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Rhodium(III)-Catalyzed Asymmetric [4+1] and [5+1] Annulation of Arenes and 1,3-Enynes: Distinct Mechanism of Allyl Formation and Allyl Functionalization

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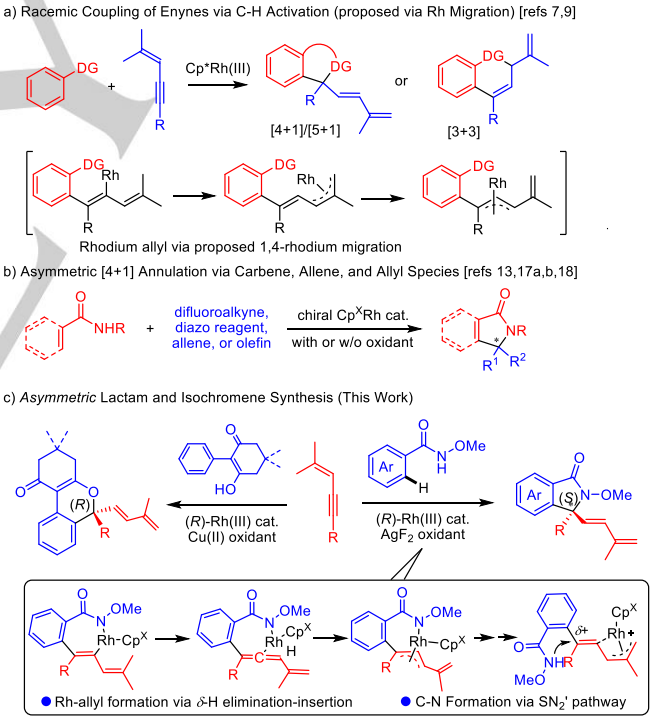
Abstract: Metal allyl species are versatile intermediates in a number of coupling reactions. However, Rh(III) π-allyls have been rarely elaborated in the context of asymmetric C-H functionalization. Reported herein is chiral Rh(III) cyclopentadienyl-catalyzed enantioselective synthesis of lactams and isochromenes via oxidative [4+1] and [5+1] annulation, respectively, between arenes and 1,3-enynes. The reaction proceeds *via* a C-H activation, alkenyl to allyl rearrangement, and nucleophilic cyclization cascade. The mechanistic details of the [4+1] annulation of *N*-methoxybenzamide and an 1,3-enyne have been elucidated by a combination of experimental and computational methods. DFT studies indicate that following the C-H activation and alkyne insertion, a Rh(III) alkenyl intermediate undergoes δ-hydrogen elimination of the allylic C-H via a six-membered ring transition state to produce a Rh(III) enallene hydride intermediate. Subsequent hydride insertion and allyl rearrangement affords several rhodium(III) allyl intermediates, and a rare Rh(III) η^4 ene-allyl species with π-agostic interaction undergoes SN_2'-type external attack by the nitrogen nucleophile, instead of C-N reductive elimination, as the stereodetermining step.

Introduction

Catalytic activation of C-H bonds has found widespread applications in synthesis of value-added organics.[1] Given structural diversity of the substrates, the properties of M-C bond need to be accordingly adjusted to ensure sufficient metal-substrate interactions. To this end, high-valent Cp*Rh(III) catalysts have been extensively employed in C-H activation, where the polarized Rh(III)-C interacts efficiently with diverse π-bonds.[2] Ideally, the M-C species possesses both thermodynamic stability and kinetic reactivity. In most C-H activation systems, the thermodynamic stability of the M-C species is ensured by cyclometalation, and the kinetic reactivity is imparted by the general organometallic propertied of the M-C bond.[1,2] Significantly, the thermodynamic and kinetic paradox may be reconciled in metal π-allyls species, which are versatile intermediates in various catalytic processes such as allylic substitutions[3] and allylic C-H activation.[4-6]

In 2014, Lam reported the first Rh(III)-catalyzed C-H activation and [5+1] annulation between arenes and 1,3-enynes,[7a] where a π-allyl intermediate was proposed to be a key intermediate.[8] Later, Lam[7] and our group[9] extended the coupling to [4+1][7c,9] and [3+3][7b] annulation for synthesis of five- or six-membered heterocycles, respectively (Scheme 1a), where the enyne may function as a versatile C1 or C3 synthon. Despite the system development, the mechanistic profile remains ambiguous with respect to both allyl formation and functionalization. The initial π-ally species was conventionally proposed to be generated via 1,4-rhodium migration from the alkenyl to the allylic position, followed by allyl-to-allyl rearrangement (Scheme 1a).[7-9] In particular, during the 1,4-migration the allylic C-H bond cleavage was proposed to be realized via a C-H activation pathway, although other mechanistic manifolds remain possible. On the other hand, the product-forming step in all these systems was proposed to be C-O/C-N reductive elimination or nucleophilic attack at the π-allyl carbon adjacent to the arene ring.[7-9]



Scheme 1 Allyl Species in Rhodium-Catalyzed Annulation.

