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Expanded Scope in Ethylene−Alkyne Cross-Metathesis: Coordinating Heteroatom Functionality at the Propargylic Position

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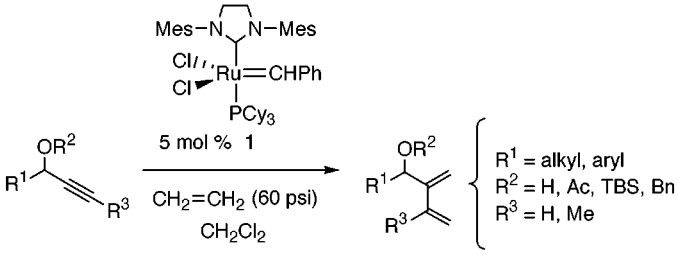
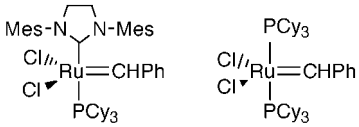
ABSTRACT



The Grubbs 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene-substituted ruthenium complex 1 catalyzed ethylene−alkyne cross-metathesis and was shown to tolerate free hydroxyl groups and coordinating functionality at the propargylic and homopropargylic positions. Hindered and enantiomerically enriched 1-substituted alkynes also react efficiently under the reported conditions.

Alkene−alkyne metathesis offers an economical synthesis of 2-substituted dienes. Important work in the area has been conducted by the groups of Blechert[1] and Mori.[2] However, a variety of alkynes are not reactive enough for practical use. Alkynes substituted with heteroatom functionality in the propargylic (and homopropargylic) position react with alkenes using Grubbs benzylidene catalyst **2** provided that the heteroatom is suitably protected (as an ester or carbonate). Protection helps guard against unwanted chelation to metal alkylidenes which may decelerate or shut down catalysis. Propargylic substitution also impedes the rate of cross-metathesis. Functional groups such as alcohols, ethers, and silyl ethers either do not react at all or perform very poorly in ene−yne cross metathesis.[2b,3] In this report, we demonstrate expanded reaction scope in an intermolecular alkyne metathesis with ethylene using the Grubbs 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ruthenium carbene **1**.



As with alkene metathesis, suitably positioned heteroatom functionality in the molecule may interfere with catalysis by trapping the metal alkylidene as a chelate. This chelative interaction may be stabilizing and may kinetically compete with alkene binding. As a result of this, even intramolecular reactions such as ring closing metathesis (RCM) may be thwarted.[4] It may be possible to overcome chelation by

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

(2) (a) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388. (b) Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron* **1999**, *55*, 8155. (c) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356.

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(4) (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324. (b) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.

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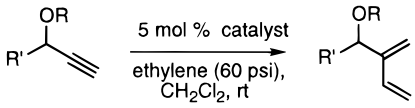
heteroatoms, particularly oxygen-containing functional groups, by choice of catalyst. The well-defined ruthenium carbene complexes developed by Grubbs and co-workers are weak Lewis acids and poorly oxophilic.[5] Recently, the electron-rich imidazolidine carbene ligand has been used in metal-catalyzed reactions.[6] On introduction of the new catalyst **1**, Grubbs et al.[7] demonstrated that RCM is possible in cases where the previous catalyst **2** performs with poor results. Given these observations, we set out to prepare 2-substituted dienes independent of propargylic substituent (or chirality). Cases that are known to be difficult[2b,3] were the first to be examined.

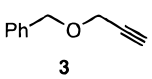
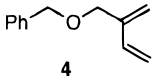
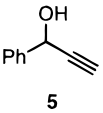
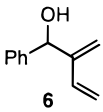
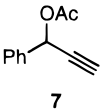
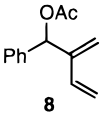
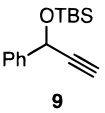
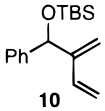
To obtain a better understanding of the substrate scope, the reactivities of catalysts **1** and **2** were examined using various problematic substrates (Table 1). Our standard reaction conditions for ethylene metathesis include 5 mol % of catalyst and an initial concentration of 0.25 M alkyne in CH_2Cl_2 at 60 psi of ethylene pressure.[8] Substrates were chosen which lacked reactivity or which required long reaction times with catalyst **2**. A diminution in the rate of metathesis was evident with catalyst **2** compared to catalyst **1**. After the indicated time period, the reactions were stopped and monitored for conversion. Table 1 reports yields based upon GC analysis. Alkynyl ethers are unreactive in alkyne−ethylene cross-metathesis.[2b] Higher ethylene pressure and catalyst **2** fail to provide useful yields of **4** (entry 1), but catalyst **1** gives nearly quantitative conversion. Free alcohols are resistant to cross-metathesis using catalyst **2** (even at elevated ethylene pressure),[3] but catalyst **1** gave clean[9] and quantitative conversion to **6** (entry 2). Grubbs et al.[7] have shown that a free alcohol undergoes RCM with catalyst **1**.

