Ruthenium-Catalyzed Cycloisomerization of 1,6-Diynes with Styryl Terminals Leading to Indenylidene Cycloalkanes

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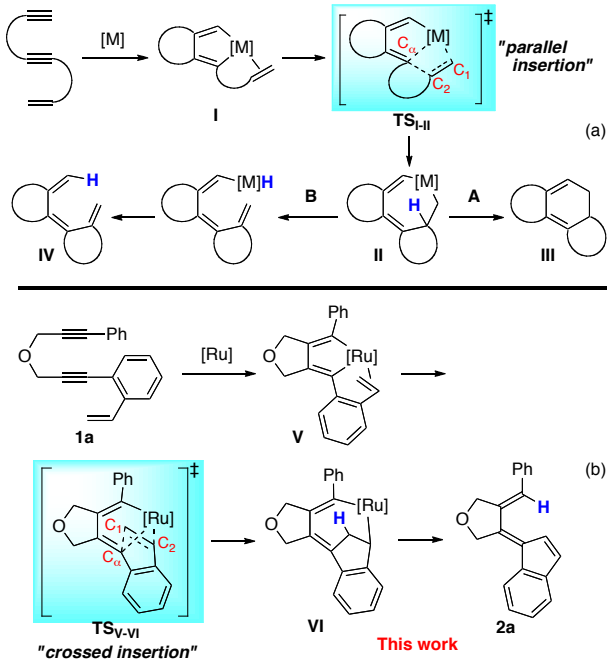
ABSTRACT: In the presence of a neutral ruthenium catalyst, Cp*RuCl(cod), 1,5,10-enediynes bearing a styryl terminal underwent cycloisomerization to afford exocyclic 1,3-dienes with an indenylidene moiety. The reaction mechanisms are proposed based on the results of control experiments and density functional calculations. The transformations of the obtained cyclization products were also investigated to demonstrate the synthetic potential of this method.

KEYWORDS: Ruthenium catalyst, cycloisomerization, enediyne, indenylidenecycloalkane, spirocycle.

Introduction

Insertion of an unsaturated molecule into the carbon–metal bond of a metallacycle intermediate is the fundamental step of diverse [*m* + *n* + *o*] cycloadditions mediated by transition-metal (TM) complexes.[1] Among them, the TM-catalyzed [2 + 2 + 2] cyclization of enediynes is a powerful method that provides access to fused cyclohexadienes, which can then be readily functionalized to afford diverse molecular scaffolds (Scheme 1a, path A).[2] In this synthetically valuable transformation, a pendant alkene is normally inserted into the adjacent carbon–metal bond of a metallacyclopentadiene intermediate in a parallel fashion to form two new bonds: M–C_1 and Cα–C_2 (**I** → **TS$_{I\text{-}II}$** → **II**). Thus, subsequent C–C bond-forming reductive elimination from the resultant metallacycloheptadiene intermediate **II** affords a fused cyclohexadiene product **III**. Alternatively, β-H elimination from **II** is followed by C–H bond-forming reductive elimination to generate 1,3,5-triene **IV** (Scheme 1a, path B). However, the latter cycloisomerization process has rarely been reported.[2g,3] In the literature precedents of such a [2 + 2 + 2] cyclization, tethers with more than three atoms have been widespread as shorter tethers suffer from a significant energetic penalty associated with the formation of strained small rings.[4]

In contrast, we serendipitously discovered that relevant 1,5,10-enediyne **1a** possessing an *o*-phenylene tether between the central alkyne and the terminal alkene underwent an unprecedented cycloisomerization at ambient temperature in the presence of neutral ruthenium catalyst Cp*RuCl(cod) (Cp* = η^5-C_5Me_5, cod = 1,4-cyclooctadiene), leading to indenylidenecycloalkane product **2a** (Scheme 1b). This reaction mode is strikingly different from conventional enediyne cycloisomerization as depicted in Scheme 1a. Moreover, the indenylidene formation from the 1,5-enyne moiety is distinctive from previous 1,5-enyne cycloisomerization and enyne metathesis: the former usually generates 6-*endo* cyclization products or bicyclo[3.1.0]alkenes and the latter involves C–C bond fission.[5,6] The theoretical investigation into the mechanism of this intriguing transformation (*vide infra*) suggested that alkene insertion occurred in a crossed manner with concomitant formations of M–C_2 and Cα–C_1 bonds (**V** → **TS$_{V\text{-}VI}$** → **VI**) and that the resultant unusual metallacycloheptadiene **VI** ultimately converted into **2a** *via* 1,5-H transfer.



