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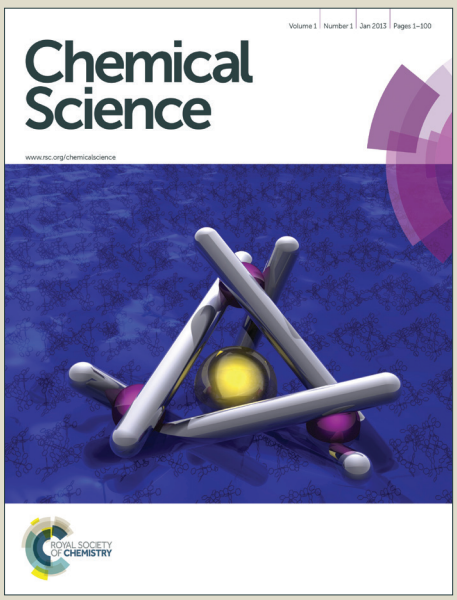

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Edge Article

Rhodium-Catalyzed C-H Functionalization-Based Approach to Eight-membered Lactams

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

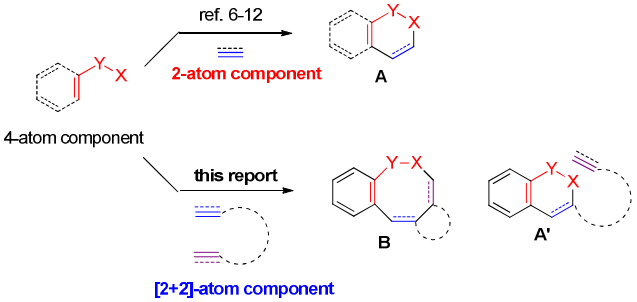
DOI: 10.1039/b000000x

A Rh(III) catalyzed formal [4+2+2] cyclization of *N*-pivaloyloxy benzamides **1** with 1,6-allene-enes **2** by C-H functionalization is reported. The reactions occur at room temperature and are compatible with air and moisture with a tolerance of many synthetically useful functional groups. The follow-up modifications of the products have been demonstrated. After careful mechanistic studies and DFT calculation, a reaction mechanism was proposed.

Introduction

It is well known that medium-sized rings are hard to synthesize due to entropic and enthalpic reasons.[1] Among them, eight-membered lactams are found in many natural products and bioactive molecules.[2] The normal approach to these molecules often require harsh conditions (such as high temperatures and highly diluted solutions), at least stoichiometric amount of metal reagents, or pre-functionalized starting materials by several steps.[3] Therefore, developing a catalytic procedure for the efficient synthesis of eight-membered lactams under mild conditions is still desired.

In principle, [2+2+2+2] or [4+2+2] cyclization would be the most straightforward yet challenging approach to the eight-membered lactams.[4] On the other hand, in recent years, directed Rh(III)-catalyzed C-H functionalization reactions have been extensively studied.[5] Among them, the formal [4+2]-cyclization between arenes or alkenes with a proper directing group and unsaturated compounds such as alkenes, alkynes or allenes facilely affording six-membered products have been well established.[6-12] We envisioned a strategy for the efficient construction of eight-membered rings if a [2+2]-atom component, i.e., a molecule contains two unsaturated carbon-carbon bonds, is applied instead of alkenes, alkynes or allenes. The challenge is the highly unfavorable selectivity for the formation eight-membered ring since it is much easier to form six-membered rings (A' vs. B) with the participation of just one C-C π-bond (Scheme 1). Herein, we wish to report the realization of such a concept by applying an allene-ene as the [2+2]-atom component catalyzed by $[Cp^*RhCl_2]_2$ with *N*-pivaloyloxy benzamides as the [4]-atom component under very mild conditions.



Scheme 1 Rh(III)-catalyzed cyclization: [4+2] vs [4+2+2]

Results and Discussion

After some trial and error with compounds bearing at least two unsaturated C-C bond, we identified such a reaction, in which 3-(trimethylsilyl)-1,2,6-heptatriene **2a** acts as a [2+2]-atom component while *N*-pivaloyloxybenzamide **1a** behaves as the [4]-atom component. When **1a** was treated with **2a** in a mixed solvent of MeOH and water (v/v 20/1) under the catalysis of $[Cp^*RhCl_2]_2$, the expected [4+2+2] cyclization product, i.e., the benzo-fused eight-membered lactam **3a**, was indeed formed in 75% NMR yield although together with the [4+2] regioisomeric mixture[13] of two products **4aa** and **5aa** with the isolated carbon-carbon double bond being reacted as the minor products (Table 1, Entry 1). The structure of **3a** was confirmed by X-ray diffraction study (Scheme 2),[14] indicating that the allene unit has been reacted first. After screening the solvent, we found that MeOH was the best (Table 1, Entries 1-5). Moisture, air and 4Å MS had very little influence on the yield (Table 1, Entries 6-7). Then, the base effect was investigated and 30 mol% of K_2CO_3 was found to be the optimal (Table 1, Entries 2 and 8-13). Control experiments showed that no reaction occurred in the absence of $[Cp^*RhCl_2]_2$ or bases. Finally, the reaction of **1a** and **2a** in methanol under the catalysis of $[Cp^*RhCl_2]_2$ with 30 mol% K_2CO_3 as base at room temperature was chosen as the optimal reaction conditions for further study (Table 1, Entry 11).

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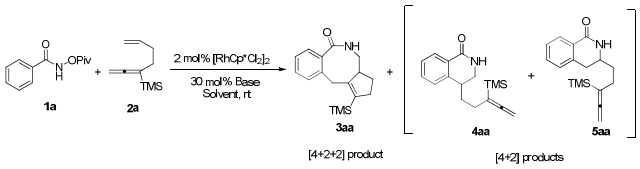
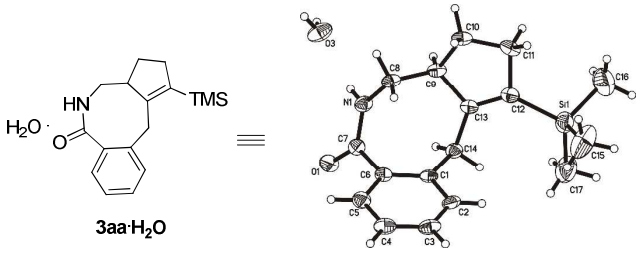
Table 1 Optimization of reaction conditions: the Rh-catalyzed cyclization of **1a** with **2a**[a]



