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Ethylene-Promoted Intermolecular Enyne Metathesis

Anthony J. Giessert, Nicholas J. Brazis, and Steven T. Diver*

Department of Chemistry, University at Buffalo, the State University of New York,
Amherst, New York 14260

diver@nsm.buffalo.edu

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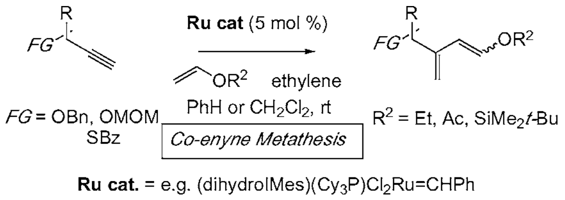
ABSTRACT

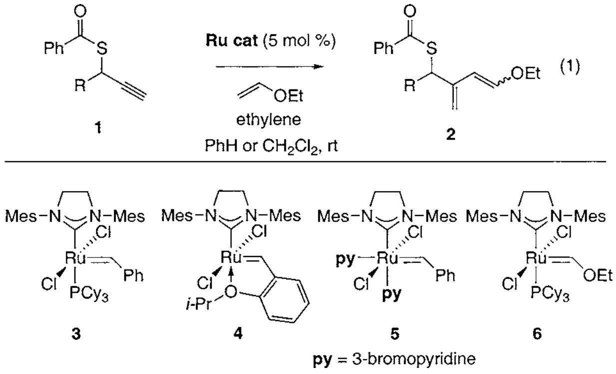


Intermolecular enyne metathesis between functional group-rich alkynes and vinyl ethers was promoted by ethylene cometathesis. The concentration of ethylene was optimized to suppress the competing formation of butadiene through background ethylene metathesis. The role of ethylene appears to be both protective and rate enhancing.

Enyne metathesis is a synthetically useful diene synthesis.[1] The cross selectivity of the intermolecular reaction,[2] the functional group tolerance of the ruthenium carbenes, and increasingly challenging synthetic applications have elevated the utility of enyne metathesis. In several instances, previous shortcomings have been surmounted by the use of the more reactive second-generation Grubbs catalyst. In the course of studying intermolecular enyne metatheses with vinyl ethers, we found that certain alkynes failed to react using the carbene complex **3**. We surmised that the generated ruthenium Fischer carbenes **6** were too unreactive with these more functional group-rich alkyne substrates. In this report, we describe the use of ethylene as a helping alkene to promote reactivity in intermolecular (cross) enyne metathesis, thereby increasing the applicability of the intermolecular reaction to problematic substrates (eq 1).

Ethylene has been used to promote catalyst longevity in ring-closing enyne metathesis. Mori demonstrated the usefulness of ethylene in ring-closing metathesis, a result that has been widely embraced in the field, especially for difficult ring-closing metatheses.[3] Poor reactivity was overcome by conducting the reaction under an ethylene atmosphere. Mori and co-workers[3] suggested that the influence of ethylene was to prevent side reactions of the vinyl carbene species and would open up degenerate reactions of the active ruthenium methylidene that would prevent catalyst decomposition and other mischief.

Scheme 1. Ethylene-Promoted Cross Enyne Metathesis



Use of ethylene to promote or influence the course of cross metathesis is expected to be problematic due to competitive

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(1) Reviews: (a) Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133−154. (b) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1−18.

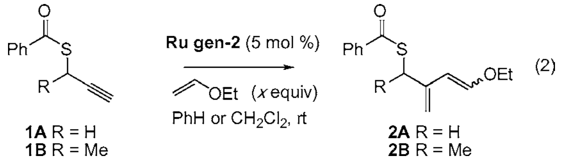
(2) Stragies, R.; Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2518−2520.

(3) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082−6083.