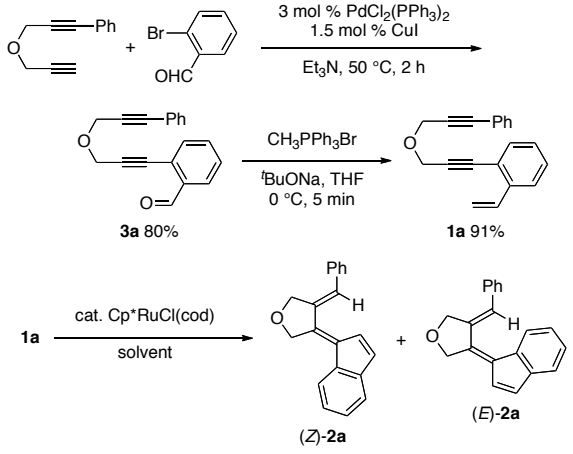
Scheme 1. (a) Conventional [2 + 2 + 2] cyclization (path A) and cycloisomerization (path B) of enediynes, and (b) newly discovered cycloisomerization of 1,5,10-enediyne **1a** leading to indenylidene cycloalkane **2a**.

Because cycloisomerizations proceed with partial reorganization of atom connectivity (isomerization), all atoms contained in the starting material are retained in the final product.[7] Therefore, cycloisomerizations have received considerable

attention as perfectly atom-efficient chemical transformations. As a TM-catalyzed cycloisomerization leading to indenes, Rautenstrauch-type pentannulations involving an initial 1,2-group shift have been developed,[8] due to the prime importance of indene scaffolds found in bioactive molecules and materials.[9] However, our cycloisomerization significantly differs from previous methods as it has a distinct reaction mode as mentioned above and provides a ready access to unique exocyclic dienes containing an indenylidene moiety, which can be readily transformable, from simple acyclic enediynes. Herein, we present our study on unprecedented cycloisomerization of 1,6-diynes with a styryl terminal *via* an unusual mode of alkene insertion into the ruthenacycle intermediate.

Results and Discussion

The preparation of substrates is straightforward: for example, the representative enediyne **1a** was obtained in two steps, Sonogashira coupling of the corresponding 1,6-diyne with *o*-bromobenzaldehyde and subsequent Wittig reaction of **3a**, as outlined in Scheme 2. Enediyne **1a** was then subjected to our previous [2 + 2 + 2] cyclization conditions using ruthenium complex Cp*RuCl(cod) as a catalyst since this complex is readily accessible and generally provides good results in our previous studies.[10] (10 mol %) and **1a** were stirred in 1,2-dichloroethane (DCE) at room temperature for 24 h, affording new products (*Z*)- and (*E*)-**2a** with a *Z*/*E* ratio of 60:1 (Table 1, entry 1). Purification with silica gel chromatography afforded **2a** in 71% yield. The same reaction was conducted in DCE for 10 h and analyzed the *Z*/*E* ratio at a half conversion. Accordingly, the ratio was estimated as 6.7:1 and therefore, it is assumed that the longer reaction time caused the selective decomposition of the minor isomer to increase the *Z*/*E* ratio to 60:1.



Scheme 2. Preparation and cycloisomerization of enediyne **1a**.