Besides employing enynes as coupling partners, insertion of allenes,[10] dienes,[11] or diazo reagents[12] also leads to Rh(III) allyls in C-H activation systems. In addition, C-H activation of allylic olefins also provides direct and complementary entry to rhodium[5] and iridium[6] allyls that can be functionalized by various nucleophiles under oxidative conditions. Despite the progress, rhodium and iridium allyls have been rarely elaborated in asymmetric C-H activation.[13] With the powerful role of chiral cyclopentadienyl (Cp^x) rhodium(III) catalysts in asymmetric C-H activation as pioneered by Cramer[15a] and Rovis,[15b]

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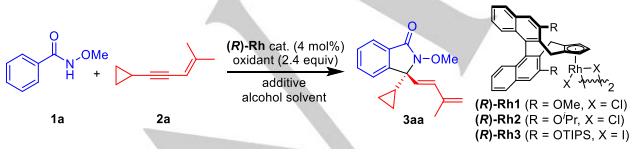
asymmetric Rh(III) catalysis has demonstrated increasing potential in construction of highly enantioenriched aromatics.[13-18] In previous asymmetric C-H activation systems, alkenes,[15] alkynes,[16] and diazo[17] compounds are predominant coupling partners. In particular, alkenes[15a-f] and alkynes[16] typically react as a C2 component. On the other hand, in the very few reports of Cp^{x}Rh(III)-catalyzed asymmetric [4+1] annulation systems, only diazo compounds,[17a,b] difluoroalkynes,[18] allenes,[13] and alkene[19] have been employed as coupling reagents (Scheme 1b), which stays contrast to various reports of racemic [n+1] annulation reactions.[7-10,20]

The ambiguity of mechanism of initial allyl formation in these anulation systems in general, the relative rarity of rhodium catalyzed enantioselective allylic functionalization, and the mechanistic details of the enantioselective control during allylic functionaliztion inspired us to conduct systemetic studies. We now report asymmetric [4+1] and [5+1] annulation of two calsses of arenes with 1,3-enynes (Scheme 1c). This system can be challenging in terms of enantioselective control since, beside the rarity of Rh-allyls in asymmetric C-H activation, nucleophilic allylic functionalization is considered to be the stereo-determining step, which differs from migratory insertion or reductive elimination that constitutes majority of the stereodetermining step in previous Cp^{X}Rh(III) catalyzed C-H activation systems. Combination of experimental and theoretical studies on the [4+1] annulation system unravel distinct pathways of allyl formation and allyl functionalization.

Results and Discussion

We initiated our studies with optimization of the [4+1] annulation of *N*-methoxy benzamide (**1a**) with 1,3-enynes **2a** using a Cramer's chiral catalyst (*R*)-**Rh1** (Table 1). By following modified racemic reaction conditions, a coupling occurred in the presence of a Cu(II) oxidant to give product (*S*)-**3aa** in good yield but low enantioselectivity (entry 1). Examination of different metal oxidants indicated that silver oxidants generally offered better enantioselectivity (entries 2-5), and AgF_2 seemed a superior oxidant (70% ee). Screening of alcoholic solvents revealed that 3-pentanol allowed isolation of **3aa** in high yield and good enantioselectivity (entry 10). Lowering the reaction temperature to 10 °C further increased the enantioselectivity (entry 11), and both high yield and excellent enantioselectivity (85% ee) were secured when the amount of HOAc was doubled. Gratifyingly, catalysis using (*R*)-**Rh2** further improved the enantioselectivity (entry 12), while essentially no reaction occurred when the (*R*)-**Rh3** was used (entry 14).

Table 1. Optimization of the Reaction Conditions. [a,b]



Entry	Oxidant (2.4 equiv)	Additive (equiv)	Solvent	*T* (°C)	Yield[b] (%)	ee (%)
1	$Cu(OAc)_2$	AgOAc(0.2)	MeOH	rt	86	47
2	AgOAc	--	MeOH	rt	45	64
3	Ag_2CO_3	HOAc (1.0)	MeOH	rt	71	55
4	AgF	HOAc (1.0)	MeOH	rt	40	65
5	AgF_2	HOAc (1.0)	MeOH	rt	45	70
6	AgF_2	HOAc (1.0)	EtOH	rt	60	77
7	AgF_2	HOAc (1.0)	*i*-PrOH	rt	51	76
8	AgF_2	HOAc (1.0)	TFE	rt	43	47
9	AgF_2	HOAc (1.0)	*t*-BuOH	rt	57	78
10	AgF_2	HOAc (1.0)	3-PentOH	rt	84	79
11[c]	AgF_2	HOAc (2.0)	3-PentOH	10	71	85
12[c,d]	AgF_2	HOAc (2.0)	3-PentOH	10	70	90
13[c,d]	AgF	HOAc (2.0)	3-PentOH	10	65	80
14[c,e]	AgF_2	HOAc (2.0)	3-PentOH	10	0	--

[a] Reactions were carried out using **1a** (0.1 mmol), **2a** (0.15 mmol), **Rh1** (4 mol%), oxidant (2.4 equiv) and additive (0.2−2.0 equiv) in a solvent (1 mL) for 48 h under air. [b] Isolated yields. [c] 72 h. [d] **Rh2** (4 mol%). [e] **Rh3** (4 mol%). 3-PentOH = 3-pentanol.TFE = CF_3CH_2OH.

