An Unusual Ruthenium-Catalyzed Dimerization of Propargyl Alcohols

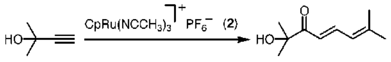
Barry M. Trost* and Michael T. Rudd

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

Received May 10, 2001

Metal-catalyzed dimerizations of terminal alkynes have been extensively explored with numerous different metals.[1−3] Typically, the products are enynes derived from tail-to-tail or head-to-tail couplings. In some cases, mechanisms invoke alkylidenemetal complexes—a mechanistic scenario that derived further support by dimerization to 1,2,3-butatrienes. During the course of our studies of Ru-catalyzed reactions of alkynes, we noted the presence of a minor product during reactions involving propargyl alcohols. In this paper, we report this product corresponds to an unprecedented pathway and optimization of the reaction to make it synthetically useful.

Treatment of 3,3-dimethylpropargyl alcohol as in eq 1 (10 mol % **2**, 30 mol % CSA (camphorsulfonic acid), acetone, water, 60 °C, 1 h) gave a product corresponding to a dimer in 60% yield.

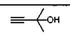
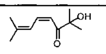
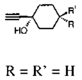
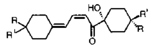
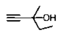
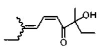
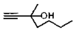
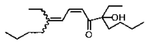
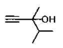
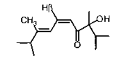
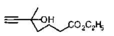
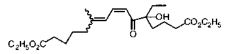
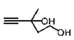
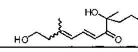


(1)

1 **3**

Infrared spectroscopy showed both hydroxyl (3463 cm^{-1}) and conjugated carbonyl (1676, 1625 cm^{-1}) absorptions, the latter confirmed by the ^{13}C NMR peak at δ 203.1. The presence of a conjugated diene was also apparent in the ^{13}C NMR spectrum (δ 145.4, 137.1, 119.5, and 114.4) as well as in the ^{1}H NMR spectrum [δ 7.76 (dd, $J = 14.8$, 11.7 Hz, 1H), 6.34 (d, $J = 14.8$ Hz, 1H), 6.06 (d, $J = 11.7$ Hz, 1H)]. The latter also indicated all four methyl groups of a dimer were intact [δ 1.94 (s, 3H), 1.92 (s, 3H), 1.39 (s, 6H)]. These data indicate the structural formula **3**[4] for the dimer. Subsequent study indicated that CSA was not required for the reaction. Ruthenium catalysts lacking a Cp-like group were ineffective in promoting the reaction.[5]

Table 1. Representative Examples of Ru-Catalyzed Dimerization of Propargyl Alcohols

Entry	Propargyl Alcohol	Method	Product	Yield[g]
1		A[a]		77%
				
2	R = R' = H	B[b]	R = R' = H	55%
3	R, R' = OCH_2CH_2O	C[c]	R, R' = OCH_2CH_2O	65%
4	R = Ph, R' = H	C[c]	R = Ph, R' = H	76%
5	R = CN, R' = H	D[d]	R = CN, R' = H	60%
6	R = H, R' = CN	D[d]	R = CN, R' = H	55%
7	R, R' = O	C[c]	R, R' = O	70%
8		A[a]	 [e]	55%
9		B[b]	 [e]	65%
10		B[b]		65%
11		C[c]	 [e]	63%
12		C[c]	 [f]	70%

[a] Reaction performed at 3 M using 7 mol % **2** in 10 vol % acetone in THF, 1 equiv H_2O, −20°, 4 h. [b] As in footnote *a*, but using 10 mol % **2.** [c] As in footnote *a*, but using 10 mol % **2** at 0°. [d] As in footnote *a*, but using 10 mol % **2** at 60° and 0.1 M. [e] A 1:1 *E* :*Z* mixture at the γ,δ double bond. [f] A 2:1 *E* :*Z* mixture at the γ,δ double bond. [g] Isolated yield of pure product.

