Reaction Mechanism

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Metalla-Claisen Rearrangement in Gold-Catalyzed [4+2] Reaction: A New Elementary Reaction Suggested for Future Reaction Design

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Abstract: We report here computational evidence for a metalla-Claisen rearrangement (MCR) in the case of gold-catalyzed [4+2] cycloaddition reaction of yne-dienes. The [4+2] reaction starts from *exo* cyclopropanation, followed by MCR and reductive elimination. The cyclopropane moiety formed in the first step is crucial for a low barrier of the MCR step. In addition, the importance of an appropriate combination of the tether group and the terminal substituent on alkyne in the yne-diene substrates was studied. The mechanism of rhodium-catalyzed [4+2] reaction of yne-dienes was also investigated to see whether an MCR mechanism is involved or not. The findings and new understanding hereby reported represent an important advance in the catalysis field.

Introduction

Cope and Claisen rearrangements as well as other related [3,3]-sigmatropic rearrangements are textbook reactions, and are widely used in synthesis. Some of these rearrangements were also found in biological processes.[1,2] Cope rearrangement is related to all carbon substrates, while Claisen rearrangement uses heteroatom (such as N, O, S) embedded substrates (Figure 1A–B). Similar to aza- and thio-Claisen rearrangements, when metal atom is involved in the substrates, the corresponding reactions are called metalla-Claisen or metalla-Cope rearrangement (MCR) (Figure 1C–D). MCR has been observed on allylvinylzinc reagents.[3a–c] Though some investigations on Re-, Os- and Rh-Claisen rearrangements were performed on theoretical models,[3d–e] no such processes were found in real reactions for d-transition metals, to the best of our knowledge.

Transition-metal-catalyzed intra- and intermolecular [4+2] reactions are powerful methods to synthesize six-membered carbocycles between inactive dienes and alkynes, alkenes and allenes.[4] Scheme 1 shows the two possible mechanisms of the metal-catalyzed [4+2] reaction of yne-dienes. The widely accepted mechanism is pathway I, which starts with diene coordination by metal, followed by oxidative cyclometallation and reductive elimination. In addition to this, pathway II including *exo* cyclopropanation, MCR and reductive elimination is also possible. We previously studied Rh-catalyzed [4+2] reaction of ene/yne-dienes and proposed pathway I was the preferred one.[5] But for yne-dienes, we did not investigate whether pathway II was favored or not.

In this paper, we report our answer to this question and the reasons behind this. A major part of this paper will show that pathway II is favored compared to pathway I in gold-catalyzed [4+2] cycloaddition of yne-dienes, which was discovered by Fürstner and co-workers in 2007.[11–13] Three examples of the Au-catalyzed [4+2] reactions reported by the Fürstner group are shown in Scheme 2. Both pathways I and II, together with another pathway involving direct cationic cyclization (see the Supporting Information) have

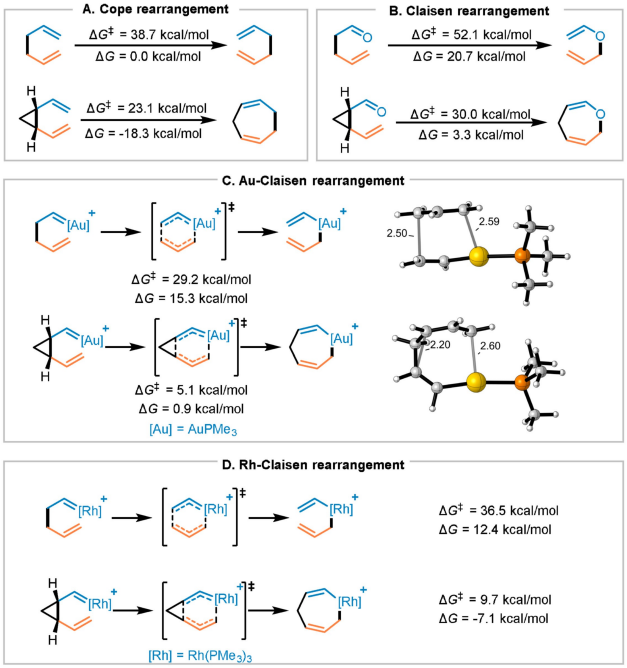

Figure 1. Thermodynamic and kinetic data computed at ωB97M-V/def2-QZVP/SMD(DCM)//BMK-D3BJ/def2-SVP level.[6–10] (A) Cope rearrangement. (B) Claisen rearrangement. (C) Au-Claisen rearrangement. (D) Rh-Claisen rearrangement.

