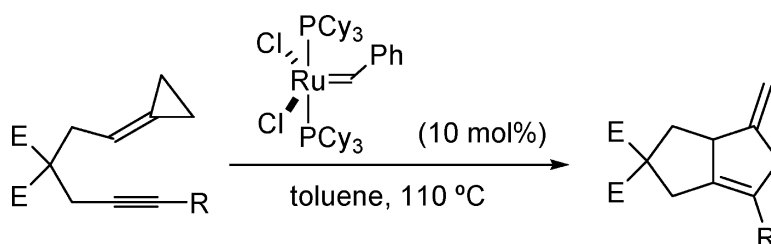Communication

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Ruthenium-Catalyzed [3 + 2] Intramolecular Cycloaddition of Alk-5-ynylidenecyclopropanes Promoted by the "First-Generation" Grubbs Carbene Complex

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Received April 5, 2004; E-mail: qojoselm@usc.es

The transition-metal-catalyzed [3 + 2] cycloaddition of methylenecyclopropanes (MCPs) to unsaturated bonds, pioneered by Noyori and Binger,[1] constitutes an attractive strategy for the construction of five-membered rings.[2] The intramolecular palladium- or nickel-catalyzed version of the reaction, which has been investigated for MCPs of type **1**, gives rise to interesting cyclopentane-containing bicycles such as **3** (Scheme 1).[3] Our group has recently demonstrated that the isomeric alkynylidenecyclopropanes **2**, which are easily assembled from simple precursors, likewise undergo palladium-catalyzed [3 + 2] cycloaddition to give this type of cyclopentenyl adducts (Scheme 1).[4] These cycloadditions probably involve initial formation of a Pd−trimethylenemethane species of type **A** followed by intramolecular carbometalation onto the alkyne and final reductive elimination.

In the course of our studies to determine the metathetic reactivity of ynylidenecyclopropanes such as **2**, we discovered that their intramolecular cycloaddition to **3** can also be catalyzed by the "first-generation" Grubbs carbene complex **4**. In recent years there have been several reports of new ruthenium-promoted transformations,[5] but to the best of our knowledge, we present here the first examples of [3C + 2C] cycloadditions to have been catalyzed by a ruthenium complex.[6]

Our exploration of this reaction began after noting that treatment of enyne **2a** with the well-known Ru−benzylidene **5** gave not only the expected product from ring-closing enyne metathesis (**6a** in 32% unoptimized yield)[7] but also a small amount of the cyclopentene adduct **3a** (Table 1, entry 1). The novelty of this nonmetathetic behavior of **5**[8] prompted us to investigate whether use of the "first generation" Grubbs catalyst **4** might afford better yields of cycloaddition products, owing to its lower enyne metathesis activity. As is shown in Table 1, this did indeed turn out to be case. Treatment of **2a** with **4** (20 mol %) in CH₂Cl₂ at 40 °C gave the cycloadduct **3a** in 36% yield (entry 2); most of the remaining reaction mass was unreacted starting material, but we also detected small amounts of the product due to intramolecular enyne metathesis, diene **6a** (less than 5%), and the cross-metathesis enyne **7a** (less than 10%). Performing the reaction in 1,2-dichloroethane at 80 °C afforded a slightly higher yield of the desired cycloadduct (43%; entry 3), while refluxing in toluene enabled **3a** to be isolated in 59% yield (65% based on recovered starting material; entry 5).
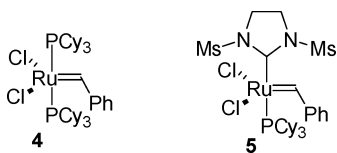
Remarkably, increasing the substrate concentration had a marked impact on the efficiency of the cycloaddition reaction: heating a 0.1 M solution of **2a** in toluene at 110 °C in the presence of 10%
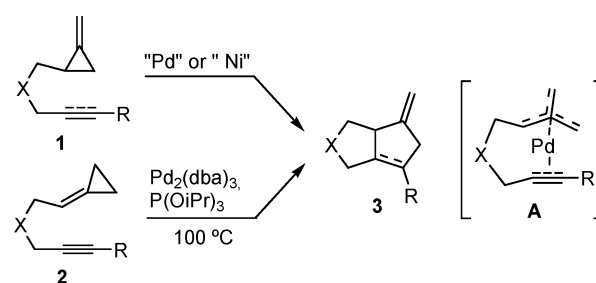
Scheme 1

