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Mechanistic Insights into the Ru(II)-Catalyzed Intramolecular Formal [3 + 2] Cycloaddition of (*E*)-1,6-Enynes

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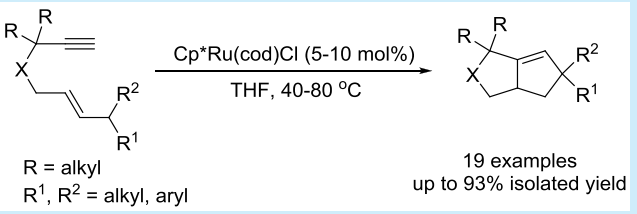
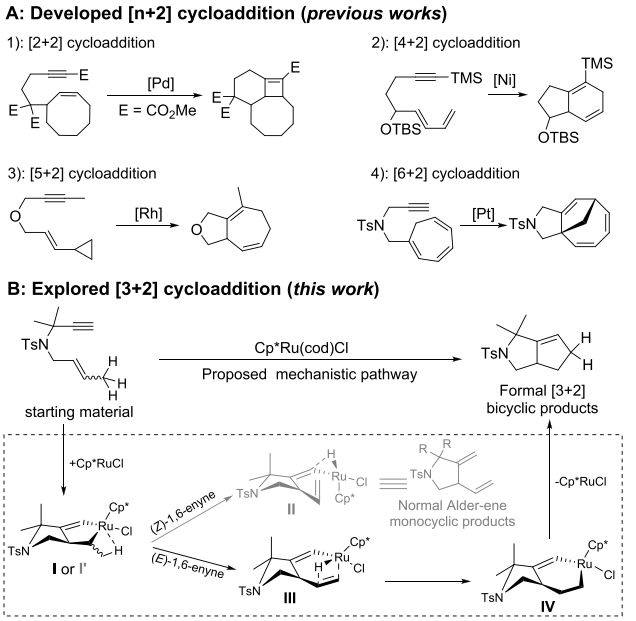
Supporting Information

ABSTRACT: Design of a unique reaction pathway in transition-metal-catalyzed 1,6-enynes cyclization to construct valuable synthetic motifs is a significant challenge in organic chemistry. Herein, we report a Ru(II)-catalyzed formal [3 + 2] cycloaddition as an efficient method to prepare unprecedented bicyclo[3.3.0]octenes from readily available (*E*)-1,6-enynes. Mechanistic studies based on the deuterium labeling experiments and the DFT calculation disclose a reasonable mechanistic pathway, where a ruthenacyclopentene generated by an ene−yne oxidative cyclization undergoes a sequential ß-hydride elimination and intramolecular hydroruthenation to form a ruthenacyclohexene, producing the desirable bicyclo[3.3.0]octenes.



Transition-metal-catalyzed enyne cyclizations have been extensively employed as useful synthetic tools in the construction of a variety of natural products, pharmaceutically molecules, and also industrially relevant products.[1] Since the pioneering work reported by Trost on the palladium-catalyzed cycloisomerization of 1,6-enynes in the middle 1980s,[2] numerous reports and well-documented reviews involving various metal complexes have emerged as conceptual processes in enynes cyclization reactions,[1,3] and the related new cyclization reactions have continuously appeared in literature until recently.[4] Of all these significant contributions, the intramolecular [*n* + 2] (*n* = 2, 4, 5, 6) cycloadditions of enynes are especially attractive due to the ubiquitous feature in the facile syntheses of polycyclic molecules with 4−8 membered rings (Scheme 1A).[5] The first intramolecular [2 + 2] cycloaddition of enynes was reported by the Trost group, where the enynes with an electron-withdrawing motif at the acetylenic carbon could be converted into the cyclobutenes (Scheme 1A$_1$).[5a,6] The initial success of the intramolecular [4 + 2] cycloaddition of dienynes was reported in 1989 through the use of a nickel(0) complex (Scheme 1A$_2$).[7] Shortly after Trost also found that the CpRu(MeCN)$_3$PF$_6$ effectively promoted the [4 + 2] cycloaddition of yne-enones.[8] The pioneering work on the intramolecular [5 + 2] cycloaddition involving the enynes structures was established by the Wender group through the use of the *in situ* formed cationic rhodium species [Rh(PPh$_3$)$_3$]OTf (Scheme 1A$_3$).[9] Subsequently, a series of 1,6-enynes containing the cyclopropyl group on the alkene side could be used for the construction of cycloheptadienes via this similar intramolecular [5 + 2] cycloaddition. The single example of intramolecular [6 + 2] cycloaddition of trienynes was reported by the Tenaglia group,

