JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Ruthenium Hydride-Promoted Dienyl Isomerization: Access to Highly Substituted 1,3-Dienes

Joseph R. Clark, Justin R. Griffiths, and Steven T. Diver*

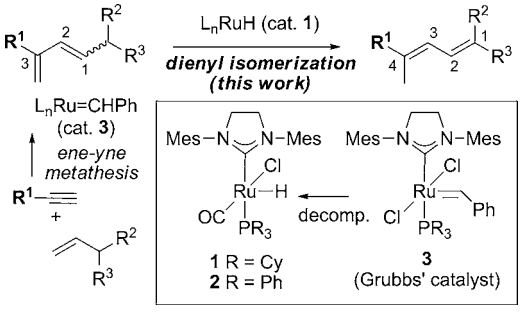
Department of Chemistry, University at Buffalo, the State University of New York, Buffalo, New York 14260-3000, United States

Supporting Information

ABSTRACT: Ruthenium hydrides were found to promote the positional isomerization of 1,3-dienes into more highly substituted 1,3-dienes in a stereoconvergent manner. The reaction can be conducted in one pot starting with terminal alkynes and alkenes by triggering decomposition of the Grubbs catalyst into a ruthenium hydride, which promotes the dienyl isomerization. The presence of an alcohol additive plays a helpful role in the reaction, significantly increasing the chemical yields. Mechanistic studies are consistent with hydrometalation of the geminally substituted alkene of the 1,3-diene and transit of the ruthenium atom across the diene framework via a π-allylruthenium intermediate.

The catalytic ene−yne cross-metathesis promoted by the Grubbs ruthenium carbenes has emerged as a useful carbon−carbon coupling to access the 1,3-diene motif.[1] Conjugated 1,3-dienes appear in a variety of bioactive natural products and lend themselves to further synthetic elaboration. Ene−yne metathesis is a powerful method for coupling nearly equimolar amounts of alkyne and alkene, fulfilling the criteria of an atom-economical cross-coupling reaction.[2] However, there are limitations of the intermolecular ene−yne cross-metathesis. For instance, it produces limited substitution patterns on the 1,3-diene. Normally the 1,3-diene has 1,3-disubstitution (see the reactant in Scheme 1), and there is no direct isomerization

Scheme 1. Dienyl Isomerization



of the 1,3-diene into a *more highly substituted* 1,3-diene. In this report, we describe a formal 1,5-hydride shift mediated by a ruthenium hydride complex that accomplishes "dienyl isomerization", that is, the conversion of a 1,3-diene into a new 1,3-diene (Scheme 1). In addition, conversion of alkynes and alkenes into dienyl isomerization products can be achieved through a tandem metathesis/dienyl isomerization sequence starting from Grubbs catalyst **3**. Dienyl isomerization of 1,3-dienes obtained through ene−yne metathesis provides stereoconvergent access to diene substitution patterns that cannot be produced by ene−yne metathesis.

The synthesis of highly substituted 1,3-dienes through tandem catalytic reactions[3] extends the scope of diene substitution patterns accessible in a stereoconvergent process. Ene−yne metathesis is a useful catalytic method for 1,3-diene synthesis, but it cannot be used to produce 1,1,4-trisubstitution or 1,1,4,4-tetrasubstitution on the resulting diene. Because these diene substitution patterns appear in a variety of bioactive natural products, a catalytic method that could access them from simple alkene and alkyne reactants would be useful. Induced decomposition of Grubbs complex **3** into a ruthenium hydride allows these reactions to be coupled to give dienyl isomerization (Scheme 1), which could potentially use a single source of ruthenium catalyst.[3a] Though dienyl isomerization was observed previously in one case, the catalyst was undefined and the reactivity was limited because the *E* and *Z* isomers could not each be converted to product.[4] Overcoming the reactivity difference of individual stereoisomers poses a challenge but would provide a stereoconvergent catalytic process. Last, though isomerization of alkenes is well-known,[5] that of conjugated dienes is not.

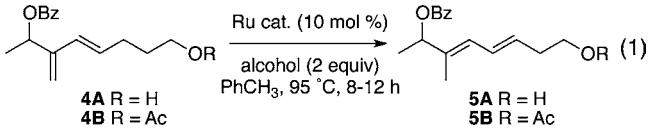
Initial studies were directed to the optimization of catalysts to effect the conversion of both *E* and *Z* dienes to the dienyl isomerization product. Typically, mixtures of *E* and *Z* dienes are obtained from ene−yne cross-metathesis. Earlier studies suggested that a metal hydride may promote dienyl positional isomerization, but each geometric isomer did not react to give the product.[4] Since primary alcohols are known to result in conversion of Grubbs ruthenium carbenes into ruthenium hydrides,[6] our initial screening efforts focused on some common ruthenium hydrides that are known to bring about alkene positional isomerization (Table 1).

