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Ru(II)-Catalyzed RCM Reactions with Electrophilic Diene Substrates

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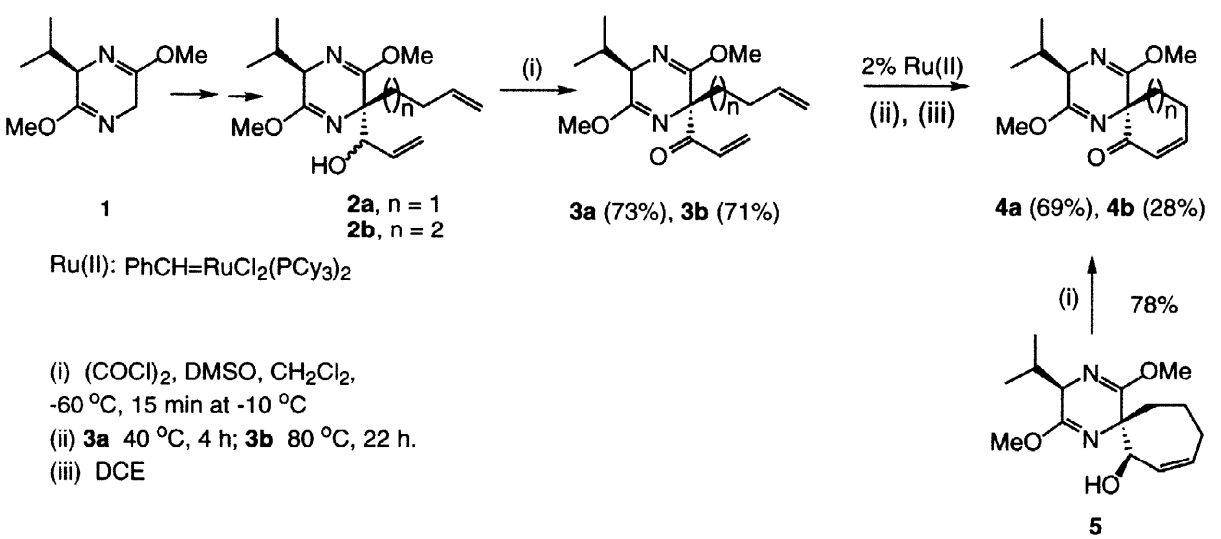
Abstract: Electrophilic dienes from α,β-unsaturated ketones readily undergo the Ru(II)-benzylidene initiated RCM reaction. Cyclohexenone spirane formation was faster than cycloheptenone spirane formation. The products were pure stereoisomers. The products after hydrolysis were α,β-unsaturated oxo derivatives of cyclic α-amino acids. © 1998 Elsevier Science Ltd. All rights reserved.

Recent reviews highlight the importance and wide applicability of ring closing metathesis (RCM) in the construction of cyclic structures.[1-4] It is desirable to elucidate further the chemistry of such cyclization reactions in order to gain a better understanding of electronic as well as of steric influences which may act to promote, retard or even prevent ring formation.[5,6]

Ruthenium alkylidene catalysts are compatible with a wide variety of functional groups in the substrates undergoing ring closure.[1,4] The catalyst most tolerant to functional groups appears to be a benzylidene derivative $PhCH{=}RuCl_2(PCy_3)_2$. The high compatibility, however, is reflected in a somewhat reduced activity as compared with other members of the ruthenium alkylidene family of catalysts in initiating the reaction. Grubbs, in a recent study of substituent effects in dienes on the RCM, concluded that steric effects of an alkyl substituent up to an isopropyl group were allowed on the inner carbon of the terminal olefinic bond. Dienes with an electron-withdrawing group on the inner olefinic carbon failed to undergo RCM at a significant



1 **2a**, n = 1 **2b**, n = 2 **3a** (73%), **3b** (71%) **4a** (69%), **4b** (28%)

Ru(II): $PhCH{=}RuCl_2(PCy_3)_2$

(i) $(COCl)_2$, DMSO, CH_2Cl_2, -60 °C, 15 min at -10 °C
(ii) **3a** 40 °C, 4 h; **3b** 80 °C, 22 h.
(iii) DCE

5

Scheme 1

PII: S0040-4039(98)01651-7

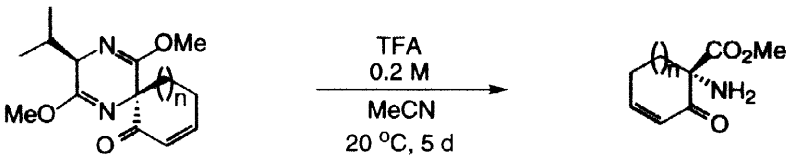
rate. The failure was, in part, ascribed to the steric bulk of the electron-withdrawing group, but the emphasis was on the deactivation caused by electron withdrawal.[7] The steric effects can be significantly reduced when a carbonyl group is inserted into the chain to form an α,β-unsaturated amide, ester or ketone. A ketone has generally the most electrophilic double-bond. The literature describes a case where two olefinic chains were tethered to an amino nitrogen with one of the chains attached as an acrylamide; the RCM reaction proceeded well under appropriate conditions.[8] Additional and related examples of RCM reactions of α,β-unsaturated carbonyl compounds exist for the stronger alkylidene ruthenium catalysts.[1-4,7]