Scheme 1. Transition-Metal-Catalyzed Intramolecular [*n* + 2] Cycloadditions of Enynes



where PtCl$_2$ was used to construct the cyclopentane fused bicyclo[4.2.1]nona-2,4,7-trienes derivatives (Scheme 1A$_4$).[5t]

Despite the great achievements with these developed transformations, to the best of our knowledge, the intramolecular [3 + 2] cycloaddition reaction of 1,6-enynes is still

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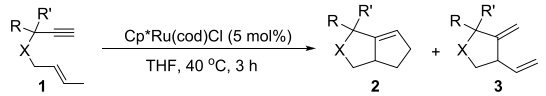
challenging (Scheme 1B). One of the main restrictions lies in the fact that this intramolecular [3 + 2] cycloaddition needs the participation of a saturated C(sp^3)−H bond rather than the above-observed participation of the carbon−carbon single/double bonds in the intramolecular [n + 2] (n = 2, 4, 5, 6) cycloadditions.[10] This limitation means a compulsory demand via a 1,2-hydrogen shift that must undergo the cleavage of a saturated C(sp^3)−H bond. Another restriction ascribes the corresponding competing cyclization reaction to convert into the normal Alder-ene monocyclic products (gray part in Scheme 1B). Therefore, based on valuable information in the mechanistic study of normal Alder-ene process,[11] a systematic adjustment of the sterically hindered effect in 1,6-enynes with the suitable substituent at the propargylic position could favor the conformational match of the [Ru]−H bond and the pseudoequatorial alkene in ruthenium hydride intermediate **III**,[12] thus leading to the formation of the ruthenahexene intermediate **IV** via hydroruthenation process of **III**. This is a reasonable solution to overcome the above restrictions for the formation of the desirable bicyclic products via the release of the ruthenacyclohexene **IV**. In this contribution, we realize this intramolecular formal [3 + 2] cycloaddition reaction of (*E*)-1,6-enynes is mechanistically unusual relative to that of the $AgSbF_6$-catalyzed intermolecular cyclization of alkenes and alkyne,[13] providing a series of bicyclo[3.3.0]octenes in good yields under mild reaction conditions. As presented in this study, the deuterium labeling experiments and the control experiments, together with the DFT calculations, disclose its catalytic mechanism of this intramolecular [3 + 2] cycloaddition process.

In our proof-of-concept experiments, we first examined the reaction feasibility in the proposed mechanistic pathway of the intramolecular [3 + 2] cycloaddition by adjusting the substituents at the propargylic position of the selected (*E*)-1,6-enynes. The reactions were carried out through the use of 5% mol of the electron-rich Cp*Ru(cod)Cl as a catalyst since the reported Cp*Ru(cod)Cl could efficiently catalyze various enyne cyclization reactions.[14] As shown in Table 1, we initially found that the reaction of the tosylamide **1aa** without a substituent at the propargylic position did not occur, whereas those of **1ab** and **1ac** with a monosubstituent at the propargylic position only afforded the normal Alder-ene monocyclic **3ab** and **3ac** (entry 1 versus entries 2−3).[11b,15] To our delight, the reaction of **1ad** could steadily produce the clean bicyclic **2ad** in 89% isolated yield, even if in 1 g level of scale (84%) (entry 4; also see Supporting Information for the optimization of reaction conditions). This finding indicates that the methyl groups at the propargylic position are able to meet a proposed spatial orientation of the [Ru]−H bond and pendent C═C double bond in the intermediate **III**, which is indicative of an interesting contribution of the *gem*-dialkyl effect reported by Thorpe and Ingold in 1915.[16] A further attempt by using **1ae** with a cyclic substituent at the propargylic position also afforded the desirable bicyclic **2ae** in 85% isolated yield (entry 5), supporting this *gem*-dialkyl effect. However, the sole *gem*-dialkyl effect is not sufficient since the reaction of the *O*-linked **1af** did not produce the bicyclic **2af** instead of **3af**, and those of the *C*-linked substrates (**1ag**−**1ah**) also only gave the normal Alder-ene monocyclic products (**3ag**−**3ah**) (entries 6−8), indicating a sensitive hydroruthation process for the tethering atom of enynes. These comparisons elaborated an integrated contribution of a spatially configurational sp^3 hybridized *N*-linker and the assistance of the *gem*-dialkyl effect for the intramolecular [3 + 2] cycloaddition, which is distinctly different from the common *homo*-hydroalkynylative cyclization adducts and *homo*-[2 + 2 + 2] cycloadducts process reported by Tenaglia's group.[17]