The effect of solvents was examined to speed up the reaction and improve the product yield. In polar solvents such as THF, acetonitrile, and DMF, the reaction was accelerated to give higher yields although the stereoselectivity was considerably diminished (entries 2–5). In particular, the reaction was completed within 3 h in DMF at room temperature, even with a decreased catalyst loading (5 mol %), to afford inseparable mixtures of (*Z*)- and (*E*)-**2a** in high combined yields and a *Z*/*E* ratio of 5:1 (entry 5). The use of a protic solvent, MeOH, resulted in low conversion and **2a** was not detected. On the other hand, the use of a less polar solvent, toluene, resulted in a good yield and improved stereoselectivity, even though the reaction required 6 h to proceed to completion (entry 6). When the reaction was performed in toluene at 50 °C, **1a** was completely consumed within 2 h, affording (*Z*)- and (*E*)-**2a** in 89% combined yield without lowering stereoselectivity (entry 7). Judging from the yield and stereoselectivity, the reaction conditions for entry 7 were used for further investigation of the substrate scope. This cycloisomerization is scalable: the reaction of **1a** could be performed on a gram scale without loss of yield or stereoselectivity (entry 8). It should be noted that (*Z*)- and (*E*)-**2a** are kinetic products: the reaction progress of **1a** in toluene-d_8 was monitored by ^{1}H NMR to observe the constant (*Z*)/(*E*) ratio of 8:1 throughout the reaction. Moreover, the isolated (*Z*)-**2a** was completely recovered when subjected to the cycloisomerization conditions (3 mol % Cp*RuCl(cod), DMF, 50 ˚C, 3 h), without loss of stereochemistry. The major product (*Z*)-**2a** was characterized by ^{1}H/^{13}C NMR and mass spectroscopy, and its stereochemistry was elucidated by X-ray crystallographic analysis of the corresponding Diels-Alder product (*vide infra*).

Table 1. Optimization of reaction conditions.[a]

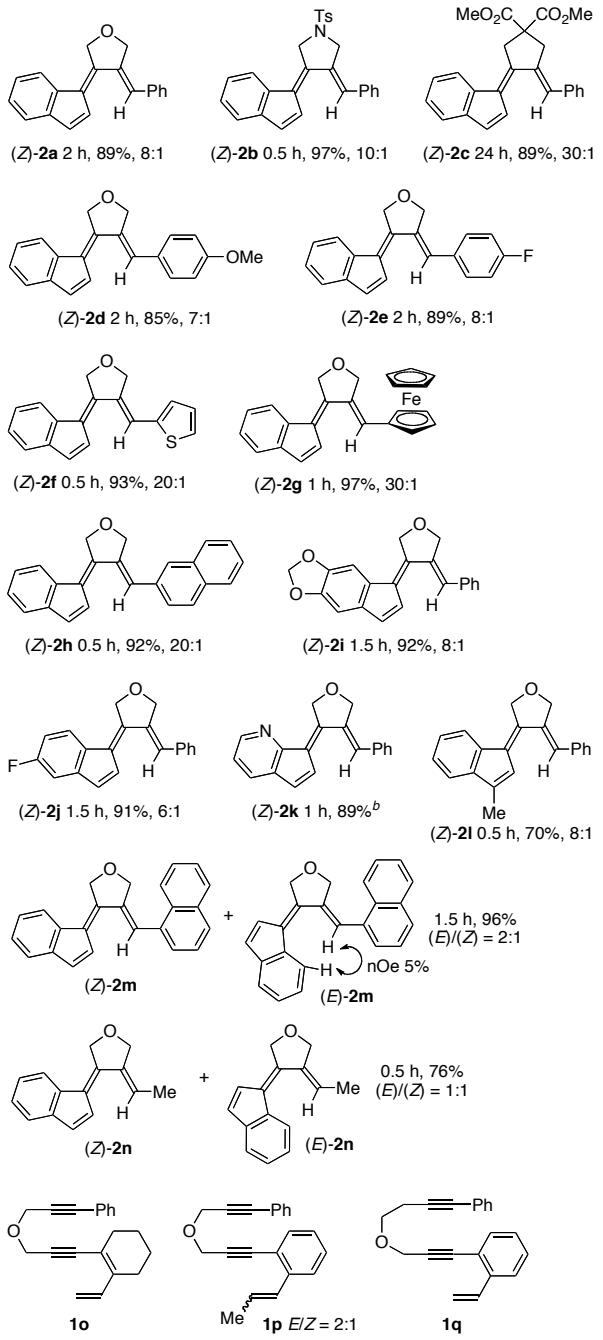
Entry	Solvent	Time/h	Yield/%[b]	*Z*/*E* ratio[c]
1	DCE	24	71	60:1
2	THF	2.5	92	5:1
3	MeCN	2	75	5:1
4	DMF	1	93	5:1
5[d]	DMF	3	95	5:1
6	toluene	6	87	8:1
7[e]	toluene	2	89	8:1
8[f]	toluene	1.5	95	8:1

[a] **1a** (0.3 mmol), Cp*RuCl(cod) (10 mol %), solvent (1.5 mL). [b] Isolated yields. [c] Crude ratio determined by ^{1}H NMR analysis. [d] Cat. 5 mol %. [e] 50 °C. [f] **1a** (1.36 g, 5.0 mmol).

