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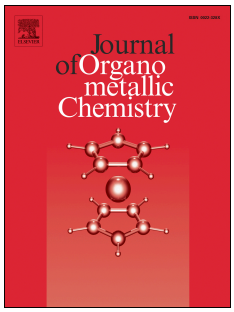

Computational insights into the mechanisms of Ru-catalyzed cycloisomerization of 2-ethynylaniline and 2-(2-propynyl)tosylanilide: The role of pyridine in assisting the metal-vinylidene formation

Abosede Adejoke Ogunlana, Jianping Zou, Xiaoguang Bao

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Computational Insights into the Mechanisms of Ru-Catalyzed Cycloisomerization of 2-Ethynylaniline and 2-(2-Propynyl)tosylanilide: The Role of Pyridine in Assisting the Metal-Vinylidene Formation

Abosede Adejoke Ogunlana, Jianping Zou,* and Xiaoguang Bao*

College of Chemistry, Chemical Engineering and Materials Science, Soochow University, 199 Ren-Ai Road, Suzhou Industrial Park, Suzhou, Jiangsu 215123, China.

E-mail: jpzou@suda.edu.cn; xgbao@suda.edu.cn

Abstract

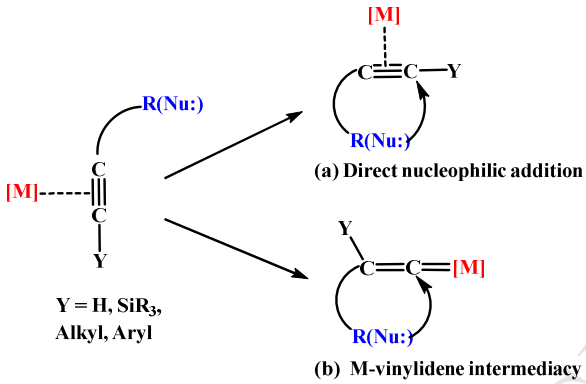
Mechanistic studies of ruthenium-catalyzed cycloisomerization of 2-ethynylaniline and 2-(2-propynyl)tosylanilide were carried out using DFT calculations. A pyridine assisted hydrogen transfer pathway was unveiled for the formation of Ru-vinylidene complex. The proposed pathway was applied to rationalize the origin of the regioselectivity, *5-exo vs 6-endo* cyclization, in the ruthenium catalyzed cycloisomerization of 2-(2-propynyl)tosylanilide. The cycloisomerization of 2-(2-propynyl)tosylanilide in the presence of pyridine produced a *6-endo* cyclized product via the Ru-vinylidene intermediate assisted by pyridine while its absence afforded a *5-exo* cyclized product via a direct nucleophilic addition. This study sheds more light on alternative pathways for reactions involving alkyne-vinylidene species.

Keywords: DFT, ruthenium, vinylidenes, regioselectivity, cycloisomerization, pyridine.

1. Introduction

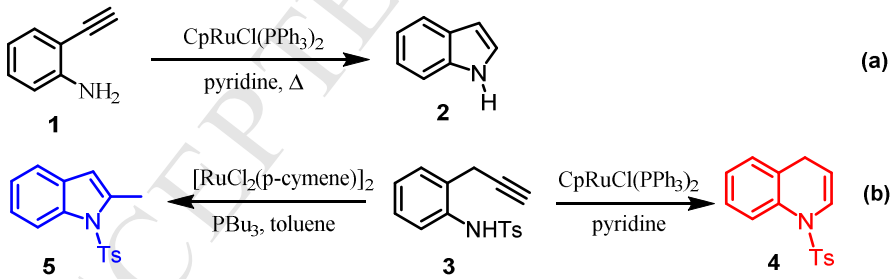
Transition-metal-catalyzed intramolecular cyclization of aromatic alkynyl amines/amides has attracted considerable research attention due to its convenient construction of nitrogen containing heterocycles [1], such as indole, quinoline and isoquinoline derivatives. This class of organic compounds is prevalent in manifold of biologically active compounds and synthetic organic materials. A large number of transition metal-based catalysts, such as Ru [2], Rh [3], Au [4], Ag [5], Cu [6], Pd [7], Ir [8], Pt [9], Zn [10], Mo, W, Cr [11], In [12], Hg [13] and Fe [14] have been reported to catalyze the intramolecular cyclization of aromatic alkynyl amines/amides. From a mechanistic point of view, these reactions can be generally classified into two types. The first type involves taking advantage of the tethered nucleophilic group of alkynyl amines to undergo the direct nucleophilic addition to the alkyne moiety after π-alkyne activation by transition metals (Scheme 1a) [15]. For instance, the group of Sakamoto proposed that a direct nucleophilic addition of the amine moiety in 2-ethynylaniline to the terminal alkyne carbon occurred in the Cu-catalyzed cyclization of 2-ethynylamines to form indoles [15a]. Moreover, a combined experimental and computational study carried out by the group of Gevorgyan [15b] supported the direct *5-endo-dig* cyclization over the metal-vinylidene formation in Au-catalyzed cycloisomerization of propargylic pyridines. This direct cyclization is also consistent with the mechanism proposed by the group of Wong [15c, 15d] in Ru-catalyzed cycloisomerization of propargylic pyridines using DFT calculations. The second type employs the intermediacy of metal-vinylidene species of terminal alkynylamines which subsequently undergo cyclization (Scheme 1b) [16]. In this regard, the Tanaka group [16a] has reported the intermediacy of Rh-vinylidenes in Rh-catalyzed cycloisomerization of 2-silylethynylphenols and 2-silylethynylanilines to give 3-silylbenzofurans and 3-silylindoles, respectively. Meanwhile, a great number of reports have been well documented for the formation of the key metal-vinylidene intermediate via the direct 1,2-H shift [17]. For example, the direct 1,2-H shift has been investigated for the formation of metal-vinylidene intermediate by Vastine and Hall [17f] using DFT calculations. A theoretical study on the isomerization of internal alkynes to vinylidenes via a direct 1,2-aryl shift has been carried out by Takano and co-workers for group 8 transition-metal complexes [17g]. More recently, the Saito's group [17h] has reported the formation of

Ru-vinylidene intermediate by 1,2-carbon migration in ruthenium catalyzed cycloisomerization of 2-alkynylanilides.



