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Ethylene metathesis of sulfur-containing alkynes

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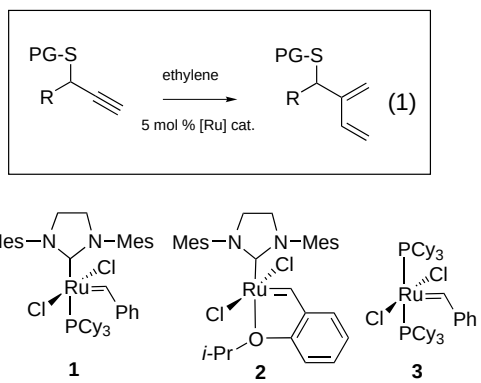
Abstract—Enyne metathesis of sulfur-containing alkynes and ethylene has been achieved. High yields were obtained by use of thiol esters in the alkyne partner for the cross metathesis with ethylene. The necessary reactivity and functional group compatibility were achieved through the use of the Grubbs' second generation benzylidene carbene catalyst. © 2002 Elsevier Science Ltd. All rights reserved.

There have been tremendous advances in alkene metathesis due largely to functional group compatibility of the ruthenium carbenes developed by Grubbs. With the supporting dihydroimidazole carbene ligand, the ruthenium carbenes are more active in alkene metathesis[1] and more tolerant of potentially coordinating functional groups like alcohols and ethers. Despite these recent advances and the widespread utilization of metathesis, there has been little application of metathesis to unsaturated organosulfur compounds.[2,3] The earliest examples[2a,b] described ring-closing metathesis (RCM) using both the Grubbs and Schrock catalysts. To the best of our knowledge, there have been no applications using sulfur-containing alkynes. The limited number of examples of metathesis with sulfur-containing substrates can be partly explained by the fact that middle to late transition metals used as catalysts may interact favorably with the soft sulfur atom (e.g. Pearson hard–soft acid–base theory).[4] In metathesis, any stabilization of species on the catalytic reaction coordinate could deplete active catalyst and shut down catalysis. Previous work suggested that the Grubbs' catalyst **1**, possessing the strong sigma-donating *N*-heterocyclic carbene ligand, could overcome coordination by oxygen in enyne metathesis.[5] In this communication, cross metathesis of sulfur-containing alkynes with ethylene employing ruthenium carbene **1** is reported (Scheme 1).



Scheme 1.

Lack of reactivity or lack of turnover in some alkenes bearing coordinating functionality has been attributed to chelated metal carbenes.[6] Coordination depends on the proximity of functional groups to the intermediate metal carbenes and can result in stabilized chelated structures or result in catalyst decomposition. How catalyst **1** overcomes or averts these problems in enyne metathesis is not well understood, although recent mechanistic studies explaining the high activity of **1** in alkene metathesis[1b,c] provide some important clues. Our investigation was prompted by the question whether potentially coordinating sulfur functionality could be tolerated by the new catalyst **1** as it pertains to synthetic effort in our group directed toward the synthesis of sulfur-containing natural products. Of more general interest is the question under what circumstances is sulfur permissible in ruthenium-catalyzed alkene–alkyne metathesis.

Initial enyne metathesis of propargyl thioethers with ethylene gas[7] gave disappointing results. Using catalyst **1** (5 mol%), the benzyl ether **4A** gave only 3% conversion (gc) after 6 h, reaction conditions that result in complete conversion of the ether **6** to its diene.[5] This is

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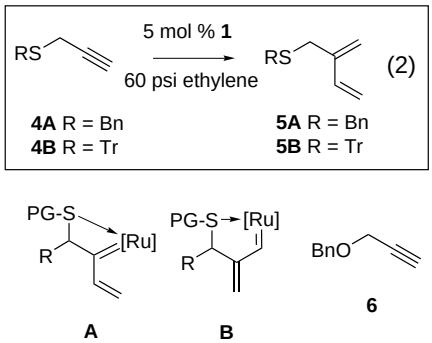
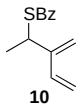
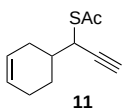
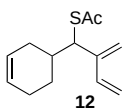
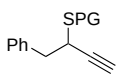
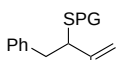
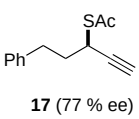
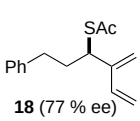


Scheme 2.

plausibly explained by coordinative stabilization of the regioisomeric ruthenium vinylidene intermediates, **A** and **B** (Scheme 2). Even the bulky trityl protecting group gave poor conversion. Trityl ether **4B** provided a 10% conversion after 24 h. The Lewis basicity of sulfur is thought to be responsible for the stability of the putative chelates. Reduction of the Lewis basicity of sulfur was believed to be possible through choice of protecting group. In particular, we considered thiol esters because of their ready availability and because of their facile conversion into other sulfur-containing functionality.