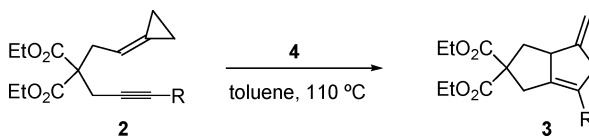**Table 1.** Ruthenium-Catalyzed Intramolecular Alkylidene−Cyclopropane−Alkyne Cycloadditions

entry	[Ru] (%)	solvent (mM)	T (°C)	time	yield (3a) (%)
1	**5** (10)	CH₂Cl₂ (10)	30	24 h	8
2	**4** (20)	CH₂Cl₂ (10)	40	2 h	36
3	**4** (20)	Cl₂(CH₂)₂ (10)	84	4 h	43
4	**4** (20)	toluene (10)	30	4 h	−
5	**4** (20)	toluene (10)	110	4 h	59
6	**4** (10)	**toluene (100)**	**110**	**45 min**	**78**
7	**4** (5)	toluene (100)	110	3 h	54[a]
8	**4** (2)	toluene (100)	110	3 h	34[b]

[a] 73% based on recovered **2a**. [b] 75% based on recovered **2a**.

of carbene complex **4** led to total consumption of starting enyne and provided the desired cycloadduct in 78% yield (entry 6). The reaction can also be achieved using lower catalyst loadings, although it leads to partial recovery of the starting enyne (entries 7 and 8).

Having established a functional cycloaddition protocol, we looked at the influence of the terminal substituent of the alkyne on the efficiency of the reaction. Substrates **2b**−**2f** underwent cycloaddition in moderate to good yields (Table 2). However, the reaction is quite sensitive to the steric bulk of the substituent, with the result that complete consumption of enynes **2c**−**2e** required the use of a slightly higher catalyst loading. The presence of TMS at the alkyne terminus inhibited the cycloaddition process (entry 8, **2g**). In all these reactions the minor products included traces of cross-metathesis enynes **7**.

With regard to the reaction mechanism, we first confirmed that **6a** is not an intermediate in the process because prolonged heating

**Table 2.** Effect of Alkyne Substituent on the Ruthenium-Catalyzed Intramolecular Cycloaddition of **2**

entry	R (substrate)[a]	catalyst (%)	time (min)	yield (%)
1	CH_3 (**2a**)	10	45	78
2	H (**2b**)	10	240	47[b]
3	CH_2CH_3 (**2c**)	10	300	56
4	CH_2CH_3 (**2c**)	15	90	73
5	$(CH_2)_4CH_3$ (**2d**)	15	120	67
6	CH_2OTBS (**2e**)	15	205	62
7	CH_2OH (**2f**)	10	300	26
8	$SiMe_3$ (**2g**)	10	300	–

[a] Substrates were prepared following procedures described in ref 4. [b] This reaction was carried out in refluxing dichloroethane; in toluene at 110 °C we obtained lower yields of the cycloadduct.

of this compound in toluene, either in the presence or absence of **4**, did not lead to the adduct **3a** (**6a** remains mostly unchanged). A particularly relevant issue concerns the specific ruthenium species responsible for initiating the cycloaddition reaction. Since it is known that **4** decomposes upon heating at high temperatures,[9] we speculated that the catalytically active species could be one (or more) of the resultant thermolyzed ruthenium derivatives, presumably a non-carbene species. This was not the case, however, as preheating of a solution of **4** in toluene (2 h, 110 °C) prior to addition of the enyne inhibited the cycloaddition.

