Ruthenium-Catalyzed Tandem [2 + 2 + 2]/[4 + 2] Cycloaddition of 1,6-Heptadiyne with Norbornene

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Summary: *The ruthenium(II)-catalyzed reaction of a substituted 1,6-heptadiyne with norbornene gave a tandem [2 + 2 + 2]/[4 + 2] cycloaddition product as a single stereoisomer along with a [2 + 2 + 2] cycloadduct. CpRu(cod)Cl catalyzes both [2 + 2 + 2] cycloaddition of the heptadiyne and norbornene and subsequent [4 + 2] cycloaddition of the resultant cyclohexadiene and norbornene. The second [4 + 2] cycloaddition step was effectively improved by use of an indenyl complex, (η^5-C_9H_7)$Ru(PPh_3)_2Cl$, to afford the tandem adducts in moderate to good yields.*

Transition-metal-catalyzed cyclotrimerization of alkynes is a viable route to highly substituted benzene derivatives.[1] Cyclotrimerization of 2 equiv of an alkyne with an alkene is also catalyzed by transition metals to produce cyclohexadiene,[2] which is a potential diene component for Diels−Alder reaction. Such Diels−Alder-type [4 + 2] cycloadditions are generally promoted by heat, pressure, or Lewis acid,[3] and recently, several transition-metal catalysts were found to promote [4 + 2] cycloaddition of nonactivated Diels−Alder partners.[1] In this conjunction, we found that several organoruthenium complexes **1** having a planar auxiliary ligand promotes both [2 + 2 + 2] cycloaddition of 1,6-heptadiyne derivatives **2** with norbornene[4] and subsequent [4 + 2] cycloaddition of the resultant cyclohexadiene **4** with the second norbornene molecule to afford an interesting polycyclic compound **3** as a single stereoisomer along with **4** (Scheme 1). Herein, we wish to report this novel tandem [2 + 2 + 2]/[4 + 2] cycloaddition.

In the presence of CpRu(cod)Cl (**1a**) (10 mol %), malonate derivative diyne **2a** and 20 equiv of norbornene were refluxed in dichloromethane for 7 h. Separation of products by silica-gel chromatography gave an unexpected tandem [2 + 2 + 2]/[4 + 2] cycloadduct **3a** in 45% yield along with a [2 + 2 + 2] cycloadduct **4a** (20%) (Table 1, entry 1). The structure of **3a** was confirmed based on the following spectral features. The ^{1}H NMR spectrum and the parent peak of the mass spectrum (*m*/*z* 396, M^+) indicate that the product is the 1:2 adduct of **2a** and norbornene. In the ^{13}C NMR spectrum, there are two sp^2 peaks (δ 172.5 and 131.3) and eight sp^3 peaks (δ 57.0, 52.7, 41.1, 36.0, 29.5, 28.1, 22.0, and 12.8), and no coupling was observed between the bridgehead proton H_a and the *endo*-proton H_b in the ^{1}H NMR spectrum (Scheme 1). These observations support the highly symmetrical exo−exo structure of **3a**.[5] Finally, a satisfactory elemental analysis was obtained.

The present method is an interesting route to the novel rigid polycyclic system **3a**, which is potentially a key component of functionalized artificial molecules.[6]

