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Ruthenium-Catalyzed Hydrative Cyclization of 1,5-Enynes

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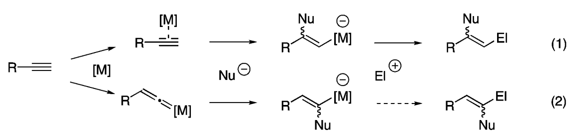
Transition-metal-catalyzed alkyne addition is a process of wide utility for the formation of carbon−carbon and carbon−heteroatom bonds with high regio- and stereocontrol.[1] While numerous strategies have been developed to effect carbofunctionalization via a 1,2-addition process (eq 1), such a reaction enabling a multicomponent coupling has remained elusive in the 1,1-mode due to the susceptibility of the putative vinylmetal intermediate to a protic quench (eq 2).[2,3] Given the facility with which metal vinylidenes are available from alkynes and the versatility of a metal−carbon σ-bond, such tandem 1,1-addition reactions would be of significant utility in organic synthesis. Herein, we describe a ruthenium-catalyzed hydrative cyclization of 1,5-enynes that occurs through a 1,1-difunctionalization of terminal alkynes.



Our initial studies focused on testing the feasibility of an internal Michael acceptor to intercept the vinylmetal species emanating from an attack of a nucleophile to the vinylidene complex (Scheme 1). The addition of benzoic acid to **1** under ruthenium catalysis,[4] however, did not provide **3**, but resulted in the formation of **2** in 70% yield. The exclusive *Z*-selectivity of **2** suggests that the reaction involves **B** as the intermediate rather than **C**, which is required for cyclization.[5] Noting the reports on ruthenium-catalyzed anti-Markovnikov hydration,[6] we reasoned that this problem of geometric isomerism might be circumvented by targeting **D** arising from tautomerization of either water adduct **B** or **C**. Subsequently, the acylmetal species would then undergo a C−C bond-forming cyclization with the pendant alkene to form **5**, overriding a reductive elimination pathway to **4**.[7]

On the basis of the mechanistic proposition, hydrative cyclization of **1** was examined using various ruthenium catalysts (Table 1). Following literature protocols,[6] **1** was subjected to conditions known to promote anti-Markovnikov hydration (entries 1−3). These catalyst systems, however, induced neither cyclization nor hydration, returning mainly starting material (ca. 80%). In contrast, employing non-half-sandwich ruthenium complexes and dppm produced the desired cyclopentanone **5** along with the Markovnikov hydration adduct **6** and reduced products **7**−**9** (entries 4 and 5).[8] Further screening revealed the combination of [(p-cymene)$RuCl_2$]$_2$ and dppm (entry 6) to be a superior catalyst which improved the yield of **5** to 64% while minimizing formation of the byproducts. The use of dppm as the ligand proved to be critical as reactions with other mono- and diphosphine ligands gave poor results (entries 7−10).

To gain insight into the active catalyst, all of the reagents employed in entry 6 of Table 1 were reacted in the absence of **1** (Scheme 2). This reaction led to decomplexation of *p*-cymene from the ruthenium center and formation of **10**, which upon anion

Scheme 1 Addition−Cyclization of **1** via Ru Vinylidene Catalysis

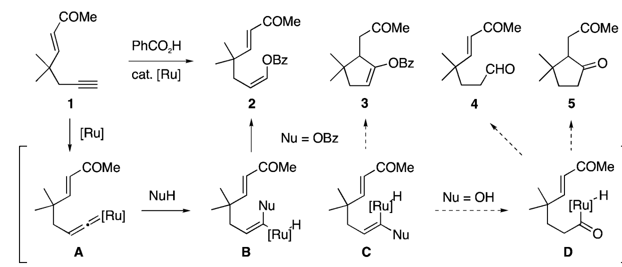
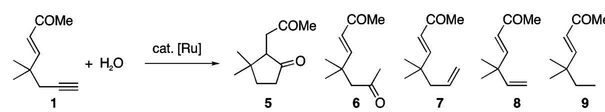


