J|A|C|S
COMMUNICATIONS

Published on Web 06/28/2006

Ru-Catalyzed Cyclization of Terminal Alkynals to Cycloalkenes

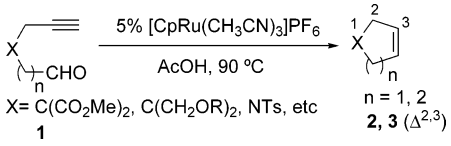
Jesús A. Varela, Carlos González-Rodríguez, Silvia G. Rubín, Luis Castedo, and Carlos Saá*

Departamento de Química Orgánica y Unidad Asociada al CSIC, Facultad de Química, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain

Received February 13, 2006; E-mail: qocsaa@usc.es

Transition metal catalysts occupy a central role in improved or newly developed cyclization reactions. For example, internal alkynals undergo cycloisomerization to cycloalkenones through Rh-catalyzed intramolecular hydroacylation,[1] conversion to *exo*-and *endo*-cycloalkenols through Ni-catalyzed reductive and Ni and Pd-alkylative processes[2] and through Rh-catalyzed arylative cyclizations,[3] and transformation into cyclic alkenyl ethers or conjugated cyclic ketones by π-complexation to electrophilic Pd[4] or Rh complexes.[5] However, some of these procedures fail to cyclize terminal alkynals, which have accordingly received much less attention. Here we describe a new, efficient Ru-catalyzed cyclization of terminal alkynes **1** to cycloalkenes **2** (Scheme 1).[6,7]

Scheme 1. Ru-Catalyzed Cyclization of Terminal Alkynals **1**



Heating the 5-alkynal **1a** (n = 1, X = $C(CO_2Me)_2$) in a 5% solution of the catalyst $[CpRu(CH_3CN)_3]PF_6$ in AcOH afforded, after 24 h at 90 °C, the cyclopentene **2a**, with one carbon less than **1a**, in excellent yield (Table 1, entry 1).[8] Heating at higher temperatures led to faster reactions, but with increasing amounts of the isomeric cyclopentene **3a** (entries 2 and 3). Using the more electron-rich, sterically more demanding catalyst $[Cp^*Ru(CH_3CN)_3]PF_6$ gave similar results (entries 4 and 5). Interestingly, addition of 5% dppf to the reaction mixture led exclusively to **2a** in 85% yield (entry 6).[8b]

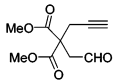
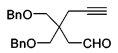
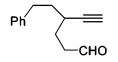
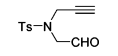
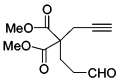
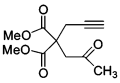
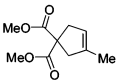
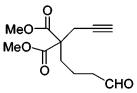
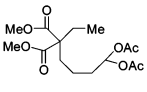
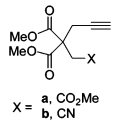
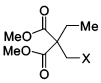
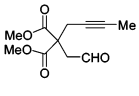
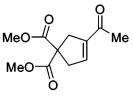
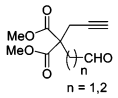
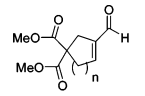
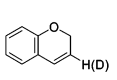
Table 1. Ru-Catalyzed Cyclization of Alkynal **1a** [X = $C(CO_2Me)_2$, n = 1] in Acetic Acid

entry	catalyst[a]	T (°C)	time	yield (%)[b]	**2a**:**3a**
1	$[CpRuL_3]PF_6$	90	24 h	95	95:5
2	"	130	1.5 h	96[c]	60:40
3	"	150	50 min	93[c]	50:50
4	$[Cp^*RuL_3]PF_6$	90	5.5 h	95[c]	80:20
5	"	150	50 min	92[c]	50:50
6	$[Cp^*RuL_3]PF_6$ + 5% dppf	90	8 h	85	100: 0

[a] L= CH_3CN, dppf= diphenylphosphinoferrocene. [b] Isolated yields. [c] GC yields.

Other terminal 5-alkynals with alternative 3,3-disubstitution (**1b**), with 4-monosubstitution (**1c**), or with nitrogen at skeletal position 3 (**1d**) and the terminal 6-alkynal **1e** behaved similarly affording cyclopentenes **2b** and **2c**, 2,5-dihydropyrrole **2d**, and cyclohexene **2e**, respectively, in good to excellent yields (Table 2, entries 2−5). To go into the reaction with more detail, a series of experiments with several substrates were performed. When the alkynone **4** was used, the corresponding cyclopentene **5** was obtained in moderate yield (Table 2, entry 6),[9] indicating that an oxidative addition of the ruthenium to the aldehyde C−H bond is unlikely.

