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Alkenol−Alkyne Cross Metathesis

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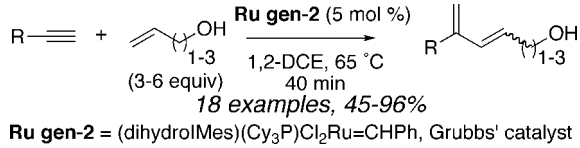
ABSTRACT

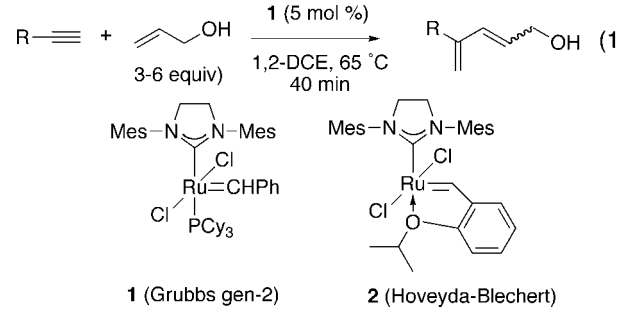


Allyl alcohols and their homologues were used in the enyne cross metathesis to prepare hydroxy-functionalized dienes. An isomerization was found to occur under prolonged heating, and a method for conversion to (*E*)-diene product is also reported.

Enyne metathesis has become a useful method for diene synthesis.[1] In particular, the cross enyne metathesis between an alkene and alkyne is attractive because it joins two simple unsaturated reactants into a diene building block that can be employed in further transformation. A major concern in synthetic applications of metathesis has been the choice of protecting groups for hydroxyl groups, especially in the allylic position.[2] Oxygen functionality, though tolerated by the Grubbs ruthenium carbenes, may chelate to the metal carbene,[3] slowing catalysis or resulting in decomposition. In alkene metathesis, allylic alcohols are tolerated but also may result in destruction of the metal carbene. We were interested in incorporating alcohol functionality into the diene product and wanted to learn whether allylic alcohols posed difficulties in enyne metathesis. In this report, we show that free hydroxyl functionality is tolerated in the alkene reactant in cross enyne metathesis (eq 1 in Scheme 1).

With no literature on enyne metathesis to guide us, we looked to previous work in alkene metathesis.[4] Hoye and Zhao[5a] found that there was an accelerating effect for tertiary allylic alcohols versus their hydrocarbon analogues in ring-closing alkene metathesis (RCM) with the first generation Grubbs carbene. At the same time, secondary allylic alcohols, though they react faster in RCM, also have a decomposition mechanism available that results in truncation of the unsaturated moiety and its conversion to a methyl ketone (eq 2 in Scheme 2).[5a,b] Subsequently, Paquette and Efemrov[5b] observed the truncation during a "routine" ring-closing alkene metathesis. Hoye had also found that allylic ethers initiated more slowly than the corresponding allylic alcohol. Yet in

Scheme 1. Allyl Alcohol−Alkyne Cross Metathesis



(1) Enyne reviews: (a) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1–18. (b) Mori, M. Ene-Yne Metathesis. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2, pp 176−204. (c) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382.

(2) Gennari summarizes the range of results found in complex molecules: Caggiano, L.; Castoldi, D.; Beumer, R.; Bayon, P.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2003**, *44*, 7913–7919.

(3) (a) Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron* **1999**, *55*, 8155–8167. (b) Kulkarni, A. A.; Diver, S. T. *J. Am. Chem. Soc.* **2004**, *126*, 8110–8111.

(4) The mechanistic interpretation of enyne metathesis has been closely intertwined with that of alkene metathesis. To a first approximation, the initiation abilities of alkenes will determine their success in either alkene or enyne metathesis.

(5) (a) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123–1125. (b) Paquette, L. A.; Efremov, I. *J. Am. Chem. Soc.* **2001**, *123*, 4492–4501. (c) Michaelis, S.; Blechert, S. *Org. Lett.* **2005**, *7*, 5513–5516.

