Theoretical investigation on Rh(III)-catalyzed switchable C–H alkenylation of enamide with enone and Rh(I)-catalyzed decarbonylative version of 1,2,3,4-tetrahydroquinoline with anhydride

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Abstract: The mechanism is investigated for Rh(III)-catalyzed C–H alkenylation of enamide with enone and Rh(I)-catalyzed decarbonylative version of 1,2,3,4-tetrahydroquinoline with anhydride. The former contains β-C(sp²)−H activation of enamide, 1,2-migratory insertion of enone, β-hydride elimination or protodemetalation with additional HCl. The diastereoselectivity is kinetically controlled favoring alkenylation N-(2Z,4E)-butadiene while the regio-divergence is switchable to alkylation. The latter is composed of rate-limiting oxidative addition of anhydride to Rh(I), C8-selective C–H activation after ligand exchange producing tBuCO₂H and six-membered rhodacycle, decarbonylation releasing CO as new carboxylate ligand and reductive elimination of Rh-alkenyl precursor leading to C8-alkenylnated product. The whole process with huge heat release is favorable thermodynamically and all barriers capable to overcome under microwave assistance. The positive solvation effect is suggested by decreased absolute and activation energies in solution compared with in gas. These results are supported by Multiwfn analysis on FMO composition of specific TSs, and MBO value of vital bonding, breaking.

Keywords: C–H alkenylation; regioselectivity; decarbonylation; 1,2-migratory insertion; rhodacyclic

1. Introduction

As important natural products and bioactive molecules, enamides are widely used to be efficient intermediates in organic synthesis. Among many attractive features, the most sought-after field is direct olefinic β-C(sp²)−H functionalization including alkylation [1–3] and alkenylation [4]. The alkyl radicals were often featured with E-stereoselectivity in alkylation while activated alkenes were coupling partners in alkenylation. Thus C–C bond generation catalyzed by transition metal via C–H activation has received wide interest in recent years. Wherein rhodium(III) catalysts aroused extensive concern with unique advantages as reviewed in reaction assisted by removable directing group [5] and direct C–H arylation of various acyclic enamides with arylsilane [6]. Another interesting aspect is strategies with allylic alcohols in C–H activation through regulation of organometallic selectivity reactivity [7,8]. Recently, many C–H alkylation and alkenylation with allylic alcohols have been achieved for various substrates using rhodium catalyst [9,10].

On the other hand, 1,2,3,4-tetrahydroquinolines are vital active molecules biologically and important compounds pharmacologically. Many efforts were devoted to C–H activation or functionalization of 1,2,3,4-tetrahydroquinolines in past few decades. Particularly in the presence of palladium, rhodium catalysts, the
regioselective alkylation [11,12] can be enabled via introduction of N-directing
group. Shi [11] reported aromatic C−H bond activation directed by an N-alkyl
acetamino group. Jiang [12] achieved direct synthesis of 8-aryl tetrahydroquinolines
via ortho-arylation of aryureas in water. The arylation [13,14] was also available
such as Wang’s direct C7 alkylation of indolines via sequential C−H and C−C
activation and Yang’s C8-selective C−H alkenylation and alkylation with styrenes
and allylic alcohols. The Rh(I)-catalyzed decarboxylative alkenylation of 1-
(pyridine-2-yl)-1,2,3,4-tetrahydroquinoline with cinnamic anhydride was obtained
by Zhang [15]. Mohit Kumar reported four examples of Ru(II)-catalyzed C8–H
alkenylation of N-Piv-1,2,3,4-tetrahydroquinoline with internal alkynes [16].
However, these advances still have limits in substrate generality and functional
group tolerance. Then diverse carboxylic acids demonstrated as advantageous
coupling reagents appeared in transition metal-catalyzed decarboxylative and
decarboxylative coupling reaction [17–19]. The use of alkenyl carboxylic acids as
alkenyl sources in decarboxylative alkenylation received much attention.

Many advantages have been shown for alkenyl C(sp²)−H functionalization [20].
Based on novel rhodium(III)-catalyzed tunable C4 alkylation and alkenylation of
indoles developed by Punniyamurthy [21] and persistent attention on enamides, a
breakthrough was Luo’s rhodium(III)-catalyzed β-C(sp²)−H alkenylation and
alkylation of acyclic enamides with allyl alcohols [22]. Compared with this was
decarboxylative functionalization of (hetero)arene C−H bonds depending on C2-
selective C−H alkenylation and polyenylation of imidazoles and directed
trideuteromethylation with CD₂CO²D of Walsh group [23,24]. Especially their Rh(I)-catalyzed C8-selective C−H alkenylation of N-(pyrimidin-2-yl)-1,2,3,4-
tetrahydroquinolines [25]. Although excellent regioselectivity and stereoselectivity
was achieved, there is no report about detailed mechanistic study explaining the
origin of critical step. How the N-(2Z,4E)-butadiene and (Z)-β-C(sp²)−H alkylated
enamide presented in switchable mode under the promotion of rhodium(III)? Why
the catalytic activity of rhodium(I) strongly influenced by installable and removable
N-directing group? To solve these puzzled problems in experiment, an in-depth
theoretical study was necessary for these strategy leading to diverse functionalized
enamides and C8-alkenylated and arylated 1,2,3,4-tetrahydroquinolines.