The results for ethylene metathesis for a group of alkyne thiol esters are presented in Table 1. As illustrated in Table 1, thiol esters provide a sufficiently attenuated electronic environment on sulfur to permit catalyst turnover as evidenced by the excellent chemical yields. The thiol acetates and thiol benzoates were prepared by Mitsunobu reaction on the alkynols.[8] Ethylene metatheses were conducted using 60–80 psi ethylene and 5 mol% **1**.[9] 2-Propyne thiol benzoate **7** reacted to complete conversion after 24 h, which provides the standard reaction time used throughout the table. In entry 3, the catalyst **2**[10] gave similarly high conversion compared to **1**, although catalyst **3** performed poorly (entry 4). Propargylic substitution was well tolerated for normal alkyl groups (entries 2–3, 6–8). With the cyclohexenyl substituent (entry 5), higher temperatures were necessary; however only 64% conversion was realized with 5 mol% catalyst **1** and 70 psi ethylene after 24 h. The rate of conversion slowed considerably after just a few hours, probably due to accelerated rate of catalyst decomposition at this temperature.[6b,c] Higher conversion was achieved simply by spiking the reaction with an additional 5 mol% **1** after 3 h and then stopping the reaction after 7 h total reaction time. In this way, 99% conversion was achieved to provide **12** in 98% isolated yield obtained as a 1:1 mixture of diastereomers. No difference between thiol benzoates and thiol acetates was apparent (entries 6, 7). Because of the potential for racemization due to the hard–soft Lewis acid–base interaction of the sulfur atom with the ruthenium catalyst, metathesis of an enantiomerically-enriched thiol ester was investigated. Thiol ester **17** (77% e.e., HPLC, Chiracel OD-H) was converted to its diene **18**, which was obtained of the same enantiomeric purity as the alkyne substrate as determined by HPLC (Whelk-o, entry 8).

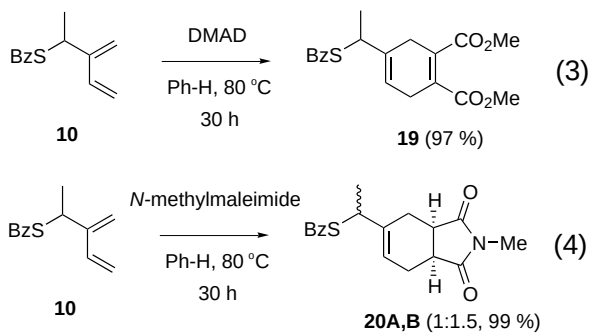
Table 1. Ethylene metathesis with alkyne thiol esters

Entry	Alkyne	Product	yield,[a] (conversion)[b]
1	 **7**	 **8**	95 % (99 %)
2	 **9**	 **10**	87 % (99 %), cat. **1**
3			(99 %), cat. **2**
4			(11 %), cat. **3**
5	 **11**	 **12**	98 (99 %)[c]
6	 **13** PG = Ac	 **14** PG = Ac	97 %
7	**15** PG = Bz	**16** PG = Bz	99 % (99 %)
8	 **17** (77 % ee)	 **18** (77 % ee)	97 %

(a) Isolated yield after 24 h reaction time using 5 mol % **1**. (b) Conversion was determined by gc and is not corrected for response factor. (c) after 7 h with an additional 5 mol % **1** added after 3 h; reaction heated at 45 °C.

The diene products of Table 1 are useful substrates for the Diels–Alder reaction. The thermal [4+2] cycloaddition of crude **10** with dimethylacetylene dicarboxylate (DMAD) gave a 97% yield of the 1,4-cyclohexadiene **19** (Scheme 3).[11] Similarly, cycloaddition of **10** with *N*-methylmaleimide gave a 1:1.5 mixture of diastereomers **20** in quantitative yield (Eq. (4) in Scheme 3).

In conclusion, the first examples of sulfur-containing alkynes undergoing intermolecular metathesis with ethylene have been documentated. Sulfur located in the propargylic position was selected as a test case to explore the viability of enyne metathesis in sulfur-containing natural product synthesis. Applications of



Scheme 3.

metathesis to the synthesis of sulfur-containing natural products are in progress.