The substrate scope was investigated by performing the cycloisomerization of various enediynes under the optimized reaction conditions (Table 2). Cycloisomerization products (*Z*)-**2b** and (*Z*)-**2c**, which bear a tosyl amide and malonate moiety, respectively, were obtained in good yields with higher stereoselectivity than that observed for **2a**. Ether-tethered enediynes **1d** and **1e**, having a *p*-methoxyphenyl and *p*-fluorophenyl terminal, respectively, showed similar reactivity as the parent enediyne **1a**, affording (*Z*)-**2d** and (*Z*)-**2e** in comparable yields and stereoselectivity. On the other hand, products (*Z*)-**2f**, (*Z*)-**2g**, and (*Z*)-**2h**, having a 2-thienyl, ferrocenyl, and 2-naphthyl terminal, respectively, were formed in high yields with high *Z*/*E* ratios of 20:1–30:1. In addition, 1,3-dioxole and fluorobenzene tethers were compatible to afford (*Z*)-**2i** and (*Z*)-**2j** in similar yields and *Z* selectivity as observed

for **2a**, indicating that the electronic effect of the phenylene tether is negligible. Significantly, enediyne possessing a 3-vinyl-2-pyridyl terminal instead of a styryl terminal afforded azaindenylidene product (*Z*)-**2k** as an exclusive regioisomer. An α substituent on the styrene was also tolerated: enediyne **1l** with a 2-methylstyrene moiety afforded (*Z*)-**2l** in 70% yield, with a moderate *Z*/*E* ratio of 8:1.

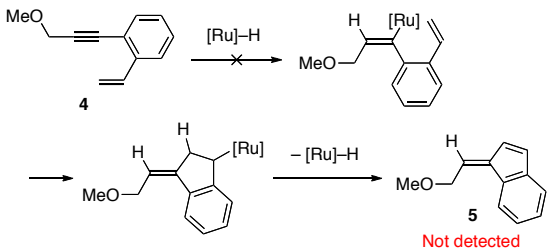
Table 2. Scope of enediyne substrates.[a]



[a]All reactions were performed with 10 mol % Cp*RuCl(cod) in toluene at 50 °C. *Z*/*E* ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. [b](*Z*)-**2k** was exclusively formed.

In all the above examples, (*Z*)-isomers were selectively formed, with the *Z*/*E*-ratios ranging from 6:1 to 100:0. In striking contrast, enediyne **1m** possessing a 1-naphthyl terminal underwent cycloisomerization under the optimized conditions to afford a 2:1 mixture of (*E*)- and (*Z*)-**2m** (Table 2). The stereochemistry of the major isomer (*E*)-**2m** was inferred from its ^{1}H NMR data: significant low-field shifts were observed for the vinylic proton and the indenyl aromatic proton at the 7 position (δ 8.39 and 8.28 ppm, respectively), and a nuclear Overhauser effect (nOe) correlation was also observed between these protons. Moreover, complete loss of stereoselectivity was observed for the cycloisomerization of enedyne **1n** with a methyl terminal, affording a 1:1 mixture of (*E*)- and (*Z*)-**2n** in 76% combined yield. The controlling factor for the stereoselectivity is unclear at this stage. Moreover, when cyclohexene analog **1o** was subjected to the standard reaction conditions, no reaction occurred in 24 h. In this case, **1o** was recovered in 87% yield. This result suggests that aromatic rings as enyne tethers are imperative for the present cycloisomerization. In contrast to α-methylstyrene derivative **1l**, the reaction of β-styrene derivative **1p** (*E*/*Z* = 2:1) resulted in a very low conversion (<10% NMR) after 24 h under the standard reaction conditions. ^{1}H NMR analysis of the crude reaction mixture revealed that 83% of **1p** remained, with no change in the *E*/*Z* ratio. Enediyne **1q** containing a 1,7-diyne moiety was also completely inactive, and was recovered intact.