Scheme 1. Two mechanistic pathways for the transition-metal-catalyzed cycloisomerization of alkynylamines to synthesize nitrogen containing heterocycles.

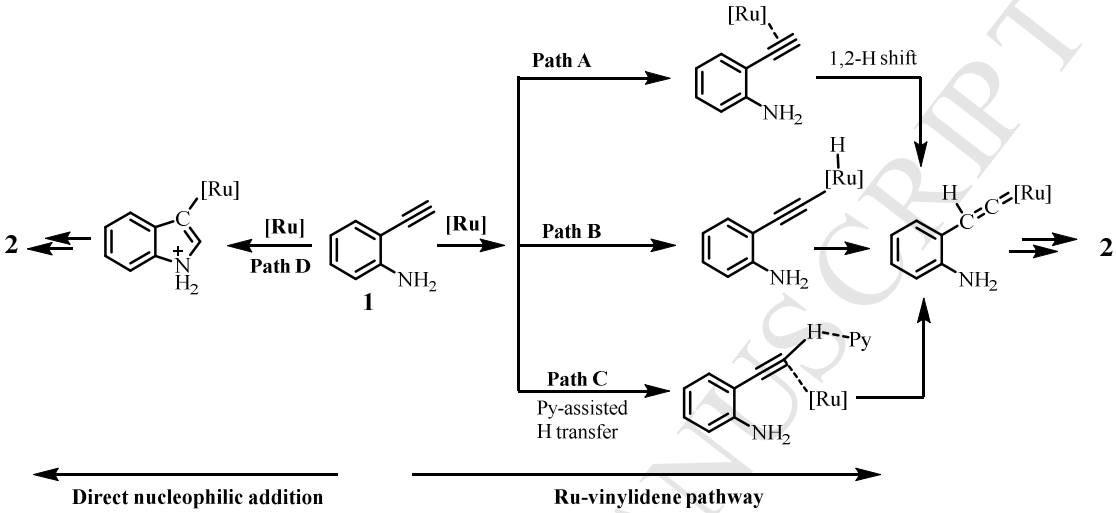
In particular, the Saá's group [2c] reported an efficient ruthenium(II) catalyzed cycloisomerization of 2-ethynylaniline **1** which led to the synthesis of indole using pyridine as solvent (Scheme 2a). It was interesting that the same ruthenium catalyst catalyze the cycloisomerization of 2-(2-propynyl)tosylanilide **3** in the presence of pyridine to produce a dihydroquinoline product **4,** while the cycloisomerization of **3** by another Ru(II) catalyst, $[RuCl_2(p\text{-cymene})]_2$, afforded an indole product **5** in the absence of pyridine (Scheme 2b).



Scheme 2. The Ru(II)-catalyzed cycloisomerizations of 2-ethynylaniline and 2-(2-propynyl)tosylanilide.

Based on the intermediacy of Ru-vinylidene complex, the mechanism of the reaction might follow the commonly proposed direct 1,2-H shift (Scheme 3, *path A*). [16, 17a-e] Also, studies [17a-e] have shown that the oxidative addition of alkyne C-H bond into Ru center to afford a hydrido-alkynyl complex, followed by 1,3-H shift is another viable pathway (*path B*). In addition, we envisaged that pyridine as a solvent could also act as a proton shuttle in assisting the cycloisomerization reaction. This led us to propose a new mode of Ru-vinylidene formation via

the pyridine assisted hydrogen transfer (PAHT) pathway (*path C*). On the contrary, the mechanism could bypass the formation of the Ru-vinylidene complex to undergo a direct nucleophilic addition after the initial activation of the alkyne moiety by the ruthenium catalyst, to afford the indole product (*path D*) [15].



Scheme 3. Possible mechanistic pathways for the Ru-catalyzed cycloisomerization of **1**.

In order to better understand the mechanism of the ruthenium catalyzed cycloisomerization reactions and the reason(s) for the different regioselective products obtained, a comprehensive mechanistic study of the ruthenium catalyzed cycloisomerization of 2-ethynylaniline and 2-(2-propynyl)tosylanilide was carried out by DFT calculations. An indirect mode of Ru-vinylidene formation via the PAHT pathway was proposed in this work. In addition, the proposed pathway could be applied to explain the origin of the regioselectivity, *5-exo vs 6-endo* cyclization, in the ruthenium catalyzed cycloisomerization of 2-(2-propynyl)tosylanilide.

2. Computational Method

All calculations were carried out using Gaussian 09 [18] program package with the ωB97XD [19] density functional method which includes empirical dispersion and long range correction. This method among others has been reported to be effective for computations involving ruthenium metal [20]. The LANL2DZ basis set together with LANL2DZ pseudo potential [21] were utilized for the ruthenium atom while the 6-31G(d,p) basis set [22] was employed for other atoms in the geometry optimization. Vibrational frequency analysis was carried out on the optimized geometry to characterize them as minima (no imaginary frequency) or transition states (one imaginary

frequency). Intrinsic reaction coordinate calculations [23] confirmed that the optimized transition states connect to their respective reactants and products. The Gibbs free energies were evaluated at 298.15 K and 1 atm. To consider solvation effects, single-point energy calculations using the SMD solvation model [24] were performed based on the optimized gas-phase geometries. Larger basis set (LANL2TZ(f) for Ru atom and 6-311++G(d,p) for other atoms) were utilized for such single-point energy calculation. In accordance with the experimental conditions, pyridine and toluene solvents were employed for reactions involving alkynyl amine and amide respectively. It is known that DFT calculations could overestimate the entropic effect [25]. The translational entropy correction in solution was incorporated using the method proposed by Whitesides et al. [26] Unless specified otherwise, the solvation Gibbs free energy was used for discussion and it was obtained from the addition of the solvation single-point energy and the thermal correction to the Gibbs free energy. In order to reduce computational costs, the simplified phosphine ligand PMe_3 was used to replace the experimentally used PPh_3/PBu_3 ligand. The CYLview software was employed to show the 3D structures of the studied species [27].