Entry	Solvent	Base	t (h)	NMR Yield[b]/%	
				3aa	**4aa+5aa**
1	MeOH/H_2O[c]	NaOAc	11	75	12
2	MeOH	NaOAc	21	80	14
3	DCE	NaOAc	21	58	17
4	DCM	NaOAc	21	65	21
5	Toluene	NaOAc	21	44	17
6[d]	MeOH	NaOAc	14	80	16
7[e]	MeOH	NaOAc	14	74	15
8	MeOH	KOAc	14	68	14
9	MeOH	CsOAc	14	69	14
10	MeOH	Na_2CO_3	14	69	14
11	MeOH	K_2CO_3	14	81 (72)[f]	14
12	MeOH	Cs_2CO_3	14	76	14
13	MeOH	K_3PO_4	11	73	13
14[g]	MeOH	-	11	-	-
15[h]	MeOH	K_2CO_3	13	75	14
16[i]	MeOH	K_2CO_3	13	72	13
17[j]	MeOH	K_2CO_3	13	18	7
18[g,k]	MeOH	K_2CO_3	13	-	-

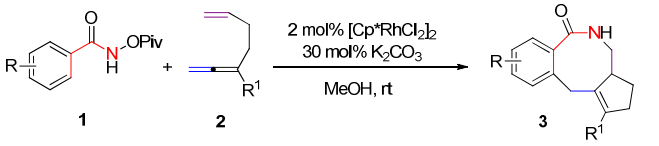
[a] The reaction was conducted with **1a** (0.2 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (0.004 mmol), K_2CO_3 (0.06 mmol), MeOH (1.2 mL) and monitored by TLC. [b] Determined by ^1H NMR using dibromomethane as internal standard. [c] The ratio of MeOH/H_2O was 20/1 (1.2 mL/ 0.06 mL). [d] Under N_2 atmosphere. [e] Under N_2 atmosphere and 4 Å MS was added. [f] Isolated yield is in the bracket. [g] Recovery of **1a** was 98% with **2a** disappeared. [h] 10 mol% K_2CO_3 was added. [i] 50 mol% K_2CO_3 was added. [j] 1 equiv. K_2CO_3 was added. [k] The reaction was conducted in the absence of the Rh(III) catalyst.



Scheme 2 ORTEP representation of **3aa**

When the reaction was conducted on a gram-scale, **3aa** was also formed in 62% yield (Table 2, Entry 2). The reaction of substrates with electron-donating groups such as methyl, *tert*-butyl and methoxy or electron-withdrawing groups such as COOMe, Cl, Br, CF_3 and NO_2 in the *para* position of the aryl unit all gave corresponding lactams **3ba-3ia** in moderate to good yields, showing the potential for further elaboration (Table 2, Entries 3-10); when *o*-methyl *N*-pivaloyloxy benzamide **1j** was used, lactam **3ja** could also be formed in a lower yield (23%) with full conversion, most probably due to the steric effect (Table 2, Entry 11). It is important to note that silyl group could be replaced with aryl groups with either electron-withdrawing or electron-donating substituents, a hetero-aryl and even an alkyl group, showing the broad substrate scope (Table 2, Entries 12-16). The structure of **3ae** was further confirmed by X-ray diffraction study (see p 26 in the Supporting Information).[15] It should be noted that **4-** and **5**-type by-products were also formed as by-products as judged by ^1H NMR analysis (Table 2).

Table 2 The reaction scope[a]



Entry	R	R^1	Time (h)	Yield of **3**, %	NMR yield of [**4**+**5**][b], %
1	H (**1a**)	TMS (**2a**)	2	68 (**3aa**)	11
2[c]	H (**1a**)	TMS (**2a**)	2	62 (**3aa**)	N.D.[d]
3	4-Me (**1b**)	TMS (**2a**)	2	57 (**3ba**)	10
4	4-^{t}Bu (**1c**)	TMS (**2a**)	2	47 (**3ca**)[e]	8
5	4-OMe (**1d**)	TMS (**2a**)	2	55 (**3da**)	10
6	4-CO_2Me (**1e**)	TMS (**2a**)	2.5	60 (**3ea**)	10
7	4-Cl (**1f**)	TMS (**2a**)	2	50 (**3fa**)	10
8	4-Br (**1g**)	TMS (**2a**)	2	50 (**3ga**)	11
9	4-CF_3 (**1h**)	TMS (**2a**)	3	53 (**3ha**)	11
10	4-NO_2 (**1i**)	TMS (**2a**)	12	62 (**3ia**)	7
11	2-Me (**1j**)	TMS (**2a**)	48	23 (**3ja**)	8
12	H (**1a**)	Ph (**2b**)	5	56(**3ab**)[f]	N.D.
13	H (**1a**)	*p*-ClC_6H_4 (**2c**)	18	63 (**3ac**)[g]	N.D.
14	H (**1a**)	*p*-$MeOC_6H_4$ (**2d**)	10	45 (**3ad**)[h]	N.D.
15[i]	H (**1a**)	3-thienyl (**2e**)	48	47 (**3ae**)[j]	N.D.
16[k]	H (**1a**)	Bu (**2f**)	14	34 (**3af**)	N.D.

[a] The reaction was conducted with **1** (1 mmol), **2** (1 mmol), $[Cp^*RhCl_2]_2$ (0.02 mmol), K_2CO_3 (0.3 mmol), and MeOH (6 mL) and monitored by TLC. [b] Determined by ^1H NMR using dibromomethane as internal standard. [c] Reaction was conducted on 6 mmol scale. [d] Not determined. [e] 97% purity. [f] 94% purity. [g] 92% purity. [h] 91% purity. [i] Reaction was conducted at 55 °C. [j] 90% purity. [k] **1a** (1.5 mmol), **2f** (1 mmol) and $[Cp^*RhCl_2]_2$ (0.04 mmol) were used.