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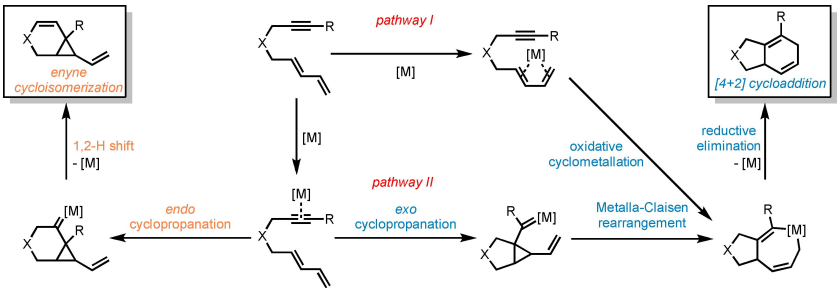
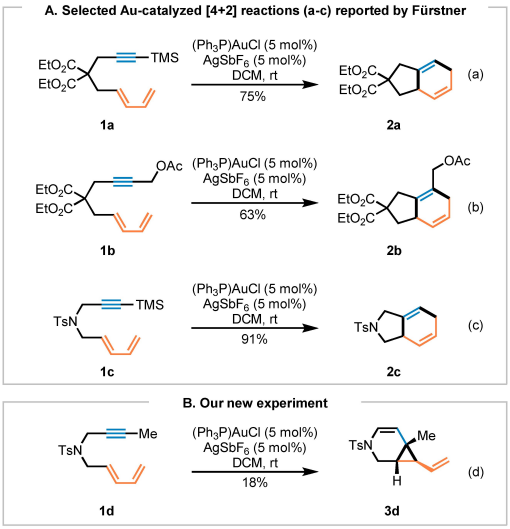


Scheme 1. The proposed reaction pathways for the metal-catalyzed [4+2] reaction of yne-dienes and the competing enyne cycloisomerization pathway.



Scheme 2. Experimental results of Au-catalyzed [4+2] cycloaddition and enyne cycloisomerization of yne-dienes.

been proposed by Fürstner, but no experimental or theoretical studies have been carried out to elucidate which one of these pathways was favored.

In this work, we report our density functional theory (DFT) calculations to answer this mechanistic question, leading us to provide the first evidence for an Au-Claisen rearrangement in a real (not a theoretical) reaction. We believe that this finding and understanding of the Au-Claisen rearrangement represent important advances in organometallic chemistry and reaction development, which could further inspire chemists to interweave MCR in their future design of new reactions. Also, we will test whether pathway II works for the Rh-catalyzed [4+2] reaction of yne-dienes.

To make sure that pathway II involving MCR is the favored one in Au-catalyzed [4+2] cycloaddition of yne-dienes, we must in principle exclude all other possible pathways and understand their competing pathways as well. We have performed all of these in this investigation, finding that the Au-catalyzed reaction of yne-dienes did not always give [4+2] products. In the successful [4+2] reactions, as represented by three examples in Scheme 2A, when the tether between the yne and diene in the yne-diene substrates has $X=C(CO_2Et)_2$ (simplified as carbon or C tether in later on discussions), R can be either an alkyl or a silyl group (reactions a–b, from Fürstner group, the TMS group in the final products was proposed to be lost during workup). However, when the tether has X=NTs (Ts=*p*-toluenesulfonyl), simplified as nitrogen or N tether in later on discussions, R group must be a silyl group (reaction c, from Fürstner group). No understanding of this was given in the original experimental report. During our study of effects of tether and substituent in yne-dienes (see below), we further predicted that, under the catalysis of Au, enyne cycloisomerization should be favored compared to the [4+2] reaction for substrates with N tether and R=alkyl (reaction d in Scheme 2B).[14] We were happy to verify this prediction by our new experiment, showing that cyclopropanation product was found but no [4+2] product can be detected in the reaction mixture (see Supporting Information for experimental details). The mechanism of this competing reaction is also proposed and shown in Scheme 1, which involves an *endo* cyclopropanation and [1,2]-hydrogen shift. Therefore, computational study of how [4+2] reaction and this cycloisomerization compete is required.

