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Ruthenium-Catalyzed Three-Component Coupling via Hydrative Conjugate Addition of Alkynes to Alkenes: One-Pot Synthesis of 1,4-Dicarbonyl Compounds

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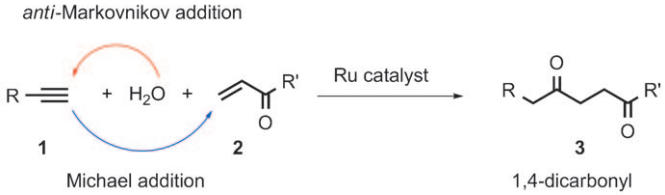
Dedicated to Professor Eun Lee on the occasion of his retirement and 65th birthday

The addition reaction of alkynes catalyzed by transition metals is a useful method for the formation of a wide variety of carbon–carbon and carbon–heteroatom bonds.[1] A readily conceivable merit of this powerful process is the prospect of carrying out multicomponent coupling reactions by capturing the incipient metal alkenyl intermediate for further bond formations. While an array of such strategies has indeed been practiced utilizing the 1,2-addition of transition metal alkyne π-complexes,[2] a less common approach involves a 1,1-addition, wherein an alkyne engages in the multicomponent reaction (MCR) process through catalysis mediated by a metal vinylidene complex. In our previous studies, this type of geminal addition was demonstrated to be feasible in intramolecular settings, thus leading to the development of a range of novel addition–cyclization reactions.[3] We questioned if the same mechanistic mode could be operative in intermolecular processes, thus achieving carbon–carbon bond formation between an alkyne and an alkene with concomitant addition of water (Scheme 1). Herein we report the results of our investigation of a ruthenium-catalyzed hydrative conjugate addition of alkynes to alkenes that affords 1,4-dicarbonyl compounds. This three-component reaction represents a process of high atom economy, which furnishes a product of well established utility.[4]



Scheme 1. Ruthenium-catalyzed three-component coupling reaction.

Based on the findings from the hydrative cyclization in which $[Ru_3Cl_5(dppm)_3]PF_6$ (dppm = bis(diphenylphosphino)-methane) proved to be the most effective catalyst,[3a] our investigation started with testing the efficacy of this trinuclear ruthenium complex in the reaction of 4-phenylbutyne (**1a**), water, and methyl vinyl ketone (**2a**; Scheme 2). Subjecting the mixture of **1a** and **2a** (5 equiv) in wet dioxane (1:2 = v/v) to the same reaction conditions employed for the cyclization process gave the desired 1,4-diketone **3aa** in 29% yield. However, monoketones **4aa** (14%) and **5a** (7%) were also generated, which presumably arose from simple two-component reactions, Michael addition and Markovnikov hydration,[5,6] respectively. In contrast, the reactions using ruthenium complexes such as [CpRu(dppm)Cl][7] and $[CpRu(PRPh_2)_2(CH_3CN)]PF_6$ (R = 2-(diphenylphosphino)-6-*tert*-butylpyridine)[8] known to mediate vinylidene catalysis did not produce diketone **3aa** but induced *anti*-Markovnikov hydration to give aldehyde **6a** in low yield, whilst recovering unreacted alkyne **1a**.

With the initial results, we set out to optimize the trinuclear complexes $[Ru_3Cl_5(dppm)_3]X$ (X = Cl, PF_6) and examine whether they are active catalysts or simply precursors of mononuclear complexes.[9] Thus, the trinuclear complex $[Ru_3Cl_5(dppm)_3]Cl$ was heated at reflux in acetonitrile to

