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Ruthenium-Catalyzed Intramolecular [2+2+2] Cyclization of Allene–Yne–Enes: Construction of Fused-Tricyclic Skeletons

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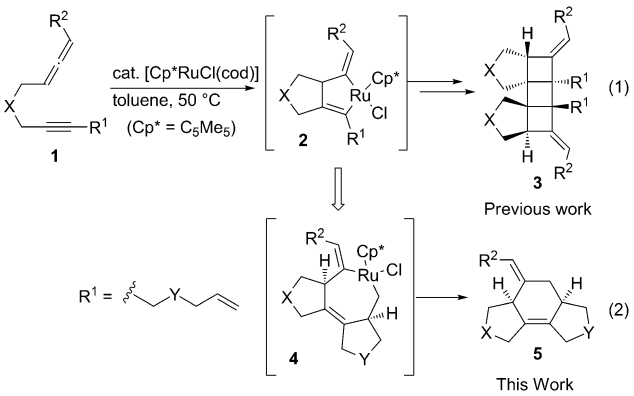
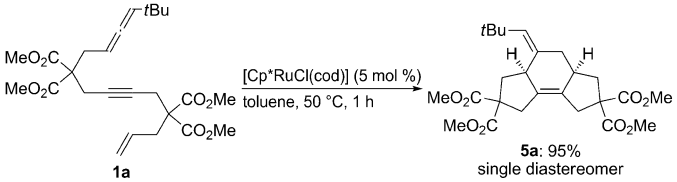
A transition metal-catalyzed [2+2+2] three-component cycloaddition is one of the most powerful methodologies for construction of a polycyclic skeleton in a one-pot operation.[1,2] Numerous examples of an intermolecular or intramolecular [2+2+2] cycloaddition with alkynes or alkenes, as an unsaturated bond component, have been reported to date.[1] However, [2+2+2] cycloaddition of substrates including an allene as a coupling partner is still limited to several examples.[3–8]

We have previously reportedc a ruthenium(II)-catalyzed cyclodimerization of allenynes **1** that afford pentacyclic compounds **3**.[9] The reaction proceeds through the formation of ruthenacyclopentene intermediate **2**, from which reductive elimination followed by dimerization of the resulting cyclobutene derivative affords **3**. In this regard, we envisaged that if the reaction of allenyne **1**, which possesses an unsaturated bond as an R^1 substituent, was carried out in the presence of a ruthenium catalyst, insertion of the unsaturated bond into the ruthenium–carbon bond of **2** would proceed to give ruthenacycle **4**, and subsequent reductive elimination would afford tricyclic compound **5** (Scheme 1). Here, we report ruthenium(II)-catalyzed intramolecular [2+2+2] cyclization of allene–yne–ene, which affords 5,6,5-fused tricyclic skeletons.[10,11]



Scheme 1. Ruthenium-catalyzed cyclization of allenyne through ruthenacyclopentene intermediate.



Scheme 2. [Cp*RuCl(cod)]-catalyzed [2+2+2] cyclization of allene–yne–ene **1a**.

To study the feasibility of the above method, the simple substrate **1a** was treated with 5 mol% of [Cp*RuCl(cod)] in toluene at 50°C (Scheme 2). As a result, an expected 5,6,5-fused tricyclic compound **5a** was obtained in 95% yield as a single diastereomer.

Encouraged by this result, we set out to investigate the scope and limitations of the [2+2+2] cyclization of allene–yne–enes. First, the effects of substituents on the allene and alkene moieties were examined (Table 1). Cyclization of **1b** with a methallyl group instead of an allyl group afforded the corresponding cyclized product **5b** in quantitative yield as a single stereoisomer (Table 1, entry 1). On the other hand, when the substrate **1c** bearing an *E*-crotyl group as a tethered alkene was treated with [Cp*RuCl(cod)] catalyst, the tricyclic compound **5c** was produced in low yield (Table 1, entry 2). Allene-yne-enes **1d**–**1f** were also subjected to the same reaction conditions, however, no desired cyclic compounds were obtained and only starting materials were recovered (Table 1, entries 3–5). The reaction of allene-yne-ene **1g** with a methyl group on the allene moiety gave the corresponding tricyclic compound **5g** in 36% yield along with the triene derivative **6**, which was obtained through β-hydride elimination from ruthenacycloheptene intermediate **4** (Table 1, entry 6).