In what follows, we will first discuss the computed free energy surfaces of pathway II and cycloisomerization pathway in the reaction of yne-diene catalyzed by Au. Then wavefunction analysis is used to provide insights into the Au-Claisen rearrangement in pathway II. After that, the effects of tether and substituent in the yne-diene substrates on the competition of [4+2] and cycloisomerization reactions will be discussed. Finally, we try to answer whether and why Rh-catalyzed [4+2] reaction of yne-dienes does/does not involve MCR.

Results and Discussion

[4+2] vs. Enyne Cycloisomerization for Au

The DFT computed Gibbs free energy profile for the favored pathway, pathway II of [4+2] reaction of yne-diene **1a** by a model catalyst of $Au(PMe_3)^+$ is shown in Figure 2 (the experimental tether with $X=C(CO_2Et)_2$ was replaced by $X=C(CO_2Me)_2$ in the calculations). The other two pathways proposed by Fürstner were found to be disfavored kinetically and were ruled out for further discussions (details are

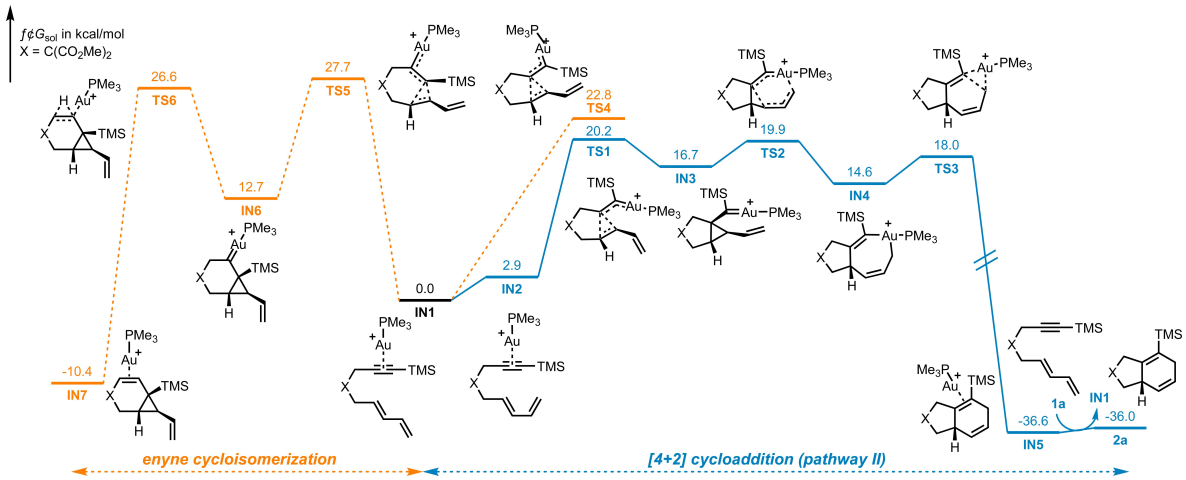


Figure 2. Gibbs free energy profiles of [4+2] and enyne cycloisomerization reactions at ωB97M-V/def2-QZVP/SMD(DCM)//BMK-D3BJ/def2-SVP level.[6–10]

given in the Supporting Information). The catalytic cycle of [4+2] reaction starts from ligand exchange of the [4+2] cycloadduct/Au complex **IN5** (coming from the previous catalytic cycle) and yne-diene **1a** to give complex **IN1**, which is a neutral process thermodynamically. This intermediate undergoes geometry change of its diene moiety from a *s-trans* conformation to a *s-cis* conformation to form intermediate **IN2**. Then **IN2** is converted to **IN3** through *exo* cyclopropanation via **TS1**, in which the TMS group is *trans* to the forming cyclopropane (the alternative transition state **TS4** suffers from an additional increase of $\Delta\Delta G^{\neq}$ of 2.6 kcal mol^{-1}). After that, **IN3** undergoes an Au-Claisen rearrangement with an activation free energy of 3.2 kcal mol^{-1}. The final step in the [4+2] pathway is reductive elimination via **TS3**, with an activation free energy of 3.4 kcal mol^{-1}. Therefore, the rate-determining step in the [4+2] reaction is the *exo* cyclopropanation, with an overall activation free energy of 20.8 kcal mol^{-1} (20.2 kcal mol^{-1} coms from **IN1** to **TS1** and 0.6 kcal mol^{-1} from ligand exchange).