Scheme 1, cycle A, outlines a mechanistic rationale based upon metallacycle formation in analogy to the enyne chemistry[6,7] and cyclotrimerization of alkynes.[8] This rationale makes the prediction that the *Z* isomer **4** should be the precursor of the observed *E* isomer **3**. Indeed, running the reaction as above but lowering the temperature to room temperature with a reaction time of only 5 min still gave a 50% yield of dimer but now as a 2:3 mixture of *Z*:*E* isomers (**4** :**3**). Remarkably, the reaction proceeds at −78° (1 h) to give a 75% yield of a 7:3 ratio of **4**:**3**. Switching to THF at room temperature gave none of the *E* isomer **3**, but now produced a 1.4:1 ratio of the *Z* isomer **4**[4] and an aldehyde **5**[4,9] in 75% yield. The latter may be readily understood as resulting from cycle B of Scheme 1. Use of methylene chloride at room temperature only gave **4**, but the yield dropped to 40%. Since in acetone we obtained only **3** and **4** and in THF only **4** and **5**, we examined mixtures of these two solvents to optimize formation of **4**. Using 10 vol % acetone in THF at −20 °C with 7 mol % catalyst **2** gave a 25:1 mixture of **4** and **5** which were isolated in 77 and 3% yields, respectively. Refluxing a solution of pure **4** in

---

(1) For recent Ru-catalyzed reactions, see: Pavlik, S.; Gemel, C.; Slugovc, C.; Mereiter, K.; Schmid, R.; Kirchner, K. *J. Organomet. Chem.* **2001**, *617*, 301; Tenorio, M. A. J.; Tenorio, M. J.; Puerta, M. C.; Valerga, P. *Organometallics* **2000**, *19*, 1333; Bassetti, M.; Marini, S.; Tortorella, F.; Cadierno, V.; Diez, J.; Gamasa, M. P.; Gimeno, J. *J. Organomet. Chem.* **2000**, *593*, 292; Le Paih, J.; Derien, S.; Dixneuf, P. H. *Chem. Commun.* **1999**, 1437; Matsuzaka, H.; Ichikawa, K.; Ishii, T.; Kondo, M.; Kitagawa, S. *Chem. Lett.* **1998**, 1175; Qu, J.-P.; Masui, D.; Ishii, Y.; Hidai, M. *Chem. Lett.* **1998**, 1003; Slugovc, C.; Mereiter, K.; Zobetz, E.; Schmid, R.; Kirchner, K. *Organometallics* **1996**, *15*, 5275; Yi, C. S.; Liu, N. H. *Organometallics* **1996**, *15*, 3968; Bianchini, C.; Frediani, P.; Masi, D.; Peruzzini, M.; Zanobini, F. *Organometallics* **1994**, *13*, 4616; Bianchini, C.; Peruzzini, M.; Zanobini, F.; Frediani, P.; Albinati, A. *J. Am. Chem. Soc.* **1991**, *113*, 5453. For a review, see: Tokunaga, M.; Wakatsuki, Y. *Yuki Gosei Kagadu Kyokaishi* **2000**, *58*, 587; *Chem. Abstr.* **2000**, *133*, 73620.

(2) Al: Dash, A. K.; Eisen, M. S. *Org. Lett.* **2000**, *2*, 737. Ir: Ohmura, T.; Yorozuya, S.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2000**, *19*, 365. U: Wang, J. Q.; Dash, A. K.; Berthet, J. C.; Ephritikhine, M.; Eisen, M. S. *Organometallics* **1999**, *18*, 2407. Hf: Yoshida, M.; Jordan, R. F. *Organometallics* **1997**, *16*, 4508. Cu: Balcioglu, N.; Uraz, I.; Bozkurt, C.; Sevin, F. *Polyhedron* **1997**, *16*, 327. Ti: Varga, V.; Petrusova, L.; Cejka, J.; Hanus, V.; Mach, K. *J. Organomet. Chem.* **1996**, *509*, 235. Rh: Baidossi, W.; Goren, N.; Blum, J.; Schumann, H.; Hemling, H. *J. Mol. Catal.* **1993**, *85*, 153; Kovalev, I. P.; Yevdakov, K. V.; Strelenko, Y. A.; Vinogradov, M. G.; Nikishin, G. I. *J. Organomet. Chem.* **1990**, *386*, 139. Ni: Giacomelli, G.; Caporusso, A. M.; Lardicci, L.; Marcacci, F. *Chim. Ind. (Milan)* **1981**, *63*, 482. Rh with propargyl alcohols: Schmitt, H. J.; Singer, H. *J. Organomet. Chem.* **1978**, *153*, 165; Schäfer, H. A.; Marcy, R.; Rüping, T.; Singer, H. *J. Organomet. Chem.* **1982**, *240*, 17; Nishida, T.; Ninagawa, Y.; Itoi, K.; Fujita, Y. *Bull. Chem. Soc. Jpn.*. **1983**, *56*, 2805; Singer, H.; Steigerwald, M. *J. Organomet. Chem.* **1996**, *508*, 267.