Attempts to isomerize **4A** without any additive led to incomplete reaction (Table 1, entry 1). The product **5A** was contaminated with aldehyde-containing side products. On the basis of this result, and knowing that dehydrogenation of alcohols occurs by ruthenium hydrides,[7] we reasoned that an alcohol additive might suppress the oxidation of alcohol **5A** under the catalytic conditions. Improved conversion and chemical yield were found using the alcohol additive 1-butanol (entry 2). For diene reactant **4B**, which does not possess a free

Received: November 20, 2012
Published: February 21, 2013

   dx.doi.org/10.1021/ja4011207 | J. Am. Chem. Soc. 2013, 135, 3327−3330

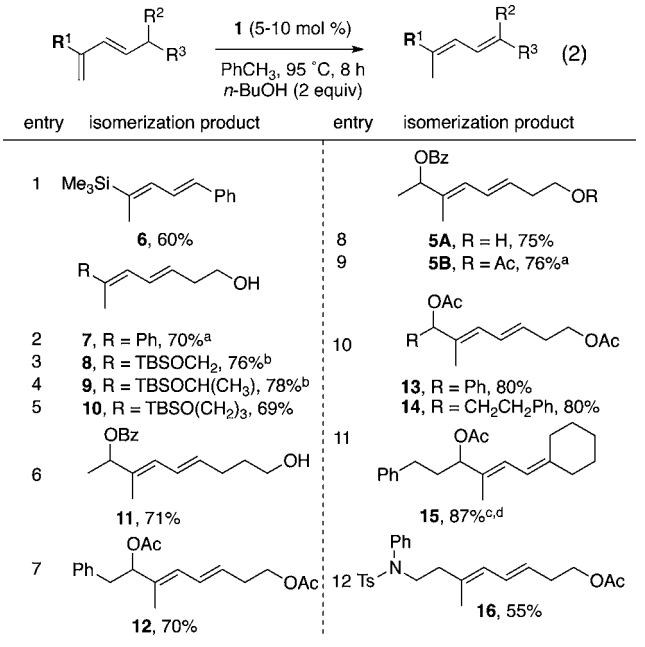
Table 1. Screening of Catalysts and Alcohol Additives



entry	reactant	Ru cat.	alcohol	% conv.	%5[a]
1	**4A**	**1**	none	60	40
2	**4A**	**1**	1-butanol	100	75
3	**4B**	**1**	1-octanol	100	65
4	**4B**	**1**	2-propanol	80	70
5	**4B**	**1**	cyclohexanol	100	80
6	**4B**	**1**	*tert*-butanol	10	10
7	**4B**	**1**	phenol	10	10
8	**4B**	**1**	1-butanol	97	80
9	**4B**	**2**	1-butanol	100	70[b]
10	**4B**	$RuHCl(CO)(PPh_3)_3$	1-butanol	10	n.d.[b,c]
11	**4B**	$RuHCl(CO)(PCy_3)_2$	1-butanol	25	n.d.[c]
12	**4B**	$RuH_2(PPh_3)_4$	1-butanol	10	n.d.[c]

Conditions: 0.05 M diene in toluene, 95 °C, 6–12 h. [a]NMR yields vs mesitylene as an internal standard. [b]Semihydrogenation was also observed. [c]Not detected.

Table 2. Dienyl Isomerization of 1,3-Dienes



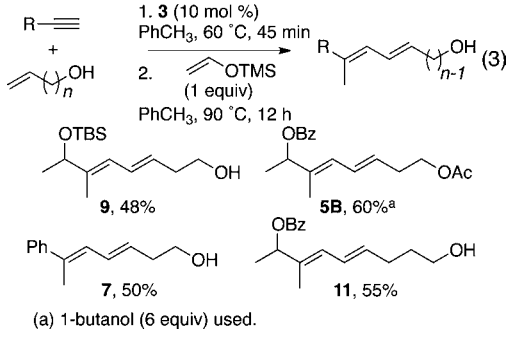
Unless otherwise noted, products were isolated as pure *E* isomers. [a]5 mol % **1** was used. [b]5.5:1 *E*/*Z*. [c]NMR yield. [d]Isolated in 56% isolated yield after saponification of the acetate.