The enyne cycloisomerization pathway is disfavored since the rate-determining transition state **TS5**, corresponding to the *endo* cyclopropanation, is higher than **TS1** by 7.5 kcal mol^{-1} in terms of Gibbs free energy (the followed [1,2]-H shift via **TS6** is also disfavored). This agrees with experimental results that no such a product were observed for **1a** (Scheme 2).

In-depth Analysis of Au-Claisen Rearrangement

To better understand this Au-Claisen rearrangement in the [4+2] reaction, activation free energies for several reference reactions were calculated (Figure 1). The parent Cope rearrangement in DCM (dichloromethane) is difficult with a computed activation free energy of 38.7 kcal mol^{-1}.[15] When a cyclopropane tether is introduced, the Cope rearrangement becomes easier with a computed activation free energy of 23.1 kcal mol^{-1}, due to the strain release from the cyclopropane tether. For Claisen rearrangement, a similar conclusion can be reached.[16] When gold-carbene is introduced, the corresponding Claisen rearrangement becomes easier by 9.5 kcal mol^{-1} compared to parent Cope rearrangement, with a computed activation free energy of 29.2 kcal mol^{-1}. This process is endergonic, suggesting that Au=C and C–C bonds in the reactant are stronger than the Au–C and C=C bonds in the product. When a cyclopropane tether is introduced, the Au-Claisen rearrangement has an activation free energy of 5.1 kcal mol^{-1}, which is 18.0 kcal mol^{-1} lower than that required for the Cope rearrangement of divinylcyclopropane. Similar results were found for Rh-Claisen rearrangement. This implies that strain release could be one of the driving forces for the Au- and Rh-Claisen rearrangements with a cyclopropane tether. Below is our analysis.

The low activation free energy of the above Au-Claisen rearrangement with a cyclopropane tether also prompted us to check whether the gold atom in the seven-membered ring has an oxidation state of +III, which is usually difficult to be reached ($Au^{3+}/Au^{+} = 1.36$ V).[17,18] We proposed that **IN4** is more represented by a Au^{I}-allyl cation structure instead of Au^{III} as that formally drawn in Scheme 1 and Figure 2. Intermediate **IN4** carries two significantly different Au–C bonds, where $d_{Au\text{-}C6} = 2.14$ Å and $d_{Au\text{-}C1} = 2.02$ Å (Figure 3). These are also revealed by the computed Wiberg bond indexes (WBI).[19] Phosphorous ligand is known to has strong *trans*-influence, i.e., the bond in its *trans*-position is weakened and lengthened. But in **IN4** the Au–C1 bond in the *trans* position to PMe_3 is shorter than the Au–C6 bond, suggesting an intrinsic difference of the two bonds. Natural bond orbital (NBO)[20] analysis in **IN4** shows that Au contributes 29.1 % of the Au–C1 bonding orbital and 55.3 % of Au–C6 bonding orbital, in which the latter indicates an inverted ligand field,[21] at least for the allyl ligand (C6). Based on above result, we suggest that **IN4** is better described as a complex of Au^{I} and an allyl cation, instead of an allyl anion coordinated Au^{III} species. Similarly, **IN3** can be regarded as an allylic carbocation, as demonstrated by