In light of this clear configurational unit of substrates, a series of sulfamide-tethered 1,6-enynes containing an sp^3 hybridized *N*-linker and the dimethyl substituents at the propargylic position were further investigated as shown in Table 2. The results showed that the reactions with all the tested (*E*)-1,6-enynes could steadily produce the correspond-

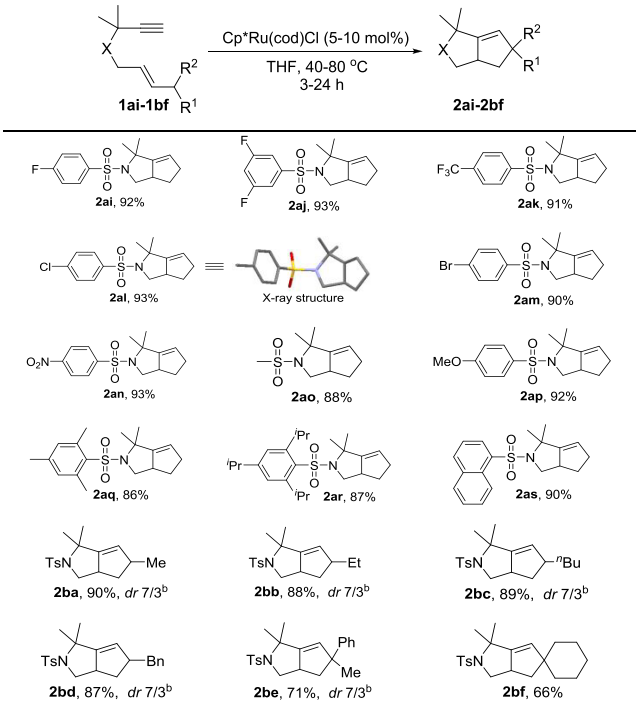
Table 1. Evaluation of Ru(II)-Catalyzed Cyclization of (*E*)-1,6-Enynes[a]



entry	enyne: X, R, R′	% yield of **2**[b,c]	% yield of **3**[b,c]
1	**1aa**: NTs, H, H	ND (**2aa**)	<5 (**3aa**)
2	**1ab**: NTs, H, Me	ND (**2ab**)	55 (**3ab**)
3	**1ac**: NTs, H, Ph	ND (**2ac**)	39 (**3ac**)
4	**1ad**: NTs, Me, Me	89 (**2ad**)	ND (**3ad**)
5	**1ae**: NTs, −$(CH_2)_5$−	85 (**2ae**)	ND (**3ae**)
6	**1af**: O, −$(CH_2)_5$−	ND (**2af**)	82 (**3af**)
7	**1ag**: $C(CO_2Et)_2$, Me, Me	ND (**2ag**)	76 (**3ag**)
8	**1ah**: $C(CH_2O)_2CO$, Me, Me	ND (**2ah**)	73 (**3ah**)

[a]Reaction conditions: enyne **1** (0.4 mmol), Cp*Ru(cod)Cl (0.02 mmol), 40 °C, THF, 3 h. [b]Isolated yield. [c]ND = Not detected.

Table 2. Ru(II)-Catalyzed Intramolecular Formal [3 + 2] Cycloaddition Reaction[a]



[a]Reaction conditions 1: enyne **1ai**−**1bd** (0.4 mmol), Cp*Ru(cod)Cl (0.02 mmol), 40 °C, THF, 3 h. Reaction conditions 2: enyne **1be**−**1bf** (0.2 mmol), Cp*Ru(cod)Cl (0.02 mmol), 80 °C, THF, 24 h. [b]Dr was determined by crude NMR.

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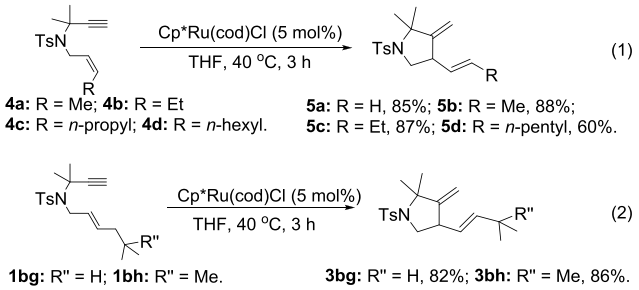
ing bicyclo[3.3.0]octenes (**2ai**–**2bf**) in good to excellent isolated yields, where a representative structure of **2al** was determined by its X-ray structure (CCDC: 1908820; see Supporting Information for the single crystal X-ray structure). In addition, it was found that the substrate scope is well-tolerant of the alkene side chain of (*E*)-1,6-enynes, where the enynes featuring different substituents on the alkene side chain could undergo this [3 + 2] cycloaddition to provide the corresponding bicyclic products (**2ba**–**2bf**). It was also notable that the reactions of **1be**–**1bf** required enhanced loadings of catalyst (10 mol %) at higher temperature (80 °C) with a prolonged reaction time (24 h).