Next, we turned our attention to investigation of the effect of the linker structure (Table 2). When the substrate **1h** containing a fluorenyl group between the alkyne and alkene moieties was subjected to the above-mentioned reaction conditions, the cyclized product **5h** was obtained in 83% yield (Table 2, entry 1). The reaction of allene-yne-enes **1i** and **1j** containing a nitrogen atom and an oxygen atom, respectively, in the linker between the alkyne and alkene moieties proceeded stereoselectively to give the corresponding tricyclic compounds **5i** and **5j** (Table 2, entries 2

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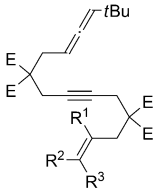
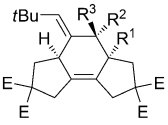
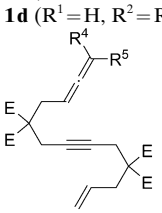
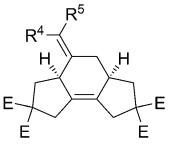
Table 1. Effects of substituents on the allene and alkyne moieties.[a]

Entry	Substrate[b]	t [h]	Yield [%][c]
			
1[d]	**1b** (R^1=Me, R^2=R^3=H)	2	**5b**: quant
2	**1c** (R^1=R^3=H, R^2=Me)	48	**5c**: 22 (67)
3	**1d** (R^1=H, R^2=R^3=Me)	25	**5d**: - (52)
			
4	**1e** (R^4=R^5=H)	23	**5e**: - (81)
5	**1f** (R^4=R^5=Me)	43	**5f**: - (72)
6	**1g** (R^4=Me, R^5=H)	1	**5g**: 36[e]

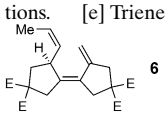
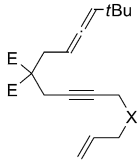
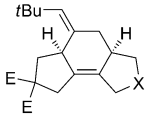
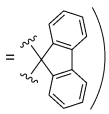
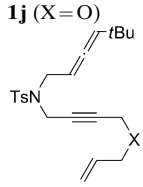
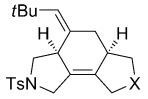
[a] Reaction conditions: [Cp*RuCl(cod)] (5 mol%), toluene, 50°C. [b] E=CO_2Me. [c] Values in parentheses are the yields of recovered starting material **1**. [d] The reaction was carried out under reflux conditions. [e] Triene **6** was also produced in 33% yield.  **6**

Table 2. Effects of the different linker moieties.[a]

Entry	Substrate[b]	t [h]	Yield [%]
			
1	**1h** (X = )	49	**5h**: 83
2	**1i** (X=NTs)	21	**5i**: 59
3	**1j** (X=O)	2	**5j**: 25
			
4	**1k** (X = )	42	**5k**: 79
5	**1l** (X=NTs)	20	**5l**: 71
6	**1m** (X=O)	1	**5m**: 14

[a] Reaction conditions: [Cp*RuCl(cod)] (5 mol%), toluene, 50°C. [b] E=CO_2Me.

and 3). The reaction of allenynes with a nitrogen atom in the linker between the allene and alkyne moieties **1k**–**1m** stereoselectively produced the cyclized products **5k**–**5m** in low to good yields (Table 2, entries 4–6).

The relative stereochemistry of the ring junction and geometry of the *exo*-alkene moiety in the tricyclic compounds were unambiguously determined by X-ray crystallographic analysis of **5k** to have a *Z*-configuration (Figure 1).[12]

A possible reaction course including the origin of stereoselectivity is shown in Scheme 3. First, dissociation of the