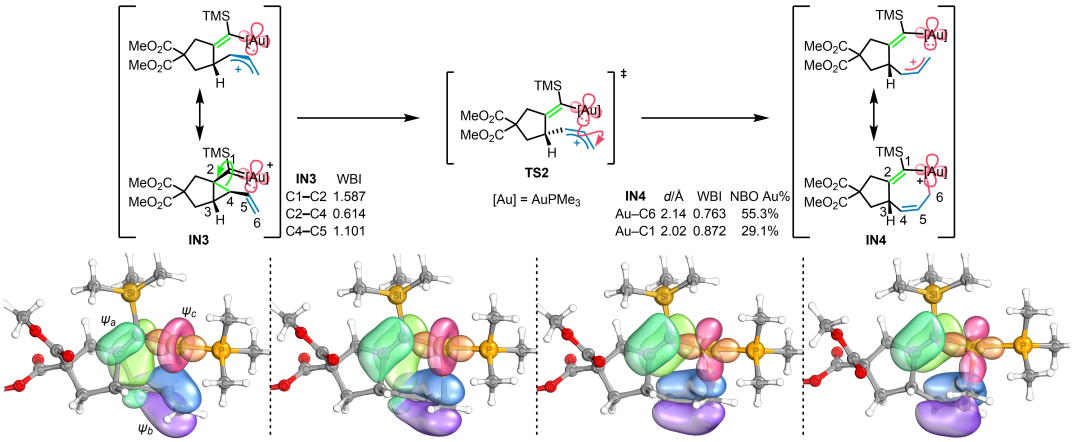


Figure 3. Wavefunction analysis of **IN3** and **IN4** and IBO analysis along the IRC of **TS2**.

NBO calculations (Figure 3). Therefore, the MCR here can be appreciated as a nucleophilic attack of Au^I to an allylic carbocation, which has a low activation free energy.

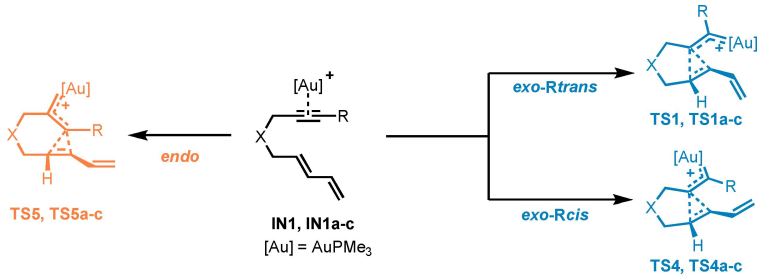
To gain more insight into the Au-Claisen rearrangement process, intrinsic bond orbital (IBO) analysis[22] were carried out along the intrinsic reaction coordinate (IRC) path of **TS2** (Figure 3). Three key IBOs, namely ψ_a, ψ_b and ψ_c were found to undergo significant displacement along the IRC (three orbitals are drawn together here and their individual changes are given in the Supporting Information). ψ_a tracks the transformation of σ(C2–C4) to π(C1–C2) in the early phase of IRC. ψ_b corresponds to delocalization of π(C5–C6) which gives an allyl type π orbital among C4, C5 and C6. ψ_c represents the transformation of Au d_{z^2} atomic orbital to σ(Au–C6) orbital. Also, it is noteworthy that the σ(Au–C6) involves mostly the $d_{x^2-y^2}$ orbital of Au. Therefore, the MCR here can be perceived as Au^I donating a pair of 5d electrons to an in situ generated allyl cation, delivering **IN4**. This also corroborates the previous description of **IN4** as an Au^I-allyl cation complex.

Tether and Substitution Effects in Au-catalyzed [4+2] Reaction

Two types of cyclopropanation (*exo* and *endo*) in yne-dienes determine the selectivity between [4+2] and enyne cycloisomerization. The relative energies of three transition states for each substrate can be appreciated by considering both electronic and steric effects of the tether (C tether corresponding to X = $C(CO_2Me)_2$, and N tether having X = NMs, Ms = methylsulfonyl. NMs is the model for NTs in DFT calculations), and R substituent in the terminal position of alkyne in the substrates.

The tether mainly affects the selectivity through electronic effect. Substrates with a N tether preferentially undergo *endo* cyclization (entry 3, Table 1), while substrates with C tether (entry 1–2) favor *exo* cyclization. These computational results match the experimental results[5,11] shown in Scheme 2. They also agree with previous calculations[23] and can be understood by polarization of alkyne's π and π* orbitals. Since N has a larger electronegativity than C atom has, the C–N(Ms)R bond possesses a

Table 1: Selected transition states for ***exo*** and ***endo*** cyclopropanation.[a]



Entry	X	R	*exo*-R*trans*	*exo*-R*cis*	*endo*
1	$C(CO_2Me)_2$	TMS	**TS1**: ***20.2***	**TS4**: 22.8	**TS5**: 27.7
2	$C(CO_2Me)_2$	Me	**TS1a**: 22.5	**TS4a**: ***16.6***	**TS5a**: 18.5
3	NMs	Me	**TS1b**: 25.9	**TS4b**: 20.2	**TS5b**: ***15.7***
4	NMs	TMS	**TS1c**: ***18.4***	**TS4c**: 19.6	**TS5c**: 19.1