In addition to the general practicability, this intramolecular [3 + 2] cycloaddition also presented an obvious substrate selectivity as shown in Scheme 2. In the cases of the 1,6-enynes

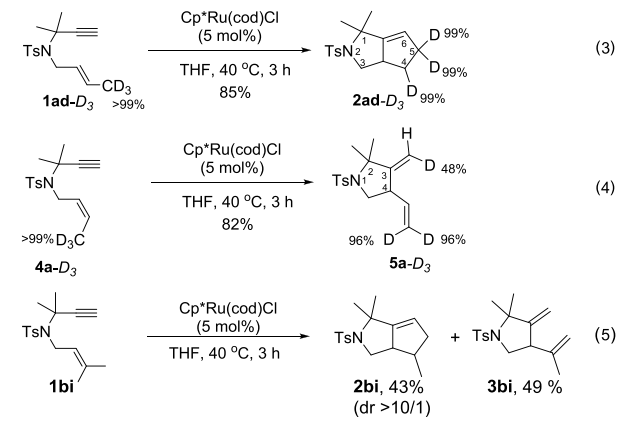
Scheme 2. Investigations of the Affecting Factors to the Ru(II)-Catalyzed Intramolecular Formal [3 + 2] Cycloaddition Reaction



bearing a (*Z*)-configured alkene as the substrate, the reactions of **4a**–**4d** under the optimal reaction conditions only afforded the normal Alder-ene monocyclic **5a**–**5d** with high isolated yields (60%–88%) (eq 1, Scheme 2), which were similar to Trost's reported results.[11] Notably, no bicyclic products clearly demonstrated the substrate's *Z*/*E*-configurational selectivity. In the cases of (*E*)-1,6-enynes equipped with bulky substituents at the allylic position (**1bg** and **1bh**), only the normal Alder-ene monocyclic **3bg** and **3bh** were observed (eq 2, Scheme 2), indicating the substrate's sterically hindered selectivity.

To disclose the nature of an orientational match between the [Ru]–H bond and pendent C=C double bond in the intermediate **III**, a deuterium labeling experiment, the [3 + 2] cycloaddition of **1ad**-D_3, was performed (eq 3 in Scheme 3). It

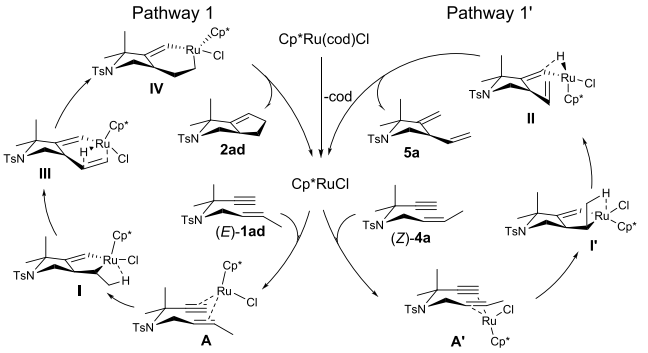
Scheme 3. Deuterium Labeling Experiments and Investigations of the Substitution Effect



was found that the tosylamide **1ad**-D_3 could be steadily converted into the deuterated **2ad**-D_3 with complete deuteration retention. This observation indicated that the reaction might go through the suggested intermediate **III** in this [3 + 2] cycloaddition, demonstrating a metal-assisted intramolecular hydrogen shift step since a 1,2-hydrogen shift occurs from the $C_5(sp^3)$–D bond to the $C_4(sp^3)$–D bond in **2ad**-D_3 that was proven by the reaction of **1ad** in D_2O without deuterium incorporation. In order to explain ruthenium hydride intermediate **II**, another deuterium labeling experiment for the reaction of (*Z*)-**4a**-D_3 was also investigated (eq 4 in Scheme 3). The result presented a similarly intramolecular hydrogen shift, suggesting the reaction undergoes the ruthenium hydride intermediate **II** to produce the deuterated **5a**-D_3. Further evidence to support the proposed ruthenium hydride intermediate **II** and **III** comes from a parallel reaction of **1bi**, where a representative **1bi** with dual methyl groups at the alkene could be efficiently converted into both bicyclic **2bi** and the Alder-ene monocyclic **3bi** (eq 5 in Scheme 3).

