

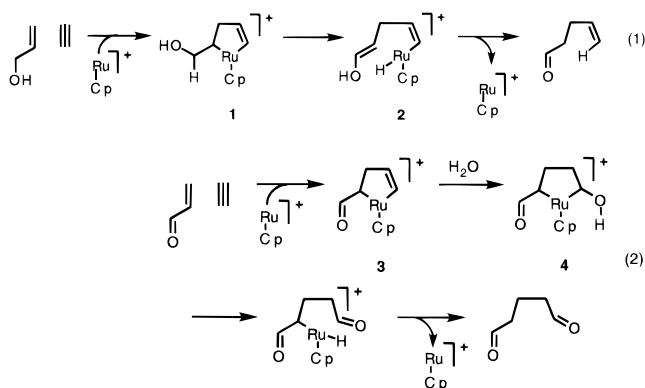
A Ru-Catalyzed Three-Component Addition To Form 1,5-Diketones

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The improvement of synthetic efficiency requires the development of more reactions wherein the product is the sum of the reactants with anything else being required only catalytically, i.e., the invention of atom economical reactions.¹ In pursuit of this goal, earlier work in these laboratories suggested that a ruthenacycle **1** is a likely intermediate in the ruthenium-catalyzed addition of alkenes and alkynes to form γ , δ -unsaturated ketones (eq 1).^{2,3} If the β -hydrogen elimination (**1** \rightarrow **2**) is blocked by



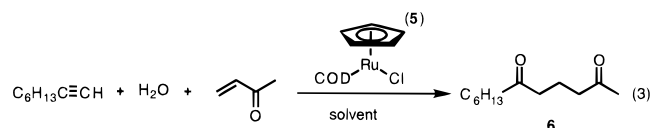
using a vinyl ketone as in eq 2, the intermediate ruthenacyclopentene **3** may undergo an addition across the double bond considering the availability of unshared electrons on Ru⁴⁺. The resultant ruthenacycle **4** may now undergo a β -hydrogen elimination wherein the overall result is the combination of an alkyne, an enone, and water to form a 1,5-diketone. These intermediates represent important precursors of ring systems by intramolecular aldol and pinacol processes as well as in their own right.⁴ We wish to report the realization of this proposed reaction.

We examined the reaction of 1-octyne with methyl vinyl ketone as our test system. Using 5 mol % of the ruthenium complex **5**⁵ as catalyst, a mixture of 1-octyne and methyl vinyl ketone was heated in 1:1 DMF-water at 100 °C in the presence of 10 mol % ammonium hexafluorophosphate for 3 h. Gratifyingly, the desired 2,6-dodecanedione **6**,⁶ mp 51–2 °C, was formed albeit in 41% yield (44% yield brsm⁷) (eq 3). Changing solvent to 1:1 *n*-propyl alcohol–water (also at 100 °C) or 1:1 isopropyl alcohol–water (at 80 °C) saw little improvement in

Table 1. Addition of 1-Alkynes, Water, and MVK To Form 2,6-Diketones

Entry	R	Yield ^a	Cmpnd No.
1	HOCH ₂ CH ₂ CH ₂	(69)	7a
2	NCCH ₂ CH ₂ CH ₂	82 (81)	7b
3	<i>t</i> -C ₄ H ₉ O ₂ CCH ₂ CH ₂	67 (51)	7c
4	CH ₂ OCH ₂ CH ₂ CH ₂	68 (57)	7d
5	(CH ₃) ₂ C(OH)	70 (59)	7e ^b
6	NH ₂ C(=O)CH ₂ CH ₂ CH ₂	(28)	7f
7		(69)	7g
8		70 (52)	7h ^b

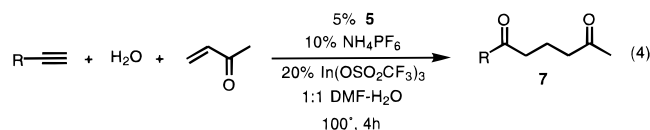
^a Yield determined by GC with dodecane as an internal standard. Yields in parentheses are for isolated pure compound (see ref 6). ^b In this case, a minor amount (<5%) of a regioisomeric product was also formed.



the former case (45% yield, 51% yield brsm⁷) and some decrease in yield in the latter case (35%, 39% brsm⁷). Interestingly, adding 10 vol % of *n*-propyl alcohol to 1:1 DMF–H₂O increased the yield to 57% (59% brsm⁷). We attribute the latter effect to better solubilization of the 1-octyne in the reaction medium while maintaining high polarity. Because of subsequent results, we also examined use of acetonitrile as an additive but only a 35% yield of the desired adduct was formed.