In previous work,[3] 1-substituted propargylic acetates were found to be less reactive than unsubstituted propargyl acetates. Acetate **7** took >22 h to reach 95% conversion using catalyst **2**, but complete conversion was realized after 2 h with **1** (entry 3). Silyl ethers are sterically hindered and gave no reaction after 8.5 h using **2**, but with catalyst **1** complete conversion occurred during this time period (entry 4). The large differences in the conversion data suggested that there was a significant rate acceleration using catalyst **1** in the ethylene−alkyne metathesis.

The reaction rates of Table 1 were accelerated with catalyst **1** and higher ethylene pressure. Reactions conducted at balloon pressure typically gave low conversions even after extended reaction times.[2b,3] The rate of conversion of alkyne **3** to **4** at 60 psi of ethylene pressure using complexes **1** and **2** is illustrated in Figure 1. A considerable rate difference was apparent. The lower yields obtained with catalyst **2** in the difficult cases of Table 1 may be attributed to the observed rate difference seen with benzyl propargyl ether **3**.

Table 1. Evaluation of Ruthenium Catalysts **1** and **2** for Various Alkynes



Entry	Substrate	Product	Time	% Conversion[a] 1	2
1	 **3**	 **4**	6.0 h	97	5
2	 **5**	 **6**	2.0 h	99	N.P.[b]
3	 **7**	 **8**	2.0 h	99	38
4	 **9**	 **10**	8.5 h	99	N.P.

(a) Determined by gc analysis; (b) N.P. = no product observed after the indicated time period.

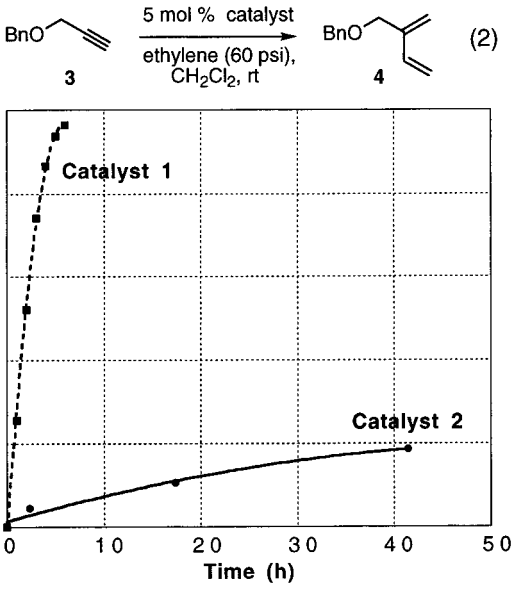


Figure 1. Rate comparison of alkyne−ethylene metathesis using catalysts **1** and **2**.

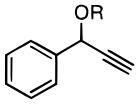
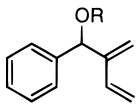
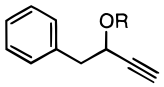
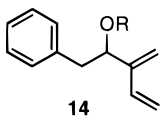
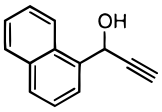
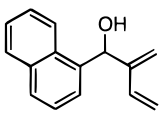
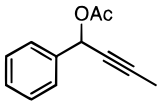
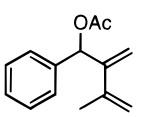
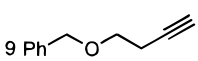
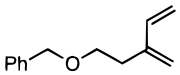
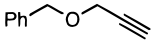
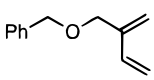
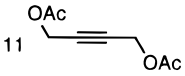
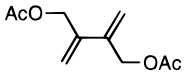
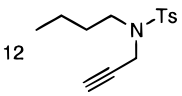
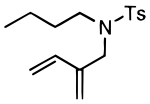
(5) (a) Nguyen S. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858. (b) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856. (c) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. Reviews: (d) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452. (e) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(6) (a) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2490. (b) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247. (c) Fürstner, A.; Theil, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204.