3. Results and Discussion

*3.1. Mechanistic study of the Ru-catalyzed cycloisomerization of **1** to form indole product.*

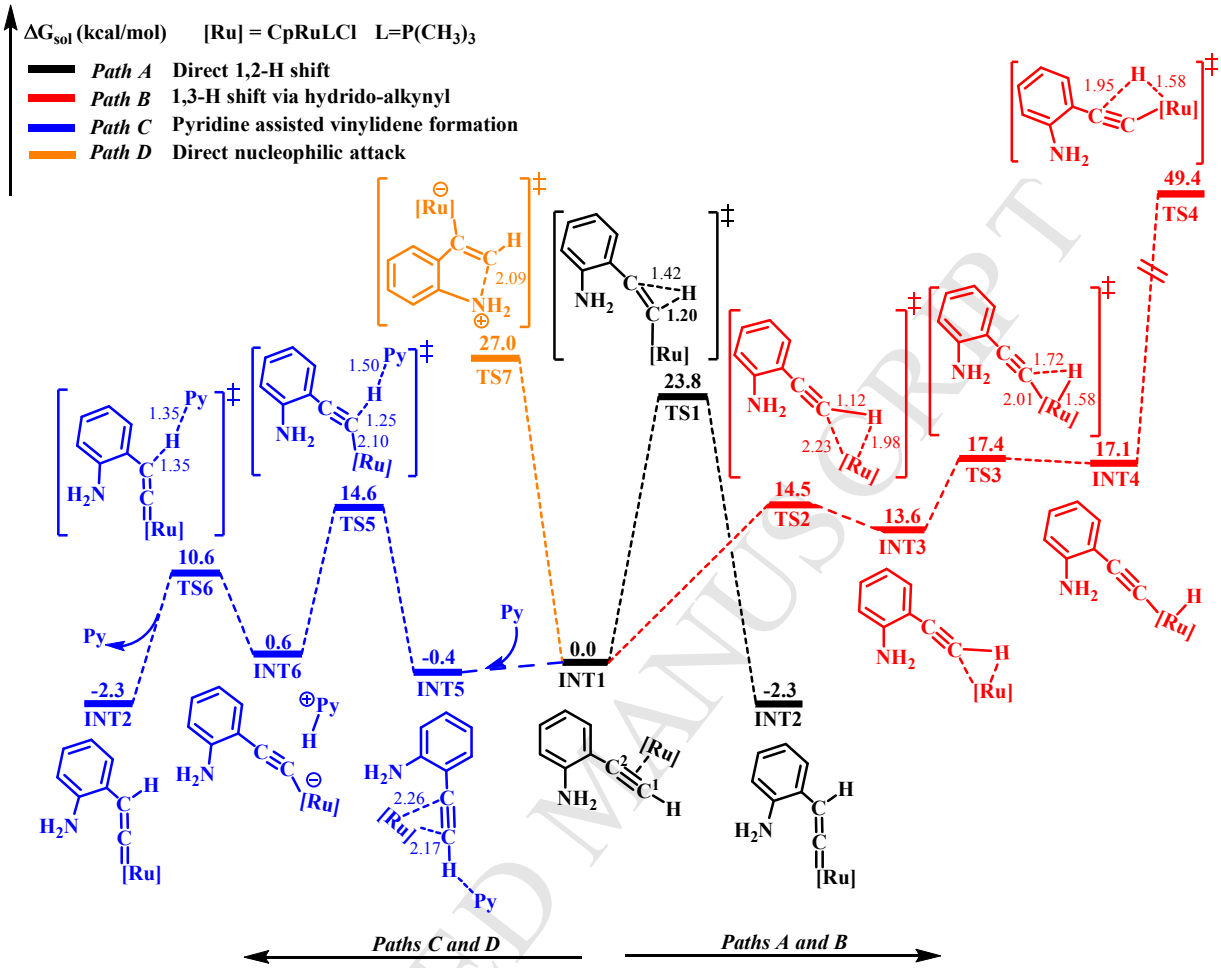
The crucial Ru-vinylidene intermediate has been proposed to account for the formation of indole product via the cycloisomerization of **1**. Initially, the formation of the Ru-vinylidene intermediate via the commonly proposed direct 1,2-H shift was computationally explored. The coordination of the alkyne moiety in **1** to the ruthenium catalyst forms an initial Ru-ethynylaniline complex **INT1,** which is characterized by a π-alkyne binding mode. Subsequently, a direct 1,2-H shift from the terminal carbon, $\mathbf{C^1}$, to the internal carbon, $\mathbf{C^2}$, would afford the Ru-vinylidene complex **INT2.** The transition state for this shift was located as **TS1**, in which the H…$\mathbf{C^1}$ and H…$\mathbf{C^2}$ bond distances are stabilized to 1.20 Å and 1.42 Å respectively. The energy barrier for this step was calculated to be 23.8 kcal/mol and the formed **INT2** is thermodynamically stable, being exergonic by 2.3 kcal/mol (Fig. 1, *path A*).

Another pathway leading to the formation of the Ru-vinylidene intermediate is the 1,3-H shift of a hydride-alkynyl complex [17d-e]. In this pathway, the initial π-bound substrate **INT1** may undergo slippage towards the σ-(C-H)-binding mode with the metal center, forming **INT3** via **TS2**

with a barrier of 14.5 kcal/mol relative to **INT1**. Next, the C-H bond oxidative addition (OA) onto the Ru center might proceed via **TS3** to offer a hydrido-ruthenium complex, **INT4.** The free energy of the OA step was calculated to be 17.4 kcal/mol relative to **INT1**. Subsequently, 1,3-H shift from Ru center to $\mathbf{C^2}$ might follow to generate the Ru-vinylidene complex. The transition state for the 1,3-H shift was located as **TS4** and the energy barrier was predicted to be 49.4 kcal/mol relative to **INT1**, implying that this step is kinetically very unfavorable. Similar energy demanding for 1,3-H shift has previously been reported by Angelis and co-workers (51.1 kcal/mol) [17d] in the DFT study of alkyne to vinylidene rearrangement of $[(Cp)(PMe_3)_2Ru(HC{\equiv}CH)]^+$. Overall, the 1,3-H shift of the hydride-alkynyl intermediate has much higher energy barrier than the direct 1,2-H shift pathway.