Importantly, *N*-pivaloyloxy-2-naphthylamide **1k** afforded tetra-cyclic product **3ka** in 48% yield with the 3-position C-H bond being exclusively functionalized (eq 1). The substituent on the internal side of the alkene moiety was also tolerated affording lactam **3ag** with a methyl group on the quaternary

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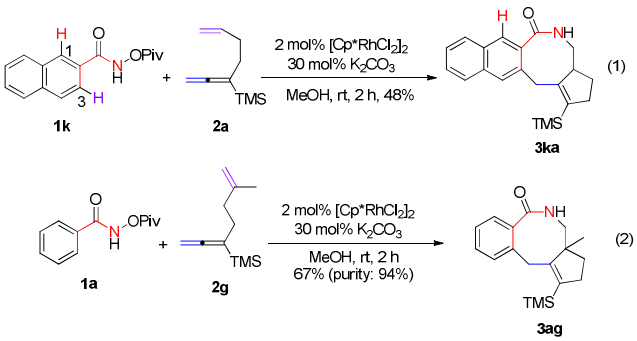
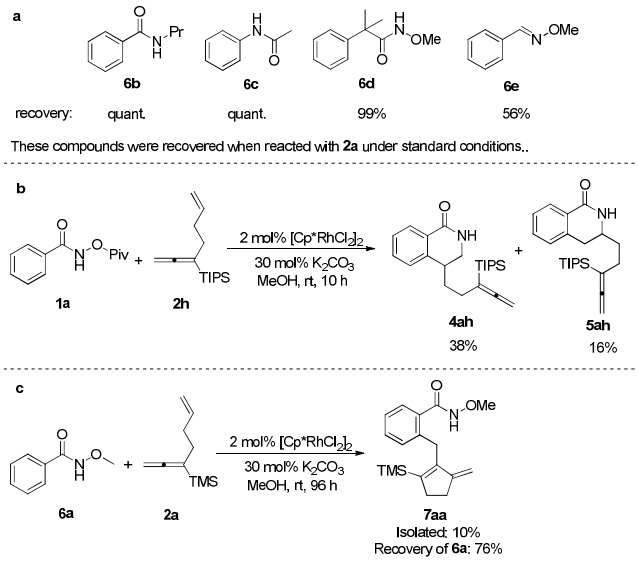
carbon center which was hard to form in 67% yield (eq 2).

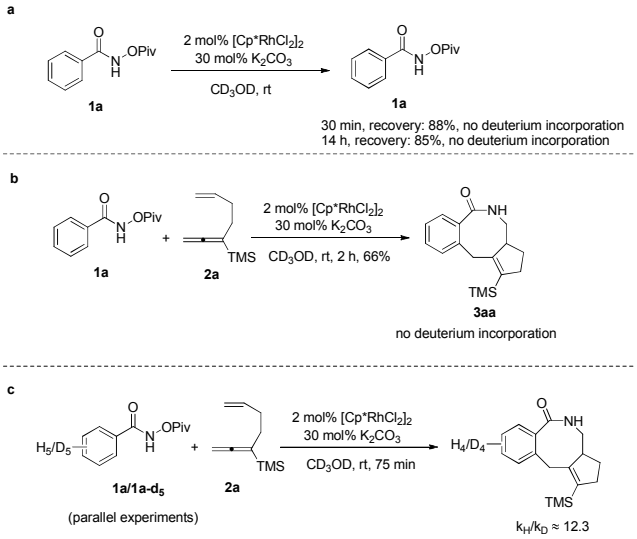


Other frequently used directing groups **6b-6e**[5] failed to yield any expected products with a high recovery of the starting materials (Scheme 3, a). The steric effect of the silyl group in the allene moiety was also observed: when TMS was replaced by the bulkier TIPS group, the allene moiety was untouched: only the isolated C-C double incorporated regioisomeric products **4ah** and **5ah** were formed (Scheme 3, b). When *N*-methoxybenzamide **6a** was used to react with **2a** under the standard conditions for 96 h, both unsaturated units were involved in the transformation, however, the most commonly observed *β*-H elimination occurred, affording a five-membered ring in the final product **7aa** in 10% isolated yield (Scheme 3, c).



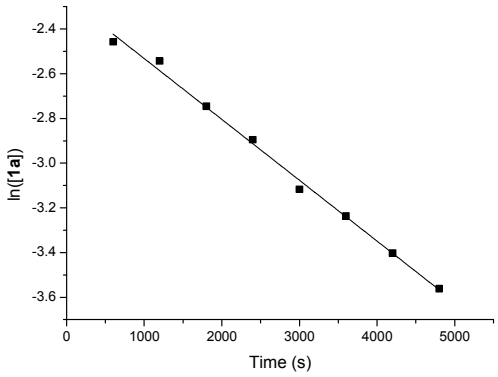
Scheme 3 Failed directing groups and steric effect

Furthermore, when the reaction of **1a** was conducted in [D_4]methanol under the standard conditions in the absence of or presence of allene-ene **2a**, no obvious deuterium incorporation was detected from the recovered **1a** and formed **3aa**, suggesting that the C–H activation step was irreversible (Scheme 4, a and b). Then the kinetic isotope effect (KIE) value of **1a** and **1a-d_5** was measured by parallel experiments. The high KIE value of 12.3 demonstrated that C-H activation must be involved in the rate-determining step (Scheme 4, c).[16]



Scheme 4 Mechanistic studies

The orders of each reactant were also measured. A linear relationship was observed for ln([**1a**]) vs. reaction time, indicating a first-order dependence of the reaction rate with **1a** [ln([**1a**])=-kt+ln([$\mathbf{1a_0}$])] (y=a+b×x in Scheme 5). A zero-order with the allene moiety **2a** ([**2a**]=-kt+[$\mathbf{2a_0}$]) (y=a+b×x in Scheme 6) was also determined by the linear relationship of [**2a**] vs. reaction time. Thus, the rate equation for this reaction is d[**3aa**] /dt= k[**1a**]^1[**2a**]^0.