(7) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

The expanded substrate scope of alkyne−ethylene cross-metathesis for a variety of alkynes is shown in Table 2. In

Table 2. Scope of Alkyne−Ethylene Metathesis Utilizing 5 mol % of Catalyst **1** at 60 psi of Ethylene Pressure

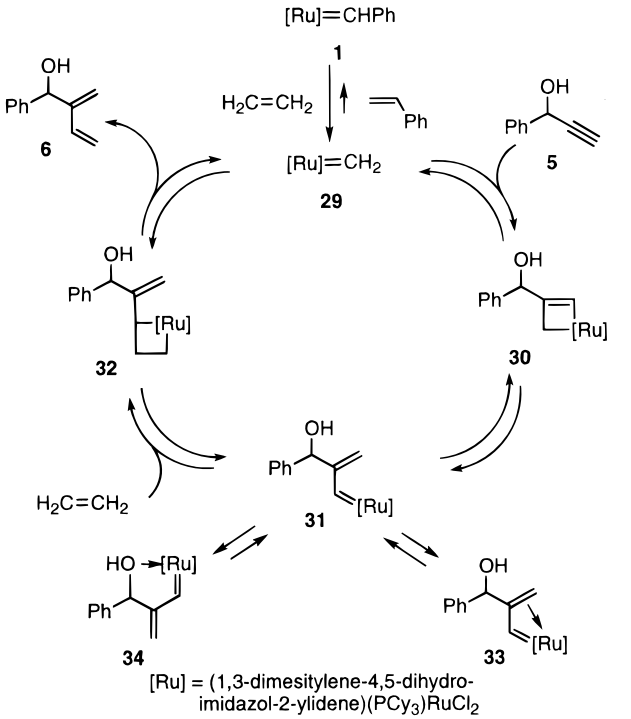
Entry	Substrate	Product	R	Time (h)	Yield[a]
1	 **11**	 **12**	**a** H	2.0	73
2			**b** Ac	2.0	92
3			**c** TBS	8.5	91
4	 **13**	 **14**	**a** H	22	58
5			**b** Ac	4.5	92
6			**c** TBS	10	96
7	 **15**	 **16**		16.5	62
8	 **17**	 **18**		16	77
9	 **19**	 **20**		4.0	62
10	 **21**	 **22**		6.0	72
11	 **23**	 **24**		4.0	69
12	 **25**	 **26**		4.0	91

[a] Isolated yield.

general, reactions with propargylic-substituted alkynes gave good to excellent yields using 5 mol % of **1** and elevated ethylene pressure (60 psi). Propargylic alcohols protected as benzyl ethers, silyl ethers, and acetates all performed well. In two cases, the effect of the propargylic substituent was evaluated (entries 1−6). The acetates **11b** and **13b** are known to perform well under elevated ethylene pressure with catalyst **2**, although the reaction times were generally > 20 h for complete conversion.[3] With catalyst **1** (5 mol %), much shorter reaction times and excellent yields were obtained, even for sluggishly reactive silyl ethers (entries 3 and 6). Despite the clean conversion by GC, lower isolated yields were obtained for the alcohols (entries 1 vs 2; 4 vs 5; 7). Lower product yields in these cases may be attributable to diene decomposition during isolation.[10] Internal alkynes also give cross-metathesis with ethylene (entries 8 and 11). The acetate **17** of entry 8 is highly substituted which results in a slower reaction.[11] The benzyl ethers in entries 9 and 10 give trace diene products by literature conditions;[2b] however, complete conversion and good yields were realized with **1**. Propargylamines protected as their sulfonamides underwent the reaction efficiently and in high yield (entry 12). With the exception of entries 4 and 8, all reactions in Table 2 went to > 95% completion by GC analysis. It can be concluded that **1** is remarkably tolerant of potentially coordinating functional groups in enyne metathesis. Since intermolecular reactions such as cross-metathesis are likely to be more sensitive to chelating traps than are intramolecular applications (e.g., RCM),[12] the effectiveness of catalyst **1** is particularly noteworthy.

A plausible catalytic cycle for alkyne−ethylene metathesis is shown in Scheme 1. Ethylene is used to generate the active

Scheme 1. Catalytic Cycle and the Role of Chelation

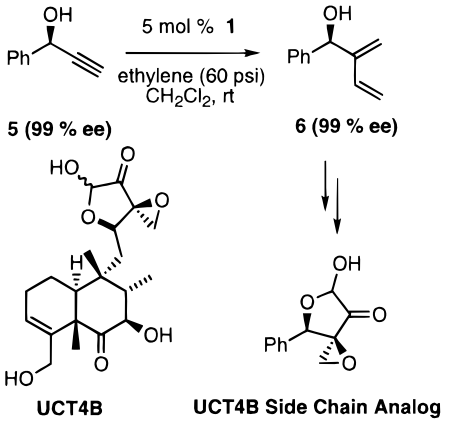


methylidene catalyst **29**[13] and is consumed stoichiometrically as a reagent. The accelerating effect of ethylene is due to higher solution concentrations at elevated pressure.[3] The slow step is probably the conversion of **31** into **32** due to the stability of vinylalkylidene **31**. Without heteroatoms at the propargylic position, coordination by the alkene (structure **33**) is the dominant stabilizing interaction.[14] Slow reactions with, for example, alcohols may be due to additional