A major effect occurred upon addition of indium salts.⁸ At a 4 h reaction time, the initial conditions gave a 43% yield (47% brsm) of the diketone **6**. Adding 10 mol % indium trichloride increases the yield to 56% (59% brsm) in the same time period. A greater improvement occurs by avoiding increasing the chloride ion concentration by using 10 mol % indium tris(triflate) where a 67% yield (69% brsm) of **6** forms. Increasing the amount of the latter co-catalyst to 20 mol % effects a further improvement of yield to 74%.

Using the latter conditions, we then explored the generality of the reaction by varying the alkyne. Table 1 and eq 4



summarize these results. The only substrate that gave poor yields was that bearing a primary carboxamide (entry 6). A possible rationale is that this functional group serves as an internal nucleophile, whose addition to the alkyne is promoted by ruthenium. Interestingly, the ester group does not create this limitation (entry 3). The nitrile (entry 2), which is a direct synthon for a primary carboxamide, represents the best substrate to date. For this reason, we explored the use of acetonitrile as a potential activating ligand, albeit to no avail. Primary (entry 1), secondary (entry 7), and tertiary (entries 5 and 8) alcohols even in a propargylic position are quite compatible.

Our previous studies indicated that substituents on the double bond greatly inhibited several of our ruthenium-catalyzed reactions.³ Thus, variation of the vinyl ketone examined replacing the methyl group by more sterically hindered sub-

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(3) Cf. Ru catalyzed Alder ene reaction; see: Trost, B. M.; Indolese, A. F.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, 117, 615. Trost, B. M.; Müller, T. J. J.; Martinez, J. *J. Am. Chem. Soc.* **1995**, 117, 1888.

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(6) This compound has been characterized spectroscopically and elemental composition established by high resolution mass spectrometry or combustion analysis.

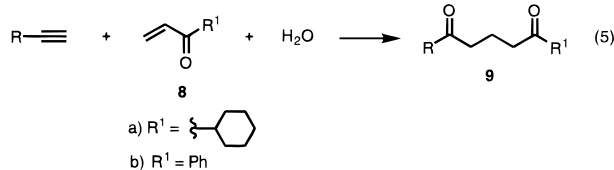
(7) brsm = based upon recovered starting material.

(8) For In co-catalysis in Pd chemistry, see: Trost, B. M.; Sharma, S.; Schmidt, T. *J. Am. Chem. Soc.* **1992**, 114, 7903. Trost, B. M.; Sharma, S.; Schmidt, T. *Tetrahedron Lett.* **1993**, 34, 7183. For In co-catalysis in Ru chemistry, see: Trost, B. M.; Livingston, R. C. *J. Am. Chem. Soc.* **1995**, 117, 9586.

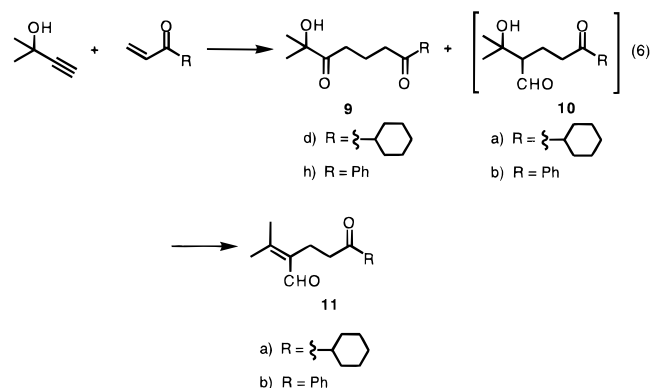
Table 2. Variation of Vinyl Ketone Acceptor