Scheme 1

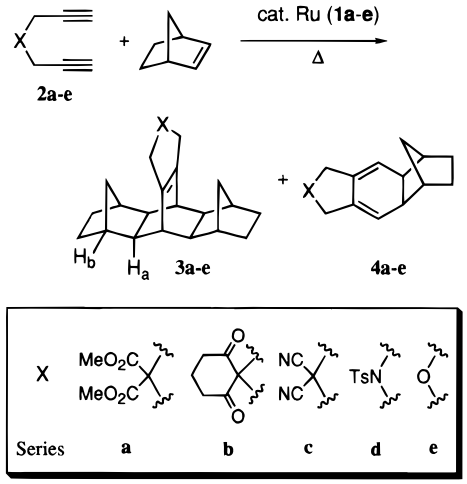

Table 1. Cycloaddition of 1,6-Heptadiynes 2a−e with Norbornene

entry	catalysts (mol %)	diynes	conditions[a]	isolated yields **3** (%)	isolated yields **4** (%)
1	**1a** (10)	**2a**	A, 7 h	45	20
2	**1a** (10)[b]	**2a**	A, 72 h	47	10
3	**1b** (10)	**2a**	A, 17 h	15	47
4	**1c** (10)	**2a**	A, 48 h	19	10
5	**1d** (10)	**2a**	A, 24 h	32	9
6	**1d** (10)	**2a**	B, 24 h	78	10
7	**1d** (5)	**2a**	B, 24 h	77	12
8	**1d** (5)	**2b**	B, 48 h	64	0
9	**1d** (5)	**2c**	B, 48 h	50	35
10	**1d** (5)	**2d**	B, 24 h	47	*c*
11	**1d** (5)	**2e**	B, 24 h	36	*c*

[a] A: CH_2Cl_2, reflux. B: $ClCH_2CH_2Cl$, 40 °C. [b] NH_4PF_6 (20 mol %) was used. [c] Trace amount.

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(2) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539.
(3) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Tetrahedron Organic Chemistry Series; Pergamon Press: Oxford, 1990, Vol. 8.
(4) For [2 + 2 + 2] cycloaddition of acetylene with norbornene, see: (a) Suzuki, H.; Itoh, K.; Ishii, Y.; Simon, K.; Ibers, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 8494. (b) Brown, L. D.; Itoh, K.; Suzuki, H.; Hirai, K.; Ibers, J. A. *J. Am. Chem. Soc.* **1978**, *100*, 8232.
(5) Meinwald, J.; Meinwald, Y. C.; Baker, T. N., III *J. Am. Chem. Soc.* **1963**, *85*, 2514.

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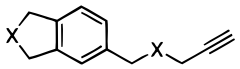
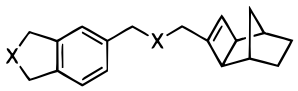
To improve the selectivity for the formation of **3a**, reaction conditions were optimized as summarized in Table 1. A cationic system "$[CpRu]^+$" (10 mol % of **1a** with 20 mol % of NH_4PF_6) improved the selectivity but the total yield was somewhat lower (entry 2). The product selectivity was reversed by use of Cp*Ru(cod)Cl (**1b**), having a more electron donating but bulkier Cp* ligand than the Cp ligand (entry 3). In this case, the [2 + 2 + 2] cycloadduct **4a** became the major product (47%). This indicates that the steric bulk of the Cp* ligand results in the facile dissociation of coordinated **4a** prior to further [4 + 2] cycloaddition (vide infra). In addition, Mitsudo-type [2 + 2] cycloaddition between the remaining alkyne terminus of a self-cyclodimerization product **5** and norbornene gave **6** in 21% yield.[7]

The corresponding phosphine analogue $CpRu(PPh_3)_2Cl$ (**1c**) was less reactive and gave poor results (entry 4). Thus, cod is superior to PPh_3 as a leaving ligand. In contrast, an indenyl analogue of the above phosphine complex, (η^5-C_9H_7)$Ru(PPh_3)_2Cl$ (**1d**), showed better reactivity and selectivity favorable to the desired tandem adduct **3a** (entry 5). The best result was found by use of **1d** in *1,2-dichloroethane* at 40 °C, and **3a** was selectively obtained in 78% yield (entry 6). A reduced amount of the catalyst (5 mol %) gave a similar result (entry 7). In general, the η^5-indenyl complex is known to be more active than the corresponding cyclopentadienyl analogues due to the associative ligand substitution induced by the η^5 to η^3 slippage of the indenyl ligand,[8] however, it is noteworthy that the η^5-indenyl ligand combined with PPh_3 improved not only the yield but also the product ratio favoring **3a**.