Table 2. Ru-Catalyzed Cyclization of Alkynals **1a**−**e** and **12**[a]

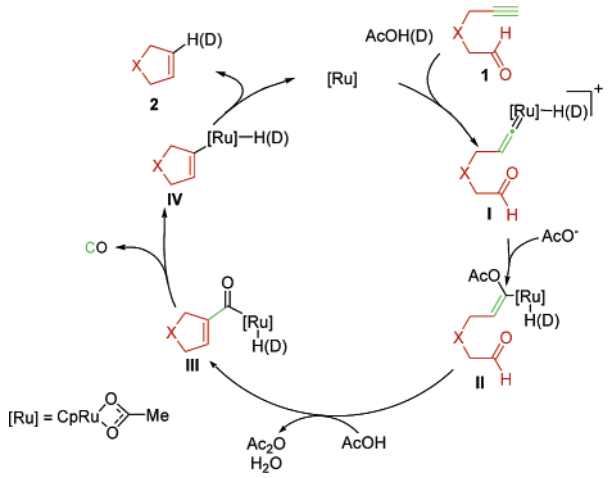
entry	alkynal		cycloalkene[b]		yield (%)[c]
1		**1a**		**2a**	90
2		**1b**		**2b**	70
3[d]		**1c**		**2c**	60
4		**1d**		**2d**	93
5[e]		**1e**		**2e**	60
6[e]		**4**		**5**	40[f]
7[e]		**1f**		**6**	52
8[e]	 X = **a**, CO_2Me; **b**, CN	**7**		**8a** **8b**	70 65
9		**9**		**10**	40
10[g]	 n = 1,2	**1a** **1e**		**11a** **11e**	75 70
11[h]		**12**		**13**	80

[a] Typical conditions: alkynal **1** (0.1 M), 5% $[CpRu(CH_3CN)_3]PF_6$, AcOH, 90 °C, 24 h. [b] For 5-alkynals, up to 5% of the product was isomer **3**. [c] Isolated yields. [d] $[Cp^*Ru(CH_3CN)_3]PF_6$ was used as catalyst. [e] Reaction performed at 130 °C. [f] Ketone **8c** (X = COMe) was also obtained in 30% yield. [g] CpRu(dppm)Cl in ^{i}PrOH/H_2O was used as catalyst. [h] Deuteration studies on **12**, performed in AcOD at 90 °C, gave deuterated **13** with more than 95% deuterium incorporation.

When the tether between the alkyne and the aldehyde was enlarged, such as alkynal **1f**, the noncyclized ketal **6** with loss of one carbon was observed (Table 2, entry 7). Other alkynes with terminal functional groups other than aldehyde behaved similarly (Table 2, entry 8).[10] The results from the last two entries seem to indicate that the carbon lost during the reaction is most likely the terminal alkyne carbon. This evidence was reinforced when the reaction of internal alkynal **9** only gave the conjugated ketone **10**, in which all the carbons of the starting material are present (Table 2, entry 9). Interestingly, terminal alkynals **1a**,**e** are able to cycloisomerize to conjugated aldehydes **11a**,**e** (all the carbons of

10.1021/ja0610434 CCC: $33.50

Scheme 2. Possible Mechanism of the Decarbonylative Ru-Catalyzed Cyclization of Terminal Alkynals **1**



the starting material remained) by just using CpRu(dppm)Cl as catalyst in ^{i}PrOH/H_2O as solvent (Table 2, entry 10).[11]

To explain the above results on the basis of the findings of Wakatsuki[10a,b] and in our own deuteration studies with alkynal **12** (Table 2, entry 11),[8b] we hypothesize the mechanism shown in Scheme 2. When heated in AcOH, the cationic catalyst [CpRu-$(CH_3CN)_3$]PF_6 most likely generates an active Ru complex[12,13] that after coordination with **1** gives the Ru(II) vinylidene species **I**,[6b,e,7] which upon nucleophilic addition of the acetic acid would afford the vinyl Ru species **II**. Next, and only for the cases of aldehydes **1a**−**e**, **12**, and the ketone **4**, an aldol-type condensation would then give the acyl Ru hydride **III**.[14] In the case of alkynal **1f**, probably the formation of a cycloheptene by an aldol-type reaction between the vinyl Ru species and the aldehyde is not favored, while the ester and nitrile groups of **8a** and **8b** are not enough electrophiles for the aldol-type reaction. Then, the next step would be the decarbonylation (*being the terminal carbon of the alkyne the one lost as CO*) followed by reductive elimination to afford the observed cycloalkenes **2** and **5**[15] in the case of alkynals and alkynone, respectively. Decarbonylation without cyclization occurred (not shown in Scheme 2) for alkynal **1f** and ester and nitrile **7a**,**b**, respectively, to give compounds **6** and **8a**,**b**. The conjugated aldehydes **11** observed when CpRu(dppm)Cl was used as catalyst (Table 2 entry 10) can also be explained according to the proposed mechanism if reductive elimination from **III** occurred (no decarbonylation takes place in this case due to the bidentate nature of dppm ligand). Nevertheless, the conjugated ketone **10** obtained from internal alkyne **9** would probably arise from a total different mechanism (hydration of internal alkyne activated with a metal acting as a Lewis acid) due to the impossibility of the formation of vinylidene species.

In conclusion, we have discovered a new Ru-catalyzed cyclization of terminal alkynals to give cycloalkenes. Under appropriate catalytic conditions, cycloisomerization to conjugated aldehydes may be observed. Both processes involve catalytic Ru vinylidenes. On the basis of the findings described herein, we envisage new possibilities of C−C bond formation catalyzed by transition metal vinylidenes. Research in this direction is currently underway.