Monitoring of the room-temperature reaction of enyne **2a** with catalyst **4** (10 mol %) by ^{31}P NMR in CD_2Cl_2, allowed the observation of a relatively rapid disappearance of the characteristic singlet of **4** at 37.2 ppm[10] along with the simultaneous appearance of a new ^{31}P signal at 31.8 ppm, with complete conversion within 1 h. The ^{1}H NMR spectrum of the reaction mixture revealed the presence of an approximate 1 to 9 ratio of the cross-metathesis product **7a** and unaltered starting enyne **2a**. On these bases, we inferred that the new ^{31}P signal was due to the cyclopropylidene ruthenium carbene **9**. This conclusion was supported by the finding that the alkylidenecyclopropane **8** reacts with stoichiometric amounts of **4** to give quantitatively the cross-metathesis alkene **10** and the ruthenium cyclopropylcarbene **9** (Scheme 2).[11]

Scheme 2
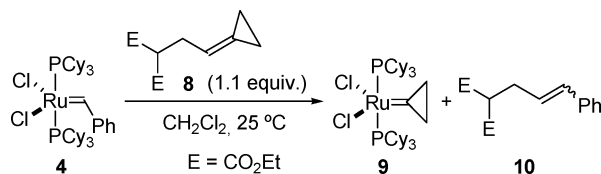
Interestingly, heating enyne **2a** under reflux in toluene for 45 min in the presence of ruthenium complex **9** (10 mol %) provided the desired bicyclo[3.3.0]octane **3a** in 82% yield.[12] The above observations suggest that the cyclopropylcarbene **9** could be the actual (pre)catalyst of the cycloaddition,[13] although catalysis by a ruthenium species directly generated from **4** in the presence of the enyne cannot be ruled out completely.

To confirm whether the responsible catalytic species could be a non-carbene derivative,[8] we checked the viability of inducing the cycloaddition reaction using these types of complexes. Compound **2a** was heated under reflux in toluene in the presence of [(p-cymene)RuCl_2]_2 but did not produce the cycloadduct. However,

when the reaction was performed in the presence of 10% of $Cp*Ru(CH_3CN)_3PF_6/Et_4NCl$ or $Cl_2Ru(PPh_3)_3$, the desired adduct was obtained in 11% and 35% yield, respectively (77% based on recovered enyne). Despite the low yields, these preliminary results seem to reinforce the hypothesis that the cycloaddition reaction is promoted by a non-carbene ruthenium species generated under the reaction conditions and that presumably it occurs by a different mechanism than in the case of palladium.

In conclusion, we have discovered a novel, nonmetathetic application of the Grubbs carbene complex in the first [3C + 2C] cycloaddition process catalyzed by a ruthenium complex. Further studies to obtain new mechanistic insights and to expand the scope and synthetic utility of the method are underway.

Supporting Information Available: Experimental procedures and spectroscopic data for the reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The disappearance of the carbene CH resonance of **4** at 19.8 ppm can also clearly be observed in the ^{1}H NMR spectra.

(11) See Supporting Information for experimental details.

(12) NMR monitoring of the progress of the reaction between **2a** and **9** in [D_8]toluene revealed no changes below 60 °C. However, heating to 70 °C induced the slow disappearance of the ^{31}P singlet at 31.8 ppm, which is characteristic of **9**, with the concomitant emergence of several new phosphorus signals (see Supporting Information) and parallel formation of the cycloadduct (as deduced from ^{1}H NMR). Increasing the reaction temperature to 110 °C brought the reaction to completion.

(13) It is interesting to note that preheating of a solution of **9** in toluene at 70 °C for 45 min generated a catalytically inactive residue. The ^{31}P NMR spectrum of this heated residue showed numerous signals.

JA0480466