Propargyl Alcohols as Synthons for Allenols in Conjugate Addition

Barry M. Trost,* Lars Krause, and Moshe Portnoy

Department of Chemistry, Stanford University
Stanford, California 94305-5080

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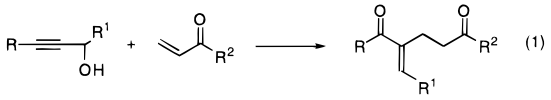
Enolate chemistry constitutes one of the most important tools for structural elaborations.[1] Unlike saturated carbonyl compounds wherein enolization can be accomplished by simple α-deprotonation, allenols (or allenolates) which are the enols (or enolates), formally arising by α-deprotonation of α,β-unsaturated carbonyl compounds cannot be derived in such a fashion.[2] An ingenious solution to this problem for the equivalent of an aldol reaction involves a Michael-induced carbonyl addition illustrated by the Baylis−Hillman reaction.[3,4] This strategy is limited to electrophilic partners that do not interfere with the nucleophilic trigger. Thus, performance of this type of reaction with a Michael acceptor as the electrophile, which is similar in type to the Michael acceptor that becomes the nucleophile, is impossible.[5] The mechanism of the ability of ruthenium to catalyze additions of oxygen nucleophiles to alkynes, which appears to be manifold, may offer a strategy to effect the net equivalent of this transformation. Based upon the work of Dixneuf,[6] a catalytic cycle for the in situ formation of a ruthenium-complexed allenol, which may be captured by a Michael acceptor, may be envisioned as outlined in Scheme 1. We report herein our studies designed to achieve the overall objective outlined in eq 1.



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The initial studies were performed with propargyl alcohol **1** and methyl vinyl ketone (MVK) and are summarized in eq 2 and Table 1. Attempts to use ruthenium complexes that were successful for additions of carboxylic acids to alkynes gave, at best, only trace amounts of the desired adducts. Our previous experiences with the coordinatively unsaturated ruthenium catalyst derived from complex **3** led us to examine its use as our catalyst.[7] Indeed, the initial run proved gratifying (entry 1). The desired product **6a**[8] was isolated in 50% yield along with that derived from regioisomeric addition **7a**[8] isolated in 26% yield. Decreasing the amount of the catalyst decreased the amount of **7a** (entry 2). Most significantly, adding indium triflate as a cocatalyst had the largest beneficial effect on this ratio (entries 3−7). With 20 mol % of the cocatalyst, the highest ratio was observed (entries 3 and 4). Reducing the amount of the cocatalyst as well as ammonium hexafluorophosphate to 5 mol % each (entry 7) saw the same ratio as in the absence of cocatalyst (entry 2) but with a higher yield. The reaction performed equally well at 80 °C as at 100 °C (entry 6 vs 5). The possibility that indium triflate simply affected pH by formation of small amounts of triflic acid was tested by adding CSA (**5b**), which gave reasonable yields but not as high a regioselectivity (entry 8). The standard conditions thus became

Scheme 1. Working Hypothesis

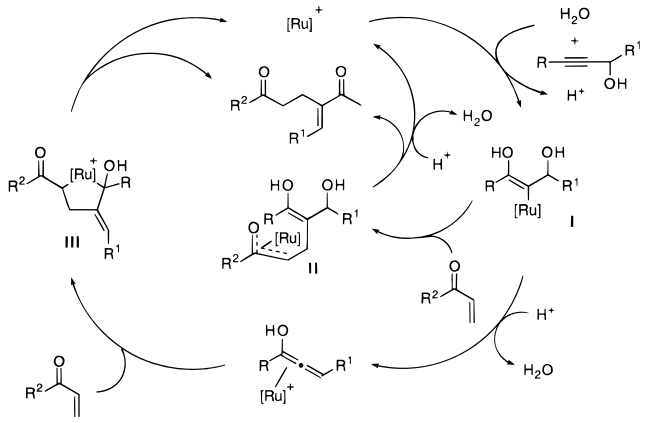
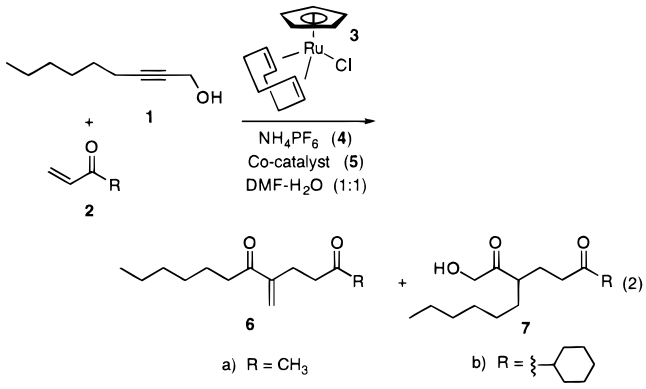