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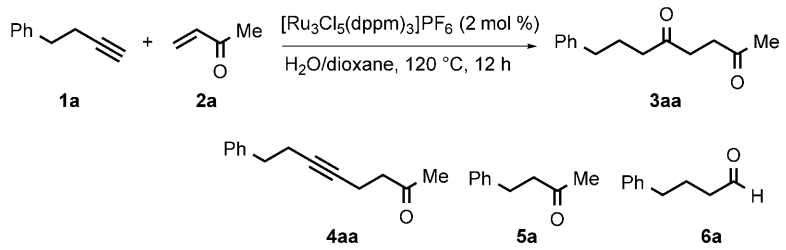
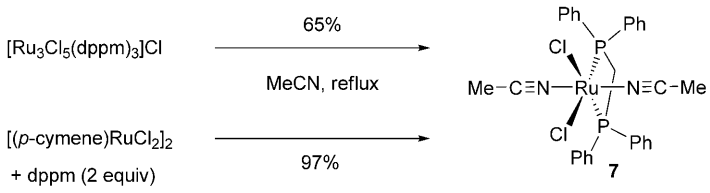


Scheme 2. Ruthenium-catalyzed hydrative conjugate addition of alkyne to enone.

obtain the mononuclear complex $[RuCl_2(dppm)(NCCH_3)_2]$ (**7**) as a yellow solid in 65% yield (Scheme 3). Alternatively, the same complex **7** could also be prepared in higher yield from the reaction of $[RuCl_2(p\text{-cymene})]_2$ with dppm in acetonitrile. An X-ray crystallographic analysis revealed complex **7** to be a C_{2v}-symmetric octahedral complex with a



Scheme 3. Synthesis of ruthenium catalyst $[RuCl_2(dppm)(NCCH_3)_2]$ (**7**).

square-planar disposition of dppm and chlorine ligands (Figure 1).[10] Gratifyingly, the new ruthenium complex was found to be more effective in the three-component coupling as shown in Scheme 1; the desired 1,4-diketone **3aa** was formed in 65% yield with formation of the alkynylation product **4aa** in only 6% yield. It was noteworthy that neither simple alkyne hydration product (e.g. **5a** or **6a**) was generated in this reaction.

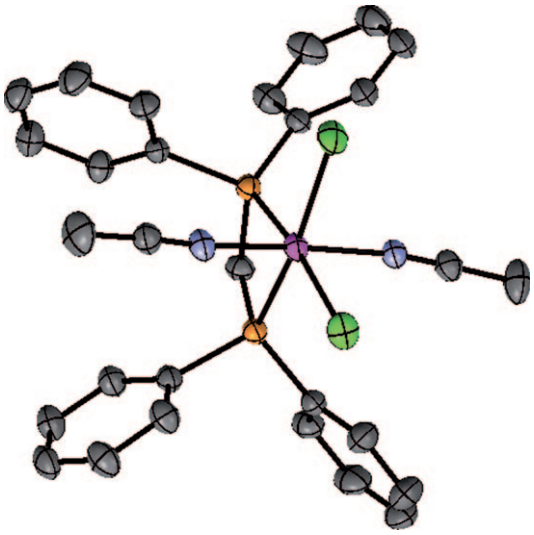


Figure 1. X-ray single crystal structure of $[RuCl_2(dppm)(NCCH_3)_2]$(**7**).

With the mononuclear ruthenium complex **7** in hand, the scope of the three-component reaction was evaluated with an assortment of alkynes and α,β-unsaturated carbonyl compounds. As summarized in Table 1, the new catalyst proved to be effective in the hydrative Michael addition of a variety of terminal alkynes to conjugated ketones and aldehydes to furnish 1,4-dicarbonyl compounds as products. In general, alkyl-substituted alkynes gave rise to 1,4-diketones **3** as the major or exclusive products, whereas simple alkyne Michael addition adducts **4** were preferentially formed from the reactions of alkenyl and aryl alkynes (Table 1, entries 5–7).[11] The reaction conditions were tolerant of a range of functional groups such as ethers, nitriles, esters, carboxylic acids, alcohols, enones, and imides. In the case of an alkyne with propargylic branching (e.g. **1d**, Table 1, entry 4), the reaction was sluggish and afforded 1,4-diketone **3da** in low yield with no alkynyl ketone formation. While 1,5-enyne **1m** produced 1,4-diketone **3ma** in 55% yield without cyclization, interestingly, the reaction of demethylated free alcohol **1n** led to the formation of alkynone **4na** as the sole product in 63% yield; this suggests a possible influence of the allylic alcohol on the partition between ruthenium alkynyl and vinylidene reaction manifolds (Table 1, entry 13 vs. 14). Ethyl vinyl ketone (**2b**) exhibited reactivity similar to that of methyl vinyl ketone (**2a**; Table 1, entry 15). With the more reactive phenyl vinyl ketone acceptor (**2c**),[12] the reaction gave only the diketone **3ac** product (Table 1, entry 16). By contrast, alkynylation was a dominant pathway when the same alkyne was treated with acrolein (**2d**; Table 1, entry 17). Except for the reaction of **1l** (Table 1, entry 12), the formation of simple hydration products (e.g. **5** and **6**) was negligible (<5%) in all cases.