With the establishment of the optimized reaction conditions, we next investigated the scope of this coupling system (Scheme 2). Benzamides bearing electronically diversified groups at the *para* position (alkyl, alkoxyl, benzyloxy, phenoxy, halide, ester, and carbonyl groups) all coupled smoothly with enyen **2a** in good to high yields and excellent enantioselectivities (**3ba-3ma**, 88-95% ee). In addition, scale-up synthesis of **3aa** was realized in moderate yield without erosion of enantioselectivity. The absolute configuration of (*S*)-**3ka** has been established by X-ray crystallography (CCDC 1957960). The reaction worked well when *meta* Me, halogen, and CF_3 groups were installed (**3oa-3ra**, 81-94% ee). High enantioselectivity was also realized for benzamides bearing *ortho* Me, F and Cl groups under slightly modified conditions (**3sa-3ua**, 90-96% ee), and the effectiveness of these substrates suggested tolerance of steric hindrance. Different fused and heterocyclic amides such as 1-naphthyl, 1-benzothiophene, 9-fluorenone, and thiophene also reacted smoothly (**3va-3ya**). Extension of the *N*-group to *N*-ethoxybenzamide afforded product **3za** in slightly lower enantioselectivity. Unfortranatly, 3-dimethoxybenzamide, benzofuran, and 4-pyridine substrated benzamides were not sutiable for this asymmetric annulation. The scope of the enyne was next found to be decent (Scheme 3). 1,3-Enynes with various alkyl and cycloalkyl terminal groups underwent [4+1] annulations with 1-naphthyl-substituted carboxamide, furnishing the desired products in good yield and enantioselectivity (**3vb-3vf, 3vh, 3sc, 3ac**). 1,3-Enynes bearing a phenylethyl group (**2g**) or a cyclic olefin (**2i**) all reacted with comparable efficiency and selectivity (products **3vg, 3sg, 3ag,** and **3vi)**. The reaction efficiency decreased when unsubstituted *N*-methoxybenzamide was used (**3ac**, **3ag**).

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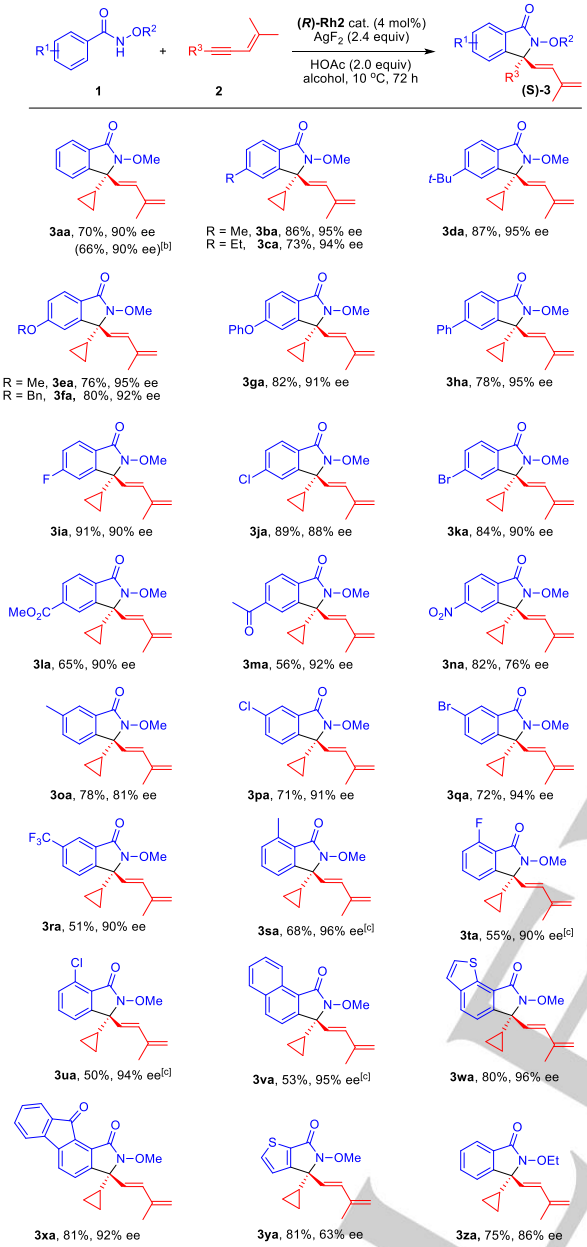
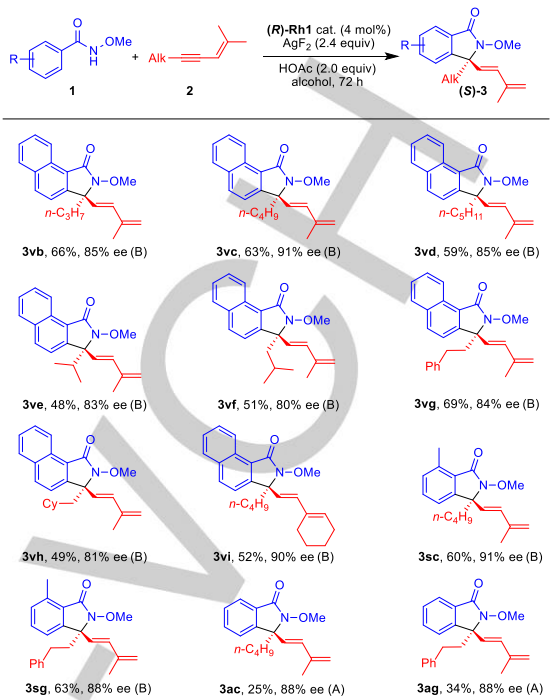