The third pathway leading to the Ru-vinylidene intermediate could take place via an indirect 1,2-H shift, assisted by the pyridine solvent. In the presence of pyridine, an initial complex **INT5** is formed in a slightly exergonic manner. Thereafter, the deprotonation of $\mathbf{C^1}$ by pyridine would occur via **TS5** to produce **INT6**. Featuring in this transition state is that the $\mathbf{C^1}$…H distance is lengthened to 1.25 Å while the H…N(pyridine) distance is shortened to 1.50 Å. In addition, the $\mathbf{C^1}$-Ru bond distance is stabilized to 2.10 Å. Subsequent protonation of the $\mathbf{C^2}$ by the pyridinium ion in **INT6** would generate the Ru-vinylidene complex **INT2** via **TS6**. The energy barrier for the pyridine assisted deprotonation step was calculated to be 14.6 kcal/mol, which is 9.2 kcal/mol lower than that for the direct 1,2-H shift. These results suggest that the PAHT pathway might be viable for the cycloisomerization reaction considered.

In addition, some reports have supported the electrophilic cyclization of nucleophile-tethered alkynes after the C≡C activation [15]. In this regard, the direct nucleophilic addition of the amine functional group in **INT1** to the $\mathbf{C^1}$ via **TS7** was explored computationally. The results indicate that the nucleophilic addition (NA) step would require the energy barrier of 27.0 kcal/mol (*path D*, Fig. 1). This calculated barrier is 12.4 kcal/mol higher than that along the PAHT. Among the various possible pathways explored for this reaction, it can be assumed that the mechanism of the Ru-catalyzed cycloisomerization might proceed along *path C* owing to the lowest energy barrier to afford a Ru-vinylidene intermediate in an exergonic manner.



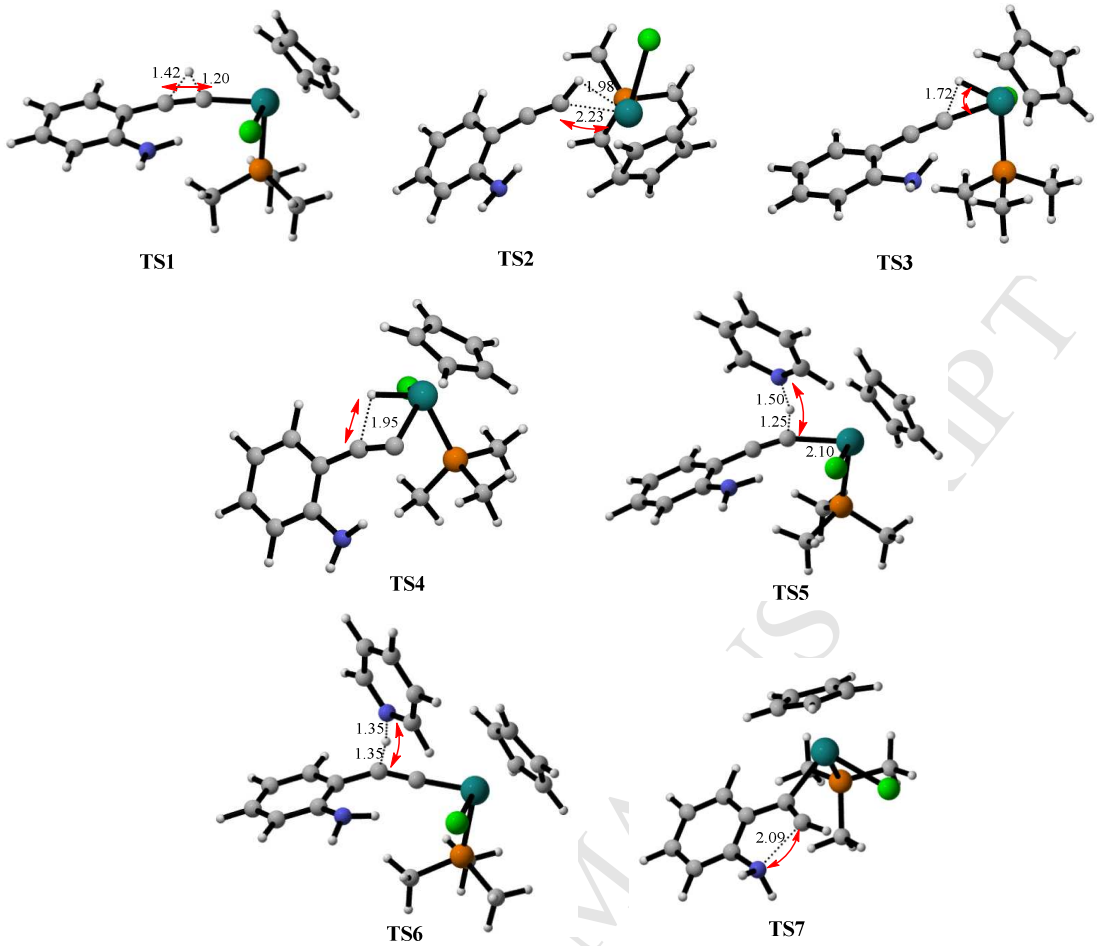


Fig. 1 Energy profiles of the various pathways considered in the Ru-catalyzed cycloisomerization of **1**. Bond distances are shown in Å and the atomic movements associated with the imaginary frequency are indicated in red arrows.

After the formation of **INT2**, the presence of an incoming pyridine would afford an intermediate **INT7**, from which NA of the amine moiety to $\mathbf{C^1}$ could occur in an intramolecular manner to furnish a *5-endo* cyclized intermediate **INT8** through a transition state, **TS8**. The NA step requires the energy barrier of 6.2 kcal/mol relative to **INT2**. Subsequently, pyridine assisted proton transfer from the ammonium nitrogen to $\mathbf{C^1}$ would occur from **INT8** to afford the product complex **INT10**, from which the indole product is released (Fig. 2). This computational result suggests that the presence of pyridine could assist in lowering the activation barrier of the formed Ru-vinylidene intermediate. Therefore, the ruthenium catalyzed cycloisomerization of **1** would follow the stepwise PAHT pathway, with the intermediacy of Ru-vinylidene complex.