hydroxyl group, several alcohols were investigated (entries 3–7). Primary and secondary alcohols were found to improve the yield of the reaction, whereas *tert*-butanol and phenol did not (no catalyst turnover; entries 6 and 7). With 1-butanol as the additive, several ruthenium hydrides were found to promote the isomerization (entries 8–12). Complexes **1** and **2** gave high conversion and reasonable yield, though some semihydrogenation product was detected with **2** (entries 8 and 9). $RuHCl(CO)(PPh_3)_3$ did not induce dienyl isomerization (entry 10), and two other common hydrides gave low conversions (entries 11 and 12). In these latter cases, mostly semihydrogenation products were observed in the crude reaction mixtures.

The scope of the diene positional isomerization was investigated using ruthenium hydride catalyst **1** and 1-butanol as an additive. This catalyst was selected because alcohol-induced decomposition of Grubbs catalyst **3** forms this ruthenium hydride.[6b] The reaction scope was studied for an assortment of 1,3-dienes obtained directly from catalytic ene–yne metathesis as *E*/*Z* mixtures[8] (Table 2; for brevity, the starting 1,3-dienes are not shown). Dienyl isomerization proceeded efficiently in cases where R^1 lacked a hydrogen (entries 1 and 2). The R^1 group (derived from the alkyne in the ene–yne metathesis step) could be linear or branched (entries 3 and 4), and free hydroxyl groups were tolerated without undergoing dehydrogenation by the ruthenium catalyst (entries 2–6). In only two cases (entries 3 and 4) were minor amounts of the *Z* isomer produced. Further positional isomerization occurring down the alkane chain was not observed. Remote oxygen functionality was well-tolerated (entries 7–10). The integrity of the propargylic chiral center was conserved throughout the process.[8,9] The isomerization occurred into secondary alkyl groups to produce the 1,1,4,4-tetrasubstitution pattern on the resulting 1,3-diene (entry 11). It is presumed that the isomerizations are driven to produce the most thermodynamically stable 1,3-diene. In all cases, the dienyl isomerization was highly regioselective, occurring away from the R^1 position.[8,10] In entries 3–12, the hydrogen at the propargylic position could have been eliminated to give a regioisomer, but this was not observed.

The ene–yne metathesis and dienyl isomerization were promoted consecutively in one pot using Grubbs catalyst **3**. The dienyl isomerization product was thought to arise from a ruthenium hydride formed in situ by decomposition of **3** in the presence of added alcohol. To evaluate this hypothesis, the ene–yne metathesis of 2-butynyl benzoate and 4-pentenol was examined using Grubbs catalyst **3**.[8] After 1 h of heating at 85 °C, a new signal was observed in the ^1H NMR spectrum at −24.8 ppm (d, J_{HP} = 21.6 Hz). After continued heating, the hydride was still present. A spiking experiment with authentic **1** showed only a single peak (no new hydride signals), verifying that the decomposition of **3** had produced **1** under the metathesis conditions. In the preparative runs shown in Scheme 2, the suspected hydride complex **1** was intentionally formed in situ at the end of the ene–yne metathesis upon the addition of vinyl trimethylsilyl ether.[6d] This resulted in dienyl isomerization. The results of the tandem sequential process are shown in Scheme 2. Advantages of this procedure include its catalyst

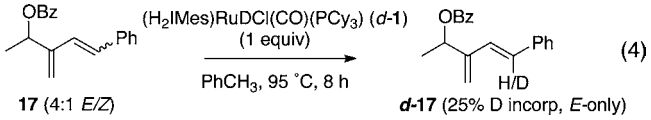
Scheme 2. Tandem Ene–Yne Metathesis/Dienyl Isomerization



dx.doi.org/10.1021/ja4011207 | J. Am. Chem. Soc. 2013, 135, 3327–3330

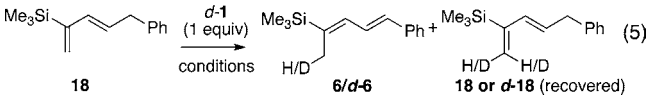
economy and the fact that the products of dienyl isomerization can be accessed starting directly from alkyne and alkene precursors.