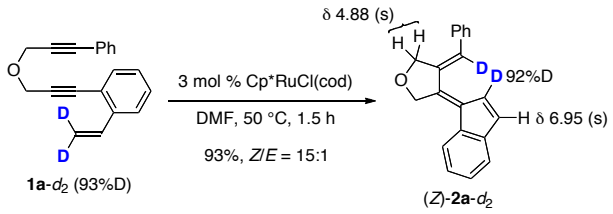
To gain insights into the reaction mechanism, several control experiments were conducted. First, 1,5-enyne **4** was subjected to the standard conditions (10 mol % Cp*RuCl(cod), toluene, 50 °C, 2 h), resulting in the recovery of **4** in 96% NMR yield (Scheme 3). Thus, the 1,6-diyne moiety is imperative for the cycloisomerization to proceed. This fact strongly supports the metallacycle mechanism rather than a metal-hydride mechanism since the latter should convert **4** to alkylideneindene **5**. A competition experiment was also conducted by adding styrene to the reaction of **1a**. When **1a** and styrene (1.1 equiv) were heated at 50 °C in the presence of 10 mol % Cp*RuCl(cod) in toluene, **1a** was totally consumed in 2 h to afford (*Z*)- and (*E*)-**2a** in 87% and 11% NMR yields, respectively. Therefore, the exogenous styrene did not affect the rate, yield, and stereoselectivity of the cycloisomerization of **1a**, indicating that intramolecular crossed insertion of the pendant alkene is more favorable than the intermolecular insertion of styrene.



Scheme 3. Elusive cycloisomerization of enyne **4** via metal-hydride mechanism.

Next, a deuterium labeling study was conducted using **1a**-d_2 (Scheme 4), and (*Z*)-**2a**-d_2 was selectively obtained. Although the vinylic proton α to the phenyl group is obscure due to the overlapping with the aromatic signals, comparison of the ^{1}H

NMR spectra of (*Z*)-**2a** and (*Z*)-**2a**-d_2 revealed that the signals due to the allylic methylene protons γ to the vinylic proton and the indenyl proton at the 3 position were altered from doublets to singlets, indicating that one of the deuterium labels of **1a**-d_2 was transferred to the vinylic position and the other deuterium label remained intact (92%D) on the indenyl 2-position. In contrast, deuterium incorporation via [Ru]–D species was *not* detected when the reaction of **1a** was performed in the presence of D_2O (2 equiv) otherwise under the same conditions. These results suggest that the involvement of metal-hydride species can be excluded. In addition, a negligible kinetic isotope effect (ca. 1.1) was observed: the cycloisomerizations of **1a** and **1a**-d_2 were separately performed in the presence of 10 mol % Cp*RuCl(cod) in toluene at ambient temperature for 6 h, resulting in 73% and 64% conversions, respectively. Therefore, the hydrogen-transfer step can be excluded as the rate-determining step (*vide infra*).



Scheme 4. Deuterium labeling experiment.

To obtain further insights into the mechanism, density functional theory (DFT) calculations were performed using the PCM (toluene) B3LYP method (Figure 1, see Supporting Information for details). For model complexes, Cp ligands were used instead of the Cp* ligands for the real complexes. According to the results of the control experiments, only metallacyclic mechanism was considered. The starting diyne complex **A** undergoes oxidative cyclization to generate the bent ruthenacycle **B**, with the dihedral angles of <Ru–Cα–Cβ–Cβ' = 30.3° and <Ru–Cα'–Cβ'–Cβ = –30.8° via $\mathbf{TS_{AB}}$ with an activation energy of $\Delta G^{\ddagger}$ = +8.3 kcal/mol. Rotation of the phenyl terminal of **B** leads to **C**, with the terminal phenyl ring being parallel to the Cp ligand. Then, **C** isomerizes to the planer ruthenacycle **D** via $\mathbf{TS_{CD}}$ with an activation energy of $\Delta G^{\ddagger}$ = +3.1 kcal/mol. The formation of **D** is highly exergonic (ΔG = –18.7 kcal/mol) because of the highly delocalized structure of this intermediate: in contrast to **B**, in which the Ru–Cα and Ru–Cα' bonds (2.04 Å) are similar to those of Ru–C single bonds and the Cα–Cβ and Cα'–Cβ' distances are shorter than the Cβ–Cβ' distance, **D** has a flat metallol-type structure with the Ru=Cα and Ru=Cα' double bonds (1.99 Å) and the similar Cα–Cβ, Cα'–Cβ' and Cβ–Cβ' bond lengths (Figure 2). A similar ruthenacycle having phenyl terminals and a Cp* ligand was previously isolated and unambiguously characterized by our group.[10,11]