Scheme 5 The determination of the order with **1a**

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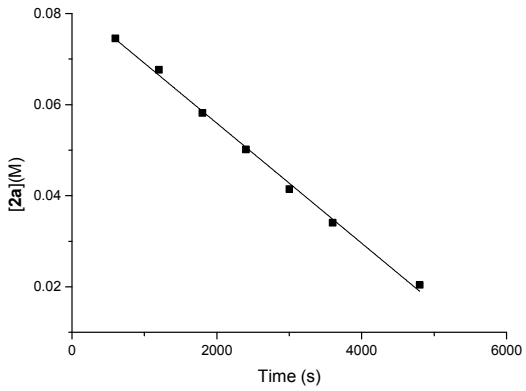
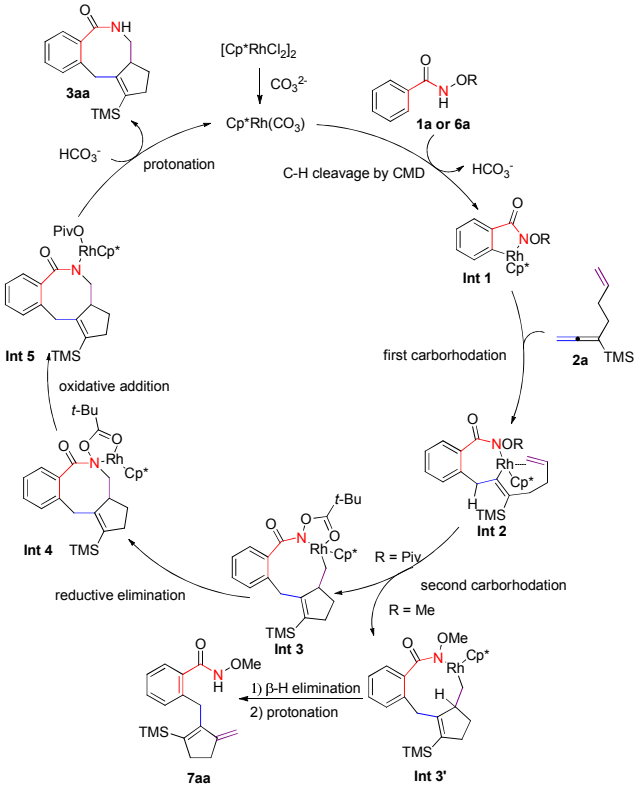


Scheme 6 The determination of the order with **2a**

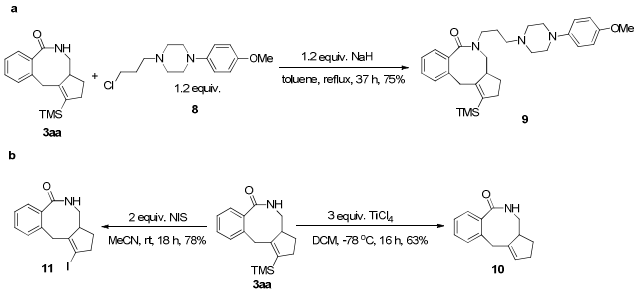
According to the experimental results above, a plausible mechanism has been proposed as shown in Scheme 7. Firstly, [Cp*Rh(CO_3)] was formed to be the catalytic species from the [Cp*RhCl_2]$_2$ dimer and CO_3^{2-}. Then base-promoted C-H bond rhodation would form rhodacyclic intermediate **Int 1**,[5-12] which is followed by the insertion of the allene moiety in the 1,6-allene-ene **2a**, affording seven-membered rhodacycle **Int 2**.[17] Subsequent cyclic carborhodation of the terminal C-C double bond would yield nine-membered rhodacyclic intermediate **Int 3** (**Int 3'**).[17] The *N*-pivaloyloxy containing intermediate **Int 3** (R = Piv) would undergo reductive elimination to form the final [4+2+2] product **3aa**. Alternatively, the *N*-methoxy intermediate **Int 3'** (R = Me) leads exclusively to the methylenecyclopentene product **7aa** by *β*-H elimination (Scheme 3, c). Thus, it is concluded that the OPiv group is important since the coordination of the carbonyl oxygen atom in the Piv group of **Int 3** with Rh(III) makes a coordination-saturated stable 18e complex, which must have prevented the *β*-H elimination, avoiding the formation of **7aa**-type product.[18]



Scheme 7 A possible mechanism

Follow-up modifications of the Products

N-Protected eight-membered benzolactams have been found to be bioactive as dopamine D_3 receptor ligands.[2i] Thus, product **3aa** has been treated with 1-(3-chloropropyl)-4-(p-methoxyphenyl) piperazine to afford the analogue **9** in 75% yield (Scheme 8, a). To further demonstrate the synthetic applications of the products, the functionalization of the TMS group in **3aa** had been conducted: a) desilylation product **10** could be formed in 63% yield by treating **3aa** with $TiCl_4$ in DCM for 16 h.[17c,19] b) The TMS group of **3aa** could be transformed to synthetically useful vinyl iodide **11**,[20] which will be useful for any elaboration based on cross coupling reactions (Scheme 8, b).



Scheme 8 Follow-up modifications of the products

Theoretical Studies on Mechanism

DFT calculations have been performed, using 3-methyl-1,2,6-heptatriene (**2a'**) as the model of substrate **2a** and *N*-acetoxybenzamide (**1a'**) as the model of *N*-pivaloyloxybenzamide **1a**, in which the TMS group in **2a** and the tertiary butyl group in

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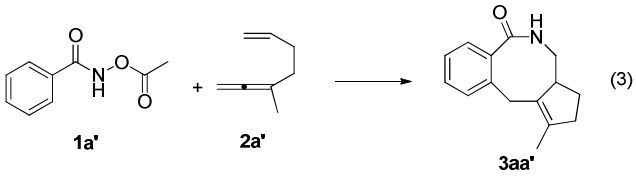
1a have both been replaced with the methyl group (eq. 3). We believe that the catalytic species involved in this reaction is a carbonate-ligated species, Cp*Rh(CO_3), which may be generated via Rh dimer dissociation and ligand exchange from $[Cp^*RhCl_2]_2$ and K_2CO_3. The energetic profiles for the initial steps of the C-H activation and the subsequent carborhodations are provided in Figure 1. The initial formation of the complex **IN1** (selected as the free energy reference) involves the coordination of the nitrogen atom in *N*-acetoxybenzamide substrate (**2a'**) with the Rh center of Cp*Rh(CO_3), which would be followed by the deprotonation of the N-H unit by the CO_3^{2-}. This N-H deprotonation step is computed to require a 12.2 kcal/mol activation barrier (**TS1**) to afford the *N*-metalated intermediate **IN2**, which is 4.5 kcal/mol less stable than the precursor **IN1**. Subsequently, **IN2** isomerizes to a more stable intermediate **IN3**, in which the Rh···$O_{hydroxyl}$ coodination in **IN2** is replaced with the Rh···$O_{carbonyl}$ coordination, with a free energy of 6.6 kcal/mol lower than the starting point (**IN1**).



(3)

The following aryl C-H activation step is realized by a concerted metalation/deprotonation (CMD) process[21a-k] (also termed as ambiphilic metal ligand activation (AMLA))[21l] via a six-membered cyclic transition state **TS2**, in which the Rh-C bond formation occurs simultaneously with the deprotonation of the ortho aromatic proton to afford the rhoda-cyclic intermediate **IN 4**. This CMD step is computed to feature the highest relative energy barrier of the whole profile (20.8 kcal/mol, **TS2**, Figure 1) and may, thus, be rate-determining. This calculated prediction is in consistent with the results of the above mentioned kinetics and deuterium exchange experiments (Schemes 3-6).