10.1021/ol035270b CCC: $25.00

ethylene metathesis.[4] The competing metathesis with ethylene would produce a butadiene byproduct, but this is largely suppressed in α,ω-enynes undergoing ring-closing metathesis since intramolecularity provides a rate advantage. Mori and co-workers indeed found competitive cross metathesis in more difficult ring closure en route to medium rings.[5] In an eight-membered ring closure, the butadiene was the major product.[5b] Entropic penalties in the ring closure permitted competitive intermolecular metathesis with ethylene. From these studies, it was not evident that an alkyne would be able to selectively react with one alkene over ethylene *in an intermolecular enyne metathesis.* Recent work by Lee et al. illustrates an influence of ethylene on selectivity of cross enyne metathesis.[6]

Table 1. Difficult Cross Metathesis



1A R = H
1B R = Me

2A R = H
2B R = Me

entry	alkyne	x	solvent	conversion (%)	time (h)
1	**1A**	9	CH_2Cl_2	23[a]	25
2	**1A**	25	CH_2Cl_2	62[a]	25
3	**1A**	9	PhH	80[a]	9
4	**1A**	9	PhH, reflux	100	20
5	**1A**	25	PhH	100	18
6	**1B**	9	CH_2Cl_2	10[a]	25
7	**1B**	9	CH_2Cl_2, reflux	46[a]	20
8	**1B**	25	PhH	45[a]	15

[a] Average of two runs.

Thiol benzoates proved to be difficult alkyne players in the cross metathesis with vinyl ethers.[7] Since we felt that these represented a challenge that would be characteristic of functional group-rich alkynes, we investigated the reaction with ethyl vinyl ether (EVE) in detail (Table 1). The same long reaction times that gave quantitative conversion in the ethylene metathesis studied previously[8] gave only low conversion in CH_2Cl_2 using excess EVE (entries 1, 2). Room-temperature reactions in benzene gave incomplete conversion, but at reflux quantitative conversion to the cross product occurred (entry 4). The long reaction times were considered problematic since catalyst longevity would be threatened. In fact, Fischer carbenes of ruthenium are known to decompose thermally.[9] The propargyl derivative **1A** is not sensitive to thermal elimination of thiol benzoic acid, so higher temperatures were explored in this case. For cheap enol ethers, large excesses (25 equiv) can be employed in benzene to achieve quantitative conversion (entry 5). With the butynyl derivative **1B**, poor conversion was observed in CH_2Cl_2 at room temperature (entry 6) and moderate conversion at reflux. The room temperature reaction in benzene using 25 equiv of EVE gave only 45% conversion in this case. Monitoring the reaction after 15 h up until 36 h revealed no further conversion, hinting that catalyst decomposition had occurred. Large excesses of EVE proved to be successful in one case, but not the other (entries 5 vs 8). Looking ahead to future applications where the enol ether must be synthesized, large molar excesses of enol ether would be impractical and wasteful. We wanted to improve the reliability of the cross metathesis with respect to various troublesome alkynes and to determine whether a sacrificial, auxiliary alkene could be used in place of large molar excesses of enol ethers.[10]

Ethylene proved to be helpful to the representatively difficult cross metatheses of eq 2. The use of ethylene as a co-added alkene seemed attractive due to its low cost and ease of removal. With two competing alkenes, two different cross metatheses are possible. Perceiving this difficulty, we comparatively evaluated the molar ratios of enol ether to ethylene to minimize the butadiene formed through competitive ethylene−alkyne metathesis. The data are presented in Table 2. At the highest ethylene pressure investigated, the amount of butadiene was surprisingly low (entries 1−3).[11] Increasing the mole fraction of enol ether (vs total alkene) reduced the butadiene **7** by a factor of 2. At equilibrium, 60 psig ethylene corresponds to a solution concentration of ca. 0.77 M.[12] At lower ethylene pressure, 4−6% of **7** was observed (entries 4−6). Lower pressure in benzene (PhH) gave only the dienol ether **2A** (entry 7), though fewer equivalents of enol ether gave about 5% undesired butadiene (entry 8). The preformed Fischer carbene initiated the reaction, giving 67% conversion after 24 h. The Hoveyda catalyst[13a,b] produced quantitative conversion, although Grubbs' pyridine solvate[13c] gave only 54% conversion, probably due to aminolysis of the thiol ester by liberated 3-bromopyridine and catalyst poisoning (entries 10, 11). Lower catalyst loading was not sufficient to obtain synthetically useful conversions (entries 12, 13). Dichloromethane was equally effective as a solvent with 9 equiv of enol ether (entry 14 vs entry 8). Balloon ethylene pressure can be used with better results in benzene than dichloromethane (entries 15, 17), but 9 equiv of EVE in benzene gives only partial conversion at balloon ethylene pressure (entry 16).