Upon coordination of the styryl alkene, **D** evolves into the less stable ruthenacyclopentadiene **E** with the Ru–Cα and Ru–Cα' single bonds and the Cα=Cβ and Cα'=Cβ' double bonds via $\mathbf{TS_{DE}}$ with an activation energy of $\Delta G^{\ddagger}$ = +12.2 kcal/mol. Because the activation energy of the reverse process ($\Delta G^{\ddagger}$ = +6.3 kcal/mol) is smaller, intermediates **D** and **E** are in equilibrium. From **E**, the unusual crossed insertion of the terminal alkene into the adjacent Ru–Cα bond occurs via $\mathbf{TS_{EF}}$ with the largest activation energy of $\Delta G^{\ddagger}$ = +19.7 kcal/mol. In $\mathbf{TS_{EF}}$, the reacting Ru–Cα bond and the styrene C=C bond were elongated by 0.071 and 0.058 Å, respectively, compared to those in **E** (Figure 2). At the same time, the distance between Cα and the alkene terminal carbon was significantly shortened from 2.637 Å to 1.942 Å. Upon insertion, the seven-membered ruthenacycle **F** is produced, and its subsequent isomerization with a flip of the indane moiety proceeds via $\mathbf{TS_{FG}}$ having a small activation barrier. The formation of **F** deserves some comments: while the usual parallel insertion of an pendant alkene into a metallacycle produces a metallacycloheptadiene (see, intermediate **II** in Scheme 1a), the unprecedented

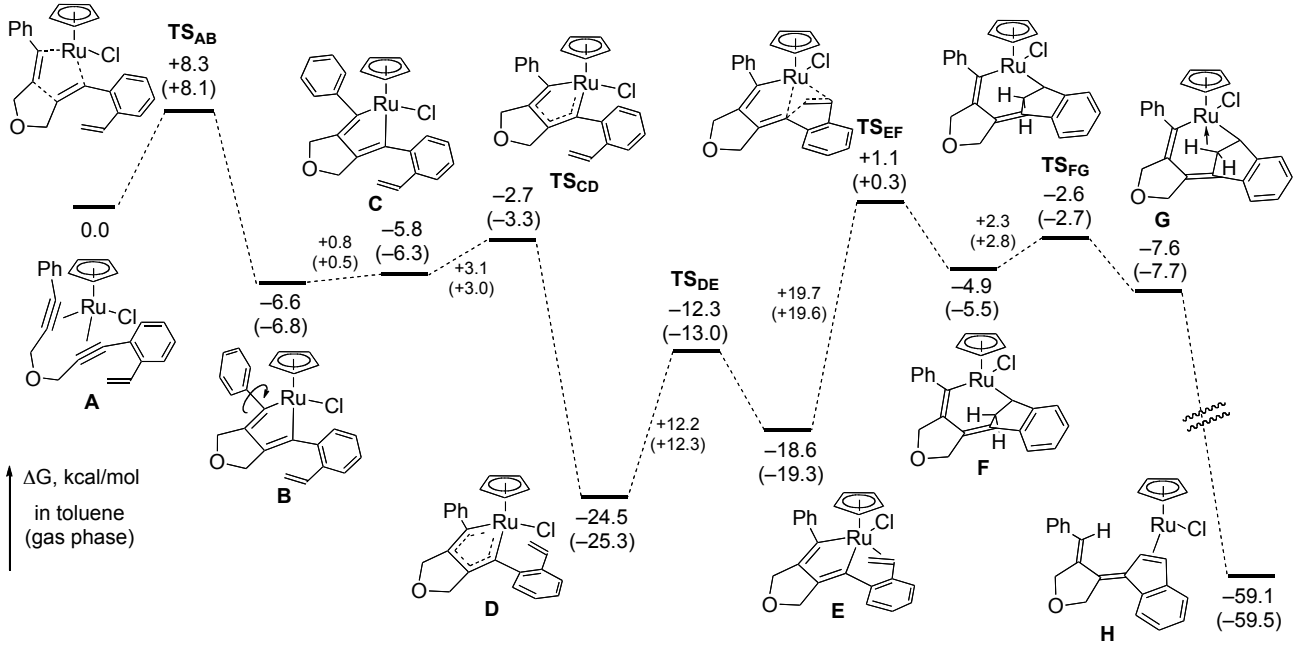


Figure 1. Energy surface for cycloisomerization of model complex **A** leading to (*Z*)-indenylidene complex **H** with relative Gibbs free energies in toluene and gas phase at 298K, 1 atm.