The dissociation of H_2CO_3 from **IN4** and the coordination of the allene moiety in the 1,6-allene-ene **2a'** affords **IN5** with a relative energy of 4.0 kcal/mol lower than the starting point. Then the coordinated distal allenic double bond undergoes an insertion into the Rh-C bond via **TS3** to provide the seven-membered rhodacycle intermediate **IN6**, in which the *N*-acetoxy moiety coordinates to Rh center with the pendant carbonyl oxygen. This cyclic carborhodation step is computed to be exergonic (ΔG_{sol} = -11.4 kcal/mol) and requires a 14.7 kcal/mol activation barrier (**TS3**, Figure 1).

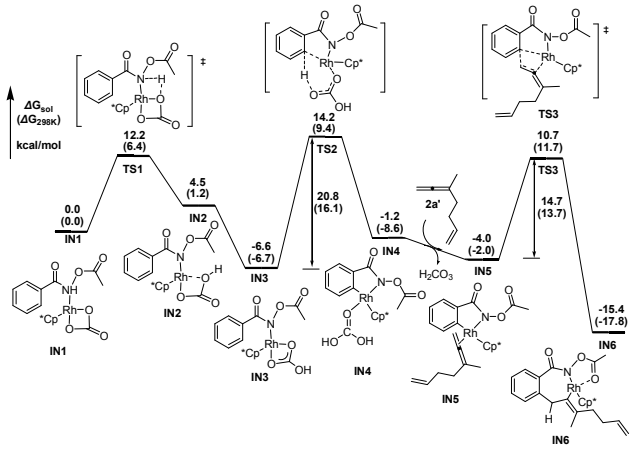
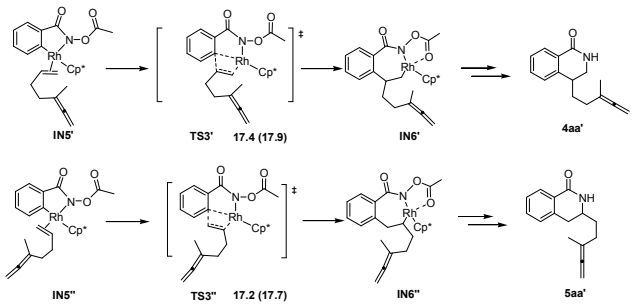


Figure 2 The energetic profiles for the C-H activation and the carborhodations of **IN1**

According to the experimental results, the [4+2] regioisomeric products **4aa** and **5aa** are obtained as the minor byproducts simultaneously with the desired [4+2+2] product **3aa**. To validate the selectivity, the pathways for the competing insertion of the isolated carbon-carbon double with either direction into the Rh-C bond have also been calculated, which are depicted in Scheme 9. The two competing insertion pathways are realized via **TS3'** and **TS3''**, respectively, with similar activation energy barriers of over 17 kcal/mol, which are about 2.5 kcal/mol higher than **TS3**, indicating that the terminal allenic double bond is more reactive than the isolated double bond in this insertion step. So the terminal allenic double bond is calculated to carborhodate preferentially, which is in accordance with experimental observations of **4aa** and **5aa** as minor by-products.



Scheme 9 The activation free energies of forming **4aa'** and **5aa'**

From the seven-membered rhodacycle **IN6**, subsequent second insertion of the terminal C-C double bond is a key step for the formation of the final eight-membered lactam **3aa** product. Besides the second cyclic carborhodation pathway, the possibility of other competitive pathways, such as C-N bond formation and β-H elimination from **IN6**, are also be investigated. The energetic profiles for possible reactions from **IN6** are presented in Figure 2. To facilitate the second cyclic carborhodation, the seven-membered rhodacycle **IN6** should first isomerize to the more stable intermediate **IN7** (11.7 kcal/mol lower in energy than **IN6**), in which the Rh center coordinates with the terminal C-C double bond instead of the carbonyl moiety in **IN6**. Then the subsequent insertion of the terminal C-C double bond into the Rh-C bond occurs via **TS4** with an activation barrier of 9.1 kcal/mol. This step is exergonic with the generation of the nine-membered

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rhodacyclic intermediate **IN8**, which is also stabilized by the coordination of the pendant carbonyl oxygen in the *N*-acetoxy moiety with the Rh center.

The activation free energy of direct reductive elimination from **IN6** is computed to be 35.5 kcal/mol (**TS5**, Figure 2), indicating that this direct C-N formation step is not favorable kinetically. Based on the mechanistic investigations of a closely related systems,[22] a more kinetically favorable pathway of C-N formation from **IN6** is discovered through a high oxidation state Rh(V) nitrene species **IN9**,[23] generated by the migration of the acetoxy moiety form N to Rh via a five-membered transition state (**TS6**, Figure 2). This migration step is computed to be slightly endergonic (ΔG_{sol} = 6.8 kcal/mol) and requires a 13.8 kcal/mol activation barrier (**TS6**). The nitrene Rh(V) species **IN9** has a Rh=N distance of only 1.867 Å, which is much shorter than the Rh-N single bond distance of 2.162 Å in **IN8**. The following reductive elimination of nitrene Rh(V) species **IN9** is much easier with a barrier of only 7.7 kcal/mol via **TS7**, affording **IN10** irreversibly with high exergonicity. Overall, the activation energy for the C-N bond formation pathway from **IN6** is 14.5 kcal/mol, as defined by the energy gap between **TS7** and **IN6**.