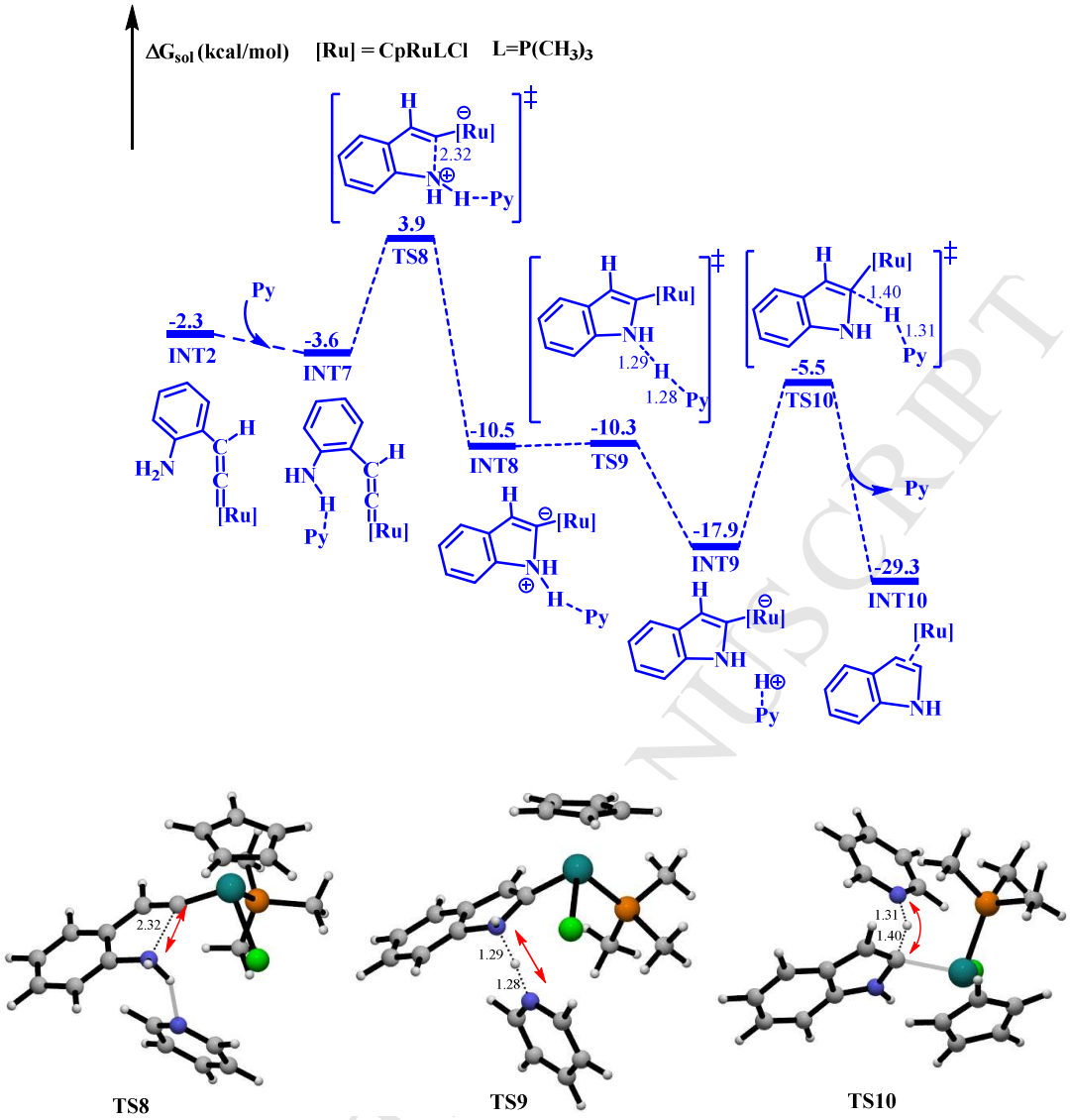
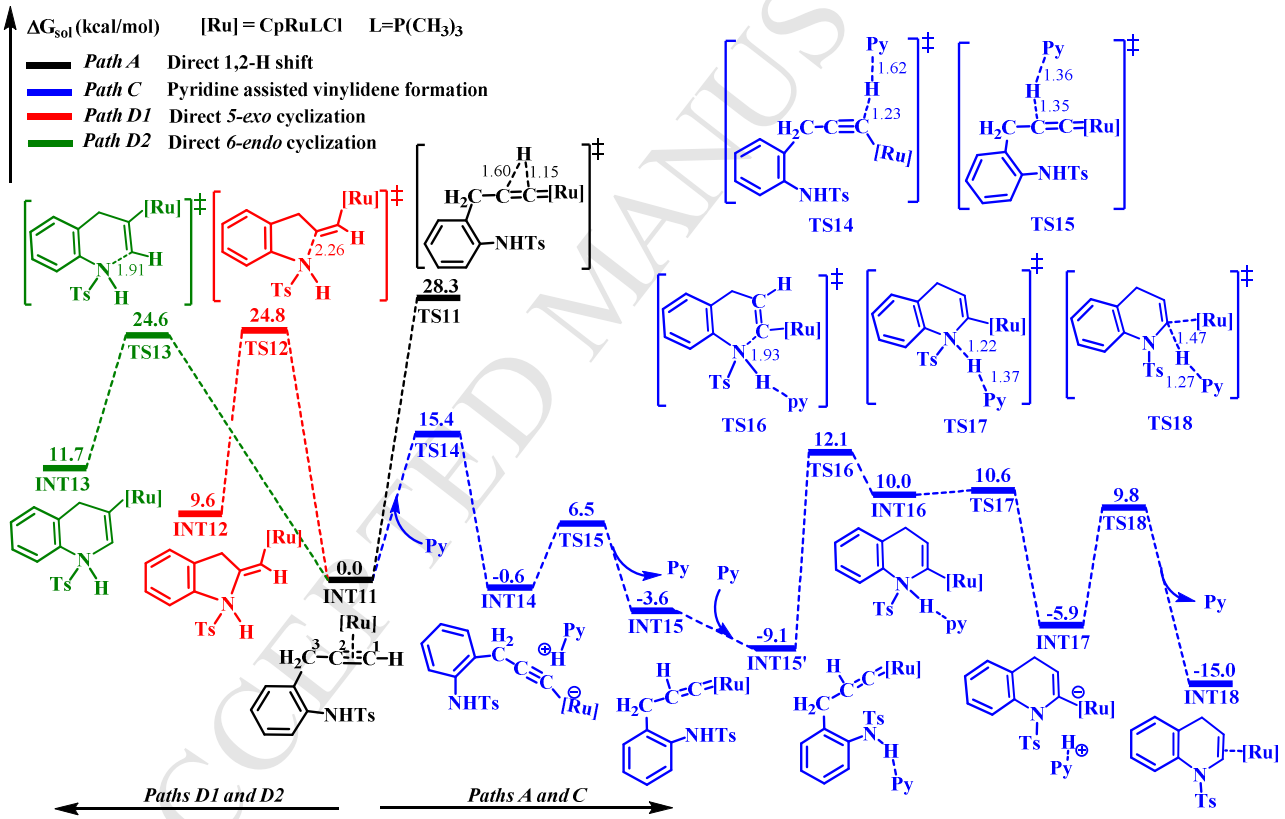


Fig. 2 Energy profile from the generated Ru-vinylidene intermediate to the final indole product. Bond distances are shown in Å and the atomic movements associated with the imaginary frequency are indicated in red arrows.

