to the Rh(III) catalyst **Rh3** significantly increased the yield without much loss of the enantioselectivity (0 °C, entry 7), and the Rh(III) chloride catalyst drastically outperformed the iodide congener (entry 6). Both high yield and excellent enantioselectivity (95% ee) were secured when the **Rh4** catalyst was used (entry 8). Variations of additive, temperature, and arene source (PhONHAc) all failed to offer improved efficiency and enantioselectivity. The absolution configuration of the product has been determined to be *(S,S)* by X-ray crystallographic

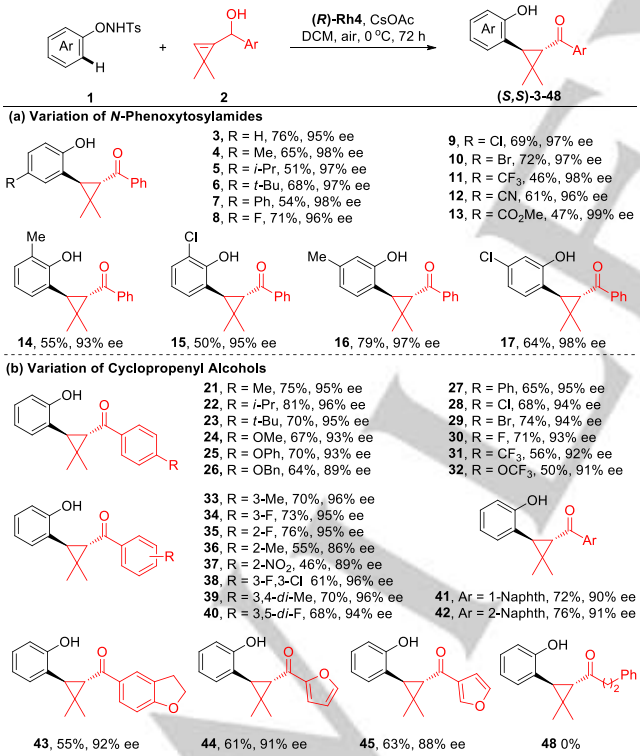
analysis of the *O*-sulfonylated derivative (vide infra). In all cases, only the *trans* product was detected.

Table 1. Asymmetric optimization studies.[a]



Entry	Catalyst (4 mol %)	Solvent	*T* (°C)	Yield[b] (%)	ee[c] (%)
1[d]	(*R*)-**Rh1**	DCM	-15	40	93
2[d]	(*R*)-**Rh1**	$CHCl_3$	-15	31	94
3[d]	(*R*)-**Rh1**	DCE	-15	35	89
4[d]	(*R*)-**Rh1**	PhCl	-15	38	89
5[d]	(*R*)-**Rh1**	DCM	0	51	91
6	(*R*)-**Rh2**	DCM	0	<5	nd
7	(*R*)-**Rh3**	DCM	0	78	89
8	(*R*)-**Rh4**	DCM	0	76	95
9[e]	(*R*)-**Rh4**	DCM	0	73	94
10[f]	(*R*)-**Rh4**	DCM	0	<5	nd
11	(*R*)-**Rh4**	DCM	25	79	89

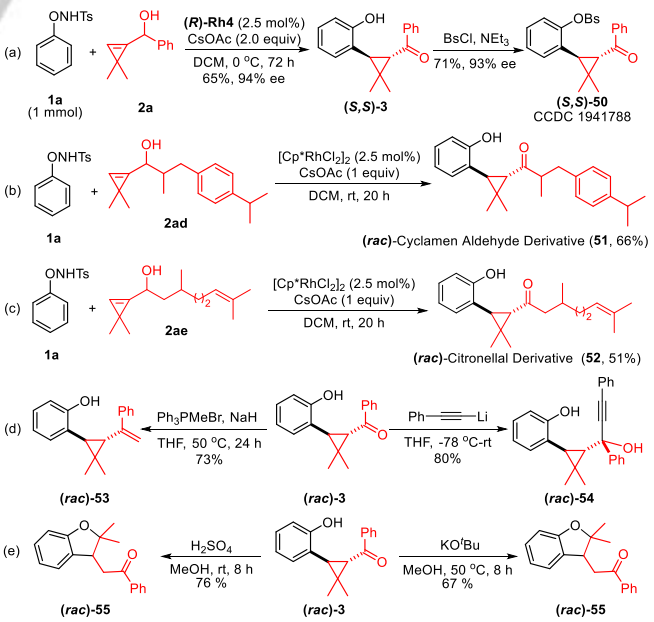
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Rh cat. (4 mol%) in a solvent (2 mL) under air, for 72 h. [b] Isolated yield after column chromatography. [c] Determined by HPLC with a chiral stationary phase. [d] Rh cat. (8 mol%) together with $Cu(OAc)_2$ (16 mol%). [e] CsOPiv was used instead of CsOAc. [f] PhONHAc was used instead of **1a**.