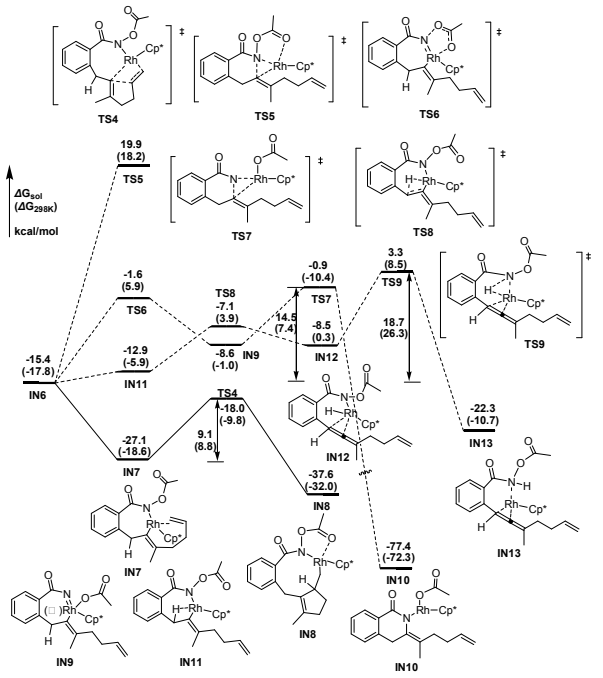

Figure 2 The energetic profiles for possible cyclic carborhodation, C-N bond formation and *β*-H elimination pathways from **IN6**

Another competitive pathway from **IN6** is the *β*-H elimination process, affording the allenation product. In this step, **IN6** should first isomerize into **IN11** (Figure 2), in which the *β*-H coordinates with the Rh center to be perfectly oriented for elimination, with the free energy increased by about 2.5 kcal/mol. The *β*-H elimination occurs subsequently via **TS8** with an activation barrier of 5.8 kcal/mol, leading to rhodium hydride species **IN12**, which is slightly higher in energy by 4.4 kcal/mol than the corresponding precursor (**IN11**). However, the following reductive elimination of the rhodium hydride species **IN12** is not as facile as the *β*-H elimination. This reductive elimination step is computed to require an activation barrier of 11.8 kcal/mol (**TS9**, Figure 2). Hence, it should overcome an activation energy of 18.7 kcal/mol totally for the allenation product generation, which is the free energy gap between **TS9** and **IN6**.

Thus, as can be deduced from the energetic data mentioned above, the second cyclic carborhodation pathway forming the nine-membered rhodacyclic intermediate **IN8** ($\Delta G_{sol}^{\neq}$ = 9.1 kcal/mol) is the most kinetically favorable among the several alternative pathways from **IN6**, which is in well agreement with the experimental observations.

Continuing with the favorable pathway from the nine-membered rhodacyclic intermediate **IN8**, there are also two competitive pathways, forming the final [4+2+2] product **3aa'** by reductive elimination and the methylenecyclopentene product **7aa'** by *β*-H elimination, respectively. The energetic profiles of both possible pathways from **IN8** are presented in Figure 3 for comparison.

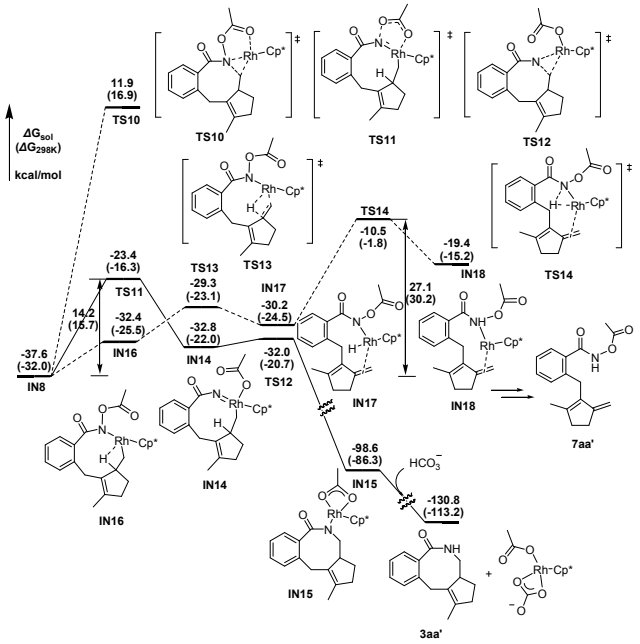

Figure 3 The energetic profiles for possible C-N bond formation and *β*-H elimination pathways from **IN8**.

Similar with the about mentioned C-N formation pathway from **IN6** (Figure 2), the migration of the acetoxy moiety from N to Rh occurs prior to the C-N bond formation, generating a high oxidation state Rh(V) nitrene intermediate **IN14**, which is 4.8 kcal/mol higher in energy than the precursor (**IN8**, Figure 3). This migration step is realized via a five-membered trasition sate **TS11**, overcoming an activation barrier of 14.2 kcal/mol. Then subsequent reductive elimination of the nitrene Rh(V) species **IN14** is very facile via **TS12** with a barrier of only 0.8 kcal/mol, exergonic largely by over 68 kcal/mol, to form the eight-membered ring in **IN15**. Then the protonolysis of the N atom of **IN15** by HCO_3^- would regenerate the catalytically active species Rh(III) and yield the final product **3aa'**, with an overall exergonicity of 130 kcal/mol.

For the *β*-H elimination process from **IN8** (Figure 3), isomerization of **IN8** into **IN16** should occur first, with the free energy increased by 5.2 kcal/mol, which is caused by the less stability of C-H···Rh coordination in **IN16** than $O_{carbonyl}$···Rh

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coordination in **IN8**. In the following step, rhodium hydride species **IN17** would be formed by *β*-H elimination of **IN16** via **TS13** with an activation barrier of only 3.1 kcal/mol. The subsequent reductive elimination of the rhodium hydride species **IN17** is highly energy demanding via **TS14**, hence, raising the barrier of the whole *β*-H elimination process of **IN8** to 27.1 kcal/mol, which is 12.9 kcal/mol higher than the alternative C-N bond formation pathway. Therefore, the final [4+2+2] product are obtained experimentally, instead of the **7**-type methylenecyclopentene product **7aa'**.

Thus, the whole catalytic cycle for the [4+2+2] cyclization mechanism is completed by DFT calculations. Shown in Figure 4 is the reaction coordinate of the most kinetically favorable pathway involving N-H deprotonation/ CMD activation of C-H bond/ first carborhodation of the distal allenic double bond/ second cyclic carborhodation of the isolated carbon-carbon double/ C-N bond formation steps. As can be deduced from the energetic data in Figure 4, the [4+2+2] cyclization reaction is calculated to occur irreversibly, as the final eight-membered lactam product lies over 122 kcal/mol below the starting point, and the CMD C-H bond activation is the rate-limiting step, with the highest relative energy barrier of 20.8 kcal/mol (**TS2**), which agrees well with the observations of the kinetics and deuterium exchange experiments (Schemes 3-6).