The ruthenium-catalyzed three-component coupling reaction could also be expanded to include conjugate enoates as acceptors (Table 2). The reaction of alkyne **1a** with methyl, ethyl, phenyl, and *tert*-butyl acrylates **8a–d** proceeded well to provide a mixture of γ-keto esters **9** and acid **10** in 58–68% combined yield. In contrast to the reactions of conjugate enones and enals (compare Table 1), the formation of an alkynylation adduct (e.g. **4**) was suppressed. A set of control experiments established that acid **10** arose from esters **9** under the reaction conditions, most likely through facilitated hydrolysis, owing to the anchimeric assistance of the γ-keto group.[13,14]

A plausible mechanism for the ruthenium-catalyzed hydrative conjugate addition is presented in Scheme 4. The catalytic cycle may be initiated with coordination of the alkyne with a ruthenium complex derived from **7**. Among the viable complexation modes of a terminal alkyne, the formation of vinylidene complex **A** can lead to *anti*-Markovnikov hydration, while σ-complex **B** and π-complex **C** undergo

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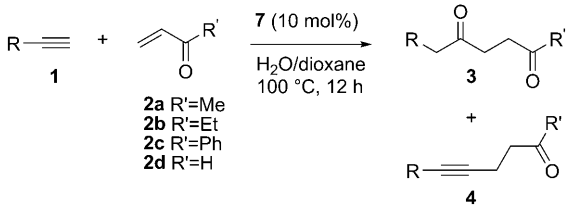
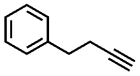
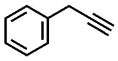
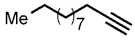
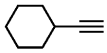
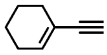
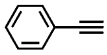
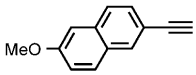
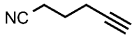
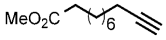
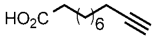
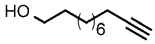
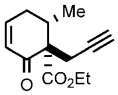
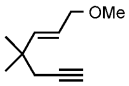
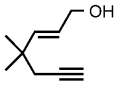
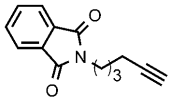
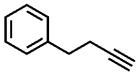
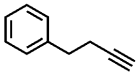
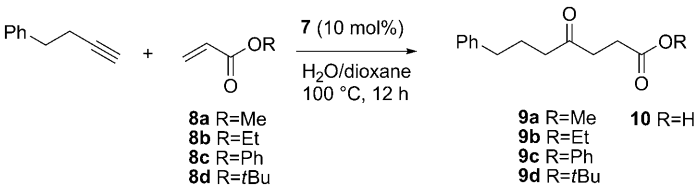
Table 1. Ruthenium-catalyzed hydrative addition of alkynes to enones and enals.