Scheme 3. Scope of asymmetric C-H cyclopropylation. Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), (*R*)-**Rh4** (4.0 mol%), CsOAc (2.0 equiv) in DCM (2.0 mL) under air at 0 °C for 72 h, isolated yield.

The scope of this enantioselective synthesis was next explored under the optimal reaction conditions (Scheme 3) and was found to be quite broad. Thus, arenes bearing various alkyl, halogen, and EWGs at the *para* position all coupled smoothly with **2a** in consistently excellent enantioselectivities (> 95% ee) and moderate to good yields (**3-13**). Introduction of *ortho* Me and Cl groups was also tolerated (**14** and **15**), suggesting compatibility with steric effect of the arene. A few *meta* substituted arene substrates coupled regioselectively with **2a** at the less hindered *ortho* site in excellent enantioselectivity (> 97% ee). The scope of the cyclopropenyl alcohol was next examined in the coupling with arene **1a**. Introduction of various electron-donating (OMe, OPh, OBn), -withdrawing (CF_3, OCF_3), and halogen groups into the *para* position of the alcohol phenyl ring was fully tolerated, with the enantioselectivity ranging from 89% to 96% ee (**21-32**). Comparably excellent enantioselectivity and good efficiency were also realized for those alcohols bearing *ortho* and *meta* substituents (**33-40**), indicative of tolerance of steric and electronic perturbation. The aryl group was also smoothly extended to 1- and 2-naphthyls and to 2- and 3-furyls (88-91% ee). In contrast to the smooth racemic coupling of alkyl-substituted alcohols, essentially no reactivity was observed in the asymmetric system (**48**), which indicates limitation of the alcohol substrate.

Synthetic applications of this coupling system were next demonstrated. Scale-up synthesis of *(S,S)*-**3** has been achieved at a 1.0 mmol scale under a reduced catalyst loading (Scheme 4a). Subsequent protection of the OH group with BsCl afforded product *(S,S)*-**50** (CCDC 1971788)[19] with essentially no erosion of the enantiopurity, which allowed determination of the absolute configuration of **3**. In subsequent racemic coupling, the reaction of **1a** with the corresponding alkyl-functionalized cyclopropenyl alcohols (**2ad** and **2ae**, derived from bioactive natural products cyclamen aldehyde and citronellal, respectively) proceeded smoothly, to afford their desired derivatives (**51-52**) in good yield (Schemes 4b, c). The ketone unit allows for further transformations (scheme 4d). Wittig reaction of **3** afforded product **53** in 73% yield. **3** could undergo nucleophilic addition with lithium phenylacetylide in high diastereoselectivity. When treated with KO^{t}Bu or concentrated H_2SO_4, **3** underwent ring opening to give dihydrobenzofuran derivate **55** in good yield (scheme 4e).