Scheme 2. Scope of Benzamides in [4+1] Annulation. [a] Reactions were carried out using **1** (0.1 mmol), **2a** (0.15 mmol), **Rh2** (4 mol%), AgF_2 (2.4 equiv), and HOAc (2.0 equiv) in 3-pentanol (1.0 mL) at 10 ºC for 72 h (**Conditions A**). [b] 0.5 mmol scale. [c] Reactions were carried out using amide (0.1 mmol), **2** (0.15 mmol), **Rh1** (4 mol%), AgF_2 (2.4 equiv), and HOAc (2.0 equiv) in EtOH (1.0 mL) at 10 ºC for 72 h (**Conditions B**).



Scheme 3. Scope of 1,3-Enynes in [4+1] Annulation System. See Scheme 2 for Conditions A or B.

To demonstrate the versatility of this oxidative annulation system, we next extended the coupling system to [5+1] annulation using 2-aryl-3-hydroxy-2-s[7a] as an arene substrate. After extensive optimization studies (Table S1 in Supporting Information), it was found that *(R)*-**Rh1** (4 mol%), $Cu(OAc)_2 \cdot H_2O$ (2.1 equiv) and AgOAc (40 mol %) favored formation of the desired [5+1] product **5ag**, and a good isolated yield (79%) and excellent enantioselectivities (92% ee) were realized with *i*-PrOH as a solvent. The generality of this oxidative [5+1] annulation was next explored (Scheme 4). Dimethyl substituted 2-aryl-3-hydroxy-2-cyclohexanediones bearing a diverse array of electron-donating (alkyl), -withdrawing (ester, acetyl, and cyano), and halogen groups at the *para*-position all coupled in good to high enantioselectivity (**5ag-5gg**, 79-92% ee). *meta* Methyl and Cl groups were also accommodated (**5hg** and **5ig**). 2-Phenyl-3-hydroxy-2-cyclohexanedione (**5jg**) and 3-phenylchromane-2,4-dione (**5kg-5lg**) were fully tolerated, and the former provided excellent enantioselectivity. The reaction was readily scaled up to 0.5 mmol (**5lg**) with slight errosion of enantioselectivity. The absolute configuration of **5lg** has been established by X-ray crystallography (CCDC 2004323) to be (*R*). Enynes containing both primary and secondary alkyl terminus were also tolerated (**5ab**, **5ae**, **5af**, and **5ah**).

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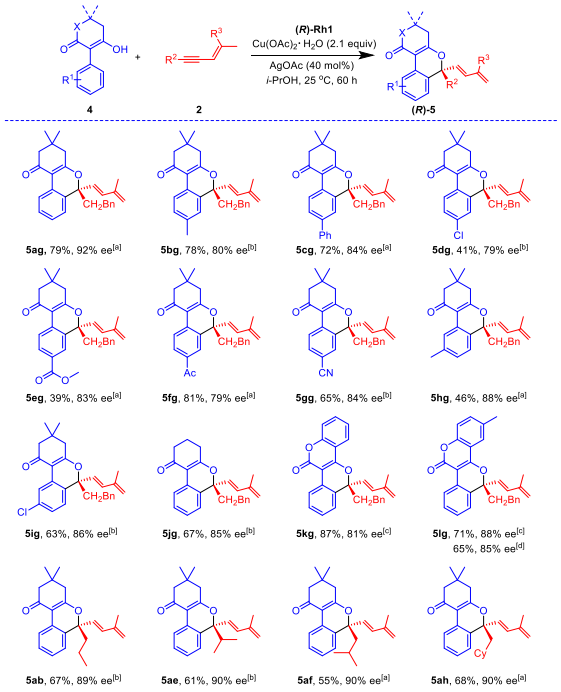
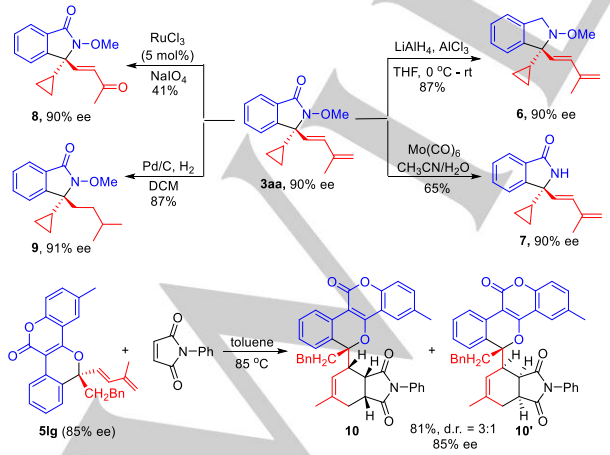