Entry[a]	Alkyne	Alkene	3[b]	4[b]
1		**1a** **2a**	65% (**3aa**)	6% (**4aa**)
2		**1b** **2a**	54% (**3ba**)	–
3		**1c** **2a**	53% (**3ca**)	15% (**4ca**)
4		**1d** **2a**	28% (**3da**)	–
5		**1e** **2a**	–	70% (**4ea**)
6		**1f** **2a**	13% (**3fa**)	44% (**4fa**)
7		**1g** **2a**	9% (**3ga**)	72% (**4ga**)
8		**1h** **2a**	73% (**3ha**)	11% (**4ha**)
9		**1i** **2a**	54% (**3ia**)	20% (**4ia**)
10		**1j** **2a**	71% (**3ja**)	0% (**4ja**)
11		**1k** **2a**	61% (**3ka**)	29% (**4ka**)
12[c]		**1l** **2a**	44% (**3la**)	–
13		**1m** **2a**	55% (**3ma**)	13% (**4ma**)
14		**1n** **2a**	–	63% (**4na**)
15		**1o** **2b**	50% (**3ob**)	11% (**4ob**)
16		**1a** **2c**	49% (**3ac**)	–
17		**1a** **2d**	22% (**3ad**)	37% (**4ad**)

[a] All reactions were performed with 0.15 mmol of alkyne, 0.75 mmol of methyl vinyl ketone, 6.0 mmol of H_2O, 10 mol% $[RuCl_2(dppm)(NCCH_3)_2]$ in 0.5 mL of 1,4-dioxane at 100 °C for 12 h. [b] Isolated yield. [c] A Markovnikov hydration adduct, methyl ketone **5l**, was formed in 15% yield, see the Supporting Information.

Table 2. Ruthenium-catalyzed hydrative conjugate addition of alkyne to acrylates.



Entry[a]	Acrylate (**8**)	γ-Keto ester **9**[b]	γ-Keto acid **10**[b]
1	methyl acrylate **(8a)**	41% **(9a)**	17%
2	ethyl acrylate **(8b)**	45% **(9b)**	19%
3	phenyl acrylate **(8c)**	30% **(9c)**	32%
4	*tert*-butyl acrylate **(8d)**	31% **(9d)**	37%

[a] All reactions were performed with 0.15 mmol of 4-phenylbutyne, 0.75 mmol of acrylate, 6.0 mmol of H_2O, 10 mol% $[RuCl_2(dppm)(NCCH_3)_2]$ in 0.5 mL of 1,4-dioxane at 100 °C for 12 h. [b] Isolated yield.

simple conjugate addition and Markovnikov hydration pathways to give rise to alkynyl adduct **4** and methyl ketone **5**, respectively. The ruthenium acyl complexes **D** and **E** emanating from hydration of **A** then add to the α,β-unsaturated carbonyl compound **2** to form ruthenium enolate **F**, which upon protonation furnishes 1,4-dicarbonyl product **3**.[15]

The novel mechanism involving a ruthenium acyl complex, arising from regioselective hydration of a vinylidene complex, is consistent with a series of observations. First, performing the reaction with a less reactive, β-substituted enone acceptor leads to the formation of a noticeable amount (>5%) of an alkene with one less carbon (e.g. **11**), probably through β-hydride elimination of **G** derived from decarbonylation of **E**.[16] Second, it has been shown by a control experiment that 1,4-diketone **3** is not produced from hydration of alkynone **4** (Scheme 5),[17] thereby indicating the distinctive mechanistic feature associated with the present three-component reaction as compared with the known synthesis of 1,5-dicarbonyls through a ruthenacycle pathway.[18] Third, an additional test has been performed to exclude the possibility of forming **3** by ruthenium-catalyzed hydroacylation of **2** with aldehyde **6**,[19] or through a Stetter-type mechanism.[20]

In summary, we have developed a new ruthenium-catalyzed three-component coupling reaction of alkynes, alkenes, and water. This process enables terminal alkynes to undergo hydration and conjugate addition to α,β-unsaturated carbonyl compounds in tandem to form synthetically useful 1,4-dicarbonyl products. The catalyst $[RuCl_2(dppm)(NCCH_3)_2]$, synthesized from commercial materials in one step, has proved to be effective in promoting both *anti*-Markovnikov hydration and Michael addition, while minimizing other alkyne activation pathways. Mechanistic studies suggest that the reaction occurs through a sequence involving formation and hydration of a ruthenium vinylidene complex, and an umpolung carbon–carbon bond-forming process of the resulting ruthenium acyl species. The unique mechanism and synthetic potential of the reaction, together with its high atom economy, should serve as a useful platform for further exploration in alkyne functionalization.