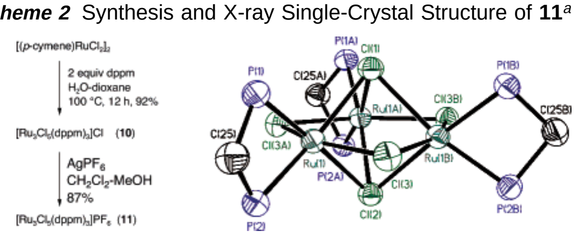
Table 1. Ruthenium-Catalyzed Hydrative Cyclization of Enyne **1**



entry	[Ru]	ligand	yield[b] 5	6	7+8+9
1[a]	$CpRuCl(PPh_3)_2$	dppm	0%	0%	0%
2[a]	$CpRuCl(PPh_3)_2$	P,N-L[c]	0%	0%	0%
3[a]	(Ind)$Ru(PPh_3)_2Cl$	−	0%	0%	0%
4	[(COD)$RuCl_2$]$_n$	dppm	29%	5%	24%
5	$Ru(PPh_3)_3Cl_2$	dppm	28%	0%	42%
6	[(p-cymene)$RuCl_2$]$_2$	dppm	64%	0%	4%
7	[(p-cymene)$RuCl_2$]$_2$	PPh_3	2%	6%	21%
8	[(p-cymene)$RuCl_2$]$_2$	dppe	47%	4%	5%
9	[(p-cymene)$RuCl_2$]$_2$	dppp	6%	9%	0%
10	[(p-cymene)$RuCl_2$]$_2$	BINAP	0%	4%	13%

[a] The reactions of entries 1−3 were carried out following ref 6. All other reactions were performed with 0.2 mmol of **1**, 10 mmol of H_2O, 10 mol % of [Ru], and 10 mol % of ligand (or 20 mol % of monophosphine) in 1.0 mL of 1,4-dioxane at 120 °C for 12 h. [b] Determined by ^{1}H NMR. [c] P,N-L = 2-Diphenylphosphino-6-methylpyridine.

Scheme 2 Synthesis and X-ray Single-Crystal Structure of **11**[a]



[a] H atoms and the two phenyl rings on P atoms are omitted for clarity.

exchange, afforded the trinuclear ruthenium **11** of 3-fold symmetry.[9] Both **10** and **11** were air and moisture stable and found to be more effective than the in situ generated catalyst for the cyclization of **1**, furnishing **5** in 76 and 80% isolated yield, respectively (2 mol % catalyst loading). However, it is unclear whether these trinuclear complexes themselves are the active catalyst or mere progenitors of mononuclear complexes.

The hydrative cyclization process was further examined with an assortment of substrates using trinuclear complex **11** as the catalyst (Table 2). A range of 1,5-enynes with α,β-unsaturated ketones,