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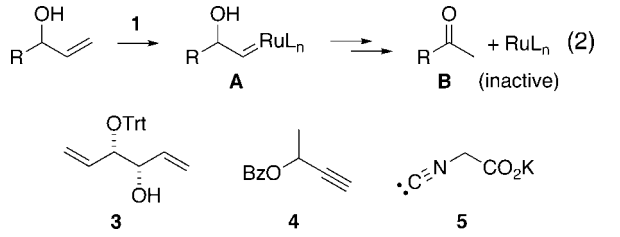
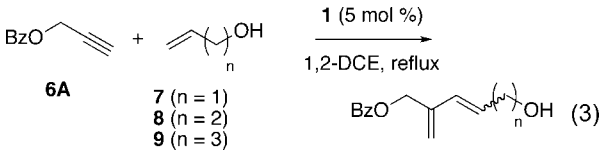
Scheme 2. Decomposition of Secondary Allylic Alcohols (Hoye and Zhao, 1999)

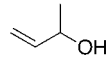
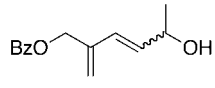


complex, highly functionalized dienes, ethers may perform better than the free alcohol.[2] Michaelis and Blechert[5c] conducted a selective cross alkene metathesis on dienol **3**, using a trityl group to block reaction on one side. These investigators attributed the chemoselectivity to steric hindrance of the bulky trityl group. Alcohol functionality in alkene metathesis is of great interest due to the potential to use aqueous solvents.[6] Very recently, Takahata and coworkers reported an accelerating effect of an allylic hydroxyl group in a ring-closing enyne metathesis using the first generation Grubbs carbene.[7] In summary, the literature from olefin metathesis suggests activation of allylic alcohols, but initiation proximal to a secondary allylic alcohol also promotes a rearrangement that is fatal to the ruthenium carbene catalyst. What is the relative significance of these observations in relation to cross enyne metathesis?

We began our studies by examining the cross metathesis between alkenols and alkyne **6A** (eq 3 in Table 1). Under

Table 1. Various 1,ω-Alkenols in Cross Enyne Metathesis[a]



entry	unsaturated alcohol (6 equiv)	product, yield, (*E*:*Z*) ratio
1	**7**	**11A** (n = 1), 74% (2.5:1)
2	**8**	**11B** (n = 2),91% (4:1)
3	**9**	**11C** (n = 3), 70% (1.5:1)
4	 **10**	 **11D**, 75% (5:1)

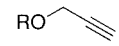
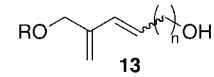
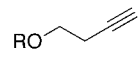
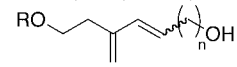
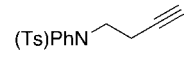
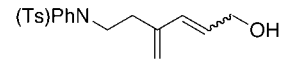
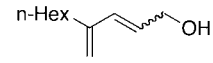
[a] Reaction conditions: alkyne (0.2 M), alkene (1.2 M), **1** (5 mol %), 1,2-dichloroethane, reflux, 40 min; isocyanide **5** (~25 mol %).

standard conditions employing 3 equiv of allyl alcohol **7** and 5 mol % of Grubbs' second generation carbene (complex **1**), complete reaction was detected in less than 10 min in refluxing 1,2-DCE. Similar reaction times were observed with the Hoveyda−Blechert carbene **2**. This proved to be a remarkably fast intermolecular metathesis, conducted under the typical conditions using an excess of the alkene reactant.[8] After 40 min, the reaction was stopped using the quenching/clean up protocol developed in our laboratory: addition of the polar isocyanide **5** (25−50 mol %)[9] as a solution in methanol. The diene **11A** was produced in 74% isolated yield as a 2.5:1 mixture of *E*/*Z* isomers.

We systematically examined the effect of distance between the free hydroxyl group and the alkene (Table 1). We found that alcohols **8**−**10** reacted effectively under the normal reaction conditions. Good isolated yields were obtained in all cases. Notably, the secondary allylic alcohol **10** (entry 4) performed well under catalytic conditions, suggesting that carbene decomposition is not a factor in these reactions, probably due to the catalyst used and the short reaction times.