chelation as in **34**.[15] The effectiveness of catalyst **1** may be explained by a combination of factors. First, it is likely that chelation is rendered less favorable in **1** due to the translabilizing effect of the electron-rich imidazolidine carbene ligand. Second, catalyst **1** is more robust and likely less prone to decomposition[16] which presumably contributes to a longer catalyst lifetime. Last, the higher concentration of ethylene helps drive **31** through the catalytic cycle by mass action. Pushing **31** forward helps minimize the amount of catalyst tied up in the presumed energy minima (e.g., **33** and **34**).

Our previous work has shown that enantiomerically enriched propargyl acetates undergo ethylene metathesis without racemization.[3] We were eager to find out whether chiral propargyl alcohols would show the same result without the need for protecting group manipulation. Thus, treatment of **5** (99% ee) with 5 mol % of **1** at 60 psi of ethylene pressure afforded dienyl alcohol **6** in 68% isolated yield (99% ee) (Scheme 2).[17] Our previous synthesis of intermediate **6** required a protection/deprotection sequence. A series of oxidations are used to gain access to enantiopure UCT4B side chain analogues.[18]

Scheme 2. Transformation of Enantiopure Alkynol



In conclusion, it has been shown that propargyl alcohols and a host of substituted alkynes undergo efficient alkyne−ethylene cross-metathesis at elevated ethylene pressure using complex **1**. To the best of our knowledge, this is the first demonstration of tolerated coordinating alcohol functionality in an intermolecular metathesis application. Dramatic rate acceleration was possible due to the combination of ethylene concentration and use of catalyst **1**. Use of Grubbs' catalyst **1** successfully overcomes chelate traps which normally slow or stop the alkene−alkyne metathesis. In addition, the catalyst displays excellent functional group compatibility with propargylic substrates which adds to the versatility of the reaction. This method offers a substantial improvement in ethylene−alkyne metathesis that broadens alkyne substrate scope and provides access to a variety of 2-substituted butadienes.

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OL006035L

(8) **Representitive Experimental Procedure for Alkyne−Ethylene Metathesis: (Table 2, entry 2).** To an oven-dried pressure tube (90 mL capacity) equipped with a magnetic stirbar was added 41 mg (50 μmol, 5 mol %) of 1,3-dimesityl-4,5-dihydroimidazol-2-ylidenetricyclohexylphosphine benzylidene ruthenium dichloride (ref 7) under argon. A solution of 174 mg of **11b** (1.0 mmol) in 4.0 mL of DCM was added to the catalyst via syringe, and the vessel was pressurized with 60 psi of ethylene (CP grade, 99.5%, Matheson) under rapid stirring. The pressure was released, and the vessel was flushed five times and then maintained at 60 psi of ethylene for 2 h. The pressure was released and the solvent removed in vacuo (rotary evaporator) to afford a dark brown oil which was purified by flash chromatography (1:4 ethyl acetate−hexanes). The product was obtained as an oil, 185 mg, 92% yield. Analytical TLC: R_f 0.44 (1:4 ethyl acetate−hexanes). Spectra were identical to those reported in ref 3.

(9) Trace styrene could be detected. No higher molecular weight products, such as dimers, were observed.

(10) For instance, conversion of **11a** (Table 2, entry 1) in the presence of 1 equiv of mesitylene internal standard was 99% after 2 h as measured using a calibrated GC method. The crude reaction mixture was subjected to column chromatography to remove the ruthenium catalyst. Fractions containing **11a** were combined after purification which indicated 80% yield with respect to internal standard as judged by GC analysis.

(11) The corresponding alcohol of **17** was less reactive giving only 44% conversion (GC) after 18 h.

(12) Higher effective molarity of alkene in RCM applications likely improves the probability that alkene will bind to the metal leading to productive metathesis.

(13) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(14) Mori, M.; Sakakibara, N,; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082.

(15) We make the distinction between the presence of alcohols (for which many metathesis applications are already known, see ref 5e) and the presence of alcohols in a potentially coordinating position with respect to intermediate ruthenium alkylidenes.

(16) For the stability of the closely related ruthenium complex containing the imidazolylidene carbene ligand, see: Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202.

(17) Enantiomeric excesses were measured by gc using a Chiradex-B capillary column (40−200 °C over 20 min, J & W Scientific, 0.25 mm × 30 m, 0.25 mm film thickness).

(18) Diver, S. T.; Ahsan, K.; Smulik, J. A., unpublished data.