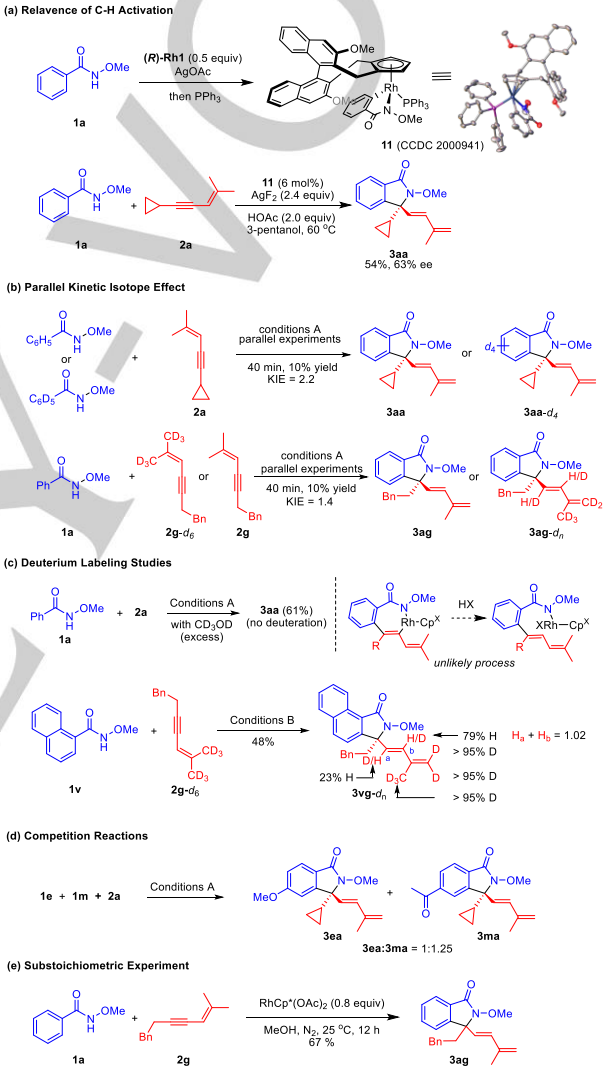
Scheme 4. Scope of Oxidative [5+1] Annulation. [a] Reactions were carried out using **4** (0.1 mmol), **2** (0.15 mmol), **Rh1** (4 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv), and AgOAc (40 mol%) in *i*-PrOH (2.0 mL) at 25 °C for 60 h (**Conditions C**). [b] Reactions were carried out using **4** (0.1 mmol), **2** (0.15 mmol), **Rh1** (4 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv), and AgOAc (40 mmol%) in *i*-PrOH (2.0 mL) at 40 °C for 48 h (**Conditions D**). [c] Reactions were carried out using **4** (0.1 mmol), **2** (0.15 mmol), **Rh1** (4 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv), and AgOAc (20 mol%) in DCM (2.0 mL) at 25 °C for 60 h (**Conditions E**). [d] 0.5 mmol scale.

Product derivatization has been carried out to demonstrate the synthetic utility of the products (Scheme 5). Chemoselective reduction of **3aa** afforded amine **6** in 87% yield. Treatment of **3aa** with $Mo(CO)_6$ led to reductive cleavage of the *N*-OMe bond (**7,** 65% yield). Oxidative cleavage of **3aa** using $NaIO_4$ in the presence of $RuCl_3$ afforded enone **8** in 41% yield. Pd/C-catalyzed hydrogenation of the diene unit delivered **9** in 87% yield. Diels-Alder reaction of **5lg** and *N*-phenylmaleimide proceeded smoothly to give adduct **10** in 81% total yield as a mixture of diastereomers. In all cases, essentially no errosion of enantiopurity was observed.



Scheme 5. Synthetic Applications of Annulation Products.

