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Ruthenium(II)-Catalyzed [2 + 2 + 2] Cycloaddition of 1,6-Diynes with Tricarbonyl Compounds

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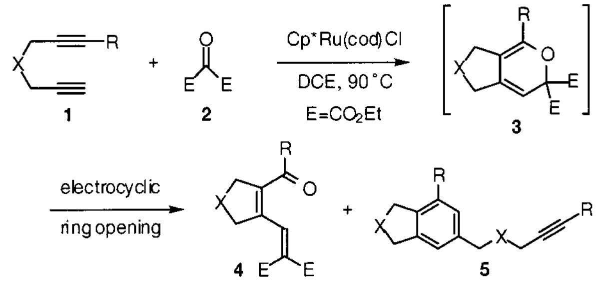
Received April 4, 2002

Transition-metal-catalyzed cycloadditions are viable tools to assemble complex cyclic molecules from unsaturated acyclic precursors.[1] Because of their intrinsic atom-economical nature, catalytic cycloadditions must play a pivotal role in the development of environmentally benign synthetic processes. In this regard, the catalyzed cyclotrimerizations of alkynes or the cocyclotrimerizations of alkynes with alkenes have received renewed attention as a powerful method to construct highly substituted carbocycles without any atomic loss.[2] In addition, nitriles or heterocumulenes such as isocyanates, carbodiimides, and carbondioxide have been known to participate in the cocyclotrimerizations with alkynes, leading to heterocyclic compounds.[2] Whereas these cycloaddition protocols involving C*sp*-heteroatom multiple bonds have been extensively investigated, C*sp*^{2}-heteroatom double bonds have been scarcely utilized to date. The cocyclotrimerizations of alkynes with ketones were realized using *stoichiometric* amounts of cobalt reagents.[3] To the best of our knowledge, only one example reported by Tsuda and Saegusa et al. exists as a *catalytic* cocyclotrimerization involving an aldehyde carbonyl group.[4] Here we wish to report the ruthenium(II)-catalyzed cycloaddition of 1,6-diynes with electron-deficient ketones.

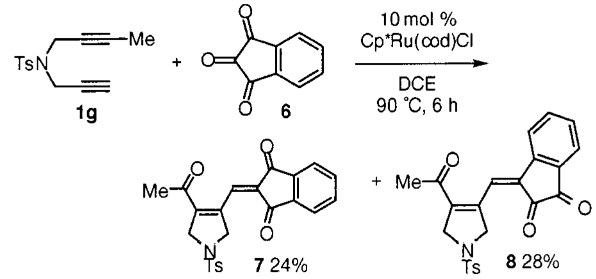
During our studies on the ruthenium-catalyzed cycloaddition of the 1,6-diynes with unsaturated molecules,[5] we found that electron-deficient nitriles can be efficiently involved into the cycloaddition with the diynes to afford bicyclic pyridines.[6] On the basis of this result, we envisaged that a highly electron-deficient C═O double bond activated with two electron-withdrawing groups might be employed for the desired catalytic cycloaddition with the diynes.[7] Actually, in the presence of 5 mol % Cp*Ru(cod)Cl, a malonate-derived diyne **1a** (X = $C(CO_2Me)_2$, R = H) and diethyl ketomalonate **2** (2 equiv) were heated in 1,2-dichloroethane (DCE) at 90 °C for 1 h to afford a dienal **4a** in 46% yield via electrocyclic ring opening of the expected cycloadduct **3a** (Scheme 1).[8] A diyne dimer **5a** was also obtained in 10% yield. Further optimization of the reaction conditions did not increase the yield of **4a**, probably due to the thermal instability of the unsaturated aldehyde moiety.

To improve the present cycloaddition, an unsymmetrical diyne **1b** having one internal alkyne termini (X = $C(CO_2Me)_2$, R = Me) was next used as a diyne substrate. In the similar manner, **1b** was effectively reacted with **2**, and the reaction completed within 2 h. To our delight, the cycloaddition proceeded in a highly regioselective manner to produce the desirable dienone **4b** in 75% yield (Scheme 1). Interestingly, the competitive dimerization of **1b** was suppressed in less than 10%. The generality of the present dienone formation was examined with respect to the diyne substrates. As summarized in Table 1, the terminal substituents bulkier than methyl group (runs 3 and 4) or the heteroatom tether groups (runs 7 and 8) required increased catalyst loadings. The present cycloaddition tolerates functionalities including esters (**1a**−**d**) and a ketone (**1e**) carbonyl group, a hydroxyl (**1f**), a tosyl amide (**1g**), and an ether (**1h**) group. These results demonstrated the wide functional group compatibility of the ruthenium catalysis. The dienone structure of the products was unambiguously confirmed by X-ray analysis (see Supporting Information).