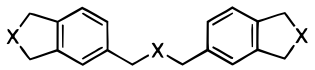
Having optimized the reaction conditions, a series of 1,6-heptadiynes shown in Scheme 1 were subjected to the tandem cycloaddition. For cyclohexanedione derivative diyne **2b** (entry 8) and malononitrile derivative diyne **2c** (entry 9), a longer reaction time (48 h) was required to complete the reaction. Thus, **2b** gave exclusively the corresponding tandem adduct **3b** in 64% yield, while a considerable amount of the [2 + 2 + 2] adduct **4c** (35%) was also formed from **2c** together with the tandem adduct **3c** (50%). In contrast to diynes having a tertiary center at the 4-position, a parent 1,6-heptadiyne with no substituent gave only trace amounts of cycloadducts under the same reaction conditions. Furthermore, diynes having a heteroatom at the 4-position **2d** and **2e** also gave pyrroline derivative **3d** and dihydrofurane derivative **3e**[9] selectively in 47% and 36% yields, respectively (entries 10 and 11). In sharp contrast to the above results, reactions with norbornadiene, which are expected to give a polymer, or benzonorbornadiene gave no cycloaddition product at all. In the former case, 97% of starting diyne **2a** was recovered intact, and in the latter, dimer **5** and trimer **7** were obtained in 77% and 17% yields, respectively.



5 X=C(CO_2Me)$_2$



6 X=C(CO_2Me)$_2$



7 X=C(CO_2Me)$_2$

A plausible mechanism of the tandem cycloaddition is outlined for the representative cyclopentadienyl complex **1a** in Scheme 2. The catalytic cycle starts with the formation of ruthenacyclopentadiene **8** from **1a** and 1,6-heptadiyne **2**. Norbornene is inserted into the ruthenium−carbon bond of **8** in order to minimize the steric repulsion between the Cp ligand and the methylene bridge of norbornene (**8** → **9** → **10**). Reductive elimination of cyclohexadiene gives the η^4-cyclohexadiene complex **11**. In the case where the bulkier Cp* ligand is present as in **1b**, the cyclohexadiene ligand dissociation was facilitated to liberate **4a** mainly. It is noteworthy that the expected [4 + 2] adduct **3a** was not formed at all by refluxing the isolated **4a**, norbornene, and **1a** (10 mol %) in CH_2Cl_2 for 24 h or stirring **4a**, norbornene, and **1d** (20 mol %) in dichloroethane at 40 °C for 24 h. Thus, the [4 + 2] cycloaddition must take place between coordinated cyclohexadiene **11** and a norbornene molecule, which inserts into the ruthenium−carbon bond in η^2-cyclohexadiene complex **12a** (**11** → **12a** → **13** → **3**). Alternatively, the ligand slippage of the indenyl ligand, $\eta^5 \rightarrow \eta^3$, promotes coordination of the norbornene to result in the [4 + 2] cycloaddition (Scheme 2, **12b**). Recently, Rh and Ni have been found to catalyze the intramolecular [4 + 2] cycloaddition between dienes and dienophiles with an electronically similar nature, which occurs only under vigorous conditions without catalysts.[1] As for intermolecular versions of [4 + 2] cycloaddition, Ti-,[10] Fe-,[11] and Rh-[12] catalyzed reactions of dienes with acetylenes were reported in addition to classical Ni catalysis of butadiene dimerization.[1] If our mechanism shown in Scheme 2 is true, the present tandem reaction would be the first example of intermolecular [4 + 2] cycloaddition between a Ru-coordinated nonactivated diene and a strained alkene, norbornene.

In summary, we have found that the ruthenium(II)-catalyzed reaction of 1,6-heptadiyne and norbornene

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(7) For CpRu(cod)Cl-catalyzed [2 + 2] cycloaddition of an acetylene with norbornene, see: Mitsudo, T.; Naruse, H.; Kondo, T.; Ozaki, Y.; Watanabe, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 580.

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(9) The lower yield of **3e** may be ascribable to its thermal unstability. The isolated **3e** slowly decomposed even at −15 °C.