Acknowledgment. This work is dedicated to Professor K. C. Nicolaou on the occation of his 60th birthday. This work was supported by the Ministerio de Educación y Ciencia (Spain) and the European Regional Development Fund (Project CTQ2005-08613), and by the Xunta de Galicia (Project PGIDT00PXI20908). S.G.R. and C.G.-R. thank the M.E.C. and the Segundo Gil-Dávila Foundation, respectively, for predoctoral grants, and J.A.V. thanks the M.E.C. for a Ramón y Cajal research contract.

Supporting Information Available: A typical procedure for the Ru-catalyzed reaction and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 11492. (b) Tanaka, K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1607. (c) Takeishi, K.; Sugishima, K.; Sasaki, K.; Tanaka, K. *Chem.—Eur. J.* **2004**, *10*, 5681. (d) See also: *Modern Rhodium-Catalyzed Organic Reactions*; Evans, A. P., Ed.; Wiley-VCH: Weinheim, Germany, 2005.

(2) (a) For a review, see: Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890. (b) For Ni *endo*-macrocyclization, see: Knapp-Reed, B.; Mahandru, G. M.; Montgomery, J. *J. Am. Chem. Soc.* **2005**, *127*, 13156. (c) For Ni *exo*-macrocyclization, see: Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 4297. (d) For Pd alkylative cyclization, see: Tsukamoto, H.; Ueno, T.; Kondo, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1406.

(3) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54.

(4) (a) Zhao, L.; Lu, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4343. (b) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764.

(5) Tanaka, K.; Sasaki, K.; Takeishi, K.; Sugishima, K. *Chem. Commun.* **2005**, 4711.

(6) For an Ru-catalyzed hydrative cyclization of ynenones, see: (a) Trost, B. M.; Brown, R. E.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 5877. See also: (b) Trost, B. M.; Fredericksen, M.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630. For an Ru-catalyzed hydrative cyclization of diynes, see: (c) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2005**, *127*, 4763. (d) Odedra, A.; Wu, C.-J.; Pratap, T. B.; Huang, C.-W.; Ran, Y.-F.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 3406. For an Ru-catalyzed hydrative cyclization of 1,5-enynes, see: (e) Chen, Y.; Ho, D. M.; Lee, C. *J. Am. Chem. Soc.* **2005**, *127*, 12184. For an Ru-catalyzed cyclocarbonylation of alkynals, see: (f) Chatani, N.; Morimoto, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 5335.

(7) For reviews on vinylidene carbene complexes, see: (a) Bruce, M. I.; Swincer, A. G. *Advances in Organometallic Chemistry*; Academic Press: New York, 1983; Vol. 22, p59. (b) Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197. For books, see: (c) *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, Germany, 2004. (d) *Topics in Organometallic Chemistry*; Bruneau, C., Dixneuf, P. H., Eds.; Springer: Berlin, 2004; Vol. 11.

(8) (a) Minor amounts of the isomer **3a** (<5%) have been observed. (b) See Supporting Information for more details and for other catalytic conditions.

(9) Reaction performed at 130 °C being the decarbonylated ketone **8c** (X = $COCH_3$) was also obtained in 30% yield.

(10) (a) Suzuki, T.; Tokunaga, M.; Wakatsuki, Y. *Org. Lett.* **2001**, *3*, 735. (b) Tokunaga, M.; Suzuki, T.; Koga, N.; Fukushima, T.; Horiuchi, A.; Wakatsuki, Y. *J. Am. Chem. Soc.* **2001**, *123*, 11917. (c) For a stoichiometric reaction, see: Bianchini, C.; Casares, J. A.; Peruzzini, M.; Romerosa, A.; Zanobini, F. *J. Am. Chem. Soc.* **1996**, *118*, 4585.

(11) Conditions developed for *anti*-Markovnikov hydration of alkynes: (a) ref 10b. For other catalytic conditions, see: (b) Grotjahn, D.; Lev, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 12232.

(12) For formation of (η^2-O_2CCH_3)Ru complexes, see: Werner, H.; Braun, T.; Daniel, T.; Gevert, O.; Schulz, M. *J. Organomet. Chem.* **1997**, *541*, 127.

(13) It has been suggested that Cp*Ru(cod)Cl, when heated with AcOH at 65 °C, forms a hydrido−Ru(IV) complex that upon coordination with alkynes gives a vinyl−Ru species. Le Paih, J.; Cuervo, D.; Dérien, S.; Dixneuf, P. H. *Synlett* **2000**, *1*, 95. We observed no products suggestive of this process.

(14) Reductive elimination products derived from intermediates **II** (vinyl acetate **IIa**) or **III** (aldehyde **11a**) did not afford the observed cycloalkene **2a** after heating their solutions in AcOH at 90 °C in the presence of the Ru catalyst. See Supporting Information S5 for details.

(15) The isomeric cycloalkenes **3** probably arise through isomerization of the Ru hydride **IV**.

JA0610434