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Intermolecular Enol Ether−Alkyne Metathesis

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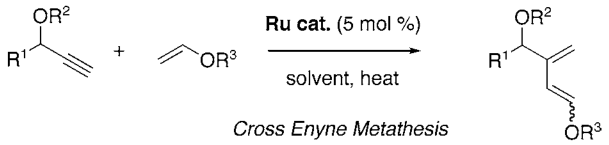
ABSTRACT



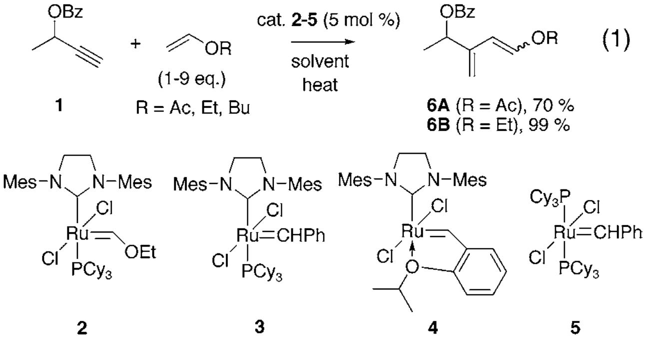
Ru cat. = (dihydroIMes)(Cy_3P)Cl_2Ru=CHPh

A new intermolecular metathesis between a variety of alkynes and alkyl enol ethers is described. The best results were obtained with the second generation Grubbs' precatalysts. The reaction occurred with a high degree of regioselectivity and provided electron-rich dienes, which underwent a variety of [4 + 2] cycloadditions.

Enyne metathesis constitutes an important and relatively new method for diene synthesis. The earliest applications of enyne metathesis were intramolecular reactions, and the development of cross (intermolecular) enyne metathesis[1] applications has occurred more recently. The intermolecular reaction involves the formal addition of a 1-alkene across the triple bond with a high degree of regiocontrol (eq 1).[1c] To date, there have been no reports of intermolecular enyne metathesis that use alkyl enol ethers as substrates, the difficulty being the stability of the putative Fischer carbene intermediates. In this communication, we show that enol ethers participate in intermolecular enyne metathesis with a variety of alkynes. The diene products in Scheme 1 are useful in cycloaddition and can be viewed as simple, accessible building blocks for organic synthesis.

Enol ethers can be problematic substrates for metathesis. In fact, living polymers obtained in ROMP are terminated by the addition of vinyl ethers and kinetic studies on metathesis use vinyl ethers to terminate the active alkylidenes by formation of the ruthenium Fischer carbene complex **B**. These species are thought to be more stable than the intermediate alkylidene (and methylidene) that is involved in alkene metathesis, and the equilibrium should favor **B** (Scheme 2). These facts suggest that the intermediacy of Fischer carbenes would be deleterious to the reaction rate of intermolecular (cross) metathesis.[2]

Scheme 1. Enol Ether−Alkyne Cross Metathesis and Carbene Complexes **2**−**5**



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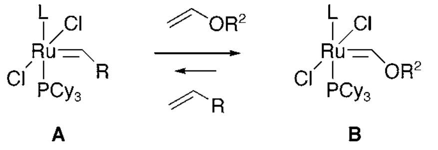
(1) (a) Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *107*, 737−738. (b) Kinoshita, A.; Mori, M. *Synlett* **1994**, 1020−1022. (c) Stragies, R.; Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2518−2520. (d) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388−12389. (e) Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron* **1999**, *55*, 8155−8167.

(2) Enol ethers in intramolecular ring-closing enyne metathesis with a chromium complex: (a) Watanuki, S.; Ochifuji, N.; Mori, M. *Organometallics* **1994**, *13*, 4129−4130. (b) Watanuki, S.; Ochifuji, N.; Mori, M. *Organometallics* **1995**, *14*, 5062−5067.

10.1021/ol034459k CCC: $25.00

Scheme 2. Equilibrium with Ruthenium Fischer Carbene Complex



(2)

Fischer carbenes of ruthenium have attracted interest due to their role in metathesis. Fischer carbenes have recently been suggested as intermediates in ring-closing enyne metathesis,[3] where intramolecularity may improve the efficiency of catalyst turnover. Ozawa demonstrated that ROMP of strained norbornenes could be triggered by using a Fischer carbene initiator,[4a,b] although in these cases the Fischer carbene does not sustain catalysis in the propagation steps. Grubbs and Louie have also characterized ruthenium Fischer carbenes and demonstrated that they initiated ROMP and can catalyze ring-closing alkene metathesis.[4c,5] Also significant from the latter study[4c] is an observed thermal decomposition pathway of Fischer carbene complexes to provide the corresponding ruthenium carbonyl hydride.