(3) For some reactions of Ru and propargyl alcohols, see: Cadierno, V.; Gamasa, M. P.; Gimeno, J.; Borge, J.; Garcia-Granda, S. *Organometallics* **1997**, *16*, 3178; Touchard, D.; Pirio, N.; Dixneuf, P. H. *Organometallics* **1995**, *14*, 4920; Werner, H.; Stark, A.; Steinert, P.; Grünwald, C.; Wolf, S. *Chem. Ber.* **1995**, *128*, 49. For a synthetic application via allenylidene intermediates, see: Trost, B. M.; Flygare, J. A. *Tetrahedron Lett.* **1994**, *35*, 4059; Trost, B. M.; Flygare, J. A. *J. Org. Chem.* **1994**, *59*, 1078; Trost, B. M.; Flygare, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 5476.

(4) New compounds have been satisfactorily characterized spectroscopically and elemental composition by combustion analysis and high-resolution mass spectrometry.

(5) The use of various other Ru^{2+} compounds resulted in no desired reaction ($(Ru(COD)(CH_3CN)_4{}^{2+}(PF_6)_2{}^{2-}$, $Ru(CH_3CN)_6{}^{2+}(PF_6)_2{}^{2-}$, $PhRu(CH_3CN)_3{}^{2+}$-$(PF_6)_2{}^{2-}$ Ru(COD)(COT) + H^+ , $Ru(ind)_2$ + H^+).

(6) Trost, B. M.; Indolese, A. F.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615. For reviews, see: Trost, B. M. *Chem. Ber.* **1996**, *129*, 1313; Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067−2096.

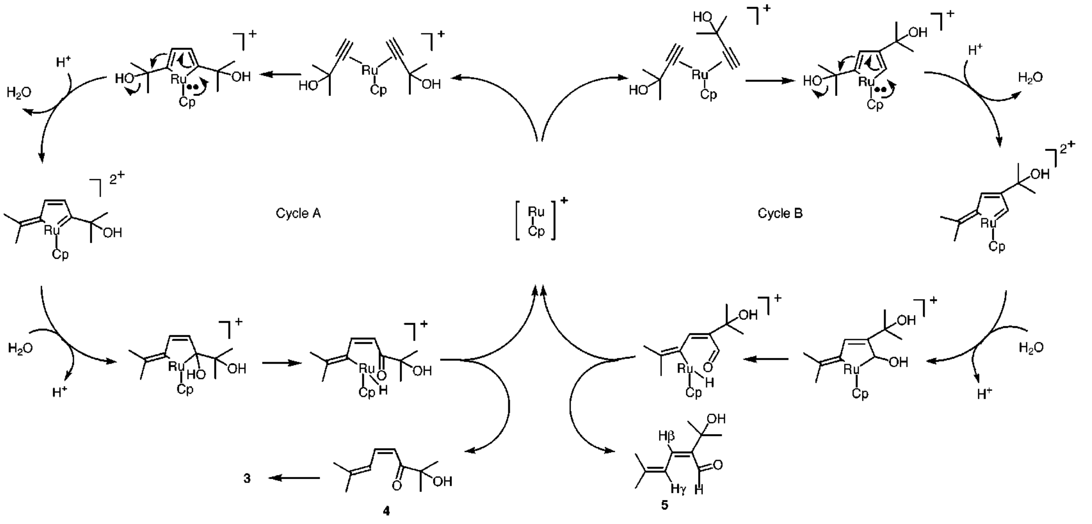
(7) For ionization of propargyl alcohols during enyne couplings, see: Trost, B. M.; Krause, L.; Portnoy, M. *J. Am. Chem. Soc.* **1997**, *119*, 11319.

(8) Lindner, E.; Jansen, R. M.; Mayer, H. A.; Hiller, W.; Fawzi, R. *Organometallics* **1989**, *8*, 2355.

(9) The geometry of the two double bonds is clearly established by nOe's. For the α,β-double bond, nOe between Hβ and sp^3-CH_3 group is 5.9% in **5** and 3.6% in **7**; nOe between Hγ and aldehydic C−H is 12.8% in **5** and 17.0% in **7**.