[a] Calculated at ωB97M-V/def2-QZVP/SMD(DCM)//BMK-D3BJ/def2-SVP level[6–10] in kcal mol^{-1}, activation free energies are relative to their corresponding intermediates **IN1**, **IN1a–c**. Favored TSs are labelled in ***bold italic***.

lower σ* orbital than that of the C–C(CO_2Me)$_2$R bond. Consequently, the former is a stronger electron-withdrawing group (EWG). It is well-known that EWGs polarize the π orbitals in such a way that the π* orbital coefficient at EWG's β-position (C1 in Figure 4A) is larger than that at α-position (C2), while the π orbital coefficient has the opposite distribution, with a larger orbital coefficient at C2 than that at C1. The polarization leads to more stabilizing interactions of π(C1–C2)→σ*(Au–P) and π(C3–C4)→π*(C1–C2) for the *endo* transition state. Also, we propose that in **TS5b**, C1 is bent against the C–NMs direction, while in **TS4b**, the bending is on the opposite direction. Due to this, the former provides better overlap and stronger hyperconjugative stabilization from the π(C1–C2)→π*(C–N(Ms)R) interaction (Figure 4B). Reaction d shown in Scheme 2 was designed to test this prediction that substrate with a C tether and an alkyl group in the alkyne moiety gives cycloisomerization product. We were happy the new experiment agreed with the prediction.[11,12]

Substrates in entries 1 and 4 have TMS as the terminal substituent and both favor *exo* cyclopropanation, despite they have different tethers. The main reason is that these reactions go respectively through R*trans* transition states **TS1** and **TS1c**. Two stabilizing factors were proposed for the preference of **TS1** over **TS4**. Firstly, TMS is a large group and **TS4** suffers from its steric repulsion with the vinyl group. This conclusion is kept when using triphenylphosphor (PPh_3) as the ligand, probably because Ph group in the ligand is far away from the reaction center (see Table S1 in the Supporting Information). The second aspect is that the hyperconjugation effect of the C–Si bond (known as the β-silicon effect)[24] is further enhanced due to a more favored bond angle (θ) in **TS1**, stabilizing the carbocation on C2 position (Figure 4C).

In summary, yne-diene substrates with C tether prefer *exo* cyclopropanation and deliver [4+2] cycloadducts, regardless of the type of substituents in the terminal position of the yne moiety. For substrates with a N tether, the *endo* cyclization is favored and the desired [4+2] reaction cannot take place, unless the alkyne has a terminal silyl group, which will again lead to *exo* selectivity in cyclopropanation step and then give [4+2] products.

Explanation for the Absence of Metalla-Claisen Rearrangement in Rh-Catalyzed [4+2] Reaction

As mentioned in the introduction part, many metal-catalyzed [4+2] reactions have been reported. Some of them might actually occur via pathway II involving MCR when yne-dienes were used as substrates. Such an issue will be discussed here for the cationic Rh-catalyzed [4+2] reaction of yne-dienes (Figure 5).[25] Based on conformation searching, **IN8** was found to be the most stable substrate-Rh complex and thus chosen to be the energy reference. The favored pathway I starts from ligand exchange to give diene/Rh/alkyne complex **IN14**, followed by oxidative cyclometallation via **TS11** with an activation free energy of 15.6 kcal mol^{-1} (from **IN8**). This step is exergonic by 14.6 kcal mol^{-1}. Then reductive elimination via **TS12** with an activation free energy of 27.8 kcal mol^{-1} gives **IN16**, a complex of [4+2] cycloadduct and the catalyst.

Pathway II involving Rh-Claisen rearrangement starts from coordination of additional phosphine ligand (another