Subjecting pure *E* and *Z* dienes individually to the conditions of Table 2 revealed that *Z*-to-*E* isomerization preceded dienyl isomerization. Pure (*Z*)-**4A** and (*E*)-**4A** were allowed to react individually under the standard conditions, and the reactions were monitored by ^{1}H NMR spectroscopy over a 12 h period.[11] The *E* isomer was converted to the isomerization product **5A** without the accumulation of any detectable intermediates. In contrast, the *Z* isomer did not directly provide product **5A**; instead, it underwent rapid isomerization to give the *E* isomer. As geometric isomerization occurred, conversion to the dienyl isomerization product **5A** began. The stoichiometric reaction of diene (*E*,*Z*)-**17** with *d*-**1** gave ca. 25% deuterium incorporation at C4 (eq 4), suggesting reversible hydrometalation of the 1,2-disubstituted alkene, which would account for the observed *Z*-to-*E* isomerization and explain the observed stereoconvergence.



Deuterium-labeling experiments using diene **18** with or without labeled external alcohol (Table 3) provided insight to

Table 3. Deuterium Labeling Studies



				% yield[a] (% D[b])	
entry	additive	time (h)	% conv.	**6**/*d*-**6**	**18**/*d*-**18**
1	none	14	80	60 (15)	20 (30)
2	CyOD	14	100	70 (30)	n.d.[c]
3	nBuOD	2.5	25	25 (20)	75 (0)

[a]NMR yields vs mesitylene as an internal standard. [b]% deuterium incorporation. [c]Not detected.

the reaction pathway and suggested a role for the added alcohol. Both cases showed significant deuterium incorporation, though greater D incorporation[12] and a better chemical yield were seen when the deuterated alcohol was present (entry 2). With no alcohol additive (entry 1), the recovered reactant showed 30% D incorporation in the geminal alkene positions, suggesting that reversible hydroruthenation of the geminally substituted end of the 1,3-diene had occurred. With an alcohol present, as in entry 2, the reaction went to full conversion, providing a 70% yield of **6** with 30% D incorporation. This is consistent with hydrometalation of the geminally substituted 1,3-diene. With an alcohol present, we were interested in identifying the D incorporation in the recovered **18**. In entry 3, stopping the reaction at 25% conversion revealed 20% D incorporation in the product, but unlike entry 1, no D incorporation was found in the recovered reactant. This finding suggests that the hydroruthenation step of the geminally substituted end of the 1,3-diene is not reversible under these conditions. With an alcohol additive, hydrometalation represents "high commitment" in the catalytic reaction, with subsequent steps, such as π-allyl formation and β-hydride elimination,[13] occurring faster than the reverse reaction.

Taken together, the observations are consistent with a π-allyl mechanism. The labeling experiments are consistent with slow hydroruthenation of the geminal alkene, leading to π-complex **B** (eq 6). Previous studies showed facile π-allylruthenium

complex formation for certain 1,3-dienes.[14] Both Ryu[14] and Krische[7] showed that an intermediate π-allylruthenium species can be intercepted by an aldehyde.[15,16] Subsequently, intermediate **B** would undergo β-elimination to give the product of dienyl isomerization and a ruthenium hydride. Relatedly, π-allylpalladium intermediates are known to undergo elimination to give dienes,[17] generally a minor side product in the Tsuji–Trost reaction. The low D incorporation is consistent with the proposed mechanism. Each turnover of a ruthenium deuteride produces a ruthenium hydride through β-elimination of **B** (eq 6), thereby introducing protium in the activated catalyst. Ligand exchange with diene reactant would carry the catalytic cycle forward.

The mechanistic studies do not rule out other possible roles of the alcohol that may also account for the higher chemical yields. For instance, with the alcohol additive present, the hydride catalyst was found to persist and was unchanged at the end of the reaction; without an alcohol, the ruthenium hydride was found to be decomposed.[8,18] The alcohol can regenerate a hydride species: dienyl isomerization in the presence of catalytic benzoquinone failed,[8,19] but in the presence of an alcohol, dienyl isomerization occurred with benzoquinone present. No spectroscopic evidence for an alcohol-activated catalyst was found, and no new hydride species were observed besides complex **1**, though it is possible that highly reactive intermediates would not be detected. Further mechanistic studies are in progress.