3.2. Origin of the regioselective Ru-catalyzed cycloisomerization of 2-(2-propynyl)tosylanilide

The unveiled role of pyridine in assisting the formation of the Ru-vinylidene complex could be applied to rationalize the origin of the regioselectivity in the Ru-catalyzed cycloisomerization of aromatic bis-homopropargylic amide to form dihydroquinoline product [2c]. Computational results showed that the direct 1,2-H shift from $\mathbf{C^1}$ to $\mathbf{C^2}$ of **INT11** will require the energy barrier of 28.3 kcal/mol to generate the key Ru-vinylidene intermediate **INT15** via **TS11** in a concerted

manner (Fig. 3, *path A*). In addition, from the initial coordination of the alkyne moiety to the Ru-catalyst, a π-alkyne complex **INT11**, the direct NA of the amide group to $\mathbf{C}^2$ via **TS12** could generate a *5-exo* cyclic **INT12** (*path D1*). The activation barrier was predicted to be 24.8 kcal/mol and the resulting **INT12** was formed in an endergonic manner. Likewise, the formation of a *6-endo* cyclic intermediate via the direct NA of the amide group to $\mathbf{C}^1$ was another possible pathway examined (*path D2*). The located transition state **TS13** would require an activation barrier of 24.6 kcal/mol to afford *6-endo* cyclic **INT13**. These results suggest that the formation of the Ru-vinylidene complex intermediate via the direct 1,2-H shift is unfavorable.



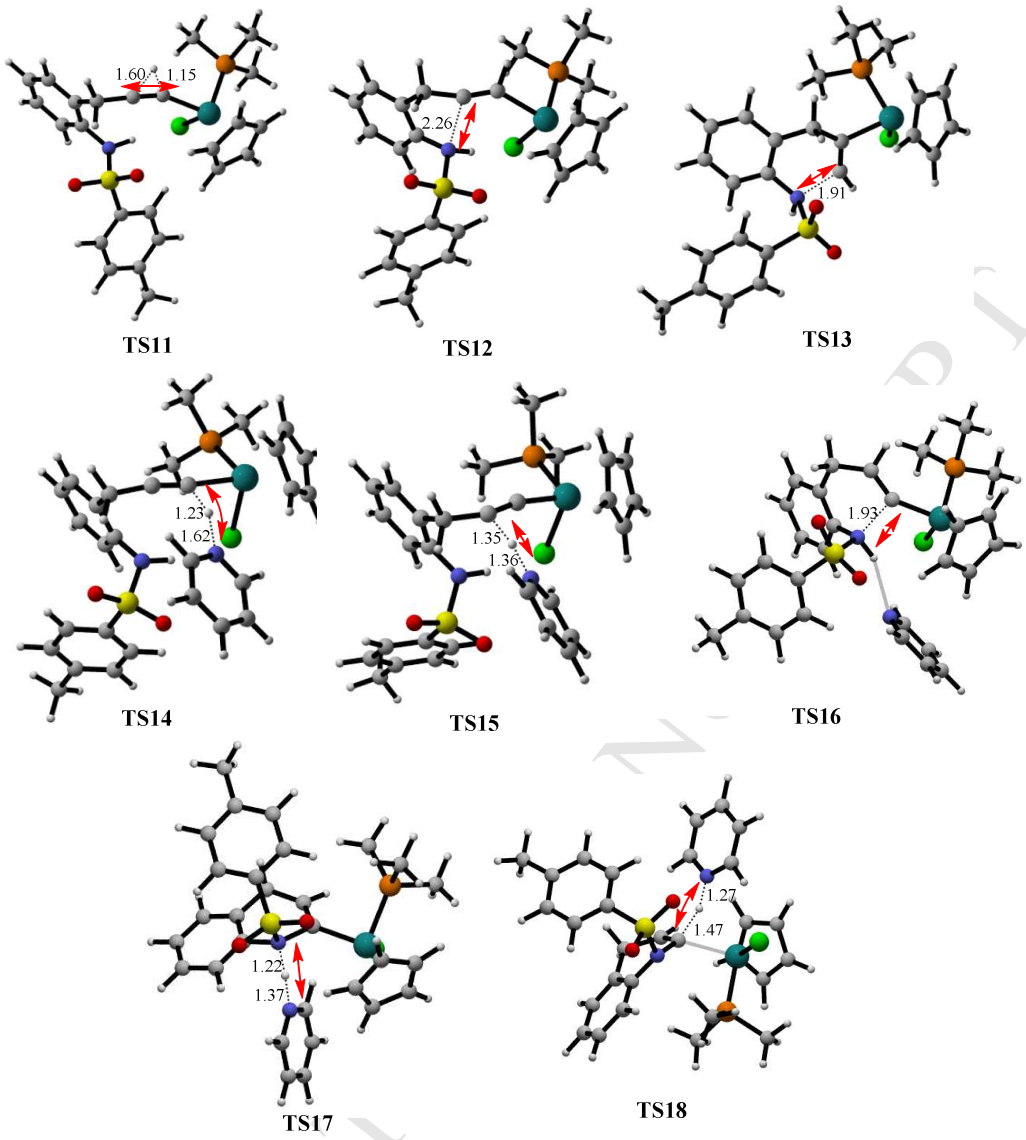


Fig. 3 Energy profile of the regioselective cycloisomerization of **3** to **4**. Bond distances are shown in Å and the atomic movements associated with the imaginary frequency are indicated in red arrows.