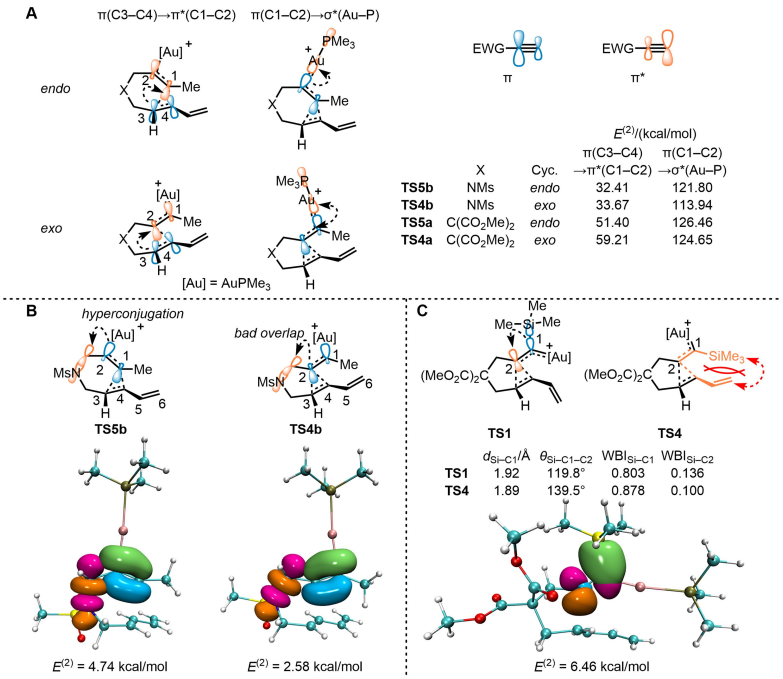


Figure 4. (A) Second-order perturbation energies ($E^{(2)}$) in **TS4a–b** and **TS5a–b**. (B) NBO overlaps and second-order perturbation energies ($E^{(2)}$) of π(C1–C2) and σ*(C2–N) in **TS4b** and **TS5b**. (C) Wavefunction analysis of **TS1** and **TS4** and overlap of σ(C1–Si) and π*(C1–C2) NBOs in **TS1**.

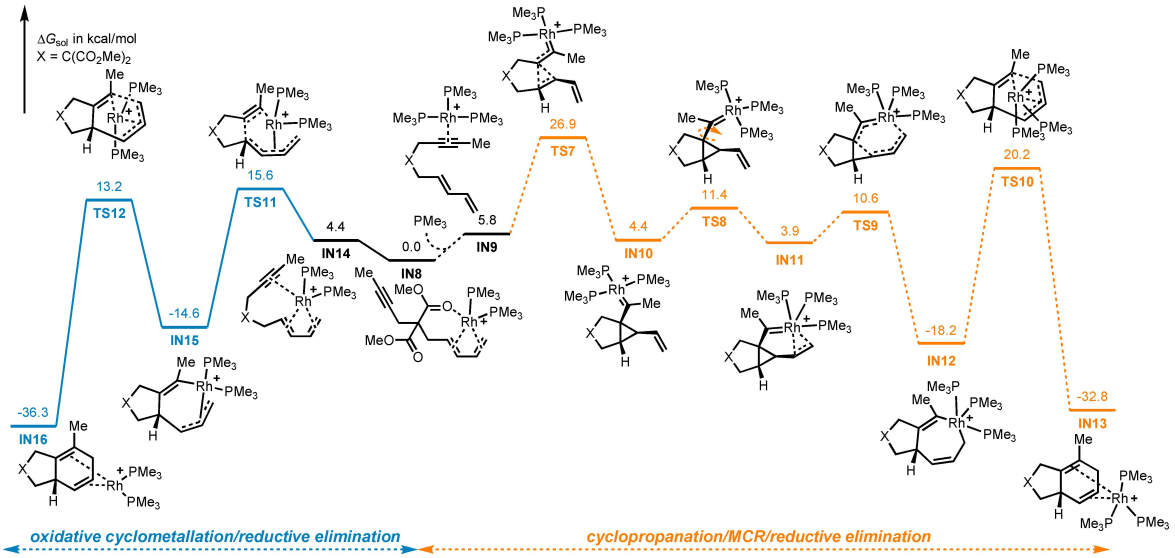


Figure 5. Gibbs free energy profiles of Rh-catalyzed [4+2] reaction at ωB97M-V/def2-QZVP/SMD(DCM)//BMK-D3BJ/def2-SVP level.[6–10]

possible process with two ligands was disfavored, see the Supporting Information). **IN9** undergoes cyclopropanation via **TS7**, with a total activation free energy of 26.9 kcal mol^{-1} (from **IN8**). **TS7** is 11.3 kcal mol^{-1} higher than **TS11** in pathway I. This can be understood by easier oxidation of Rh^{I} to Rh^{III} ($Rh^{3+}/Rh^{+} = 0.64$ V[17]) in reaching **TS11** in pathway I. Au-catalyzed cyclopropanation has an activation free energy of 16.6 kcal mol^{-1} (Table1, **TS4a**), while Rh is slightly more difficult (21.1 kcal mol^{-1} from **IN9** to **TS7**). This is consistent with experimental observations that cyclopropanation catalyzed by Rh[25,26] needs harsher conditions than that catalyzed by cationic Au.[27] The reason is attributed to stronger activation of alkyne by Au with respect to Rh (the LUMO of alkyne-Au is lower than that of alkyne-Rh, see the Supporting Information). Both factors (easy oxidation and difficult cyclopropanation for Rh compared to Au) make Rh-catalyzed [4+2] reaction favors pathway I.

