Ring-Closing Metathesis of Vinyl Chlorides for Formation of 5-, 6- and 7-Membered Carbocyclic and Heterocyclic Systems

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Abstract: Ring-closing metathesis (RCM) of olefinic vinyl chlorides can be effected using the second generation Grubb's catalyst **18** (10 mol%, deoxygenated benzene, 65 °C) to assemble a variety of carbocyclic and heterocyclic 5, 6 and 7-membered rings in high yields.

Key words: ring-closing metathesis reactions, annulations, vinyl chlorides, Grubbs ruthenium alkylidene catalyst



Scheme 1

Since the seminal discovery of functional group-compatible, well behaved and easily prepared transition metal alkylidene catalysts by the Grubbs and Schrock groups during the 1990's, the application of alkene metathesis has undergone phenomenal growth, and has rapidly become one of the most important and widely used methods in organic synthesis.¹ In particular, ring-closing olefin metathesis (RCM) has been extensively explored as an annulation strategy and has been applied to construction of both carbocyclic and heterocyclic ring systems including a number of macrocycles. Moreover, RCM chemistry has been used as a key step in total syntheses of several complex natural products. Although novel variations of metathesis have recently been described, relatively few cases have been reported involving heteroatom-substituted ole-

SYNTHESIS 2004, No. 12, pp 2058–2061 Advanced online publication: 02.04.2004 DOI: 10.1055/s-2004-822327; Art ID: Z00804SS © Georg Thieme Verlag Stuttgart · New York fins. To date, enol ethers and related derivatives have been the most widely utilized alkenes in such RCM reactions.² Nitrogen-substituted olefins such as enamides have also been used successfully.³ In addition, vinyl boronates⁴ have proven to participate in RCM reactions, but these reactions tend to be quite slow, often taking several days to go to completion. More recently, vinyl silanes⁵ have also been employed in RCM reactions.

In the course of an alkaloid total synthesis, we became interested in the possibilty of using a ring-closing metathesis reaction of a vinyl chloride as a pivotal step.⁶ Although we were unable to find any reports of such RCM reactions, Grubbs and co-workers had noted the failure of cross-coupling metathesis of vinyl halides with olefins.⁷ Despite these negative results, we decided to investigate the possibility of doing ring-closing metathesis cyclizations with vinyl halides since a number of types of olefins which do not ordinarily undergo cross-coupling do in fact participate in RCM reactions, probably due to the intramolecularity of the process.

It should be noted that some important mechanistic questions still remain regarding RCM reactions involving olefins bearing electronegative substituents. For example, it is unclear how critical it is that the transition metal catalyst initially react with the nonheteroatom-substituted olefin in order to avoid the formation of a stable Fischer-type carbene.⁸ We were concerned that this could be a potential problem in the vinyl halide metathesis chemistry, and might in fact be the reason for Grubbs' failure to effect the cross-coupling process.⁷ However, there are some documented instances where oxygen-substituted ruthenium Fischer carbenes initiate RCM processes.⁹

We have found that indeed one can effect RCM reactions with vinyl chlorides 17 to afford cyclization products 19 in high yield (Scheme 2, see below).¹⁰ The second generation Grubbs ruthenium carbene 18 proved to be the best catalyst for this transformation. The optimum reaction conditions involved treatment of a benzene solution of the vinyl chloride/olefin substrate with 10 mol% of 18 at 65 °C for 4–10 hours. At temperatures below 65 °C and at lower catalyst loadings, the reactions proved to be considerably slower, and significant amounts of starting material were recovered. In addition, it was found that deoxygenation of the system by bubbling argon through the solution prior to heating significantly improved the product yields. The methodology can be used effectively to assemble 5-, 6- and 7-membered carbocyclic and heterocyclic rings, and some specific examples are shown in Scheme 1. Interestingly, the disubstituted olefins 6 and 9 were found to react somewhat faster than the corresponding terminal systems 5 and 8, respectively (2 h vs 4–6 h).

The scope of the methodology has been explored further. For example, all attempts to form tetrasubstituted vinyl chloride products **21**, as well as the larger 8- and 12-membered rings **23** and **25**, failed and led only to recovery of starting material (Scheme 3). In addition, it was not possible to effect the RCM reactions with either vinyl bromides or vinyl triflates. It might be noted here that since our work appeared, a few research groups have reported successful RCM reactions of vinyl fluorides.¹¹





We have also performed an interesting internal competition experiment using triene **26** (Scheme 4). Thus, cyclization of **26** under our standard reaction conditions led only to cyclopentene metathesis product **27**. This transformation indicates that the vinyl chloride moiety is less reactive than mono- and disubstituted olefins in the





metathesis cyclization process. It therefore seems quite reasonable to assume that the terminal or disubstituted olefins react first to form the corresponding metallocarbenes in the RCM examples like those in Scheme 1.