Mechanistic studies have been conducted for the [4+1] annulation system (Scheme 6). To probe the C-H activation process, a chiral rhodacyclic complex **11** was prepared (Scheme 6a).[21] In the crystal structure, the relatively bulky amide directing group stays distal to the chiral ligand, which offers important basis for stereocontrol in subsequent steps. Complex **11** proved somewhat active for the coupling of **1a** and **2a** at an elevated temperature, indicating relevance of C-H activation. KIE values with respect to the arene substrate (2.2) and the enyne substrates (1.4) pointed to the conclusion that C(aryl)-H cleavage is probably involved in the turnover-limiting step (Scheme 6b).



Scheme 6. Experimental Mechanistic Studies

Next, two H/D exchange experiments have been conducted to further probe the mechanism, especially the allyl formation process. The coupling of **1a** and **2a** in the presence of CD_3OD afforded product **3aa** with no deuterium incorporation (Scheme 6c). This observation strongly argues against protonolysis of Rh-C(alkenyl) bond. Otherwise, C(alkenyl)-D would have been observed. Consequently, insertion of the N-Rh bond into protonolysis-derived diene should also be unlikely (see Supporting Information). In another study, the coupling of **1v** and hexaduterated enyne **2g**-d_6 afforded **3vg**-d_n with partial deuteration only at the two internal alkenyl positions (H_a and H_b, Scheme 6c).

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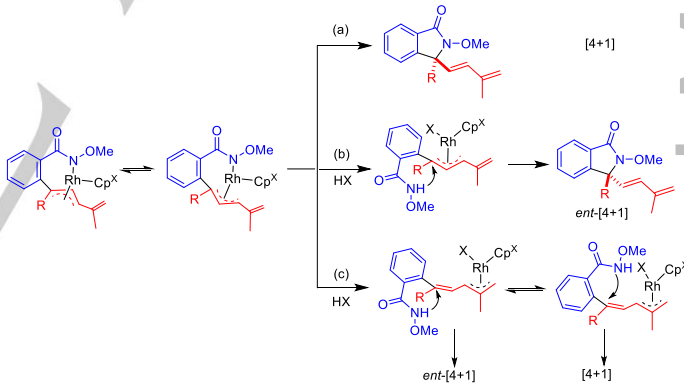
Furthermore, the sum (1.02) of H_a and H_b is essentially unity. Taken together, the labeling studies strongly suggest intramolecularity of the H/D exchange. These observations point to intermediacy of allyl species as has been previously proposed.[9] While the 1,4-rhdoium migration pathway cannot be ruled out experimentally, this migration, if present, most likely follows a σ-bond metathesis pathway so as to avoid H/D exchange with external deuterium sources.[8] In addition, the observed intraligand H/D exchange may also suggest relevance of rhodium hydride intermediate that rapidly undergoes subsequent transformation (insertion) to scramble the H and D atoms while avoiding H/D exchange with external deuterium sources.[22] The current mechanism stays in sharp contrast to a reversible protonolysis/C-H activation proposal in previous studies,[7,9] and our H/D exchange studies also provided important experimental basis for the DFT studies. Next, competition experiments using an equimolar mixture of electronically differentiated benzamides revealed that C−H activation was slightly kinetically favored for a more electron-poor amide, suggesting that the C−H activation may proceed *via* a CMD mechanism (Scheme 6d). To gain further mechanistic insight into the C−N bond formation step, a substoichiometric amount of $Cp^*Rh(OAc)_2$ was employed for the coupling of **1a** and **2a** under oxidant-free conditions, from which **3aa** was isolated in 67% yields. This observation indicates a Rh(III) to Rh(I) reductive elimination pathway instead of oxidation-induced reductive elimination.[5f,23]

DFT studies has been peformed to elucidate the mechanistic details of the couling of **1a** and **2a** using (*R*)-**Rh1** as a catalyst (Schemes 7 and 8). In the lowest energy pathway (highlighted in green, Scheme 8), by taking into account our rhodacyclic intermediate **11** with clear-cut orientation of the arene ring and the amide directing group, the Rh(III) alkenyl species **IM2** undergoes an unusual δ-hydrogen elimination[24] of the terminal allylic C-H via a six-membered ring transitions state **TS1** with an activation free energy of 25.5 kcal/mol to produce a Rh(III) enallene hydride **IM3**. In contrast, the alternative σ-bond metathesis pathway via **TS1'** is kinetically disfavored with an activation energy that is 5.0 kcal/mol higher than the **TS1**. Subsequent hydride insertion into the allene middle carbon is essentially barrierless, giving a stable η^3 allyl **IM4**. Such a δ-H elimination-hydride insertion process constitutes a novel alkenyl-to-allyl rearrangement process that has not been explored. Of note, DFT-established intermediacy of the Rh(III) allene hydride species **IM3** agrees well with our observed H/D exchange results since DFT studies explicitly indicate that **IM3** can also undergo competitive off-loop and reversible hydride insertion into the allene terminal carbon via **TS2'** with a barrier of only 0.8 kcal/mol higher than that of the constructive insertion via **TS2**. Collectively, the reversibility and the low barrier of this hydride insertion process fully accounts for our observed deuterium scrambling only at the two alkenyl positions, with no observable exchange with the external deuterium sources such as MeOD or AcOD.