Entry	R ¹	R	% Isolated Yield	Compnd No.
1		CH ₂ CH ₂ CH ₂ CN	93	9a
2		CH ₂ CH ₂ CH ₂ OH	78	9b
3		CH ₂ CH ₂ CO ₂ C ₄ H ₉ - <i>t</i>	52	9c
4		C(OH)(CH ₃) ₂	42 + 16	9d + 11a
5	Ph	CH ₂ CH ₂ CH ₂ CN	71	9e
6	Ph	CH ₂ CH ₂ CH ₂ OH	85	9f
7	Ph	CH ₂ CH ₂ CO ₂ C ₄ H ₉ - <i>t</i>	44	9g
8	Ph	C(OH)C(CH ₃) ₂	40 + 17	9h + 11b

stituents, cyclohexyl (**8a**), and a conjugated one, phenyl (**8b**), as shown in eq 5. As shown in Table 2, the isolated yields in

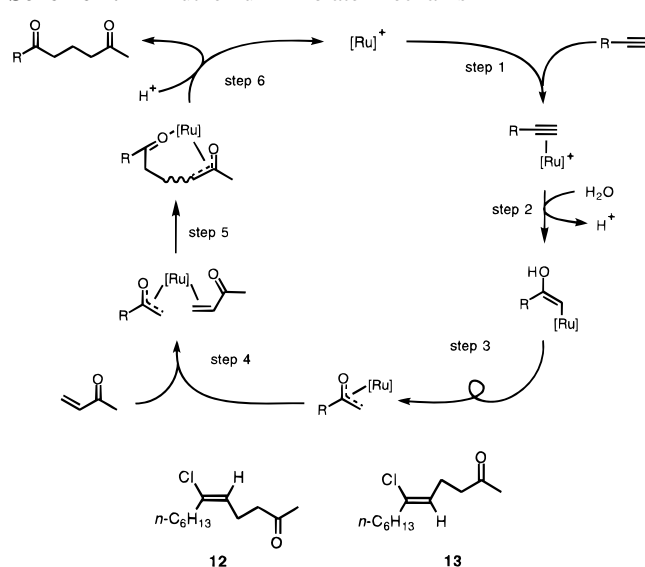


these cases are comparable to those obtained with MVK. There is one significant difference, the reactions of 3-methyl-3-hydroxy-1-butyne (eq 6) with **8a** and **8b**. In each of these cases,



a larger amount of a minor product tentatively identified as **11a** or **11b** was isolated. Their origins presumably are the regioisomeric products **10a** and **10b**, which dehydrate under the reaction conditions.

The reaction mechanism shown in eq 2 represents our initial working hypothesis. In our early studies of the reaction of MVK with 1-octyne, we identified **12** and **13** as minor products which suggested the feasibility of an alternative mechanism as outlined in Scheme 1. The ruthenium-catalyzed nucleophilic addition of water (step 2) is analogous to the elegant studies of Dixneuf on the ruthenium-catalyzed additions of carboxylic acids to alkynes to give vinyl esters.⁹ The formation of vinyl chlorides **12** and **13** then can be rationalized by such a mechanism wherein chloride competes with water as the nucleophile.¹⁰ However, the curiosity associated with this mechanism is the question of protonation of the ruthenium enolate. The fact that we do not see competitive simple hydration of the alkyne would demand

Scheme 1. A Ruthenium Enolate Mechanism

that conjugate addition via steps 4 and 5 is faster than protonation of the ruthenium enolate in this aqueous environment. At this point, the evidence does not allow unambiguous differentiation between the ruthenacycle mechanism of eq 2 and the ruthenium enolate mechanism of Scheme 1. Furthermore, the role of the indium triflate remains to be clarified although part of it may be as a chloride scavenger.¹¹

An illustrative procedure follows. A deaerated 1:1 solution of DMF–water (2 mL) was added to a mixture of CpRu(COD)-Cl (7.7 mg, 0.025 mmol), ammonium hexafluorophosphate (8.2 mg, 0.05 mmol), and indium triflate (56 mg, 0.1 mmol) followed by cyclohexyl vinyl ketone (138 mg, 1.0 mmol) and 5-hexynenitrile (52 μL , 0.5 mmol). After heating at 100 °C in a sealed tube for 4 h, the cooled reaction mixture was poured into aqueous sodium bicarbonate. The aqueous layer was extracted with ether and the latter washed with brine. After drying, evaporation, and flash chromatography (2:1 hexane–ethyl acetate), 9-cyclohexyl-5,9-dioxononanitrile was isolated as a low-melting solid, mp 32–3 °C (115 mg, 93% yield).

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Supporting Information Available: Characterization data for **7a–h** and **9a–h** (4 pages). See any current masthead page for ordering and Internet access instructions.

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