crossed insertion occurs for the ruthenacycle **E**, which has a partial biscarbene character similar to ruthenol **D**, to generate unique metallabicyclic intermediate **F**. In the generated ruthenacycle **G**, one of the methylene C–H bonds makes an agostic bond with the ruthenium center (Ru–H = 1.781 Å). Finally, this agostic proton is transferred to the vinylic carbon connected to the ruthenium center with virtually no activation barrier. Thus, normal two-step process consisting of β-H elimination and subsequent reductive elimination was bypassed. The formation of indenene complex **H** from the starting diyne complex **A** is highly exergonic, by ΔG = –59.1 kcal/mol. Therefore, the overall reaction is thermodynamically favorable. Because the largest energetic span[12] between intermediate **D** and transition state $\mathbf{TS_{EF}}$ is 25.6 kcal/mol, the overall reaction is kinetically feasible at ambient temperature, but requires heating for the efficient catalyst turnover.

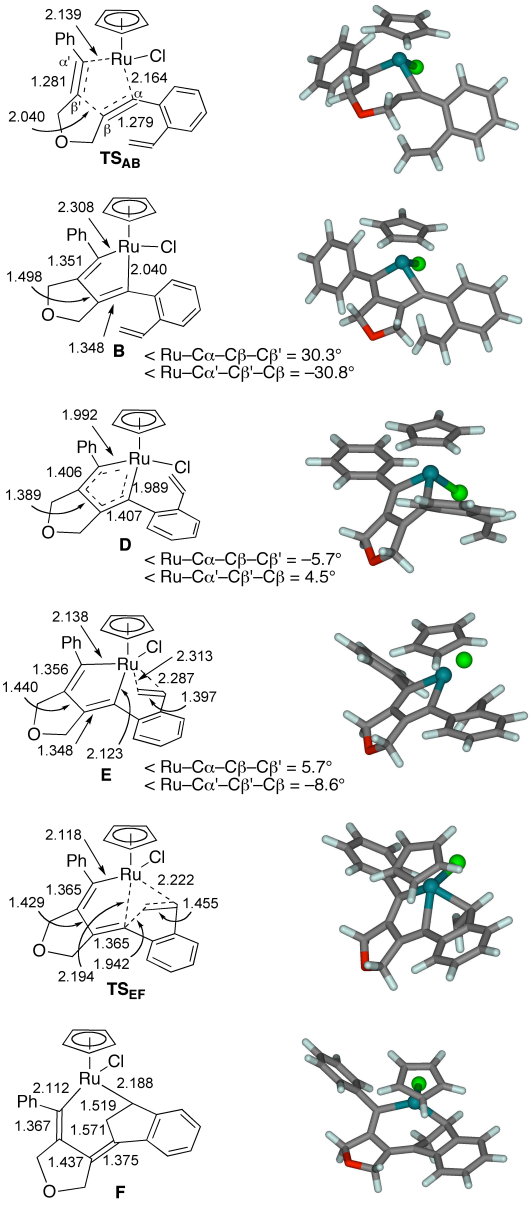
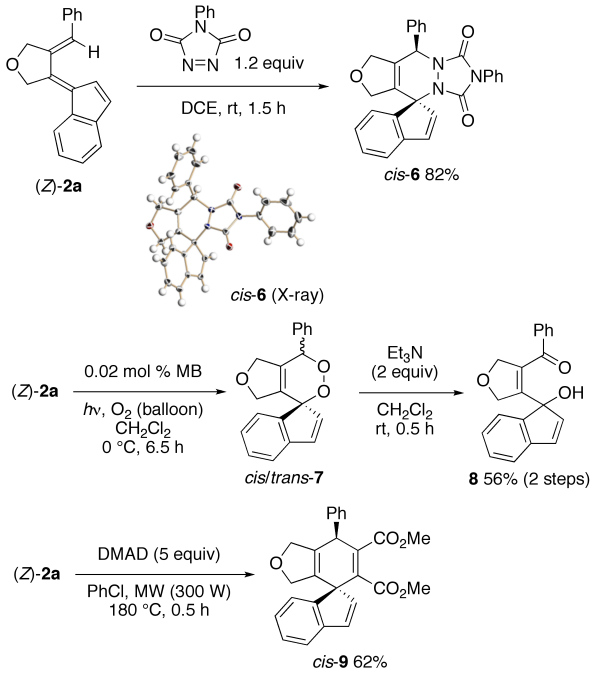


Figure 2. Representative intermediates and transition states with bond distances (Å).