The metathesis products, which can be constructed by this RCM methodology have considerable potential for a broad range of further transformations. Until quite recently transition metal-mediated couplings of vinyl chlorides were generally not synthetically useful processes. However, this situation has now changed with the discovery of Fu and co-workers that use of tri-tert-butylphosphine as the metal ligand allows efficient utilization of vinyl chlorides in Suzuki-Miyaura^{12a} and Negishi^{12b} couplings. In addition, the recent development of other reactive metal catalysts^{13a} may extend the utility of these vinyl chloride metathesis products even further. In fact, a diverse array of palladium-mediated couplings using aryl chlorides has appeared recently,¹³ although most of this chemistry has not yet been explored with vinyl chlorides. In addition, vinyl chlorides can be hydrolyzed to ketones using mercury catalysis,¹⁴ and can be oxidized under very mild conditions to a-halo ketones using our newly introduced procedure.15

Ring-Closing Metathesis of Vinyl Chlorides; General Procedure

A 100 mL flask equipped with a condenser was flame dried in vacuo. The vinyl chloride substrate (0.24 mmol) in anhyd benzene (60 mL) was added and the solution was deoxygenated by bubbling argon through the mixture using a fritted glass inlet tube for 2 h. Grubbs' second-generation catalyst **18** (10 mol%) in anhyd benzene (2 mL) was added through the condenser and the argon bubbling was continued for an additional 30 min. The mixture was heated and stirred at 65 °C for 4–10 h until TLC showed the reaction was complete. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography to afford the metathesis products listed below.

Chlorocyclohexenyl Sulfonamide 3

From substrate 1: 6 h at 65 °C; silica gel chromatography eluting with hexanes–EtOAc (5:1); yellow solid; yield: 92%; mp 72 °C.

IR (film): 2923, 2852, 1664, 1579, 1339, 1166, 1099, 970 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.64 (d, *J* = 8.2 Hz, 2 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 5.82–5.79 (m, 1 H), 3.66 (q, *J* = 2.2 Hz, 2 H), 3.15 (t, *J* = 5.7 Hz, 2 H), 2.40 (s, 3 H), 2.25–2.18 (m, 2 H).

¹³C NMR (75 MHz, CDCl₃): δ = 143.9, 133.2, 129.7, 127.5, 126.3, 122.6, 48.9, 41.8, 25.8, 21.5.

APCIMS: m/z = 272 (MH⁺, 100%).

HRMS: m/z calcd for $C_{12}H_{15}CINO_2S$: 272.0507 (MH⁺); found: 272.0504.

Chlorocyclohexenyl Benzamide 4

From substrate 2: 4 h at 65 °C; silica gel chromatography eluting with hexanes–EtOAc (3:1); yellow oil; yield: 90%.

IR (film): 3057, 2925, 1635, 1425, 1246, 1145 cm⁻¹.

¹H NMR (300 MHz, CD₃OD): δ = 7.40–7.36 (m, 5 H), 6.02 (br s, 1 H) 5.91 (br s, rotamer), 4.27 (br s, 2 H), 4.14 (br s, rotamer), 3.68 (br s, 2 H), 3.34 (br s, rotamer), 2.18 (s, 2 H).

 ^{13}C NMR (300 MHz, CD₃OD): δ = 172.5, 172.1, 136.1, 135.8, 132.2, 131.7, 129.9, 128.7, 128.1, 127.9, 127.8, 125.3, 124.8, 52.9, 47.5, 44.8, 39.7, 27.2, 26.3.

APCIMS: m/z = 222 (MH⁺, 100%).

HRMS: m/z calcd for $C_{13}H_{13}CINO$: 222.0680 (MH⁺); found: 222.0682.

Chlorocyclopentene 7

From substrate 5: 4 h at 65 °C; silica gel chromatography eluting with hexanes–Et₂O (5:1); yellow oil; yield: 88%.

From substrate 6: 2 h; yield: 96%.

IR (film): 2982, 1731, 1638, 1263, 1054, 1015 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 5.51 (t, *J* = 2.2 Hz, 1 H), 4.17 (q, *J* = 7.1 Hz, 4 H), 3.13 (q, *J* = 2.0 Hz, 2 H), 2.99 (q, *J* = 2.1 Hz, 2 H), 1.22 (t, *J* = 7.1 Hz, 6 H).

¹³C NMR (75 MHz, CDCl₃): δ = 171.0, 128.7, 123.4, 61.8, 58.0, 44.2, 39.2, 13.9.

APCIMS: *m*/*z* = 247 (MH⁺, 100).