Acknowledgements

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References

1. (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett*. **1999**, *1*, 953–956; (b) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc*. **2001**, *123*, 749–750; (c) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc*. **2001**, *123*, 6543–6554; (d) Recent review: Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res*. **2001**, *34*, 18–29.
2. (a) Armstrong, S. K.; Christie, B. A. *Tetrahedron Lett*. **1996**, *37*, 9373–9376; (b) Shon, Y.-S.; Lee, T. R. *Tetrahedron Lett*. **1997**, *38*, 1283–1286; (c) Moore, J. D.; Sprott, K. T.; Hanson, P. R. *Synlett* **2001**, 605–608.
3. Alkenes that contain sulfur functionality of higher oxidation states undergo RCM: (a) Hanson, P. R.; Probst, D. A.; Robinson, R. E.; Yau, M. *Tetrahedron Lett*. **1999**, *40*, 4761–4764; (b) Dougherty, J. M.; Probst, D. A.; Robinson, R. E.; Moore, J. D.; Klein, T. A.; Snelgrove, K. A.; Hanson, P. R. *Tetrahedron* **2000**, *56*, 9781–9790.
4. Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc*. **1967**, *89*, 1827–1836.
5. Smulik, J. A.; Diver, S. T. *Org. Lett*. **2000**, *2*, 2271–2274.
6. (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc*. **1992**, *114*, 7324–7325; (b) Coordination-induced decomposition of Schrock catalyst: Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc*. **1992**, *114*, 5426–5427; (c) Feldman, J.; Murdzek, J. S.; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8*, 2260–2265.
7. (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.
8. Corey, E. J.; Cimprich, K. A. *Tetrahedron Lett*. **1992**, *33*, 4099–4102.
9. Representative ethylene metathesis: 2-(thiobenzoylmethyl)-1,3-butadiene (**10**), entry 2 (Table 1): Into an oven-dried Fisher–Porter bottle (90 mL capacity) equipped with a magnetic stir bar was added 13 mg **1** (15.6 μmol, 0.05 equiv.), 59.4 mg **9** (0.312 mmol, 1 equiv.) and 3 mL of freshly distilled CH_2Cl_2. The vessel was purged with ethylene (4×50 psi) then maintained at room temperature under 70 psi ethylene with constant stirring for 24 h. The resulting dark colored solution was filtered through a plug of silica gel (CH_2Cl_2) and concentrated in vacuo (rotary evaporator) to yield 59 mg (87%) of **10** as a yellow oil. Analytical TLC (1:3 ethyl acetate:hexanes) R_f 0.67. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, $J=7.2$ Hz, 2H), 7.55 (t, $J=7.4$ Hz, 1H), 7.43 (t, $J=7.4$ Hz, 2H), 6.35 (dd, $J=17.7$, 11.1 Hz, 1H), 5.40 (d, $J=17.7$ Hz, 1H), 5.33 (s, 1H), 5.26 (s, 1H), 5.15 (d, $J=11.1$ Hz, 1H), 4.69 (q, $J=7.2$ Hz, 1H), 1.60 (d, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 191.5, 146.5, 136.9, 136.5, 133.3, 128.5, 127.2, 116.7, 114.6, 38.3, 21.0; FT-IR (thin film, cm^{-1}) 2929, 1657, 1449, 1209, 906, 772, 688, 645; low resolution FAB-MS, molecular ion calcd for $C_{13}H_{14}OS$ 218.1, found 241.1 (M+Na).
10. (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) Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430–432.
11. Preparation of cyclohexadiene **19** by cycloaddition: To an oven-dried Fisher–Porter bottle (90 mL capacity) equipped with a magnetic stir bar was added 25 mg (30 μmol, 0.05 equiv.) of 1,3-dimesityl-4,5-dihydroimidazol-2-ylidenetricyclohexylphosphine benzylidene ruthenium dichloride **1**, 114 mg (0.601 mmol, 1.0 equiv.) of **9**, 3 mL CH_2Cl_2, and the vessel was pressurized to 40 psi of C_2H_4. The pressure was released and subsequently flushed four times and then maintained at 70 psi ethylene for 24 h. The pressure was released and the crude brown solution was filtered through a 4 inch plug of silica gel (CH_2Cl_2) and concentrated in vacuo. The crude product **10** was transferred to an oven dried 10 mL rb flask equipped with magnetic stir bar and reflux condenser to which 70 μL (0.57 mmol, 0.95 equiv.) dimethyl acetylenedicarboxylate and 3 mL benzene was added. The solution was refluxed for 30 h, cooled and purified by column chromatography (elution 1:2 ethyl acetate–hexane) to give **19** as a colorless oil (199 mg, 97 % yield); analytical TLC (1:2 ethyl acetate–hexane) R_f 0.3. Data for **19**: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.94 (d, $J=7.0$ Hz, 2H), 7.57 (t, $J=7.5$ Hz, 1H), 7.44 (t, $J=7.5$ Hz, 2H), 5.83 (m, 1H), 4.40 (q, $J=7.5$ Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.21–2.98 (m, 4H), 1.54, (d, $J=7.5$ Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 191.3, 168.2, 168.1, 136.9, 133.7, 133.4, 132.4, 132.2, 128.6, 127.2, 119.0, 52.3, 52.2, 43.5, 28.6, 28.5, 19.5. FT-IR (thin film, cm^{-1}) 2956, 1726, 1667, 1433, 1252, 1193, 1050, 901. FAB-MS (NBA, NaI) molecular ion calcd for $C_{19}H_{20}O_5S$ 360.1, found 383.1 (M+Na).