Scheme 1



Scheme 2



In the next step, some electron-deficient ketones were subjected to the present cycloaddition. Upon reaction with the diyne **1g**, indanetrione **6** afforded the unexpected product **8** via cycloaddition at the phenacyl moiety together with the normal product **7** in the combined yield of 52% (Scheme 2). The structure of **8** was unambiguously determined by X-ray analysis (see Supporting Information). This result shows that the two phenacyl C═O double bonds activate each other by the conjugation through the benzene ring.

In contrast to the tricarbonyl compounds **2** and **6**, ethyl pyruvate and diacetyl having a ketone moiety substituted by only one electron-withdrawing group or decafluorobenzophenone having only one carbonyl group with electron-deficiency similar to that of **2** turned out to be totally ineffective. Accordingly, both sufficient electron deficiency and more than two carbonyl groups, which might form a stable chelate intermediate **9** (Scheme 3), seem essential for the ketone substrate. On the basis of this notion, a plausible mechanism for the present cycloaddition was proposed as outlined

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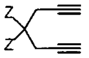
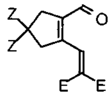
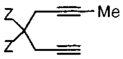
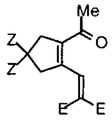
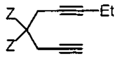
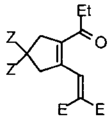
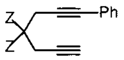
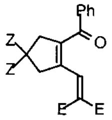
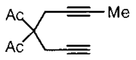
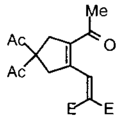
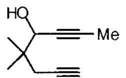
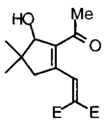
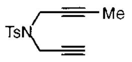
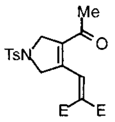
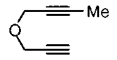
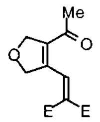
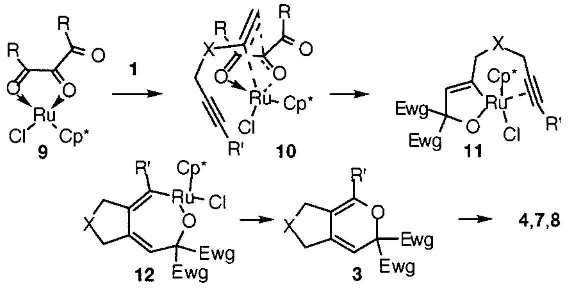
10.1021/ja0264100 CCC: $22.00 © 2002 American Chemical Society

Table 1. Cp*Ru(cod)Cl-Catalyzed Cycloaddition of 1,6-Diynes **1a**−**h** with Diethyl Ketomalonate **2** (Z = CO_2Me, E = CO_2Et)[a]

run	diyne **1**	cat. amount / *t*	**4** / yield[b]
1	 **1a**	5 mol % / 2 h	 **4a** 46%
2	 **1b**	5 mol % / 2 h	 **4b** 75%
3	 **1c**	10 mol % / 4 h	 **4c** 46%
4	 **1d**	20 mol % / 20 h	 **4d** 53%
5	 **1e**	5 mol % / 3 h	 **4e** 57%
6	 **1f**	5 mol % / 2 h	 **4f** 54%
7	 **1g**	10 mol % / 2 h	 **4g** 71%
8	 **1h**	10 mol % / 3 h	 **4h** 42%

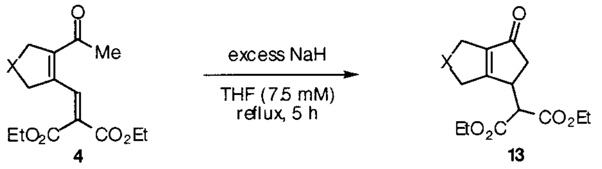
[a] All reactions were carried out with Cp*Ru(cod)Cl, diynes **1** and ketomalonate **2** (2 equiv) in DCE at 90 °C. [b] Isolated yields.

Scheme 3



in Scheme 3. The oxidative cyclization between the less hindered alkyne terminus of **1** and the ketone carboyl group in **2** or **6** starts from **9** to produce an oxaruthenacyclopentene intermediate **11** via a transition state **10**. Similar metallacycle formations were reported for related 1,2-dicarbonyl systems.[9] The insertion of the other alkyne terminus followed by the reductive elimination of **3** from **12** completes the catalytic cycle.

Scheme 4



b X=C(CO_2Me)$_2$, 77%; **g** X=NTs, 53%; **h** X=O, 32%

Finally, we attempted the intramolecular Michael addition of some cycloadducts having both an acetyl and an alkylidenemalonate moiety. As depicted in Scheme 4, the adducts **4b**,**g**,**h** were treated with NaH (10 equiv) in refluxing THF for 5 h to give the desired bicyclo[3.3.0]octenone derivatives **13b**,**g**,**h**, which are useful intermediates for the syntheses of polyquinanes and related compounds.[10]

Acknowledgment. We gratefully acknowledge financial support (09750947, 09305059, 10132222, 12450360, and 13875174) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures and analytical data for **4a**−**h**, **7**, **8**, and **13b**,**g**,**h** (PDF). X-ray crystallographic files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0264100