2. Computational details

The geometry optimizations were performed at the B3LYP/BSI level with the
Gaussian 09 package [26,27]. The mixed basis set of LanL2DZ for Rh and 6-31G(d)
for non-metal atoms [28–32] was denoted as BSI. Different singlet and multiplet
states were clarified with B3LYP and ROB3LYP approaches including Becke’s
three-parameter hybrid functional combined with Lee–Yang–Parr correction for
correlation [33–39]. The nature of each structure was verified by performing
harmonic vibrational frequency calculations. Intrinsic reaction coordinate (IRC)
calculations were examined to confirm the right connections among key transition-
states and corresponding reactants and products. Harmonic frequency calculations
were carried out at the B3LYP/BSI level to gain zero-point vibrational energy
(ZPVE) and thermodynamic corrections at 373 K, 413 K and 1 atm for each
structure in THF and 1,4-Dioxane. The solvation-corrected free energies were obtained at the B3LYP/6-311++G(d,p) (LanL2DZ for Rh) level by using integral equation formalism polarizable continuum model (IEFPCM) in Truhlar’s “density” solvation model [40–42] on the B3LYP/BSI-optimized geometries.

As an efficient method obtaining bond and lone pair of a molecule from modern ab initio wave functions, NBO procedure was performed with Natural bond orbital (NBO3.1) to characterize electronic properties and bonding orbital interactions [43,44]. The wave function analysis was provided using Multiwfn_3.7_dev package [45] including research on frontier molecular orbital (FMO) and Mayer bond order (MBO).

3. Results and discussion

The mechanism was explored for (a) Rh(III)-catalyzed switchable C-H alkenylation of enamide 1 with enone 2 leading to N-(2Z,4E)-butadiene 3 and (Z)-β-C(sp³)–H alkylated enamide 4. (b) Rh(I)-catalyzed decarbonylative alkenylation of 1,2,3,4-tetrahydroquinoline 5 with anhydride 6 producing C8-alkenylated 1,2,3,4-tetrahy-droquinoline 7 (Scheme 1). Illustrated by black arrow of Scheme 2a, a rhodacyclic intermediate i2 is generated by the reaction of 1 with model catalyst Cp*RhCl₂ via chelation assistance through β-C(sp²)–H activation. After the leaving of HCl, the coordination of enone 2 to i2 and succeeding 1,2-migratory insertion formed intermediate C with loose eight-membered ring and rigorous four-membered ring. From C, the subsequent β-hydride elimination affords alkenylated product 3 along with Cp*Rh(I) and another HCl (red arrow). Alternatively, C can undergo protodemetalation with an additional HCl to give alkylated product 4 and recovered Cp*Rh(III) (green arrow). The alkenylated 3 could be further converted into alkylated 4.

Scheme 1. (a) Rh(III)-catalyzed switchable C-H alkenylation of enamide 1 with enone 2 leading to N-(2Z,4E)-butadiene 3 and (Z)-β-C(sp³)–H alkylated enamide 4; (b) Rh(I)-catalyzed decarbonylative alkenylation of 1,2,3,4-tetrahydroquinoline 5 with anhydride 6 producing C8-alkenylated 1,2,3,4-tetrahy-droquinoline 7.

Displayed by black arrow of Scheme 2b, the oxidative addition of anhydride 6
to model Rh(I) species \( \text{Rh(CO)}_2 \text{acac} \) generates intermediate D, from which one CO ligand is exchanged by substrate 5 giving intermediate E. Then, the C8-selective C–H activation of E produces acid tBuCO\(_2\)H and six-membered rhodacycle F. The subsequent decarbonylation of F releases CO just serving as the lost carboxylate ligand and delivers Rh-alkenyl precursor in3, which proceeds reductive elimination to liberate product 7 and regenerates catalyst Rh(I) species. The schematic structures of optimized TSs in Scheme 2 were listed by Figure 1. The activation energy was shown in Table 1 for all steps. Supplementary Table S9, Table S10 provided the relative energies of all stationary points. According to experiment, the Gibbs free energies in THF and 1,4-Dioxane solution phase are discussed here.