Table 1. Initial Studies of 2-Nonyn-1-ol and Vinyl Ketones[a]

entry	R	CpRu-(COD)Cl (mol %)	NH_4PF_6 (mol %)	cocat.[b] (mol %)	temp (°C)	isolated yield (%) **6**[c]	**7**	isol. yield (%)	ratio **6**:**7**
1	CH_3	5.0	10		100	50	26	76	2:1
2	CH_3	2.5	10		100	49 (65)	13	62	4:1
3	CH_3	5.0	10	**5a** (20)	100	53 (71)	7	60	8:1
4	CH_3	2.5	10	**5a** (20)	100	59 (73)	6	65	10:1
5	CH_3	2.5	10	**5a** (10)	100	60 (73)	11	71	6:1
6	CH_3	2.5	10	**5a** (10)	80	60 (74)	14	74	4:1
7	CH_3	2.5	5	**5a** (5)	80	58 (72)	16	74	4:1
8	CH_3	2.5	10	**5b** (30)	100	51 (70)	14	65	4:1
9	C_6H_{11}	3.5	10	**5a** (20)	80	53	9	62	6:1

[a] All reactions run according to eq 2 with 1:2 ratio of propargyl alcohol to vinyl ketone. [b]Cocatalysts: **5a** = $In(OSO_2CF_3)_3$, **5b** = camphorsulfonic acid. [c]Yields in parentheses are determined by GC on the initial crude mixture.



(2)

(1) For extensive reviews, see: Schreiber, S. L., Vol. Ed. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 1. Heathcock, C. H., Vol. Ed. In *Comprehensive Organic Chemistry*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 2. Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon Press: Oxford, U.K., Vol. 3, Chapter 1.1, pp 1−64.

(2) Allenolates generated by the conjugate addition to alkynylcarbonyl compounds can be trapped, see: Hulce, M.; Chapdelaine, M. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, Chapter 1−6.

(3) For reviews, see: Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653. For a few recent references, see: Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 4317. Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron*, **1997**, *53*, 1015. For a Rh-catalyzed version, see: Sato, S.; Matsuda, I.; Izumi, Y. *Chem. Lett.* **1985**, 1875.

(4) For multistep variants, see: Leonard, W. R.; Livinghouse, T. *J. Org. Chem.* **1985**, *50*, 731. Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 274. Shono, T.; Matsumura, Y.; Kashimira, S.; Hatanaka, K. *J. Am. Chem. Soc.* **1979**, *101*, 4752.

(5) Hwu, J. R.; Hakimelahi, G. H.; Chou, C.-T. *Tetrahedron Lett.* **1992**, *33*, 6469.

(6) For a review, see: Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1997**, 507. After submission of this paper, a report of a Ru-catalyzed version of the Meyer−Schuster rearrangement appeared, see: Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **1997**, 1201.

(7) 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. A. *J. Am. Chem. Soc.* **1995**, *117*, 1888. Trost, B. M.; Imi, K.; Indolese, A. F. *J. Am. Chem. Soc.* **1993**, *115*, 8831.

(8) This compound has been satisfactorily characterized spectroscopically.

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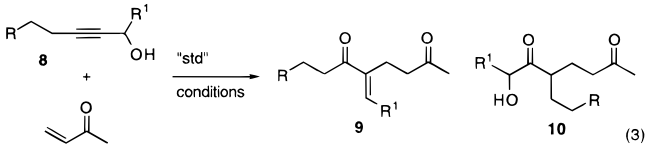
Table 2. Regioselective Ru-Catalyzed Additions of Propargyl Alcohols to MVK[a]

entry	R[b]	R[1 b]	isolated yield (%) 9	10	ratio 9:10	combined isolated yield (%)
1	(a) H	C_2H_5	55	19[c]	3:1	74
2	(b) *n*-C_4H_9	C_3H_7	48	8[c]	6:1	56
3	(c) $HOCH_2$	H	71	1	71:1	72
4	(d) N≡CCH_2	H	74	2	37:1	76
5	(e) $HOCH_2$	*n*-C_3H_7	66	2[d]	33:1	68
6	(f) $HOCH_2$	*i*-C_3H_7	71	5[d]	14:1	76
7	(g) HO	H	80	<1	>80:1	80
8	(h) $HOCH_2CH(CN)$	H	73	<1	>73:1	73

[a] Reactions performed using 2.5 mol % **3**, 10 mol % **4**, and 10 mol % **5a** in 1:1 DMF−water at 80 °C. [b] Letter signifies suffix to compound number in eq 3. [c] Obtained as a mixture of diastereomers. [d] Obtained as mainly one diastereomer.

2.5 mol % **3**, 10 mol % **4**, and 10 mol % **5a** in 1:1 DMF−water at 80 °C.