Subsequently, three possible pathways of C-N bond formation have been evaluated, namely, the C-N reductive elimination (Scheme 7a), the SN_2 substitution of π-allyl (Scheme 7b), and the SN_2' pathways (Scheme 7c). It was found that direct C-N reductive elimination of **IM4** (via transition state **RE-TS3$_S$**), which provides the (*S*) product, was highly kinetically unfavored with a calculated activation barrier of 49.4 kcal/mol, probably due to the ring strain and severe repulsion between rhodium center and cyclopropyl group. The nitrogen-dissociation–SN_2 pathway is also kinetically less favored (from **IM4** to protonated **IM5'** to transition state **SN$_2$-TS3$_R$**, with an activation barrier of 37.2 kal/mol). Significantly, we have located a lowest energy pathway of Rh-N protonolysis followed by nitrogen external attack in a SN_2' fashion. Thus, following the protonation, the resulting **IM5** allyl species is stabilized by a strong π-agostic[25] interation (Rh---C(olefin) = 2.31 Å) with the adjacent olefin. SN_2'-type attack of the nitrogen gives a diene-bound Rh(I) species, which eventually furnishes the diene product. Of note, this π-agostic interation serves to activate the proximal olefin, and the SN2' attack turns out to be stereodetermining. The (*S*)-forming transtion state (**TS3$_S$**) was found to be 2.5 kcal/mol lower in energy than the **TS3$_R$** transition state, which corresponds to an ee value of 97% and is comparable to our observed 85% ee (Table 1, entry 11). The relative stability of **TS3$_S$** over **TS3$_R$** is ascribed to reduced steric collision between cyclopropyl and cyclopentadienyl moieties. Thus, the most likely mechanism of this overall coupling system is summerized in Scheme 9.



Scheme 7. Three Possible Pathways of C-N Bond Formation

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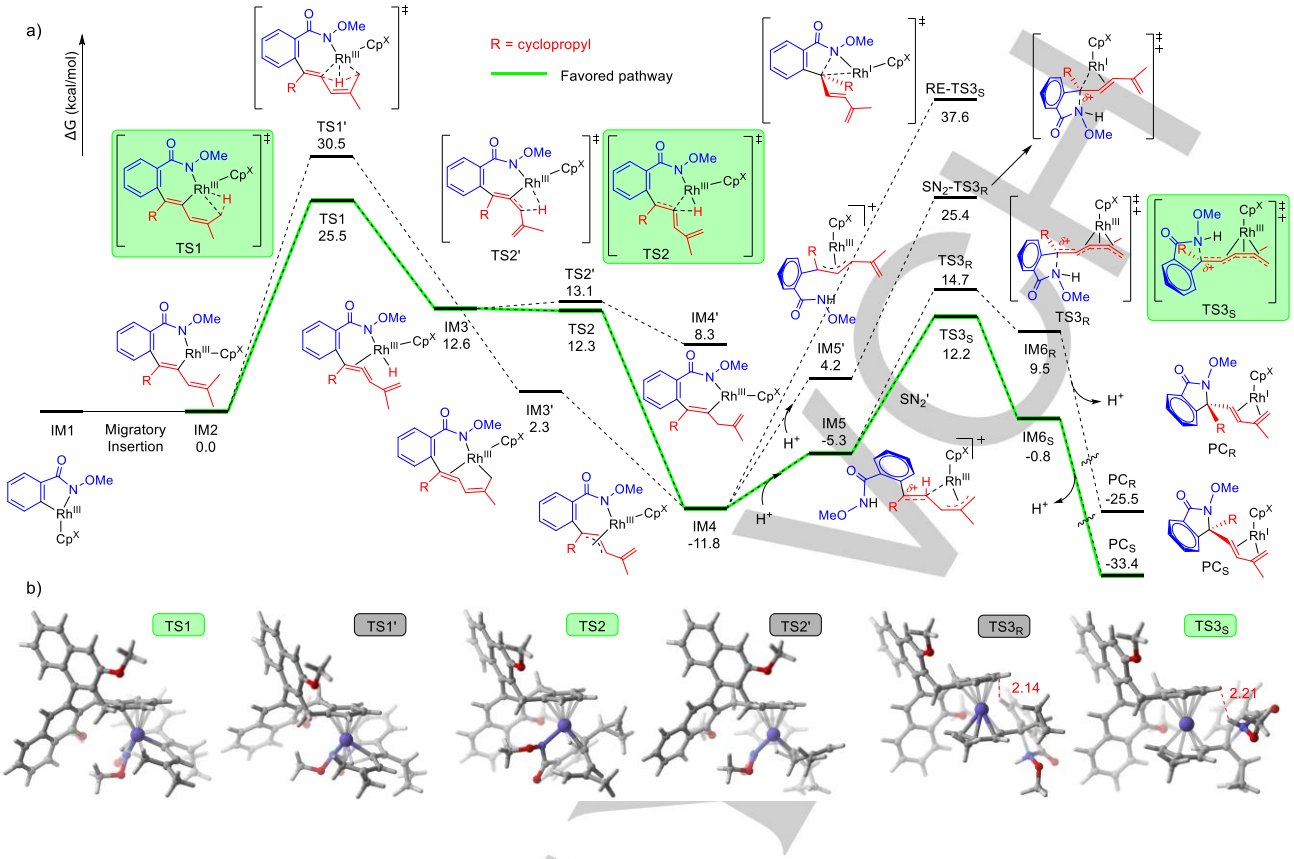
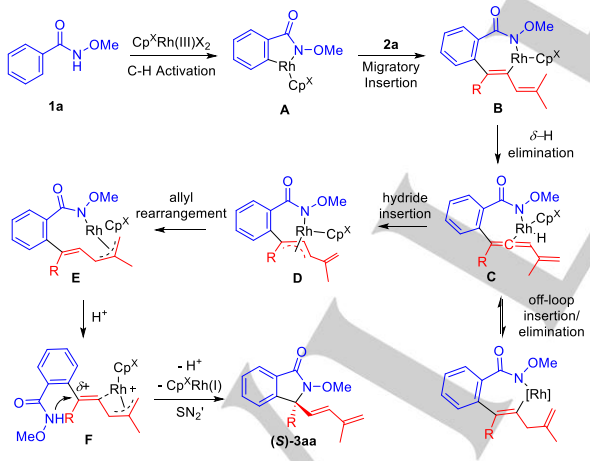