Both enol ethers and enol acetates give the intermolecular enyne metathesis with alkynes. Benzoate **1** reacted with vinyl acetate and ethyl vinyl ether (EVE) in refluxing methylene chloride to give the corresponding dienes **6A**,**B** (eq 1). The regiochemistry of the reaction was characteristic of intermolecular metathesis between 1-alkenes and terminal alkynes and was confirmed by ^{1}H NMR. Although highly regioselective, the cross metathesis shows little stereoselectivity. For example, dienyl ether **6B** was produced in a 1.7:1.0 *E/Z* ratio. The effect of vinyl ether concentration, solvent, temperature, and catalyst was investigated using alkyne **1** (Table 1).

The preformed Fischer carbene **2** catalyzed the reaction but gave lower conversions than with complex **3**. The in situ-prepared **2** gave a higher conversion, which may suggest that phosphine off-rate plays a significant role in the initiation kinetics using prepared complex **2**. Concerns about evaporative loss of EVE led us to examine butyl vinyl ether (BuVE), which expectedly worked as well as EVE (entries 3, 4). Precatalyst **4**[6] efficiently promoted the enyne metathesis, but complex **5** was less effective and gave low conversion to product. Although refluxing CH_2Cl_2 proved to be efficient, the cross reaction conducted in benzene (entries 7−12) gave shorter reaction times, usually taking only minutes. Other solvents such as THF, 1,2-dichloroethane, and toluene also worked well (99% conversion in less than 10 min). Superheated CH_2Cl_2 (sealed tube, 80 °C) gave a fast reaction (10−30 min), which suggests that temperature plays a more important role than solvent polarity for this reaction. The preformed Fischer carbene **2** provided product in refluxing benzene. The 9-fold molar excess of vinyl ether is not necessary and could be reduced to 1 equiv (entry 9). For the readily available vinyl ethers used in this study, slight molar excesses are practical. Lower catalyst loading with **3** was achieved at both 2.5 and 1.0 mol % in refluxing benzene (entries 10, 11). Vinyl acetate reacted with alkyne in refluxing benzene, giving an improved yield compared to the previous run in refluxing dichloromethane (entry 12).

Table 1. Variation of Reaction Parameters in Enol Ether−Alkyne Cross Metathesis (eq 1; R = Et, Bu)

entry	catalyst[a]	vinyl ether (9 equiv)	solvent[b]	time	conversion	yield
1	**2**	EtOCH=CH$_2$	CH$_2$Cl$_2$	12 h	47	c
2	**2**[d]	EtOCH=CH$_2$	CH$_2$Cl$_2$	12 h	99	99
3	**3**	EtOCH=CH$_2$	CH$_2$Cl$_2$	2 h	99	99
4	**3**	EtOCH=CH$_2$	CH$_2$Cl$_2$	12 h	99	95
5	**4**	EtOCH=CH$_2$	CH$_2$Cl$_2$	12 h	99	99
6	**5**	EtOCH=CH$_2$	CH$_2$Cl$_2$	12 h	12	c
7	**2**	EtOCH=CH$_2$	PhH	2 h	88[e]	c
8	**3**	EtOCH=CH$_2$	PhH	10 min	99	95
9	**3**	BuOCH=CH$_2$[f]	PhH	19 h	95	c
10	**3** (2.5%)	EtOCH=CH$_2$	PhH	0.5 h	99	c
11	**3** (1.0%)	EtOCH=CH$_2$	PhH	15 h[g]	99	c
12	**3**	AcOCH=CH$_2$	PhH	10 min	99	96

[a] Used 5 mol % catalyst based on alkyne. [b] At reflux. [c] Isolated yield not determined in these runs. [d] Catalyst prepared *in situ*. [e] 18 h, 92%. [f] Used 1 equivalent BuOCH=CH$_2$. [g] 2.5 h, 91%.

The alkyne scope of the intermolecular metathesis is summarized in Table 2.