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[4] (a) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388−12389. (b) Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron* **1999**, *55*, 8155−8167. (c) Smulik, J. A.; Diver, S. T. *J. Org. Chem.* **2000**, *65*, 1788−1792. (d) Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271−2274. (e) Tonogaki, K.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 2235−2238.

[5] (a) Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett.* **2000**, *2*, 543−545. (b) Mori, M.; Kitamura, T.; Sato, Y. *Synthesis* **2001**, 654−664.

[6] Lee, H.-Y.; Kim, B. G.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 1855−1858.

[7] Under previously reported conditions, these alkynes either did not react or decomposed. See: Giessert, A. J.; Snyder, L.; Markham, J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 1793−1796.

[8] Smulik, J. A.; Giessert, A. J.; Diver, S. T. *Tetrahedron Lett.* **2002**, *43*, 209−211.

[9] Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153−2164.

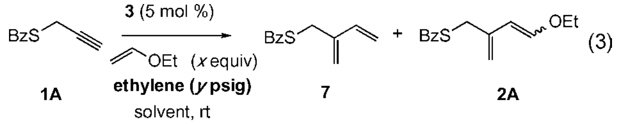
[10] Difficult metatheses have been repeated using at least two separate batches of second-generation catalyst.

[11] Fewer equivalents of enol ether and ethylene pressure (60 psig or higher) produced a greater proportion of the butadiene.

[12] Measured by NMR in CD_2Cl_2 versus mesitylene as an internal standard.

[13] (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179. (b) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973−9976. (c) Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 4035−4037.

Table 2. Ethylene-Assisted Vinyl Ether Cross Metathesis

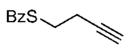
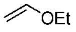
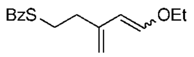
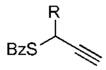
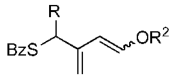
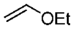
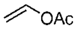
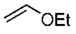
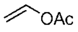
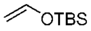
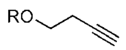
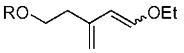
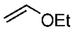
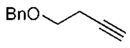
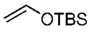
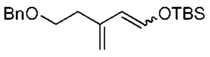
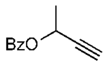
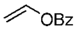
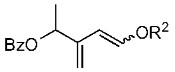
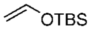
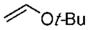


1A **7** **2A**

entry[a]	x	y (psig)	solvent	ratio	conversion (%, at t(h))
1	9	60	CH_2Cl_2	15:100	100, 20 h
2	25	60	CH_2Cl_2	8:100	100, 20 h
3	25	60	PhH	6:100	100, 20 h
4	9	10	CH_2Cl_2	7:100	82, 20 h
5	25	10	CH_2Cl_2	6:100	100, 20 h
6	25	10	PhH	4:100	100, 20 h
7	25	5	PhH	–:100	100, 20 h
8	9	5	PhH	6:100	100, 20 h
9[b]	9	5	PhH	–:100	67, 24 h
10[c]	9	5	PhH	–:100	100, 24 h
11[d]	9	5	PhH	–:100	54, 24 h
12[e]	9	5	PhH	1:100	22, 20 h
13[f]	9	5	PhH	–:100	22, 20 h
14	9	5	CH_2Cl_2	3:100	96, 20 h
15	25	g	CH_2Cl_2	–:100	52, 24 h
16	9	g	PhH	–:100	44, 24 h
17	25	g	PhH	–:100	100, 6 h

[a] Reactions in entries 1–14 were conducted in a Fisher-Porter bottle at the indicated ethylene pressure. [b] Performed with 5 mol % **6**. [c] Performed with 5 mol % **4**. [d] Performed with 5 mol % **5**. [e] Performed with 1 mol % **3**. [f] Performed with 2.5 mol % **3**. [g] Performed with balloon ethylene.