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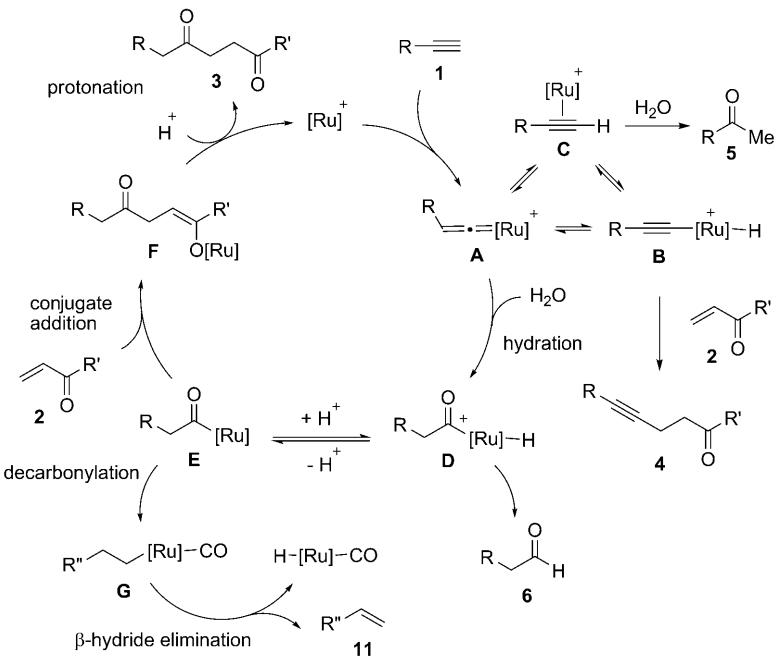
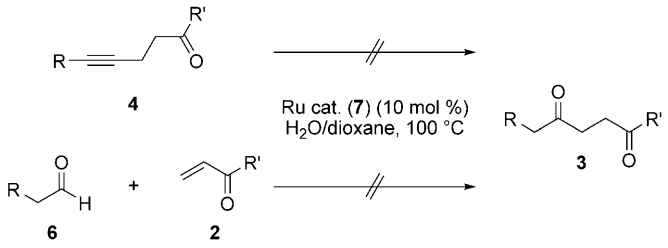
Keywords: 1,4-dicarbonyl compounds · homogeneous catalysis · ligands · multicomponent reactions · ruthenium



Scheme 4. Proposed mechanism for the ruthenium-catalyzed three-component coupling.



Scheme 5. Control experiments for mechanistic studies.

Experimental Section

General Procedure for the Ruthenium-Catalyzed Three-Component Coupling Reaction

An alkyne substrate (0.15 mmol), a Michael acceptor (0.75 mmol), $[RuCl_2(dppm)(NCCH_3)_2]$ (**7**, 0.015 mmol, 10 mol%), H_2O (0.10 mL, 6.0 mmol), and dioxane (0.25 mL) were added to a vial equipped with a screw-cap. After sealing the vial, the resulting yellow solution was heated at 100 °C. No special precautions were taken to exclude air or moisture, and the reaction was closely monitored by TLC analysis. Upon complete consumption of the starting alkyne (typically 12 to 24 h), the yellow reaction mixture was cooled to ambient temperature, dried over Na_2SO_4, filtered through a pad of silica gel, and concentrated in vacuo. Purification by flash column chromatography afforded the product in an analytically pure form.

Acknowledgements

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