In all cases, the products were obtained as mixtures of (*E*)-/(*Z*)-isomers, a characteristic of intermolecular enyne metatheses,[1c] and the ratios for each run were determined by proton NMR and can be found in the Supporting Information. Propargylic ethers and esters underwent the cross reaction with vinyl ethers without difficulty. Cross metathesis with vinyl acetate gave an excellent yield of the dienol ester (entry 2) by using optimized conditions. The potentially coordinating benzyl ether was tolerated, and bulky silyl groups gave quantitative conversion, similar to previous findings in ethylene metathesis using Grubbs' catalyst **3**.[7] Propargylic substitution does not pose a limitation (entries 5, 6, 8) and a nitrogen-containing alkyne gave the cross reaction in excellent yield (entry 7). Hydrocarbon alkynes produced the dienes efficiently with butyl vinyl ether. The cross metathesis with vinyl acetate proved to be more sensitive to catalyst loading (entries 10, 12), and in one run, polyvinyl acetate was isolated as a major byproduct. Although the reaction rate varied somewhat over the course of

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(3) (a) Clark, J. S.; Trevitt, G. P.; Boyall, D.; Stammen, B. *Chem. Commun. (Cambridge)* **1998**, 2629−2630. (b) Clark, J. S.; Elustondo, F.; Trevitt, G. P.; Boyall, D.; Robertson, J.; Blake, A. J.; Wilson, C.; Stammen, B. *Tetrahedron* **2002**, *58*, 1973−1982. (c) Schramm, M. P.; Reddy, D. S.; Kozmin, S. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4274−4277.

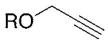
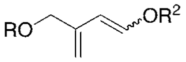
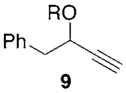
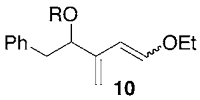
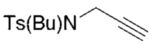
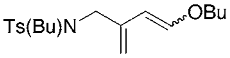
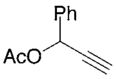
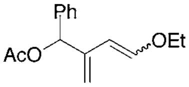
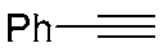
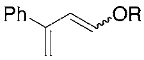
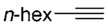
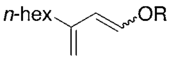
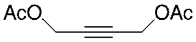
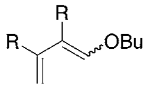
(4) (a) Katayama, H.; Urushima, H.; Nishioka, T.; Wada, C.; Nagao, M.; Ozawa, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 4513−4515. (b) Katayama, H.; Urushima, H.; Ozawa, F. *J. Organomet. Chem.* **2000**, *606*, 16−25. (c) Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153-2164.

(5) In our hands, the complex **3** did not promote alkene cross metathesis with 1-alkene and ethyl vinyl ether. See also: Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783−3784 and ref 4c.

(6) (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791−799. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179. (c) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973−9976.

(7) Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271−2274.

Table 2. Alkyne Scope in Intermolecular Vinyl Ether−Alkyne Metathesis

entry	alkyne	enol ether (9 eq.), solv.	product, yield
	 **7**		 **8**
1	**7A**, R = Bz	EVE, PhH	**8A** (R^2 = Et), 98 %
2	**7B**, R = Bz	vinyl acetate, PhH	**8B** (R^2 = Ac), 97 %
3	**7C**, R = Bn	EVE, CH_2Cl_2	**8C** (R^2 = Et), 82 %
4	**7D**, R = TBDPS	EVE, PhH	**8D** (R^2 = Et), 97 %
	 **9**		 **10**
5	**9A**, R = Ac	EVE, CH_2Cl_2	**10A** (R = Ac), 88 %
6	**9B**, R = TBS	EVE, CH_2Cl_2	**10B** (R = TBS), 38 %
7	 **11**	BuVE, CH_2Cl_2	 **12**, 92 %
8	 **13**	EVE, CH_2Cl_2	 **14**, 96 %
	 **15**		
9		BuVE, PhH	**16A** (R = Bu), 90 %
10		vinyl acetate,[a] CH_2Cl_2[b]	**16B** (R = Ac),[c] 80 %
	 **17**		
11		BuVE, PhH	**18A** (R = Bu), 86 %
12		vinyl acetate, PhH[b]	**18B** (R = Ac), 70 %
13	 **19**	BuVE, PhH	 **20** (R=CH_2OAc), 98 %

[a] Used 18 equiv of vinyl acetate. [b] Reaction was spiked with an additional 2.5 mol % **3**. [c] Conversion was found to be 80% by ^1H NMR.