Table 3. Scope of Co-Enyne Metathesis

entry	alkyne	vinyl ether[a]	diene, isolated yield	w/o ethylene[b]
1	 **8**		 **9**, 91 % (2.7:1.0 *E/Z*)	21 (1.3 : 1.0)[c]
				
2	**1A** R=H		**2A** R=H, R^2=Et, 99 % (1.9:1.0 *E/Z*)	see Table 1
3	**1A** R=H		**10** R=H, R^2=Ac, 92 % (1.0:1.0 *E/Z*)	18 (1.0:1.0)[c]
4	**1A** R=Me		**2B** R=Me, R^2=Et, 73 %[d] (3.8:1.0 *E/Z*)	see Table 1
5	**1B** R=Me		**11** R=Me, R^2=Ac, 86 % (1.0:1.3 *E/Z*)	22 (1.1:1.0)[c]
6	**1B** R=Me		**12** R=Me, R^2=TBS, (93 %)[e] (1.0:1.5 *E/Z*)	N.R.
				
7	**13** R=TBS		**14** R=TBS, 83 % (2.8:1.0 *E/Z*)	99[c]
8	**15** R=Bn		**16** R=Bn, 84 %[d] (2.6:1.0 *E/Z*)	66[c]
9	**17** R=MOM		**18** R=MOM, 91 % (2.5:1.0 *E/Z*)	99[c]
10	 **15**		 **19**, 72 % (1.0:1.5 *E/Z*)	33 (1.0:1.6)[c]
11	 **20**		 **21** R=Bz, 89 % (1.0:1.0 *E/Z*)	38 (2.6:1.0)[c]
12			**22** R=TBS, 91 % (1.6:1.0 *E/Z*)	N.R.[c]
13			**23** R=*t*-Bu, 89 % (1.3:1.0 *E/Z*)	30 (1.0:1.0)[c]

[a] Standard conditions: catalyst **3** (5 mol %), vinyl ether (9 equiv), ethylene (5 psig), benzene, rt, 12 h. [b] Yield without ethylene, ratio of (*E*)- and (*Z*)-isomers. [c] Conversion, 24 h reaction time. [d] Conversion = 99%. [e] Conversion by NMR after an additional 2.5 mol % catalyst **3** was added.

Butadiene **7**, obtained from ethylene metathesis, is not an intermediate en route to dienol **2A**. Isolated butadiene **7** was subjected to two sets of conditions to evaluate its kinetic stability under the reaction conditions. Heating **7** in benzene with **3** and 9 equiv of EVE gave no reaction. Similarly, the cometathesis employing EVE (9 equiv) and ethylene (5 psig) gave no conversion after 12 h at room temperature. The kinetic stability of butadienes has been previously observed by Blechert using the first generation Grubbs catalyst;[14] however, Lee et al.[6] showed that a 1,3-butadiene will react with excess 1-alkene with catalyst **3**, and we have made similar observations with 1-hexene. In the present case, it is likely that the Fischer carbene is not sufficiently reactive to add to the diene terminus.

The scope of the ethylene-assisted cross enyne metathesis is summarized in Table 3. The elimination-prone thiol benzoate **8** decomposes on heating, conditions previously needed to react enol ethers with alkynes.[7] Cometathesis with ethylene permits the reaction to be conducted at ambient temperature and gave quantitative conversion (91% yield, entry 1). Both enol ethers and enol acetates produce the cross products in excellent yields with the propargylic thiol benzoates. Besides increased alkyne scope for the enol ether cross metathesis, silyl enol ethers are shown to react under the cometathesis conditions (entries 6, 10, 12). The reactions are notable because the reactions fail without ethylene present and decompose on heating. The homopropargylic coordinating ethers of entries 7–9 give excellent results. Butynyl benzoate **20** reacts with EVE without ethylene, but vinyl benzoate, (*tert*-butyldimethylsilyloxy)ethylene, and *tert*-butyl vinyl ether benefit from ethylene (see right column of Table 3) and provide synthetically useful results only by cometathesis. Symmetrical internal alkynes react with enol ethers and do not require the assistance of ethylene.[7] As is typical for the cross enyne metathesis, the products were obtained as *E/Z* mixtures; the lack of stereocontrol is apparent in both the ethylene-promoted reaction and the nonethylene reactions.