In summary, a new and regioselective dienyl isomerization pathway has been described. Isomerization of the 1,3-conjugated dienes produced through ene–yne metathesis provides a stereoconvergent synthesis of a 1,3-diene with a new substitution pattern. The isomerization is promoted by a ruthenium hydride, which was identified as a decomposition product of the Grubbs catalyst in ene–yne metathesis when alkenol substrates or alcohols were used. The ruthenium hydrides may be produced directly from the Grubbs catalyst used in the metathesis step for a one-pot tandem catalytic reaction or can be added separately to trigger the isomerization. Mechanistic studies are consistent with the intermediacy of a π-allylruthenium species.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

diver@buffalo.edu

Notes

The authors declare no competing financial interest.

dx.doi.org/10.1021/ja4011207 | *J. Am. Chem. Soc.* 2013, 135, 3327–3330

■ ACKNOWLEDGMENTS

The authors thank the NSF (CHE-0848560) for support of this work and Materia for a generous gift of Grubbs' complex **3**. J.R.C. is a recipient of a Speyer Graduate Fellowship (UB Department of Chemistry).

■ REFERENCES

(1) Reviews: (a) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1. (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. (d) Diver, S. T. *Sci. Synth.* **2009**, *46*, 97.

(2) Clark, J. R.; Diver, S. T. *Org. Lett.* **2011**, *13*, 2896.

(3) (a) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365. With metathesis: (b) Alcaide, B.; Almendros, P.; Luna, A. *Chem. Rev.* **2009**, *109*, 3817. (c) Li, J.; Lee, D. *Eur. J. Org. Chem.* **2011**, 4269.

(4) Clark, D. A.; Clark, J. R.; Diver, S. T. *Org. Lett.* **2008**, *10*, 2055.

(5) (a) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390. (b) Schmidt, B. *Eur. J. Org. Chem.* **2003**, 816. Review: (c) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865.

(6) (a) Dinger, M. B.; Mol, J. C. *Organometallics* **2003**, *22*, 1089. (b) From **3**: Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546. Via Fischer carbenes: (c) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312. (d) Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Org. Chem.* **2006**, *71*, 4255.

(7) (a) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6338. (b) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14120. (c) Smejkal, T.; Han, H.; Breit, B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 10366. (d) Han, H.; Krische, M. J. *Org. Lett.* **2010**, *12*, 2844.

(8) See the Supporting Information (SI) for details.

(9) *ent*-**4B** (99% ee) was converted to *ent*-**5B** (96% ee) with negligible erosion of ee at the stereogenic center.

(10) With a free hydroxyl group in the propargylic position, the alternate regioisomer was not detected in the crude NMR spectrum.

(11) See Figures S1 and S2 in the SI.

(12) Control studies revealed that H/D exchange between the **1** and the alcohol occurred on the time scale of the experiment. Thus, deuterated alcohol was expected to increase the deuterium content of the active catalyst. The alcohols in entries 2 and 3 were also deuterated at the methine carbon.

(13) Added base (DBU or Bu_4NOAc, 1 equiv) under the standard conditions of Table 2 had a deleterious effect on the yield.

(14) π-Allyl complex formation between $(Ph_3P)_3RuCl(CO)H$ and 2-substituted-1,3-dienes has been observed: Omura, S.; Fukuyama, T.; Horiguchi, J.; Murakami, Y.; Ryu, I. *J. Am. Chem. Soc.* **2008**, *130*, 14094.

(15) The allylation chemistry is very powerful yet limited to simple diene substitution, such as 1-substituted- and 2-substituted-1,3-butadienes.

(16) Our attempts to produce a π-allyl intermediate using 1,3-dienes bearing the 1,3-disubstitution pattern did not produce an π-allylruthenium intermediate observable by ^1H NMR spectroscopy.

(17) β-Hydride elimination in π-allylpalladium chemistry: (a) Trost, B. M.; Tometzki, G. B. *J. Org. Chem.* **1988**, *53*, 915. (b) Keinan, E.; Kumar, S.; Dangur, V.; Vaya, J. *J. Am. Chem. Soc.* **1994**, *116*, 11151. Decarboxylation of a π-allyl intermediate to give 1,3-dienes: (c) Trost, B. M.; Fortunak, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 2841. Specific base-catalyzed elimination to form 1,3-dienes: (d) Takacs, J. M.; Lawson, E. C.; Clement, F. *J. Am. Chem. Soc.* **1997**, *119*, 5956.

(18) The presence of the alcohol has a negligible effect on the rate of phosphine exchange in catalyst **1** with or without a diene present.

(19) Benzoquinone is known to destroy a related ruthenium hydride: Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160.