To further elucidate the influence of the N-OR moiety on the reaction, we also investigated the possible pathways from the *N*-methoxy containing intermediate **IN8_Me**. Figure 5 presents the free energy profiles for the favored pathway of *β*-H elimination and other two competitive possibilities. **IN8_Me** should first isomerize to **IN16_Me**, in which the *β*-H atom has an agostic interaction with the Rh center and be well oriented for the following elimination. The subsequent *β*-H elimination step leads to the rhodium hydride species **IN17_Me** via **TS13_Me**, with a barrier of only 5.1 kcal/mol. The subsequent reductive elimination breaks the Rh-H bond and forms the N-H bond simultaneously by overcoming a free energy barrier of 21.5 kcal/mol (**TS14_Me**) to afford **IN18_Me**. Thus, the overall *β*-H elimination process of **IN8_Me** is facile, with a 24.6 kcal/mol activation barrier. What's more, the direct C-N bond forming process from **IN8_Me** via **TS10_Me** with an even higher activation barrier of 53.8 kcal/mol, could be ruled out safely. And the similar intramolecular oxidation of the Rh(III) species **IN8_Me** to Rh(V) nitrene intermediate by the migration of the *N*-OMe moiety via a three-center TS is also highly energy demanding (39.7 kcal/mol, **TS11_Me**). Therefore, the *N*-methoxy containing intermediate **IN8_Me** leads to the **7**-type methylenecyclopentene product by *β*-H elimination exclusively (Scheme 3c).

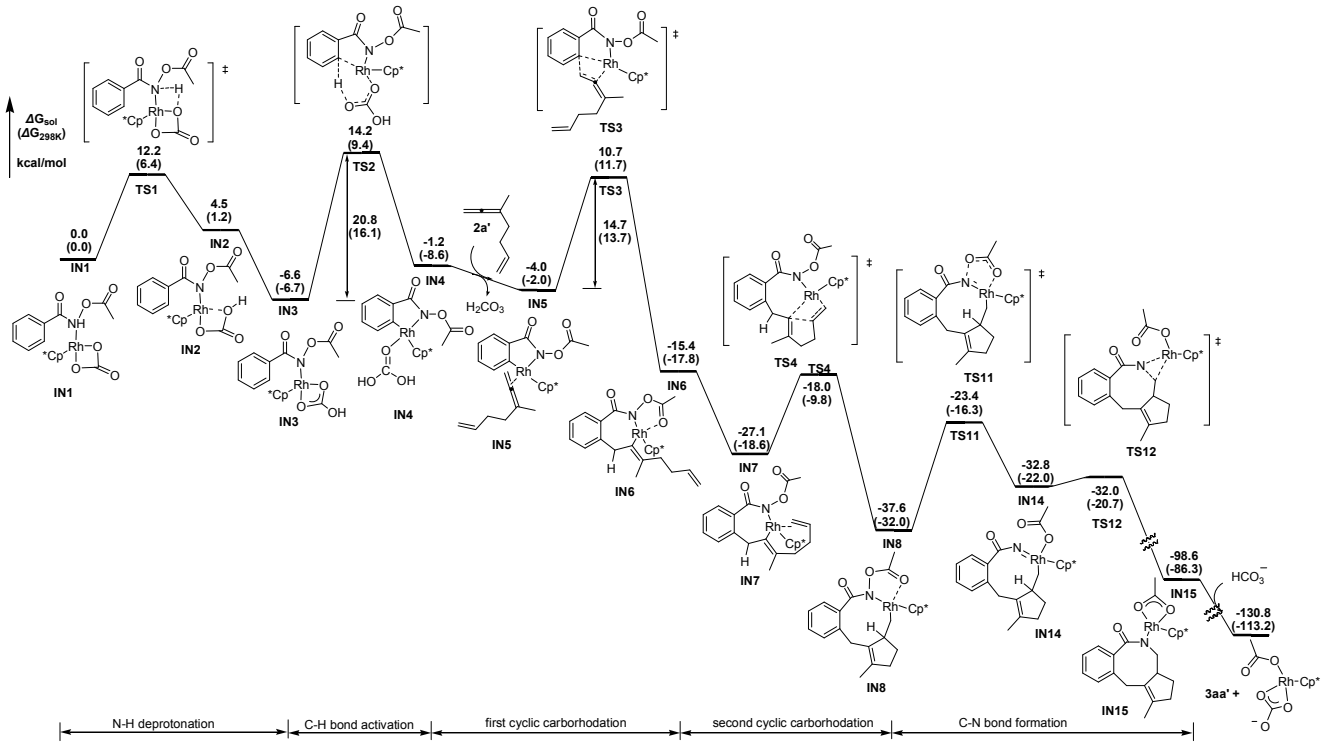

Figure 4 The summary of the free energy profile for the whole [4+2+2] cyclization reaction

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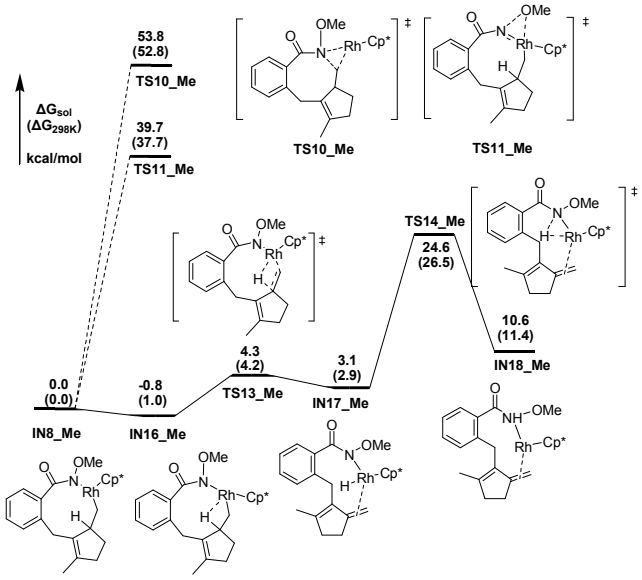

Figure 5 The energetic profiles for the *β*-H elimination pathway from **IN8_Me**

We concluded that the key factor of the influence of the *N*-OR moiety on the reaction selectivity could be attributed to the extra coordination of the carbonyl oxygen in the *N*-acetoxy moiety with the Rh center in **IN8**. First of all, this extra coordination in **IN8** facilitates the migration of the acyloxy from N to Rh, thus enable the formation of the high oxidation state Rh(V) nitrene intermediate **IN14** (Figure 3), which is the C-N bond formation precursor. Secondly, the extra stabilization of **IN8** by this kind of coordination increases the barrier of the whole *β*-H elimination process in the *N*-acetoxy containing system, avoiding the formation of the **7**-type mthylenecyclopentene product.