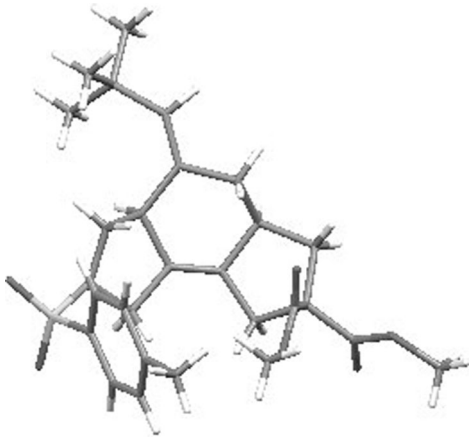
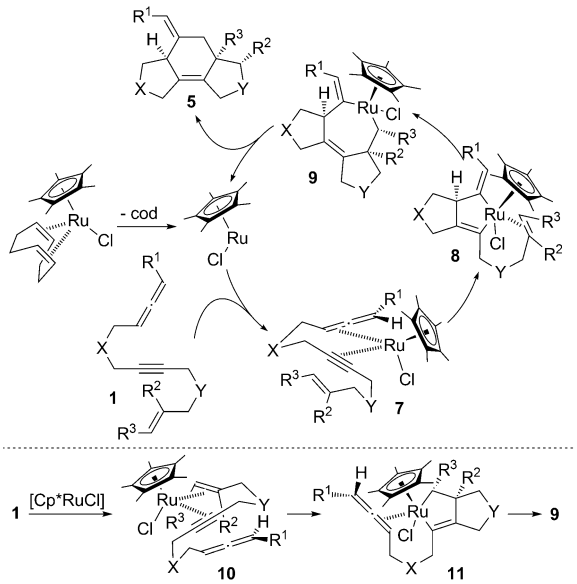


Figure 1. X-ray crystal structure of **5k**.

cod ligand from [Cp*RuCl(cod)] (Cp*=C_5Me_5) occurs to give the [Cp*RuCl] complex. The allene and alkyne moieties of **1** coordinate to the ruthenium center to give the intermediate **7**, in which the R^1 group on the allene is oriented to avoid steric repulsion by the bulky Cp* ligand. Next, oxidative cycloaddition of the alkyne and the internal double bond of the allene afford the ruthenacyclopentene **8**, and subsequent insertion of the tethered alkene proceeds to avoid steric interaction between the Cp* ligand and the substituents on the alkene moiety, thus affording the ruthenacy-



Scheme 3. Possible reaction mechanism.

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cloheptene **9** in a stereoselective manner. Finally, reductive elimination of **9** gives tricyclic compound **5**. On the other hand, an alternative pathway through a ruthenacyclopentene intermediate, which is formed from an alkyne and alkene is also possible. Thus, oxidative cyclization of an alkene and alkyne from the coordinated complex **10** affords an alternative ruthenacyclopentene **11**; then insertion of the internal double bond of the allene occurs stereoselectively to give the ruthenacycloheptene **9**. Both reaction pathways account for stereoselective formation of the cyclized product in the [2+2+2] cyclization and cannot be excluded at this stage.

In summary, we have demonstrated a ruthenium(II)-catalyzed intramolecular [2+2+2] cyclization of allene-yne-enes. The reaction proceeds via a ruthenacyclopentene intermediate formed from the allene-yne or ene-yne moiety to give tricyclic compounds in a stereoselective manner. Moreover, it was found that the progress of cyclization was strongly affected by the type of substituent on the unsaturated bonds. Further studies along this line are in progress in our laboratory.

Experimental Section

General Procedure for the [2+2+2] cyclization of allene-yne-ene

A mixture of allene-yne-ene **1** and [Cp*RuCl(cod)] (5 mol% to **1**) in degassed toluene ([**1**] = 0.1 M) was stirred at 50 °C under an atmosphere of argon (1 atm). After removal of volatiles, the residue was purified by column chromatography on silica gel to give **5**.

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Keywords: alkenes · alkynes · allenes · cyclization · ruthenium

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[12] CCDC 869537 (**5k**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The stereochemistry of **5b** and **5c** were determined by NOESY experiments, see the Supporting Information. The stereochemistry of **5a**, **5g**–**5j**, **5l**, and **5m** were assumed to be the same configuration to that of **5k** from analogy with other spectral data of **5k**.

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Intramolecular Cyclization

Nozomi Saito, Taisuke Ichimaru, Yoshihiro Sato** ——— ▮▮▮▮–▮▮▮▮

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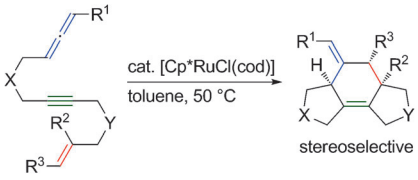

Three′s not a crowd: An intramolecular [2+2+2] cyclization between three different components, allene, alkyne, and alkene, has been realized using a catalytic amount of [Cp*RuCl(cod)] complex (cod = 1,5-cyclooctadiene), and afforded fused-tricyclic compounds in a highly stereoselective manner.