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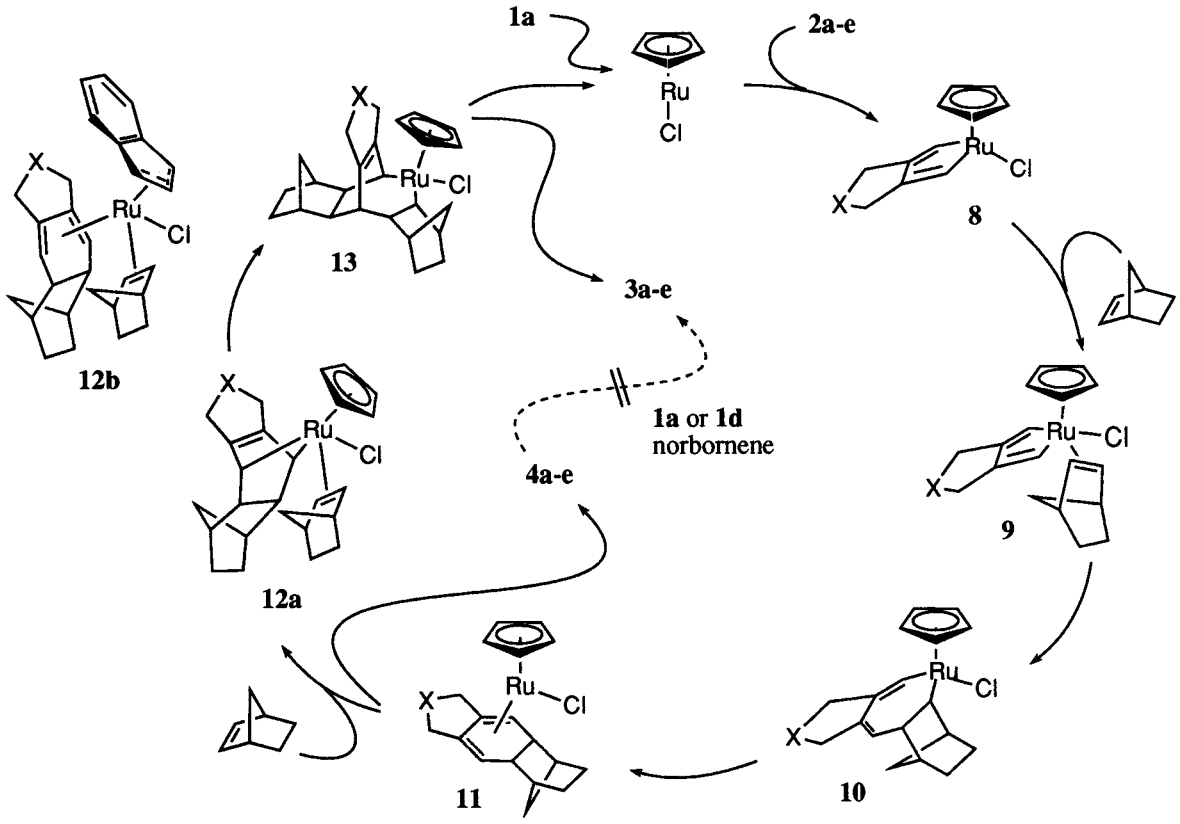
Scheme 2



gave rise to the tandem [2 + 2 + 2]/[4 + 2] cycloadduct as a single stereoisomer along with the simple [2 + 2 + 2] cycloadduct. As a catalyst, CpRu(cod)Cl, in particular, the η^5-indenylruthenium complex (η^5-C_9H_7)Ru(PPh_3)$_2$-Cl, gave the tandem adduct as the major product, and bulkier Cp*Ru(cod)Cl suppressed the second [4 + 2] cycloaddition step to afford the [2 + 2 + 2] adduct as the major product.

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Supporting Information Available: Experimental procedures and spectral data for selected compounds (3 pages). Ordering information is given on any current masthead page.

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