Because the synthesis of spirocyclic scaffolds with a quaternary carbon center has been a significant topic,[13] Diels–Alder reactions of representative cycloisomerization product (*Z*)-**2a** were investigated to demonstrate the synthetic potential of our cycloisomerization (Scheme 5). (*Z*)-**2a** was treated with 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (1.2 equiv) in DCE at room temperature for 1.5 h, affording the interesting hetero spirocyclic compound *cis*-**6** in 82% yield. Because a good-quality single crystal was obtained from *cis*-**6**, its structure was unambiguously confirmed by X-ray analysis as the phenyl and indenyl substituents are in mutually *cis* orientation.



Scheme 5. Diels–Alder reactions of (*Z*)-**2a** with triazoledione, singlet oxygen, and dimethylacetylene dicarboxylate.

The Diels-Alder reaction of (*Z*)-**2a** with singlet oxygen was then investigated (Scheme 5). In the presence of methylene blue (MB), (*Z*)-**2a** was irradiated in CH_2Cl_2 under an O_2 atmosphere at 0 °C for 6.5 h. Contrary to our expectation, endoperoxide **7** was obtained as a mixture of stereoisomers (3:2). To confirm the reason for this loss of stereochemistry, two control experiments were conducted. First, (*Z*)-**2a** was irradiated in CH_2Cl_2 under an argon atmosphere at 0 °C for 4 h, affording a mixture of (*Z*)- and (*E*)-**2a** with a *Z*/*E* ratio of 2:1. Second, the *Z*/*E* ratio became 2:1 when a mixture of (*Z*)- and (*E*)-**2a** with a *Z*/*E* ratio of 1:5 was irradiated under the same conditions. These results suggest that photo-induced rotation of the indenylidene moiety occurred prior to cycloaddition with singlet oxygen. The obtained endoperoxide stereoisomers were then treated with triethylamine in CH_2Cl_2 at room temperature for 0.5 h, affording hydroxyketone **8** via the Kornblum-DeLaMare rearrangement in 56% yield, in two steps.[14]

In addition to these highly active hetero-dienophiles, dimethyl acetylenedicarboxylate (DMAD) was used for the Diels-Alder reaction with (*Z*)-**2a** (Scheme 5). As expected, DMAD exhibited much lower reactivity, and thus, a solution of (*Z*)-**2a** and 5 equiv DMAD in chlorobenzene was heated at 180 °C for

0.5 h in a shield vessel under microwave (MW) irradiation conditions. Consequently, spirocyclic cyclohexadiene derivative *cis*-**9** was obtained in 62% yield. Because the obtained products have functional groups suitable for further transformations, cycloisomerization product (*Z*)-**2a** is a significantly versatile scaffold for diversity-oriented synthesis.

Conclusion

In conclusion, we have discovered a novel mode of cycloisomerization when 1,5,10-enediynes bearing a styryl terminal was treated with a neutral ruthenium catalyst, Cp*RuCl(cod). This reaction is considered to proceed *via* an initial oxidative cyclization of the 1,6-diyne moiety, an unusual crossed insertion of the terminal alkene into the resultant ruthenacycle, and subsequent H transfer. This unprecedented mechanism is corroborated by deuterium labeling study as well as DFT calculations of model complexes. We also demonstrated the synthetic potential of the cycloisomerization product as a versatile scaffold for diversified synthesis *via* Diels-Alder reactions.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, characterization data for all new compounds, DFT calculation data, and NMR charts (PDF)

X-ray crystallographic data for *cis*-**5** (CIF)

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In the presence of neutral and cationic ruthenium catalysts, 1,6-diynes bearing a styryl terminal underwent novel modes of cycloisomerization to afford exocyclic 1,3-dienes with an indenylidene moiety.