**Scheme 2.** Proposed reaction mechanism. (a) switchable C–H alkenylation of 1 with 2 leading to 3 and 4 catalyzed by \( \text{Cp}^*\text{RhCl}_2 \); (b) decarbonylative C–H alkenylation of 5 with 6 producing 7 catalyzed by \( \text{Rh(CO)}_2 \text{(acac)}. \)

Table 1. The activation energy (in kcal mol\(^{-1}\)) of all reactions in gas and solvent.

<table>
<thead>
<tr>
<th>TS</th>
<th>( \Delta G^{\neq \text{gas}} )</th>
<th>( \Delta G^{\neq \text{sol}} )</th>
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<tr>
<td>ts-i12</td>
<td>11.12</td>
<td>16.19</td>
</tr>
<tr>
<td>ts-i3C</td>
<td>17.63</td>
<td>19.50</td>
</tr>
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<td>ts-Ci4</td>
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<td>ts-i56</td>
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<tr>
<td>ts-in1D</td>
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<tr>
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<tr>
<td>ts-Fin3</td>
<td>40.39</td>
<td>39.60</td>
</tr>
<tr>
<td>ts-in3G</td>
<td>8.58</td>
<td>13.62</td>
</tr>
</tbody>
</table>

**Figure 1.** Relative Gibbs free energy profile in solvent phase starting from complex. (a) i1, i3, i5; (b) in1, E, F. Bond lengths of optimized TSs in Å.
3.1. β-C(sp³)−H activation/1,2-migratory insertion/C−H alkenylation

The reaction of 1 with Cp*RhCl₂ proceeds via ts-i12 as step 1 with the activation energy of 16.2 kcal mol⁻¹ relative to the starting point i1 endothermic by 10.1 kcal mol⁻¹ (black dash line of Figure 1a). The transition vector includes the approaching of O1 and C3 to Rh slightly ahead of H1 shifting from β-C3 to Cl1 ligand(2.14, 2.06, 1.38, 1.6 Å) (Figure S1a). The β-C(sp³)−H activation assisted by chelation is completed with the formation of rhodacyclic intermediate i2.

Without HCl, a complex i3 from the coordination of enone 2 to i2 is located as another the starting point of next two steps. The 1,2-migratory insertion occurs via ts-i3C with activation energy of 19.5 kcal mol⁻¹ in step 2. The transition vector contains concerted bonding of C3 to C4, Rh to C5 and cooperated cleavage of Rh···C3, elongation of C3–C4 (1.97, 2.16, 2.07, 1.44 Å) (Figure S1b). The resultant C is characterized by loose eight-membered ring and rigorous four-membered ring with Rh-C5 and Rh-O2 bond as well as sp³ C4.

The subsequent β-hydride elimination takes place via ts-Ci4 with activation energy of 9.7 kcal mol⁻¹ with respect to C in step 3 affords i4 (red dash line of Figure 1a). The transition vector corresponds to the depnovation of C4 by another Cl ligand (1.33, 1.59 Å) (Figure S1c). Once the second HCl and Cp*Rh(I) are departed, alkenylated product (2Z,4E)-3 is obatained at last. Three steps are all readily accessible with mediate barrier from kinetics and unremarkable thermal effects from thermodynamics. Thus 1,2-migratory insertion is determined to be rate-limiting of the whole process.

3.2. C−H alkylation and regioselectivity

Alternatively from C, the intermediate i5 is located binding an additional HCl and taken as starting point of the competitive C−H alkylation (green dash line of Figure 1a). This step proceeds via ts-i56 with activation energy of 15.8 kcal mol⁻¹ greatly exothermic by −36.0 kcal mol⁻¹. As suggested by the transition vector, the socalled protodemetalation includes de-coordination of Rh···C5 and slightly delayed donating H3 by Cl3 to C5 (2.43, 1.61, 1.49 Å) (Figure S1d). After protanation, C5 turns to be sp3 along with the same sp3 C4 in stable final intermediate i6 still with Rh-O2 (2.14 Å) and new Rh-Cl3, which could yield alkenylated product 4 and recovered Cp*Rh(III).

Clearly, via comparison between barriers of ts-Ci4 and ts-i56 (9.7, 15.8 kcal mol⁻¹), the excellent diastereoselectivity in experiment is kinetically controlled favoring C−H alkenylation. However, this regio-divergence is switchable considering the relative stability of i4 and i6 (1.0, −36.0 kcal mol⁻¹). Thermodynamically, the alkenylation could be further converted alkylation.

To highlight the idea of feasibility for changes in electron density and not molecular orbital interactions are responsible of the reactivity of organic molecules, quantum chemical tool Multiwfn was applied to analyze of electron density such as MBO results of bonding atoms and contribution of atomic orbital to HOMO of typical TSs (Table S11, Figure S2). These results all confirm the above analysis.
3.3. Oxidative addition/C8-selective C–H activation

Seen from black dash line of Figure 1b, the starting point is located as in1 binding anhydride 6 and Rh(CO)₃acac, from which the oxidative addition occurs via ts-in1D with activation energy of 44.6 kcal mol⁻¹ endothermic by 20.2 kcal mol⁻¹ generating D in step 1. The transition vector indicates the cleavage of anhydride bond C3-O1 and almost simultaneous coordination of C3, O1 to Rh (1.75, 2.36, 2.13 Å) (Figure S1e). As Rh(III) intermediate, the resultant D is reactive, from which the ligand exchange is easy from one CO to substrate 5 giving E with Rh-N bond taken as new starting point of next step.