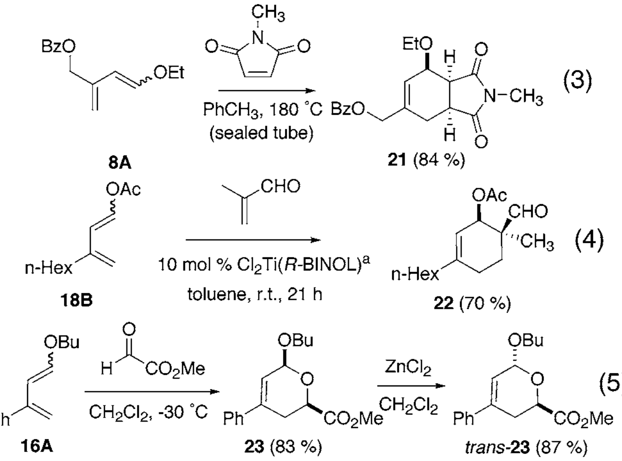
0.5 h, high conversions could be obtained at extended reaction times. The variation could not be traced to the batch of catalyst, and if the reaction rate stalled (GC analysis) the reaction could be forced to completion by adding additional vinyl acetate or by spiking with an additional 2.5 mol % **3**. With phenylacetylene and 1-octyne, it is worth noting that the reaction occurs with the same high regioselectivity characteristic of cross enyne metathesis (entries 9−12). Internal alkynes undergo the reaction (entry 13), but unsymmetrical internal alkynes gave a mixture of the four possible diastereomers.

It is evident that ruthenium Fischer carbenes can function as precatalysts for the cross enyne metathesis, but their relevance to the catalytic mechanism is presently unclear. Possible interpretations of the slow initiation of the Fischer carbene complex compared to **3** include a slower rate of phosphine dissociation or an unfavorable equilibrium with the methylidene complex. It is also noted that the Fischer carbenes can undergo competitive decomposition, which may result in either depressed reaction rates (due to a lower concentration of propagating catalyst derived from **2** or **3**) or side reactions emanating from the new ruthenium-containing byproducts. These are complications that can be identified only through more rigorous study of the reaction kinetics for the various ruthenium carbene complexes **2**−**4**.

Whether Fischer carbenes occur in pre-equilibrium or in the catalytic cycle, it seems clear that this enyne metathesis is driven by the enthalpic stability of the 1-alkoxy-1,3-dienes. This stands in contrast to the lack of reactivity of Fischer carbene complexes of ruthenium in analogous intermolecular alkene−alkene metathesis.

The products from this cross metathesis are electron-rich dienes that are useful substrates for Diels−Alder cycloaddition (Scheme 3).[8] The thermal reaction occurred with *N*-methyl maleimide (eq 3), and Mikami's catalyst[8c] was employed for asymmetric cycloaddition with methacrolein (eq 4). Using Mikami's catalyst, both (*E*)- and (*Z*)-isomers of the dienyl acetates and dienol ethers were found to react with the dienophile, although the (*E*)-isomers reacted slightly faster. The electron-rich diene **16A** gave an uncatalyzed hetero [4 + 2] cycloaddition with methyl glyoxalate, producing a mixture of diastereomers in 83 % yield. From the mixture, a single diastereomer of the dihydropyran, *trans*-**23** was obtained through equilibration with $ZnCl_2$ (eq 5). The synthesis and cycloaddition of **18B** could be conducted in one pot without removal of ruthenium catalyst and its byproducts. The three-component synthesis of the cyclic structures illustrated in Scheme 3 is notable because it is efficient, employing simple alkene and alkyne starting materials. Such rapid assembly of these structures may prove to be useful in diversity-oriented synthesis.

Scheme 3. Cycloaddition of Cross Metathesis Products



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(8) Literature yields for cycloadditions with dienol ethers use excess dienol ether and base yields on the reactive (*E*)-isomer. (a) Mandai, T.; Osaka, K.; Kawagishi, M.; Kawada, M.; Otera, J. *J. Org. Chem.* **1984**, *49*, 3595−3600. (b) Shibata, J.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1999**, 313−314. (c) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812−2820.

In summary, a new cross enyne metathesis with alkynes and vinyl ethers has been reported that permits the direct incorporation of an alkoxy group onto the diene. The catalytic, intermolecular reaction provides a viable diene synthesis and suggests that the enthalpic benefit enjoyed by enyne metathesis can overcome equilibrium with stabilized carbenes. Whether the Fischer carbenes are catalytic species awaits further mechanistic studies that are ongoing in our group.

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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.

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