The presence of ethylene increases the lifetime of the Fischer carbene complex. In the absence of ethylene, Fischer carbene **6** is completely decomposed after 24 h at room temperature. When the same experiment was conducted under ethylene, the orange color of the Fischer carbene persisted for several days. Proton NMR indicated the

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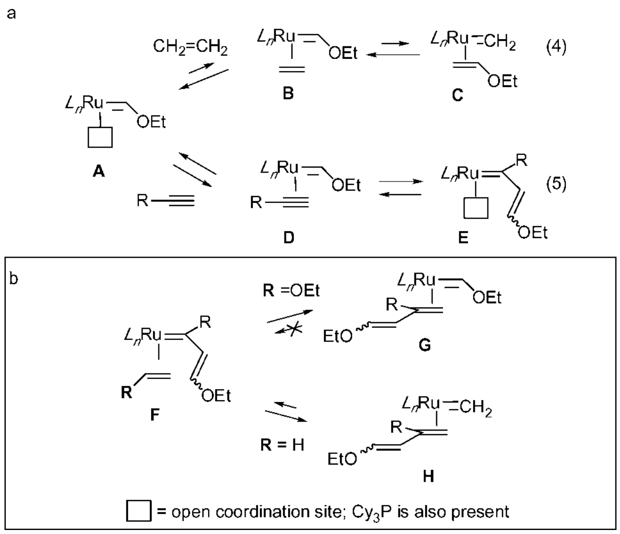
(14) Ruckert, A.; Eisele, D.; Blechert, S. *Tetrahedron Lett.* **2001**, *42*, 5245–5247.

persistence of **6** over this period. After 48 h, 60% of the Fischer carbene **6** was still present. Thus, the role of ethylene may be as simple as stabilizing the Fischer carbene complex, such that its decomposition rate is reduced sufficiently for sustainable catalysis at room temperature, where the rate of reaction is relatively slow (compared to the rate in refluxing benzene).[7] This converges with the proposition of Mori,[3] based on observations in ring-closing enyne metathesis with the first generation Grubbs carbene.

The interaction of a 14-electron Fischer carbene intermediate with ethylene would likely lead to formation of the methylidene, but this has not been observed by NMR under various ethylene pressures. While this observation does not rule out a methylidene mechanism, it does suggest that the Fischer carbene is considerably more stable than the methylidene.[9] With respect to catalysis, the equilibrium with ethylene to provide the methylidene may be substantially uphill (eq 4, Scheme 2). In contrast, alkyne binding and conversion to the vinyligous Fischer carbene is roughly isoenthalpic on the basis of carbene stability alone (eq 5). On the basis of this hypothesis, the role of ethylene, while certainly protective, may also accelerate catalyst turnover by providing an alternate methylene transfer path (panel b, lower path, Scheme 2). This explains why, to a rough approximation, high concentrations of enol ether duplicate the effect of co-added ethylene.

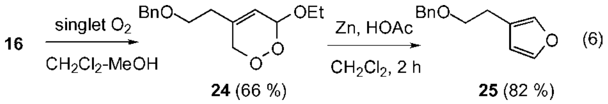
Scheme 2. Important Equilibria in the Co-Enyne Metathesis



Additional experiments are required to test these mechanistic proposals, but they provide a reasonable explanation for catalysis. The notion that ruthenium methylidene is the reactive carbene and that increased ethylene pressure provides a higher concentration of the methylidene **C** as the active catalyst cannot be ruled out.

Synthetically, the cometathesis provides access to 3-substituted furans through simple oxidative transformation with singlet oxygen. The cycloaddition occurs in good yield, and peroxyacetal **24** can be isolated and fully characterized. Reduction with zinc dust and 2 equiv of acetic acid provided furan **25** in high yield.

Scheme 3. Oxidative Transformation of Co-metathesis Product



In conclusion, the use of ethylene to overcome unreactive or poorly reactive alkynes in intermolecular enyne metathesis with enol ethers is reported. The use of a co-added alkene to improve the efficiency of the metathesis without significant competing intermolecular ethylene-alkyne metathesis was surprising. The role of ethylene appears to be protective and may assist in methylene transfer, thereby helping catalyst turnover. Further exploration of these issues and studies on the reaction mechanism are ongoing in our labs.

Acknowledgment. The authors thank Bryan Schertzer for measurements of solution concentration of ethylene and Dr. Alice Bergman (UB Instrumentation Center) for assistance with mass spectra. We gratefully acknowledge the National Cancer Institute (R01CA090603) for financial support of this work.

Supporting Information Available: Experimental procedures and full characterization data for compounds **2A**, **2B**, **9**−**12**, **14**, **16**, **18**, **19**, and **21**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035270B