Alternatively, the key Ru-vinylidene intermediate could be formed via the assistance of pyridine solvent. The deprotonation of $\mathbf{C^1}$ by pyridine (**TS14**) and the protonation of $\mathbf{C^2}$ via **TS15** would generate **INT15**. The highest $\Delta G^{\ddagger}$ for this path via **TS14** was calculated to be 15.4 kcal/mol (Fig. 3, *path C*), indicating that the pyridine assisted formation of the Ru-vinylidene complex is more favorable than the direct 1,2-H shift pathway. Thereafter, NA of the amide moiety to $\mathbf{C^1}$ in the presence of pyridine would take place via **TS16** to generate a 6-membered ring intermediate **INT16**. The predicted barrier for this step was calculated to be 15.7 kcal/mol relative to **INT15**.

Subsequently, pyridine assisted proton transfer from the amide group to $\mathbf{C^1}$ would take place via **TS17** and **TS18** to generate the product complex **INT18**, from which the final dihydroquinoline product is liberated.

Therefore, the mechanism of the cycloisomerization of **3** to **4** would follow the PAHT pathway to generate the dihydroquinoline product via the intermediacy of a Ru-vinylidene complex. This is in agreement with the experimental findings reported by Saá's group [2c].

For the cycloisomerization of 2-(2-propynyl)tosylanilide (**3**) to 2-methylindole **(5**) in the absence of pyridine, the aforementioned routes were analyzed. Initially, the cymene ligand in the ruthenium catalyst would be displaced by an incoming phosphine ligand to afford a π-alkyne complex **INT19**. Next, the direct NA via **TS19** to afford a *5-exo* cyclic **INT20** was investigated from **INT19.** Computational result showed that the energy barrier for this route is 17.2 kcal/mol relative to **INT19** and the **INT20** formed is thermodynamically stable (Fig. 4). In addition, the formation of a *6-endo* cyclic intermediate via the direct NA was also considered. The transition state was located as **TS20**. The energy barrier for the formation of *6-endo* cyclic intermediate was predicted to be 28 kcal/mol, which is ca. 11 kcal/mol higher than that of the formation of *5-exo* cyclic intermediate. Moreover, the formed **INT21** is thermodynamically unstable relative to **INT19**. Thus, for **3**, the intramolecular nucleophilic attack to $\mathbf{C^2}$ to afford the *5-exo* cyclic intermediate is more likely to occur than attack to $\mathbf{C^1}$.

In the absence of pyridine, the direct 1,2-H shift pathway was explored to yield the intermediacy of Ru-vinylidene, from which the *6-endo* cyclized **INT23** might be produced. The corresponding transition state was located as **TS21**, in which the H…C^1 distance is lengthened to 1.16 Å while the H…C^2 distance is shortened to 1.59 Å. The energy barrier was calculated to be 22.1 kcal/mol, which is ca. 5 kcal/mol higher than the direct NA pathway to form the *5-exo* cyclic intermediate (Fig. 4). Therefore, both the direct *6-endo* cyclization and the Ru-vinylidene pathway are less favorable than the direct NA pathway leading to the *5-exo* cyclic intermediate. Hence, in the absence of pyridine, the mechanism of the Ru-catalyzed cycloisomerization of **3** would regioselectively afford 2-methyl indole via the direct NA pathway.