Via ts-Ein2, the C8-selective C-H activation of E proceeds with the activation energy of 25.2 kcal mol⁻¹ relative to E endothermic by 13.2 kcal mol⁻¹ in step 2. This detailed motion can be demonstrated by the transition vector of ts-Ein2 (Figure S1f). That is H1 transferring from C8 to O2 and concerted closing of Rh to C8 (1.53, 1.14, 2.4 Å). The Rh-O1 coordination becomes weak yet still existing (2.1 Å). Therefore a six-membered rhodacycle F is produced with stable Rh-N and Rh-C8 bond after the leaving of tBuCO₂H acid from in2.

3.4. Decarbonylation/reductive elimination

Initiated from F, the following decarbonylation happens via ts-Fin3 in step 3 with a barrier of 39.6 kcal mol⁻¹ endothermic by 16.7 kcal mol⁻¹ delivering in3 as a Rh-alkenyl precursor. The transition vector is composed of remarkable C2–C3 fracture and Rh-C2 bonding (1.7, 2.31 Å) (Figure S1g). Comparatively, the single Rh-C3 bond remains strong together with the shortening of C3–O3 from double to triple (2.0, 1.18 Å). This denotes the release CO can just serve as the new carboxylate ligand of Rh(III).

Subsequently, the reductive elimination of in3 takes place via ts-in3G with activation energy of 13.6 kcal mol⁻¹ forming G exothermic by −38.3 kcal mol⁻¹ in step 4. According to the transition vector, the Rh–C2, Rh–C8 are breaking and C2–C8 is linking (2.05, 2.12, 1.97 Å) (Figure S1h). Once the bonding site of C2 is handed over from Rh to C8, the formal single C2–C8 bond reveals the accomplish of final alkenylation. G is rather stable attributed to the binding of regenerated Rh(CO)₃acac and C8-alkenylate product 7.

The oxidative addition is determined to be rate-limiting. Although the barriers of step 1 and step 3 are somewhat high, they are both capable to overcome under the microwave assistance in experiment 140 °C. Furthermore, the temporary heat absorption due to the production of intermediates with reactive Rh(III) species converts to huge heat release at last with recovered Rh(I) species. Thankfully, the whole process is favorable thermodynamically.

4. Conclusions

Our DFT calculations provide the first theoretical investigation on Rh(III)-catalyzed switchable C-H alkenylation of enamide with enone. The rhodacyclic intermediate is generated through β-C(sp²)–H activation of enamide with Cp*RhCl₂. After the leaving of first HCl, the 1,2-migratory insertion of enone forms intermediate with loose eight-membered ring and rigorous four-membered ring. The
subsequent β-hydride elimination affords N-(2Z,4E)-butadiene along with Cp*Rh(I) and second HCl. Alternatively with additional HCl, protodemetalation could give (Z)-β-C(sp²)–H alkylated enamide and recovered Cp*Rh(III). The diastereoselectivity is kinetically controlled favoring alkenylation while the regio-divergence is switchable with alkenylation converted alkylation thermodynamically.

For Rh(I)-catalyzed decarbonylative alkenylation of 1,2,3,4-tetrahydroquinoline with anhydride, the rate-limiting step is initial oxidative addition of anhydride to Rh(CO)₂acac. After the ligand exchange from one CO to 1,2,3,4-tetrahydroquinoline, the C8-selective C–H activation produces acid tBuCO₂H and six-membered rhodacycle. The subsequent decarbonylation releases CO serving as new carboxylate ligand and delivers Rh-alkenyl precursor, which proceeds reductive elimination to liberate C8-alkenyalted product and regenerated Rh(I). The whole process with huge heat release is favorable thermodynamically and all barriers capable to overcome under microwave assistance.

The positive solvation effect is suggested by decreased absolute and activation energies in THF and 1,4-Dioxane solution compared with in gas. These results are supported by Multiwfns analysis on FMO composition of specific TSs, and MBO value of vital bonding, breaking.

**Author contributions:** Conceptualization, NL; methodology, NL; software, NL; validation, NL; formal analysis, NL; investigation, NL; resources, NL; data curation, NL; writing—original draft preparation, NL; writing—review and editing, NL; visualization, NL; supervision, CM; project administration, CM; funding acquisition, XL. All authors have read and agreed to the published version of the manuscript.

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