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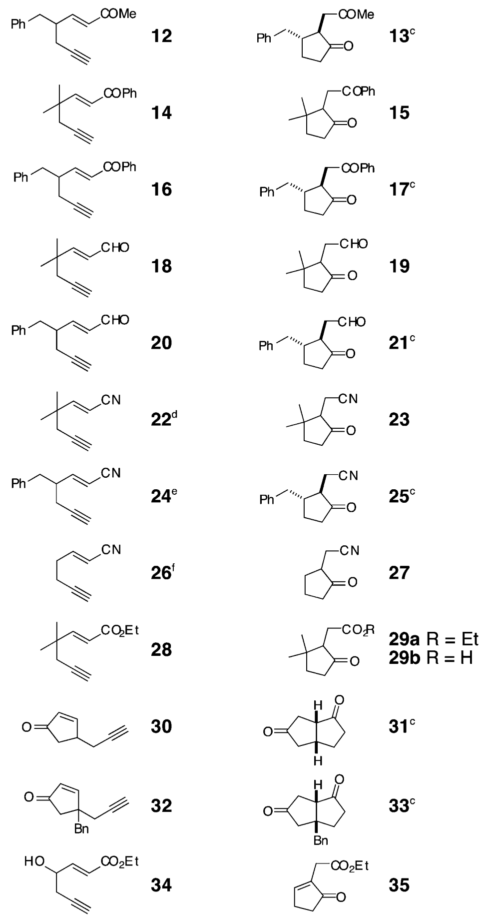
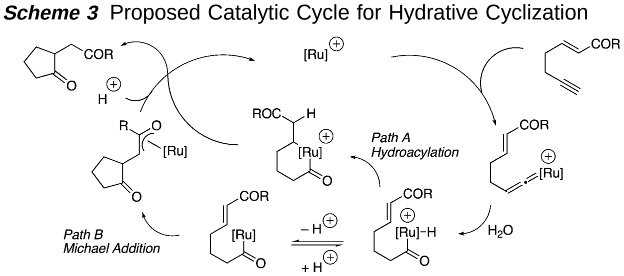
Table 2. Ruthenium-Catalyzed Hydrative Cyclization of 1,5-Enynes[a]



entry	reactant	product	yield[b]
1	12	13[c]	69%
2	14	15	72%
3	16	17[c]	63%
4	18	19	48%
5	20	21[c]	47%
6	22[d]	23	74%
7	24[e]	25[c]	81%
8	26[f]	27	68%
9	28	29a R = Et 29b R = H	46% 23%
10	30	31[c]	52%
11	32	33[c]	75%
12	34	35	53%

[a] All reactions were performed with 0.2 mmol of substrate, 10 mmol of H_2O, and 2 mol % of **11** in 1.0 mL of 1,4-dioxane at 120 °C for 12 h. [b] Isolated yields. [c] A single diastereomer was obtained as the product. [d] E:Z = 5:1. [e] E:Z = 1:1. [f] E:Z = 1:2.

Scheme 3 Proposed Catalytic Cycle for Hydrative Cyclization



aldehydes, nitriles, and esters participated well in the reaction to give the cyclopentanone derivatives as the product. In most cases, the combined yield of the uncyclized products analogous to compounds **6**−**9** was less than 5%. Notably, **34** was converted to **35** (entry 12) presumably through a β-elimination after cyclization, despite the presence of the internal hydroxyl group which could form a dihydrofuran.[10]

The mechanism of the hydrative cyclization is proposed in Scheme 3, in which the catalytic cycle involves the formation of a ruthenium vinylidene, an anti-Markovnikov addition of water, and cyclization of an acylmetal species onto the alkene. Although the cyclization may occur through a hydroacylation[11] or Michael addition (paths A and B),[12] the requirement of an electron-withdrawing substituent on the alkene and the lack of aldehyde formation suggest the latter pathway to be the more likely mechanism.[13]

In summary, we have developed a new ruthenium-catalyzed method for the tandem formations of C−O and C−C bonds via 1,1-difunctionalization of alkynes. This reaction achieves an umpolung cyclization in which a terminal alkyne is hydrated and undergoes an intramolecular Michael addition. While mirroring the Stetter reaction,[14] the new process proceeds through an acyl ruthenium species catalytically generated from hydration of a vinylidene complex. Efforts are currently directed at further expanding the scope of the transformation.

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Supporting Information Available: Experimental details and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) A mechanism, whereby a Ru alkylidene rather than an acyl Ru is formed and undergoes a cycloaddition with the alkene followed by β-hydride and reductive eliminations to give the product, cannot be excluded. For an example of a Ru α-hydroxyalkylidene, see: (a) Esteruelas, M. A.; Gómez, A. V.; Lahoz, F. J.; López, A. M.; Oñate, E.; Oro, L. A. *Organometallics* **1996**, *15*, 3423. For a mechanistically related example, see: (b) Kim, H.; Lee, C. *J. Am. Chem. Soc.* **2005**, *127*, 10180.

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