Here we just simply analyze why Rh-Claisen rearrangement is also easy, even though this does not happen. Though the Rh-carbene has less character of carbocation than that of Au,[28] Rh has more coordination sites. Stronger interaction between Rh and the olefin moiety occurs, enabling Rh to further stabilize the forming allyl cation in the Rh-Claisen transition state and leading to a low barrier of 6.7 kcal mol^{-1} (**IN11** to **TS9**). Based on this, we hypothesized that many other MCRs could have similar properties and have low activation barriers when cyclopropane tether is used. For the common MCRs, introducing substituents could be a way to lower the activation free energies shown in Figure 1, as the traditional Cope and Claisen rearrangements do.

Conclusion

In summary, we provide here the first computational evidence of Metalla-Claisen rearrangement (MCR) in a real reaction, the Au-catalyzed [4+2] reaction of yne-dienes. DFT calculations showed that this [4+2] starts from Au-catalyzed *exo* cyclopropanation of alkyne to diene, followed by easy Au-Claisen rearrangement and reductive elimination. The Au-Claisen rearrangement can be regarded as a process of an Au^{I} specie attacking an allylic carbocation intramolecularly, due to the presence of a cyclopropane tether. In addition, we revealed that the tether and terminal R group in yne-dienes influence the [4+2] reaction through both electronic and steric effects. For substrates with a C tether, R can be either an alkyl or a silyl group. But R group must be a silyl group for substrates with a N tether. Otherwise, the corresponding substrate would give enyne cycloisomerization product. These conclusions are supported by experiments reported before and a new one in the present paper. In addition, the Rh-Claisen rearrangement is easy in the studied Rh-catalyzed [4+2] reaction of yne-dienes, though it is not the favored pathway. This is because the *exo* cyclopropanation of yne to diene (catalyzed by Rh), which is ahead of the Rh-Claisen rearrangement step in pathway II, is not favored compared to oxidative cyclometallation step in the traditional pathway I (Scheme 1). The present study also provides deep understandings of the mechanisms of Au and Rh-catalyzed [4+2] reactions, and the MCR processes. With these insights, we encourage chemists to design more MCR-embedded new reactions in the future.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Gold Catalysis · Metalla-Claisen Rearrangement · Reaction Mechanism · Rhodium Catalysis · [4+2] Cycloaddition

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[15] The computed activation free energy $\Delta G^{\neq}$ of the parent Cope rearrangement (using 1,1-dideuteriohexa-1,5-diene as substrate) in the gas phase is close to the experimental value, ca. 37.6 kcal mol^{-1} ($\Delta H^{\neq} = 33.5$ kcal mol^{-1}, $\Delta S^{\neq} = -13.8$ e.u. and $T = 298.15$ K). See: W. E. Doering, V. G. Toscano, G. H. Beasley, *Tetrahedron* **1971**, *27*, 5299–5306.
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Research Articles

Reaction Mechanism

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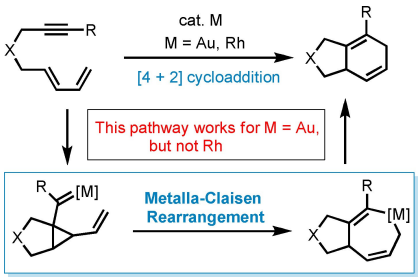
Metalla-Claisen Rearrangement in Gold-Catalyzed [4+2] Reaction: A New Elementary Reaction Suggested for Future Reaction Design



We report the first computational evidence for the involvement of metalla-Claisen Rearrangement (MCR) in the gold-catalyzed [4+2] reaction of ynedienes, together with detailed analysis of different pathways and their competition. Such a MCR does not take place when running the reaction under rhodium catalysis. The reasons behind this are hereby given.