HRMS: m/z calcd for $C_{11}H_{16}ClO_4$: 247.0731 (MH⁺); found: 247.0728.

Chlorocyclohexene 10

From substrate **8**: 6 h at 65 °C; silica gel chromatography eluting with hexanes–Et₂O (6:1); yellow oil; yield: 99%.

From substrate 9: 2 h; yield: 98%.

IR (film): 2981, 1732, 1442, 1250, 1088, 1017 cm⁻¹.

¹H NMR (360 MHz, CDCl₃): δ = 5.75–5.73 (m, 1 H), 4.16 (q, J = 2.0 Hz, 4 H), 2.78 (t, J = 2.1 Hz, 2 H), 2.15–2.11 (m, 2 H), 2.08–2.04 (m, 2 H), 1.20 (t, J = 7.1 Hz, 6 H).

 ^{13}C NMR (90 MHz, CDCl₃): δ = 170.3, 128.7, 123.2, 61.6, 54.4, 37.1, 26.4, 23.1, 13.9.

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APCIMS: m/z = 261 (MH⁺, 100 %).

HRMS: m/z calcd for $C_{12}H_{18}ClO_4$: 261.0888 (MH⁺); found: 261.0872.

Chlorocycloheptene 12

From Substrate **11**: 10 h at 65 $^{\circ}$ C; silica gel chromatography eluting with hexanes–Et₂O (5:1); yellow oil; yield: 92%.

IR (film): 2930, 1732, 1446, 1252, 1219, 1186, 1093, 1032 cm⁻¹.

¹H NMR (360 MHz, $CDCl_3$): $\delta = 5.95$ (t, J = 6.5 Hz, 1 H), 4.15 (dq, J = 1.4, 7.1 Hz, 4 H), 3.06 (s, 2 H), 2.19–2.16, (m, 2 H), 2.12–2.07 (m, 2 H), 1.68–1.65 (m, 2 H), 1.22 (t, J = 7.1 Hz, 3 H).

¹³C NMR (90 MHz, CDCl₃): δ = 170.8, 130.7, 130.2, 61.4, 55.3, 40.9, 35.7, 27.5, 21.9, 13.9.

APCIMS: m/z = 275 (MH⁺, 100%).

HRMS: m/z calcd for $C_{13}H_{20}ClO_4$: 275.1044 (MH⁺); found: 275.1027.

Chlorocycloheptene Ether 14

From substrate 13: 5 h at 65 °C; silica gel chromatography eluting with hexanes– Et_2O (8:1); yellow oil; yield: 90%.

IR (film): 3026, 2930, 2856, 1453, 1370, 1124, 1015 cm⁻¹.

¹H NMR (360 MHz, $CDCl_3$): $\delta = 7.31-7.27$ (m, 2 H), 7.20–7.18 (m, 3 H), 5.83–5.82 (m, 1 H), 4.23–4.17 (m, 2 H), 3.55–3.44 (m, 1 H), 2.81–2.70 (m, 2 H), 2.40–2.31 (m, 1 H), 2.22–2.16 (m, 1 H), 1.94–1.75 (m, 2 H).

¹³C NMR (90 MHz, CDCl₃): δ = 141.6, 128.7, 128.4, 125.9, 123.0, 73.4, 65.8, 38.5, 36.9, 31.5.

APCIMS: m/z = 223 (MH⁺, 30%).

HRMS: m/z calcd for $C_{13}H_{16}CIO$: 223.1884 (MH⁺); found: 223.0876.

Chlorocycloheptene Ether 16

From substrate **15**: 9 h at 65 $^{\circ}$ C; silica gel chromatography eluting with hexanes–Et₂O (7:1); yellow oil; yield: 88%.

IR (film): 3026, 2931, 2840, 1653, 1540, 1125, 1028 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.31–7.23 (m, 2 H), 7.20–7.16 (m, 3 H), 5.95 (dt, *J* = 1.7, 5.9 Hz, 1 H), 4.39 (d, *J* = 6.3 Hz, 1 H), 4.19–4.13 (m, 1 H), 3.61–3.57 (m, 1 H), 2.78–2.60 (m, 2 H), 2.42–2.32 (m, 1 H), 2.13–2.05 (m, 1 H), 1.94–1.88 (m, 2 H), 1.70–1.65 (m, 2 H).

¹³ C NMR (75 MHz, CDCl₃): δ = 141.9, 131.7, 128.4, 128.3, 128.1, 125.8, 79.3, 71.7, 37.4, 33.9, 32.1, 23.9.

APCIMS: *m*/*z* = 237 (MH⁺, 100).

HRMS: m/z calcd for C₁₄H₁₇ClO: 237.1041 (MH⁺); found: 237.1047.

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