The presence of alkyl substituents on the propargylic carbon had no significant effect on the reaction (eq 3, Table 2, entries



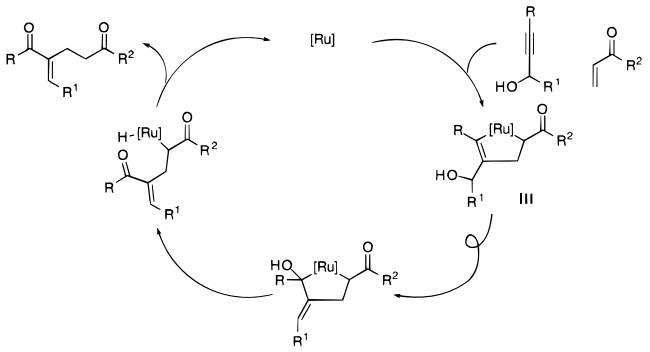
(3)

1 and 2). On the other hand, placing functional groups in the alkyl section had a significant effect on regioselectivity. For example, placement of either a hydroxyl or cyano group three carbons distant from the alkyne, i.e., **8c** or **8d** (eq 3, Table 2, entries 3 and 4), led to formation of virtually only the desired products, **9c**[8] and **9d**.[8] Enhancing steric hindrance proximal to the alkyne terminus to which the new carbon−carbon bond is formed in **8e** or **8f** generated predominately **9e**[8] and **9f**,[9] indicating retention of a high regioselectivity (eq 3, Table 2, entries 5 and 6). Reducing the tether length between the triple bond and hydroxyl group by one, i.e., **8g** (eq 3, Table 2, entry 7) or placing both cyano and hydroxy groups in the same alkyl chain, i.e., **8h** (entry 8), led to exclusive formation of single regioisomers **9g**[8] and **9h**.[8]

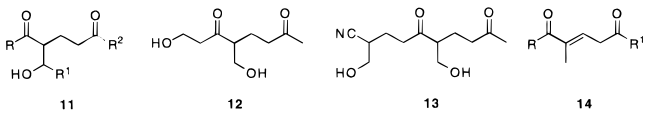
Other alkyl (or aryl) vinyl ketones may also serve as suitable acceptors. For example, cyclohexyl vinyl ketone **2b** participates analogously to MVK as shown in eq 2 and Table 1, entry 9, to give **6b**.[8] On the other hand, substitution on the vinyl group cannot be tolerated at present.

The mechanism of the reaction may follow Scheme 1. Formation of the minor product may derive by hydroxymetalation to give the opposite regioisomer corresponding to I, which then follows a route analogous to the reaction of this initial vinylruthenium species directly with MVK to give II. The effect of hydroxy and cyano substitution on controlling regioselectivity then could derive by coordination with ruthenium to stabilize intermediate I. Scheme 2 outlines an alternate, more direct formation of III, an intermediate also proposed in Scheme 1. This scheme also accounts for formation of both regioisomeric products but better accounts for the effect of functional groups on regioselectivity. In particular, the presence in *R* of a group capable of coordinating to ruthenium allows the starting alkyne to function as a bidentate ligand prior to formation of the metallacycle. This additional complexation in the precursor to

Scheme 2. Alternative Mechanism



the metallacycle should favor the pathway via III forming **9** rather than that leading to the regioisomeric product **10** wherein such bidentate coordination is not possible. A third possibility invokes the pathway previously proposed for the reaction of simple alkynes with vinyl ketones and water[9] wherein the initial product would be **11**, which then must undergo dehydration under the reaction conditions. Several arguments suggest that this pathway is not operative. First, we never see any evidence for the formation of **11** in any reaction. Thus, its dehydration



would have to be fast relative to its formation. That seems unlikely considering that the products **9g** and **9h** both possess similar functionalities that remain totally intact. Furthermore, in these two cases, the intermediates would have to be **12** and **13**. It appears unlikely that dehydration of such compounds would only occur to form **9g** and **9h**.

This new reaction offers a new paradigm for generation of a functional equivalent of an allenol or allenoate from a non-carbonyl precursor. The fact that propargyl alcohols, which are so easily derived from additions of terminal alkynes to aldehydes or by elaboration of propargyl alcohol, are the substrates make this method particularly convenient. In the present case, the formation of polyfunctional products such as **9** in a single step is quite noteworthy because of the multitude of ways it may be further elaborated and the lack of any simple alternative methods for their construction. A simple prospect is isomerization[10] of **9** (R^1 = H) to **14**, which is itself a useful structural unit. In addition to many mechanistic issues, the prospects for additional new reactions based upon this paradigm constitute exciting opportunities.

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Supporting Information Available: Typical procedure and spectral characterization for **6a**,**b**, **7a**,**b**, **9a**−**h**, and **10a** (4 pages). See any current masthead page for ordering and Internet access instructions.

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