Scheme 8. a) Profiles of Potential Energy Surface (PES) of Key Steps of 1,4-Rhodium Migration and C-N Formation. b) Snapshots of Optimized Key Transition States (bond length in angstrom in red).



Scheme 9. Global Reaction Pathway of the [4+1] Annulation Based on Experimental and DFT Studies.

Conclusion

In summary, we realized Rh(III)-catalyzed oxidative [4+1] and [5+1] coupling of benzamides and cyclohexanediones with 1,3-enynes for enantioselective synthesis of lactams and isochromenes, respetively, by integration of C-H activation and enantioselective allylic substitution. This protocol allowed access to a set of structurally diverse enantioenriched lactams and isochromenes containing a quaternary chiral center. Mechanistic studies indicated that the reaction proceeds *via* C-H activation, alkenyl-to-allyl rearrangement, and enantioselective allylic functionalization. Combined experimental and DFT studies suggested that following the C-H activation and alkyne insertion, an unusual pathway is operative for the alkenyl-to-allyl rearrangement, which stays contrast to the wildly proposed 1,4-Rh migration mechanism. Thus, the Rh(III) alkenyl intermediate undergoes δ-hydrogen elimination of the allylic C-H to produce an Rh(III) enallene hydride intermediate. Subsequent hydride insertion and allyl rearrangement affords serveral rhodium(III) allyl intermediates. Notably, a cationic η^3-allyl species undergoes stereo-determining SN_2'-type external attack by the nitrogen nucleophile instead of C-N reductive elimination. Future studies on enantioselective C-H activation through other allylic intermediates are ongoing in our laboratory.

Acknowledgements

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Keywords: asymmetric C-H activation • rhodium • enyne • allyl • lactam and isochromene

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RESEARCH ARTICLE

Rhodium(III)-Catalyzed Asymmetric [4+1] and [5+1] Annulation of Arenes and 1,3-Enynes: Distinct Mechanism of Allyl Formation and Allyl Functionalization

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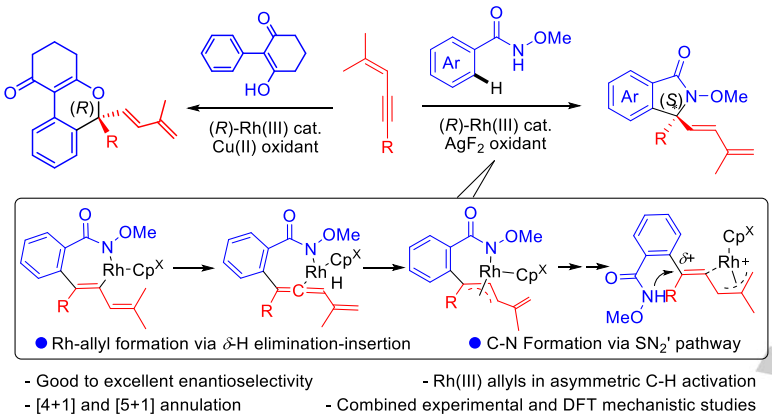

Rh(III)-catalyzed [4+1] and [5+1] annulation of *N*-methoxy benzamides and 1,3-cyclohexanediones with 1,3-enynes has been realized for enantioselective synthesis of lactams and isochromenes, respectively. DFT studies suggests an unusual pathway of alkenyl-to-allyl rearrangment and SN2'-type allylic substitution for the [4+1] annulation system.