The scope of the alkenol−1-alkyne cross metathesis is summarized in Table 2. The usual protecting groups were

Table 2. Cross Enyne Metathesis with Unsaturated Alcohols[a]

entry	alkyne	unsaturated alcohol	product, yield, (*E*:*Z*) ratio
	 **12**		 **13**
1[b]	**12A**, R = Bn	**7**	**13A** (n = 1), 69% (2:1)
2	**12B**, R = THP	**7**	**13B** (n = 1), 58% (2.1:1)
3	**12C**, R = TIPS	**7**	**13C** (n = 1), 47% (3:1)
4	**12D**, R = TBDPS	**7**	**13D** (n = 1), 53% (3:1)
5	**12E**, R = Nap	**7**	**13E** (n = 1), 69% (2:1)
6	**12E**, R = Nap	**9**	**13F** (n = 3), 74% (1.1:1)
	 **14**		 **15**
7	**14A**, R = Bz	**7**	**15A** (n = 1), 58% (3.2:1)
8	**14B**, R = Bz	**8**	**15B** (n = 2), 72% (2:1)
9	**14C**, R = Bz	**9**	**15C** (n = 3), 96% (2:1)
10	**14D**, R = TBS	**7**	**15D** (n = 1), 77% (2.3:1)
11	**14E**, R = TBS	**8**	**15E** (n = 2), 50% (1:1)
12	**14F**, R = TBS	**9**	**15F** (n = 3), 73% (1.3:1)
13	 **16**	**7**	 **17**, 45% (2:1)
14	1-octyne	**7**	 **18**, 46% (3:1)

[a] Reaction conditions: alkyne (0.2 M), alkene (1.2 M), **1** (5 mol %), 1,2-dichloroethane, reflux, 40 min; isocyanide **5** (25 mol %). [b] Reaction performed on 15 mmol scale.

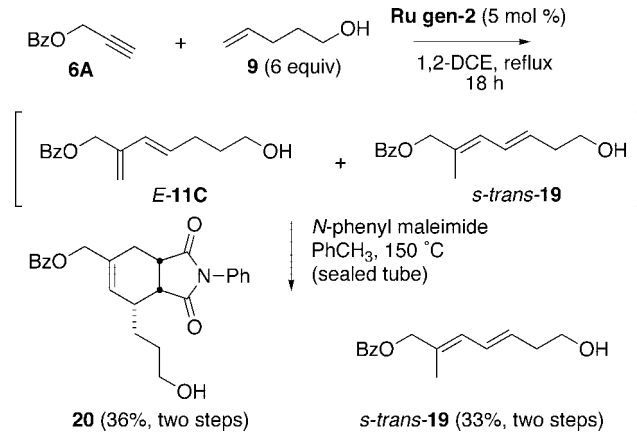
well tolerated in the propargylic position. In particular, the alkyl ethers in entries 1 and 2 have potential to chelate to intemediate carbenes, but they proved reactive. Similar results were obtained with the silyl protecting groups (entries 3 and 4). A more remote alcohol is also tolerated in the reaction

(entry 6). With oxygen functionality in the homopropargylic position (alkynes **14**), the reaction was efficient for a variety of unsaturated alcohols (allyl alcohol entries 7 and 10; and homologues entries 8, 9 and 11,12). Slightly poorer yield of the homologous diene **15E** was obtained under the standard conditions. From entry 13, it can be seen that remote nitrogen functionality results in modest yields of diene **17**.[10] However, these reactions were not reoptimized from the standard conditions. The simple hydrocarbon 1-octyne performed acceptably in entry 14.[10] The propargyl-substituted substrate **4** (Scheme 2) did not perform well in the metathesis with allyl alcohol **7** for reasons that are not completely understood. Last, the metathesis in entry 1 was performed on a 15 mmol scale, showing that the process is scaleable. In all of these cases, a mixture of *E* and *Z* isomers is obtained.

The rapid reactions led us to investigate the magnitude of the accelerated reaction rate compared to that of simple alkenes.[11] We conducted a competition experiment using propargyl benzoate **6a** and 1 equiv each of 1-hexene and allyl alcohol **7**. After heating for 20 min at 55 °C, the reaction was quenched with **5** and the crude product ratio was determined by ^{1}H NMR analysis against an internal standard (mesitylene). We found 40% (*E*)-diene derived from allyl alcohol **7** and 17% (*E*)-diene from 1-hexene. Under these conditions, this experiment shows that there is a ca. 2.3-fold rate enhancement by free hydroxyl functionality in enyne metathesis.[12] This is in accord with Hoye and Zhao's findings in the ring-closing alkene metathesis using the first generation Grubbs carbene. The finding also strongly suggests an alkylidene first mechanism with this 1-alkyne. It is the first indication that we know of that different substitution on the alkene affects rate in the cross enyne metathesis. Alkene reactivity forms the basis for the selectivity model advanced by the Grubbs group for cross alkene metathesis.[13]