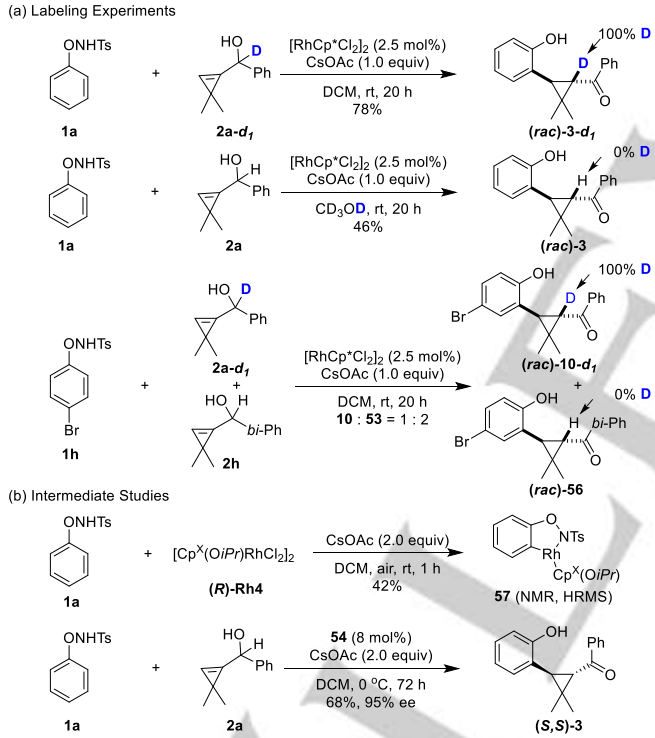


Scheme 4. Synthetic applications

Besides synthetic applications, the biological application of five *trans*-cyclopropane products was also investigated. As given in Table 2, our initial in vitro screening demonstrated that all these products displayed potent antitumor activities in a panel of human tumor cell lines, including HepG2, MCF-7, A549 and SH-SY5Y, as determined by a dose-dependent CCK8 assay. In particular, products **20** and **27** exhibited more potent inhibitory activities than the marketed anticancer drug 5-Fluorouracil. These results suggested the potential and interest of such products in broad-spectrum anticancer drug discovery. Correlation with the chemical structures of these products suggests that the introduction of aryl functional group to **3** can be beneficial in enhancing the antitumor potentiality.

Table 2. Biological Applications.

Compounds	IC_{50} (μM)			
	HepG2	MCF-7	A549	SH-SY5Y
3	41.48±8.17	>200	65.46±11.26	>200
18	31.42±1.87	26.3±1.17	38.73±2.65	35.18±1.42
20	21.25±1.38	5.2±2.93	33.0±1.08	17.35±3.19
27	25.35±1.52	25.44±2.45	35.04±1.84	34.38±1.4
30	69.47±1.31	>200	>200	>200
5-FU	51.61±0.93	31.74±1.07	39.03±3.34	2.97±0.56



Scheme 5. Mechanistic studies and proposals

A series of experiments have been conducted to probe the mechanism of this coupling system (Scheme 5). The racemic coupling between arene **1a** and a mono-deuterated alcohol (*rac*)-**2a-*d*$_1$** revealed complete transposition of the D atom to the α position of carbonyl group (Scheme 5a, above). Consistently, the coupling of **1a** and **2a** in the presence of CD_3OD resulted in no deuterium incorporation into the product, indicating that the hydrogen originates from the methine C–H. A crossover experiment using **1a** and two distinguishable cyclopropyl alcohols further reinforced this conclusion, where the corresponding two products were generated without crossover (Scheme 5a, below). The mechanism of the asymmetric coupling system was also briefly explored. A stoichiometric reaction of **1a** and (*R*)-**Rh4** allowed isolation of a rhodacycle **57** as the enantiometrically and diastereomerically pure product (Scheme 5b), which was characterized by NMR spectroscopy and mass spectrometry. Designation of **57** as a catalyst for the coupling of **1a** and **2a** afforded the *(S,S)*-**3** in 68% yield and 95% ee, indicating that the reaction follows a C–H activation pathway and the chiral environment in **57** offers sufficient control of the enantioselectivity.[21b,24]