According to the deuterium labeling experiments and the control experiments, together with the detail DFT calculations (see Supporting Information), the suggested catalytic cycles for the intramolecular formal [3 + 2] cycloaddition (pathway 1) and the Alder-ene cyclization (pathway 1′) were proposed, as shown in Scheme 4. Initially, both reaction pathways initiate

Scheme 4. Proposed Reaction Mechanism for the Intramolecular Formal [3 + 2] Cycloaddition and Alder-Ene Cyclization



through a cod dissociation and substrate coordination, followed by the ene-yne oxidative cyclization step for the formation of *tetra*-coordinated Cp*RuCl-enyne (**A** and **A′**), to produce the common ruthenacyclopentene intermediates **I** and **I′**. In the case of pathway 1 with (*E*)-**1ad** as a substrate, the transformation of **A** to the intermediate **I** goes through the transition state with the highest energy barriers of 13.3 kcal/mol obtained by a DFT calculation (see Supporting Information), which is the rate-determining step for the intramolecular [3 + 2] cycloaddition reaction. Then, the hydrogen from the pseudoequatorial methyl group in the intermediate **I** gets closer to the ruthenium center, favoring the formation of the vinyl ruthenium hydride intermediate **III** via a *β*-hydride elimination step. Finally, the intramolecular hydroruthenation step of the intermediate **III** occurs to release the ruthenacyclohexene intermediate **IV**, leading to the desired bicyclic **2ad** via a reductive elimination step. However, in the case of pathway 1′ with (*Z*)-**4a** as a substrate, the transformation of **I′** to the intermediates **II** is the rate-determining step in the Alder-ene cyclization, where the

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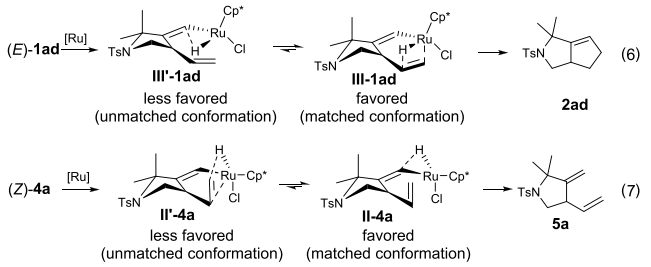
highest energy barrier of transition state is 13.7 kcal/mol detected by a DFT calculation (see Supporting Information). Due to the unmatched conformation, the intermediate **II** tends to undergo a typical ruthenium reductive elimination step to provide the Alder-ene monocyclic **5a**.[11a]

For clarity, the detailed elucidations in the formation of either bicyclic or monocyclic products were addressed, as shown in Scheme 5. In eq 6, the ruthenium hydride

Scheme 5. Proposed Reaction Intermediates



intermediate **III-1ad** is preferentially favored because of the matched conformation between the Ru−H bond and pendent C═C bond, resulting in an intramolecular hydroruthenation to produce the bicyclic **2ad**. In contrast, in eq 7, the hydroruthenation process is not favored due to the unmatched conformation induced by the pseudoaxial alkene motif, forming the Alder-ene monocyclic **5a** via the conformationally favorable **II-4a**.

In conclusion, we developed an efficient Ru(II)-catalyzed intramolecular formal [3 + 2] cycloaddition reaction of (*E*)-1,6-enynes to construct the unprecedented bicyclo[3.3.0]-octenes. During this process, the ruthenacyclopentene formed by an ene-yne oxidative cyclization step undergoes a unique mechanistic pathway to form the bicyclic products, which is consistent with the results of DFT calculations. The substrate scope investigations suggest that a wide range of (*E*)-1,6-enynes are well-tolerated in this pathway, whereas those of (*Z*)-1,6-enynes and (*E*)-1,6-enynes with the bulky substituents at the allylic position goes through an usual Alder-ene reaction pathway. This study not only highlights an abnormal reaction pathway for intramolecular enynes cycloaddition but also enriches the synthetic protocols of bicyclic organic molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02446.

General and procedural information; X-ray structure of **2al**; DFT calculation results; NMR spectra (PDF)

Accession Codes

CCDC 1908820 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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