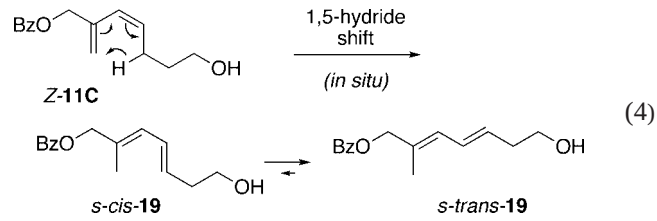
Longer reaction times affected the product distribution. Though alkyne consumption was complete in less than an hour, we investigated extended heating of the reaction in an attempt to obtain higher *E*-selectivity. On the basis of earlier work,[14] it was expected that a secondary, *E*-selective alkene−diene metathesis would upgrade the ratio of (*E*)-diene. Heating the reaction depicted in Table 1, entry 3, for an extended time period (18 h) gave an improvement of the kinetic 1.5:1 ratio of (*E*/*Z*)-**11C** (70% isolated yield, Table 1) to exclusively *E*-isomer. However, inspection of the crude ^{1}H NMR spectrum revealed that an additional product had formed with unique vinylic resonances at δ 6.38 (dd, J = 15, 11 Hz, 1H), 6.13 (d, J =11 Hz, 1H), and 5.71 (dt, J = 15, 7 Hz, 1H) ppm, consistent with a terminally substituted diene substructure (Scheme 3). On the basis of these data,

Scheme 3. Trapping of Isomerization Intermediate



we gathered that a 1,5-hydride shift had occurred. Unfortunately, this byproduct could not be separated from the diene (*E*)-**11C**.

The products were separated after an in situ cycloaddition of the (*E*)-diene. We reasoned that putative hydride shift product **19** would exist in the *s-trans* conformation, making it unreactive in the thermal cycloaddition. The thermal cycloaddition with *N*-phenyl maleimide provided cycloadduct **20** in 36% yield along with recovered **19**, obtained in 33% yield. The major (*E*)-diene **11C** underwent [4 + 2] cycloaddition cleanly, whereas the isomeric product *s-trans*-**19** was recovered unchanged from the reaction. At this stage, the products could be separated and their structures independently established by spectroscopic techniques. Diene *s-trans*-**19** presumably came from the intermediate *Z*-isomer **11C** by a 1,5-hydride shift (eq 4), though it was unclear what promoted this reactivity. Equilibrium presumably favors **19** due to greater alkyl substitution on the resulting 1,3-diene.



(4)

The causative agent for the hydride shift was investigated further. Control studies were carried out on the purified diene (*E*/*Z*)-**11C**. When this *E*/*Z* mixture was purified away from

(6) (a) Lynn, D. M.; Mohr, B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1998**, *120*, 1627–1628. (b) Connon, S. J.; Blechert, S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1873–1876. (c) Binder, J. B.; Blank, J. J.; Raines, R. T. *Org. Lett.* **2007**, *9*, 4885–4888. (d) Gallivan, J. P.; Jordan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **2005**, *46*, 2577–2580. (e) Hong, S. H.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 3508–3509. (f) Jordan, J. P.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5152–5155.

(7) Imahori, T.; Ojima, H.; Tateyama, H.; Mihara, Y.; Takahata, H. *Tetrahedron Lett.* **2008**, *49*, 265–268.

(8) Stragies, R.; Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2518–2520.

(9) Galan, B. R.; Kalbarczyk, K. P.; Szczepankiewicz, S.; Keister, J. B.; Diver, S. T. *Org. Lett.* **2007**, *9*, 1203–1206.

(10) Complete consumption of the alkyne was observed.

(11) (a) For a rate study of enyne metathesis with 1-hexene: Galan, B. R.; Giessert, A. J.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 5762–5763. (b) DFT calculations: Lippstreu, J. J.; Straub, B. F. *J. Am. Chem. Soc.* **2005**, *127*, 7444–7457.

(12) Alkene homodimerization was not detected. The reaction was run to partial alkyne conversion and gave clean conversion to the diene products of enyne metathesis. Further rate studies are being pursued.