10.1021/ja0111636 CCC: $20.00

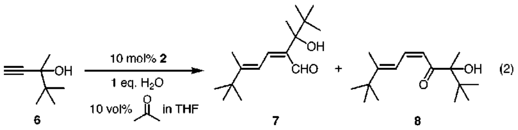
Scheme 1. A Mechanistic Rationale for Dimerization of Propargyl Alcohols

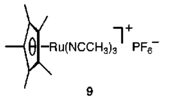


THF containing a catalytic amount of diphenyl disulfide gave pure **3** in 80% yield. Thus, either the *E* or *Z* dienone isomers can be obtained by this method.

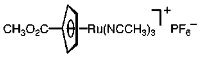
Table 1 demonstrates a broad scope for this most unusual dimerization. Tertiary propargyl alcohols are required; however, a broad range of functionality can be tolerated. Only in the case of a cyano group (entries 5 and 6) was the reaction slowed. As a result, these reactions were run more dilute at higher temperatures. Despite the requirement for higher temperatures in these two cases, only the *Z* isomer was obtained. It is to be noted that ring geometry is fully maintained in these two cases. With unsymmetrical propargyl alcohols (entries 8−12), mixtures of the *E* and *Z* isomers at the γ,δ double bond are expected and observed. Nevertheless, when branching is introduced (entry 10), only a single geometry is observed. The *E* geometry, as depicted, is assigned on the basis of a 12% nOe between the vinyl methyl group and Hβ. In only one case (entry 12) were we not able to isolate the (*Z*)-enone. Presumably, the appended primary alcohol assists the *Z*-to-*E* isomerization under the reaction conditions. Of course, the *E* isomers in all of the other cases would be readily accessible either by running the reaction under the original protocol or by performing isomerization in the presence of catalytic diphenyl disulfide.

Using a more sterically congested substrate **6** changes the course of the reaction (eq 2) wherein the aldehyde **7**[4,9] is isolated in 70% yield along with only 11% of the enone **8**. This result suggests that increasing the steric hindrance associated with the initial metallacycle of cycle A then favors cycle B. Another way to do so is to increase the steric hindrance of the catalyst. Switching from Cp to Cp* (i.e., **9**[10]) with substrate **1** does indeed shift the course of the reaction as shown in eq 3 to give 45% of lactol **10** and 15% of aldehyde **5**. The product **10** derives from ionization of the hydroxyl group of the 4-substituent in metallacycle **11** via **12** versus that of the 2-substituent via **13** to give **10** and **5**, respectively. The favoring of **12** over **13** presumably derives from increased unfavorable steric interactions between the 2-isopropylidene group and the Cp* moiety in **13**. In the absence of such steric effects, dienal **5** is normally preferred (vide supra). Further, by using an electron-deficient Cp complex **14** with propargyl alcohol **1**, a 70% yield of **5**, in addition to 14% of **4**, is obtained.[11] None of **10** is observed.

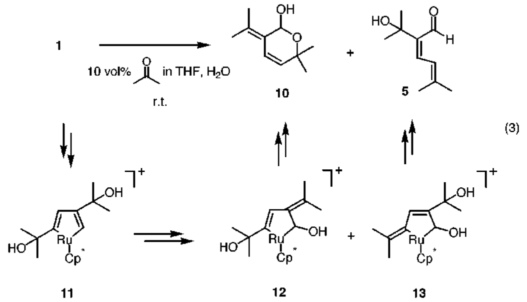




9



14



While Scheme 1 is only intended to present a working hypothesis, all of the results to date are in accord. Mechanisms invoking insertion into the alkyne C−H can also be ruled out by the fact that nonterminal propargyl alcohols do dimerize, albeit with only very low conversions at present. By appropriately modifying reaction conditions both tail-to-tail (cycle A) and head-to-tail (cycle B), products may be obtained in good yield. Furthermore, either (*E*)- or (*Z*)-enones derived from cycle A can be obtained in good yields, and either of two types of head-to-tail products illustrated by **5** and **10** can be obtained in satisfactory yields. The facility of this process is striking—it proceeds even at −78°. Such easy access to these highly functionalized products in this unprecedented fashion should provide opportunities to explore them as building blocks. These observations clearly open a new reaction manifold for exploitation.

Acknowledgment. We thank the National Science Foundation and the National Institute of Health, General Medical Sciences, for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California-San Francisco, supported by the NIH Division of Research Resources.

Supporting Information Available: Experimental procedures for the preparation of new compounds as well as characterization data are included (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0111636

---

(10) 0.1 M in 10 vol % acetone/THF.

(11) 0.01 M in 10 vol % acetone/THF (performing the reaction at higher concentrations resulted in lower yields of **5** and higher yields of **4**).