To better explore the mechanistic details, we then conducted a set of density functional theory (DFT) studies, particularly to uncover the role of the DDGs and the origin of the regioselectivity, the specific *trans*-diastereoselectivity as well as the (*S*,*S*)-enantioselectivity. Unless otherwise specified, all structures were optimized at the B3LYP level and single point energy calculations at the M06L level were performed in experimental solvent (DCM). The N−H cleavage and C−H activations occurred via **TS-1** ($\Delta G^{\ddagger}$ = 13.7 kcal/mol) and **TS-2** ($\Delta G^{\ddagger}$ = 22.3 kcal/mol via concerted metalation-deprotonation), respectively, to afford a rhodacycle **INT-3** (see the Supporting Information). Subsequent coordination and regioselective migratory insertion of olefin **2a** proceeded via **TS-3** with an energy barrier of 23.5 kcal/mol to give a seven-membered rhodacycle intermediate **INT-5**. In contrast, insertion with the other regioselectivity took place with a free energy barrier of 26.8 kcal/mol (**INT-3** to **TS-3$_{iso}$**). Therefore, formation of the intramolecular hydrogen bonding between the Ts and the OH groups plays a crucial role in controlling the insertion regioselectivity.

From **INT-5**, several possible pathways have been examined to dwell on the mechanistic details of this racemic reaction (Figure 2). In path a, the coordination of the hydroxyl group to Rh center generated a more stable intermediate **INT-6** with a free energy of -7.8 kcal/mol, followed by the oxidative addition of the N-O bond with a free energy barrier of 7.9 kcal/mol (from **INT-6** to **TS-4a**) to produce a Rh(V) nitrenoid **INT-7a**. [25,26] In path b, an alternative oxidative addition process along with the cleavage of O–N bond was involved to yield the Rh(V) species **INT-8b**, followed by intramolecular dual hydrogen transfer, in which the hydrogen on hydroxyl group was shifted to the phenol oxygen while the methine C–H of the alcohol was transferred to the NTs, to provide the **INT-9b**. Obviously, this pathway via **TS-8b** carried a relatively high free energy ($\Delta G^{\ddagger}$ = 16.4 kcal/mol), rendering it less likely compared with the path a. Besides, another reaction pathway without hydrogen-bonding assistance was also excluded sicne a relatively high free energy of 7.9 kcal/mol was involved in its transition state (see **TS-4b**). These results futher emphasized the significance of the formation of a hydrogen bonding between DDGs for this transformation. In addition, ring-opening of the cyclopropane moiety by the selective *β*–C elimination via either the Rh(III) species **TS-4c** or the Rh(V) species **TS-5c** could be ruled out because relatively high energy barriers ($\Delta\Delta G^{\ddagger}$ = 28.7 kcal/mol from **INT-5** to **TS-4c** and $\Delta\Delta G^{\ddagger}$ = 23.6 kcal/mol from **INT-7a** to **TS-5c**) were noted. Instead, nitrenoid **INT-7a** underwent irrversible, concerted proton and hydride transfer via Noyori's outer sphere mechanism with a low energy barrier of 6.5 kcal/mol (via **TS-5a**) to give intermediate **INT-8a**. It should be noted that, in an alternative stepwise pathway of OH nucleophilic addition to the Rh=N bond (via **TS-5b)** and subsequent *β*–H elimination (via **TS-6b)** was unfavorable due to the ring strain. Thus,

our calculations highlighted that the outer-sphere concerted proton-hydride transfer effectively lowers the reaction barrier and avoids the thermodynamic sink **INT-7b**. Following formation of **INT-8a**, facile C–H reductive elimination via the three-membered transition state **TS-6a** instead of enolized 1,3-Rh(III) migration ($\Delta\Delta G^{\ddagger}$ = 5.4 kcal/mol *vs* $\Delta\Delta G^{\ddagger}$ = 16.6 kcal/mol) takes place to deliver the Rh(III) phenoixde **INT-9a**, which upon protonolysis furnished the final *trans*-product together with regeneration of the Rh(III) catalyst.