Conclusions

In conclusion, we have developed the first $[Cp^*RhCl_2]_2$-catalyzed [4+2+2] cyclization between *N*-pivaloyloxy benzamides and 1,6-allene-enes forming eight-membered lactams. These reactions proceed at room temperature and are compatible with ambient air and moisture. Many arenes and allene-enes with many synthetically useful functional groups are compatible in the reactions. After careful mechanistic studies and DFT calculation, the reaction mechanism was presented in deatail and the role of the *N*-OR moiety on the selectivity for the formation of the final products is also unveiled. The formed lactams have been transformed to cyclic vinylic iodide or desilylated product as well as the analogue of dopamine D_3 receptor. With easy availability of both starting materials and new concept to facilely synthesize the 8-membered rings, which are otherwise hard to construct by other means, this [4+2+2] cyclization protocol will be of high interest in organic chemistry and related disciplines. Further studies involving three or more components and chiral [4+2+2] reaction are being carried out in our laboratory.

Experimental Section

Materials: $[Cp^*RhCl_2]_2$ was purchased from Strem. *N*-pivaloyloxy benzamides were prepared according to the literature procedures.[7c,7o] Grignard reagents were prepared from the corresponding aryl halides and magnesium. Other commercially available chemicals were purchased and used without additional purification unless noted otherwise. ^{1}H NMR spectra were recorded on a Bruker-300 MHz spectrometer (except for **2h**, a Bruker-700 MHz spectrometer was used) and ^{13}C NMR spectra were recorded at 75 MHz. All ^{1}H NMR experiments were measured with tetramethylsilane (0 ppm) or the signal of residual CHCl3 (7.26 ppm) in $CDCl_3$ as the internal reference, ^{13}C NMR experiments were measured in relative to the signal of $CDCl_3$ (77.0 ppm), and ^{19}F NMR experiments were measured in relative to the signal of residual $CFCl_3$ (0 ppm) in $CDCl_3$.

Typical Procedure for the [4+2+2] Cyclization Reactions: To a dried Schlenk tube equipped with a Teflon-coated magnetic stirring bar were added N-pivaloyloxybenzamide **1a** (221.6 mg, 1 mmol), $[Cp^*RhCl_2]_2$ (12.7 mg, 0.02 mmol), K_2CO_3 (41.3 mg, 0.3 mmol), 3-(trimethylsilyl)-1,2,6-heptatriene **2a** (166.0 mg, 1 mmol), and MeOH (6 mL) sequentially at rt. After being stirred for 2 h, the reaction was complete as monitored by TLC. Filtration through a short column of silica gel (eluent: MeOH) and evaporation afforded the crude product, which was purified by flash column chromatography on silica gel (eluent: dichloromethane/ethyl acetate = 4/1) to afford **3aa** (194.1 mg, 68%): solid; m.p. 188.2-188.9 °C (hexane/ethyl acetate); ^{1}H NMR (300 MHz, CDCl3) δ 7.77-7.65 (m, 1 H, NH), 7.48-7.33 (m, 2 H, Ar-H), 7.29 (t, *J* = 6.2 Hz, 2 H, Ar-H), 3.80 (d, *J* = 13.5 Hz, 1 H, one proton of CH_2), 3.46 (d, *J* = 13.2 Hz, 1 H, one proton of CH_2), 3.26-3.10 (m, 1 H, one proton of NCH_2), 2.96-2.75 (m, 2 H, one proton of NCH_2 + CH), 2.39-2.16 (m, 2 H, CH_2), 1.98-1.85 (m, 1 H, one proton of CH_2), 1.14-0.94 (m, 1 H, one proton of CH_2), 0.26 (s, 9 H, 3 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 150.6, 137.6, 137.2, 134.6, 130.3, 129.2, 127.4, 126.8, 52.0, 46.5, 35.7, 34.9, 28.9, -0.07; IR (neat, cm^{-1}) 3291, 3187, 3063, 2945, 2852, 1660, 1604, 1460, 1446, 1404, 1353, 1338, 1248, 1048, 1038, 1003; MS (EI, 70 eV) m/z (%) 286 (M^++1, 18.79), 285 (M^+, 62.45), 256 (100), 255 (100), 73 (100); Anal. Calcd for $C_{17}H_{23}NOSi$ (MW = 285.5): C 71.53, H 8.12, N 4.91. Found: C 71.50, H 8.14, N 4.73.

Computational Methodology. All calculations were performed with the Gaussian 09 program.[24] Geometries have been fully optimized with the density functional theory of M06 method.[25,26] The standard 6-31G(d,p)[27] basis set was used for carbon, hydrogen, nitrogen and oxygen atoms and LANL2DZ basis set[28] with effective core potential (ECP) for rhodium. Harmonic vibration frequency calculations were carried out for all the stationary points to confirm each structure being either a minimum (no imaginary frequency) or a transition structure (one

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imaginary frequency). Solvent effect has been considered by using the CPCM[29] (UAHF atomic radii) model based on the gas-phase-optimized structures. The reported relative energies are free energies at 298 K (ΔG_{298}) in gas phase and the Gibbs free energies (ΔG_{sol}) in Methanol (dielectric constant ε= 32.61), unless otherwise specified.

Acknowledgements

Financial support is acknowledged from National Natural Science Foundation (21232006 and 21472224) and National Basic Research Program (2015CB856600) of China. S.M. is a Qiu Shi Adjunct Professor at Zhejiang University. We thank Dr. Weiming Yuan in this group for reproducing the results for synthesis of **3ea**, **3ac** and **3ka**.

Notes and references

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† Electronic Supplementary Information (ESI) available: Data for new compounds and experimental procedures and theoretical studies on mechanisms. See DOI: 10.1039/b000000x/

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14. **3aa'·H$_2$O**: $C_{17}H_{23}NOSi·H_2O$, MW = 303.47, monoclinic, space group P 21/n, final R indices [I > 2σ(I)], R1 = 0.1006, wR2 = 0.2419; Rindices (all data), R1 = 0.1392, wR2 = 0.2672; a = 7.8451(6) Å, b = 10.8055(10) Å, c = 41.681(3) Å, α = 90.00°, β = 92.188(5)°, γ = 90.00°, V = 3530.7(5) Å3, T = 293(2) K, Z = 8, reflections collected/unique 15620/6440 (Rint = 0.0483), number of observations [> 2σ(I)]: 4214, parameters: 401. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC 979559.

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