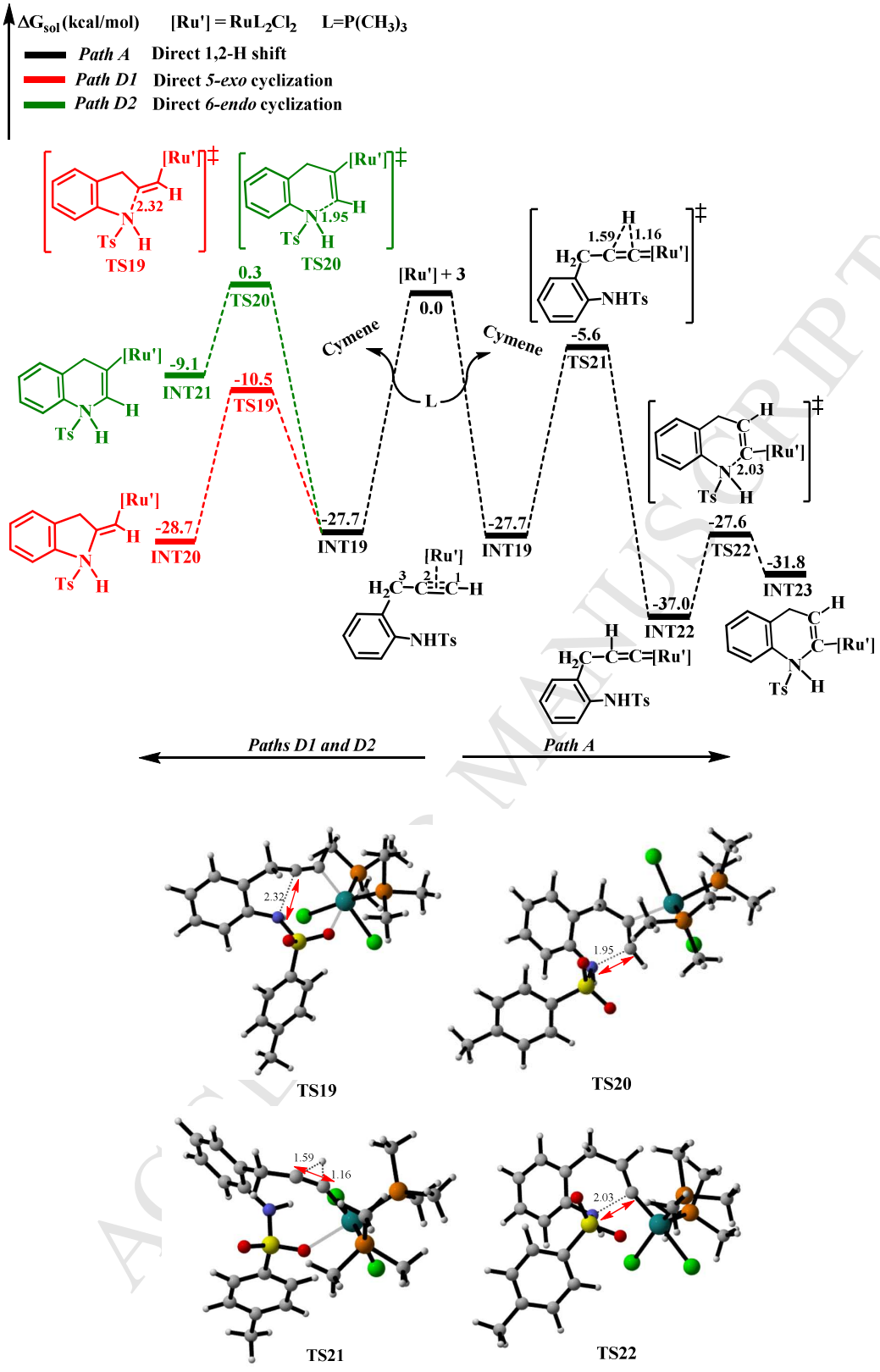


Fig. 4 Energy profile for the regioselective cycloisomerization of **3** to **5**. Bond distances are shown in Å and the atomic movements associated with the imaginary frequency are indicated in red arrows.

To elucidate the regioselectivity of **3** to **5**, the natural population analysis (NPA) for charge distribution was carried out. The results revealed that the slightly negatively charged $\mathbf{C^2}$ of **3** is readier to undergo the direct NA than the more negatively charged $\mathbf{C^1}$ (-0.01 *vs* -0.26 e respectively). Also, the $\mathbf{C^2}$ in **INT19** was found to be slightly positively charged (0.01 e). This suggests that the $\mathbf{C^2}$ of **3** will be preferably attacked by the nucleophile. In addition, frontier molecular orbital (FMO) analysis was carried out on the structures transforming from **3** to **INT20** (Fig. 5). The LUMO of **INT19** is partially located on the $\mathbf{C^2}$ with a small magnitude, and transiting to **TS19** shows that there is an increase in magnitude of the LUMO on the same carbon atom. This implies that $\mathbf{C^2}$ is more electrophilic than $\mathbf{C^1}$ thus, readier to undergo the direct NA. Therefore, in the absence of pyridine, the formation of the Ru-vinylidene complex becomes less favourable in comparison with the direct NA at $\mathbf{C^2}$, which would make the formation of the *5-exo* cyclic intermediate a feasible process. This also is in consonant with the experimental report [2c].

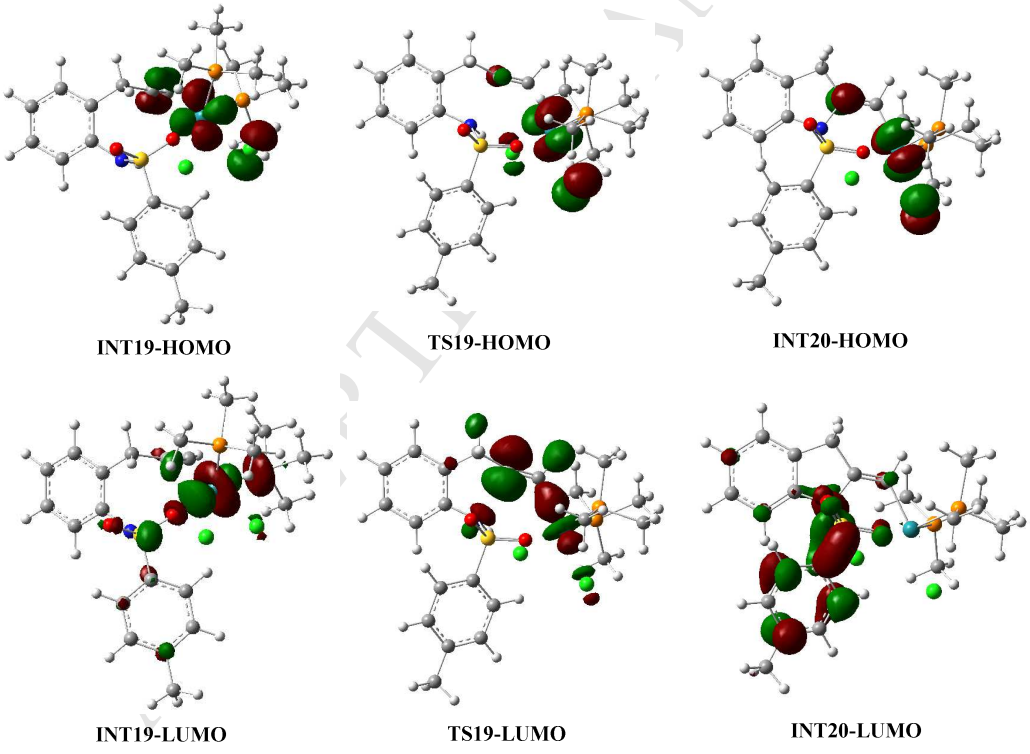


Fig. 5 FMO analysis for the transformation of **INT19** to **INT20** (isovalue=0.05).

4. Conclusion

Mechanistic studies of the ruthenium-catalyzed cycloisomerization of 2-ethynylaniline and 2-(2-propynyl)tosylanilide were carried out using DFT calculations. For the cycloisomerization of 2-ethynylaniline to indole, a new mode of Ru-vinylidene formation via the pyridine assisted hydrogen transfer (PAHT) pathway was proposed. Computational results showed that this pathway is more favorable than the previously reported pathways for the transition-metal-catalyzed cycloisomerization of alkynylamines/amides. Then, the newly proposed pathway was applied to explain the origin of the regioselectivity, *5-exo vs 6-endo* cyclization, in the ruthenium catalyzed cycloisomerization of 2-(2-propynyl)tosylanilide. The results revealed that in the presence of pyridine, the *6-endo* product would be formed via the Ru-vinylidene intermediate generated along the PAHT pathway while the absence of pyridine led to a switch in the reaction mechanism, allowing the formation of a *5-exo* product via the direct nucleophilic addition pathway. This study not only sheds more light on alternative pathways for reactions involving alkyne-vinylidene species but also underscores the effect of reaction modifications towards attaining different regioselectivities in cycloisomerization reactions.

Acknowledgments

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- A pyridine assisted hydrogen transfer pathway to form the Ru-vinylidene complex is unveiled.
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- In the absence of pyridine, the direct nucleophilic addition pathway is favourable to afford a *5-exo* cyclized product.