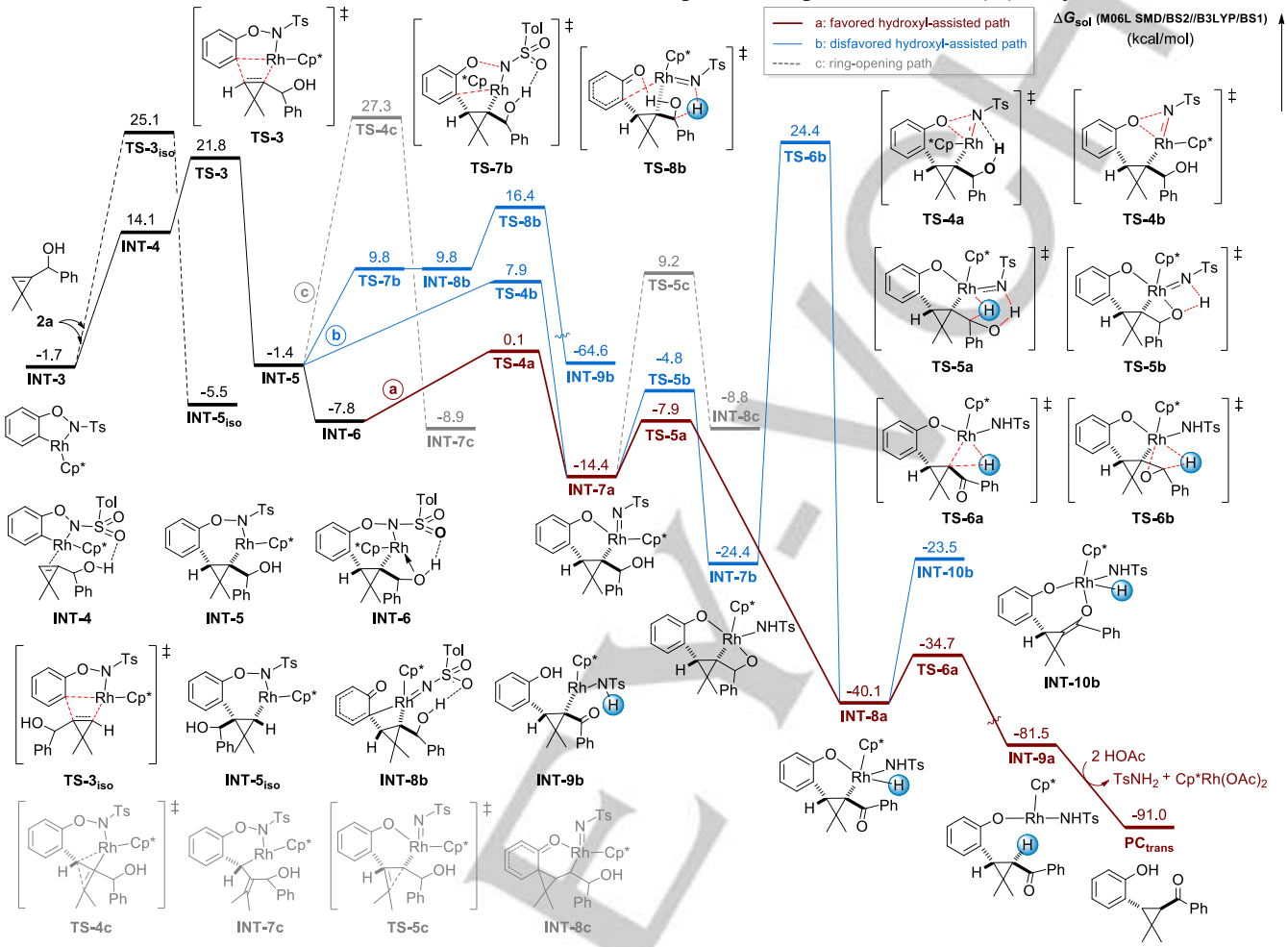
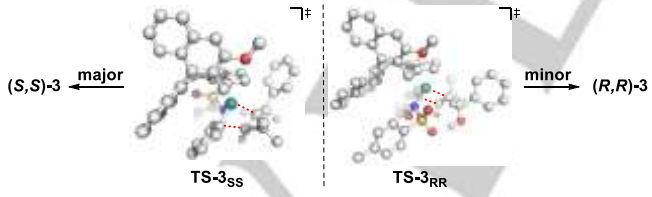


Figure 2. Computed Gibbs free energy changes of the reaction pathways for alkyne insertion, oxidative addition, Noyori-type outer sphere concerted proton-hydride transfer, reductive elimination and protonlysis in DCM.