(13) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

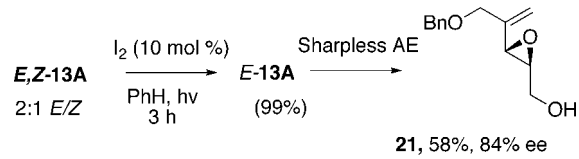
(14) Giessert, A. J.; Diver, S. T. *J. Org. Chem.* **2005**, *70*, 1046–1049.

the ruthenium catalyst and heated under the reaction conditions (DCE, reflux, 18 h), no 1,5-hydride shift product was observed, and the *E/Z* mixture was recovered unchanged. This ruled out a simple thermal isomerization and suggested that a ruthenium-derived species was causing isomerization. We considered that the longer heating periods decomposed the Grubbs carbene into ruthenium hydrides. If this occurred, then the 1,5-hydride shift would have been caused by ruthenium hydrides.

Ruthenium hydrides[15] formed in situ caused 1,5-hydride shift in crude reaction mixtures of **11C**. We conducted metathesis as defined in entry 3, Table 1, to obtain an *E/Z* mixture of **11C**. To this crude mixture was added 50 mol % of $NaBH_4$ using Schmidt's procedure[15c] to form ruthenium hydrides in situ from the Grubbs catalyst **1**. After 2 h of heating at 60 °C in 1,2-DCE, only (*E*)-**11C** and 1,5-hydride shift product **19** were observed in the crude ^{1}H NMR. This experiment illustrates that ruthenium hydrides are competent to produce the isomerization by hydride shift under typical reaction conditions.

The hydride shift did not pose a general problem in this study due to the typically short reaction times (ca. 30−40 min) using a large excess of 1,ω-alkenol. Under these conditions, the enyne metathesis is so fast that longer periods of heating are not necessary. The long periods of heating in the presence of the large excesses of alcohol are likely to account for decomposition of the metal carbenes.[5a,16] At short reaction times, this is not problematic for the enyne metathesis.

Conversion of an *E/Z* isomeric mixture to the *E*-isomer was accomplished through application of a classical isomerization method using catalytic I_2, hν (eq 5).[17] To the best of our knowledge, this equilibration has not been used to upgrade *E/Z* ratio from *E/Z* mixtures produced through nonstereoselective cross metathesis. A major shortcoming of metathesis is the low stereoselectivity, and there are few ways of dealing with this problem. The crude mixture **13A** (2:1 *E/Z*, Table 2, entry 1) was irradiated in the presence of 10 mol % of I_2 to give 99% yield of (*E*)-**13A**. This procedure is simple and very effective for converting an *E/Z* mixture to the pure *E*-isomer.



21, 58%, 84% ee (5)

The presence of the hydroxyl group near the diene permits directable, chemoselective transformation. Diene (*E*-)**13A** was epoxidized under catalytic Sharpless asymmetric conditions to give **21** in 58% isolated yield (eq 5). We foresee additional substrate-directable transformations[18] utilizing the hydroxyl group, conveniently introduced through catalytic enyne metathesis.

In conclusion, we have demonstrated that free hydroxylic functionality is permitted in the alkenes used in cross enyne metathesis. The alcohol provides a rate enhancement compared to that of simple hydrocarbon alkenes. We observed a 1,5-hydride shift in the minor (*Z*)-diene which could be minimized under short reaction times. We also used a simple (nonmetathesis) procedure for the isomerization of an *E/Z* mixture into (*E*)-diene. Last, the hydroxyl group provides a handle to direct a chemoselective epoxidation of the diene moiety. Further diene functionalization methods and detailed kinetic studies of unsaturated alcohol−alkyne metathesis will be reported in due course.

Acknowledgment. This work was partially supported by the Petroleum Research Fund (PRF AC-44202) and the NSF (CHE-601206). J.R.C. acknowledges the NSF-REU program at SUNY Buffalo (CHE-453206) for summer support. The authors thank Dr. Amol Kulkarni (U. Pitt.) for some preliminary observations, and we thank Materia (Pasadena, CA) for supplying Grubbs' catalyst.

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

OL800523J

(15) For leading references on the isomerization by ruthenium hydrides under nominal metathesis conditions, see: (a) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390–13391. (b) Schmidt, B. *Eur. J. Org. Chem.* **2003**, 816–819. (c) Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672–7687. (d) Schmidt, B.; Biernat, A. *Org. Lett.* **2008**, *10*, 105–108.

(16) (a) Dinger, M. B.; Mol, J. C. *Organometallics* **2003**, *22*, 1089–1095. (b) Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 10103–10109.

(17) Use of catalyst I_2/hν for diene isomerization: Van Rossum, A. J. G.; De Bruin, A. H. M.; Nivard, R. J. F. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1036–1042.

(18) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.