Level of theory	$\Delta\Delta G^{\ddagger}$ (**TS-3$_{RR}$**-**TS-3$_{SS}$**) (kcal/mol)	ee(%)
M06L SMD/BS2//B3LYP/BS1	0.6	51
M06 SMD/BS2//B3LYP/BS1	1.8	93
M06L SMD/BS2//M06L/BS1	2.8	99
M06 SMD/BS2//M06/BS1	1.7	92

*T = 0 °C

Figure 3. Optimized geometries, energy differences and ee values of the transition states **TS3$_{SS}$** and **TS3$_{RR}$** for the alkene insertion step in the ***(R)*-Rh4** catalyzed cyclopropanation reaction.

After the exploration of the racemic coupling system, we further rationalized the enantioselectivity of the asymmetric coupling of **1a** and **2a** catalyzed by chiral ***(R)*-Rh4** catalyst by DFT studies. Migratory insertion of the Rh-C(aryl) into the C=C bond constitutes the steterodeterming step. Two transition states **TS-3$_{SS}$** and **TS-3$_{RR}$** with respect to different stereoselectivity of olefin insertion were investigated and the differences of activation energies are given in Figure 3. Our calculations using different levels of theoretical studies confirmed that the free energy of **TS-3$_{RR}$** was consistently higher than that of **TS-3$_{SS}$**, with the energy difference between **TS-3$_{SS}$** and **TS-3$_{RR}$** ranging from 0.6 to 1.8 kcal/mol (0 °C), which correponds to a good to excellent calculated ee values (up to 99% ee). The results are indeed in line with our results in asymmetric C–H cyclopropylation. Thus, on the basis of both DFT calculations and experimental mechanistic studies, a tandem C–H activation, alkyne migratory insertion, oxidative addition, outer sphere concerted proton-hydride transfer, reductive elimination, and protonolysis process is proposed (See the Supporting Information).

Conclusion

We have developed the first Rh(III)-catalyzed and DDG-assisted enantio- and diastereoselective C–H cyclopropylation of *N*-phenoxytosylamides with cyclopropenyl alcohols as a result of ring-retentive internal redox coupling, which complements the few existing methods to synthesize *trans*-cyclopropanes. Both racemic and enantioselective reactions have also been realized with broad functional group compatibility under mild and operationally simple conditions. Subsequent derivatization of natural products and biological application of the selected products as the screening of the promising antitumor drugs further highlighted the utility of the developed protocol. Through detailed experimental and computational investigations, the role of the DDGs, the origin of the regioselectivity, the specific *trans*-diastereoselectivity, and the (*S*,*S*)-enantioselectivity have been elucidated. Significantly, Noyori-type outer sphere concerted proton-hydride transfer mechanism was identified as a key factor for controlling such *trans*-specific selectivity. Future studies on asymmetric C–H activation using other strained rings are ongoing in our laboratories and will be reported in due course.

Acknowledgements

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Keywords: Rhodium • *trans*-cyclopropane • asymmetric C–H activation • *N*-phenoxysulfonamide • cyclopropenyl alcohol

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[26] An alternative O–N cleavage pathway from **INT-6** to **INT-11b** via **TS-9b** with an relatively high energy barrier of 20.4 kcal/mol was ruled out. For details, see Figure S2 in the Supporting Information.

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RESEARCH ARTICLE

Chiral Rh(III)-catalyzed C–H activation and cyclopropylation of *O*-sulfonyl phenols have been realized in a highly enantioselective, diastereoselective, and regioselective manner with cyclopropenyl secondary alcohols as the cyclopropylating reagent. Integrated experimental and computational mechanistic studies suggest that the reaction proceeds via a Rh(V) nitrenoid intermediate that participates in Noroyi-type outer sphere concerted proton-hydride transfer to deliver such selectivity.

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Rhodium(III)-Catalyzed Enantio- and Diastereoselective C–H Cyclopropylation of *N*-Phenoxylsulfonamides: Combined Experimental and Computational Studies