In connection with our studies of constrained α-amino acids,[9-12] we had ready access to α,β-unsaturated ketones thereby providing a strongly electrophilic double-bond with low steric effects. The olefinic chains were tethered in a stereoselective manner to the C-5 carbon in the bislactim ether **1**. Conformational preferences for the diene chains are likely to be influenced by the tethering system used. In Grubbs studies of electronic effects on the RCM reaction, the malonate carbon was the common point of attachment of the diene chains.[7]

The keto substrates **3** were prepared by a Swern oxidation of the allylic alcohols **2,** which were available from previous work.[10,13,14] Swern oxidation was also a good reaction for oxidation of the cycloheptenol spirane **5**. The product was the cycloheptenone spirane **4b**. The latter was also formed in the RCM reaction from the diene substrate **3b** (*vide infra*).

2 Mol% of the ruthenium(II) complex, bis(tricyclohexylphosphine)benzylidene ruthenium dichloride [Ru(II)], was used as the catalyst precursor.[15] The reactions were effected in 1,2-dichloroethane (DCE). The cyclohexenone spirane **4a** was isolated in a 69% yield after running the reaction at 40 °C for 4 hours. Higher temperature and a longer reaction time was required for the RCM reaction yielding the cycloheptenone spirane **4b**. The latter was isolated in only a 28% yield after 22 hours at 80 °C. The electronic influence from the keto group on the double-bond is likely to be very similar in both substrates. Therefore, the difference in yields and rates is related to conformational preferences in the two substrates.

It seems relevant to compare the above metathetic reactions with RCM reactions of the parent allylic alcohols under similar conditions. Six-membered ring allylic products were isolated in *ca.* 90% yield from both **2a** and its epimeric alcohol. Analogous RCM reactions for the preparation of seven-membered ring products gave a *ca.* 60% yield, somewhat dependent on the stereochemistry at the alcohol carbon.[10] The cycloheptenol spirane **5** was one of the isomers from the latter reaction. In another series, with the allylic hydroxyl group and its double-bond moved one carbon unit away from the spirane center, six-membered ring formation proceeded readily whereas the RCM reaction failed completely for formation of the seven-membered ring.[11] Prior esterification of the hydroxyl group in the latter case, however, changed the seven-membered ring formation from a zero percentage to a high 95% yield reaction. In a related β-substituted acrolein diene substrate, six-membered ring formation has been effected by the RCM reaction despite the electrophilic state of the double-bond.[12] All these findings are best rationalized in terms of rates controlled by conformational populations biased for cyclization. The conformational factor, rather than the electronic state of the double-bond, seems more important for the control of the rate of the RCM reaction. Furthermore, it seems most likely that the RCM reaction is initiated by attack from the carbenoid catalyst on the more electron rich double-bond, or for steric reasons sometimes on the less substituted double-bond. Once the initial adduct has been formed, the electronic state of the second double-bond becomes less important. The main factor for the catalyst in the the metathetic operation will be the conformational accessibility of the second double-bond.



4a, n = 1
4b, n = 2

6a (37%), **6b** (47%)

Scheme 2

The cycloalkenone spiranes **4** were cleaved under mild acidic conditions to form unique cycloalkenone α-amino acid esters **6**.[16] The latter are exceptionally constrained α-amino acids, potentially useful as conformational probes and bioactive agents.[17] Previously we have prepared their reduced analoques, the corresponding allylic alcohols.[10]

In conclusion we have shown that electrophilic dienes from α,β-unsaturated ketones readily undergo Ru(II)-benzylidene initiated RCM reaction to form six- and seven-membered rings.

References and Notes:

1. (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413-4450; (b) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446-452.
2. Fürstner, A. *Topics in Catalysis* **1997**, *4*, 285-299.
3. Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371-388.
4. Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036-2056.
5. Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484-2489.
6. Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130-9136.
7. Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310-7318.
8. Rutjes, F. P. J. T.; Shoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677-680.
9. (a) Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 2309-2322; (b) Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 10603-10614.
10. Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 5925-5936.
11. Hammer, K.; Rømming, C.; Undheim, K. *Tetrahedron*. In press.
12. Hammer, K.; Undheim, K. *Tetrahedron: Asymmetry*. In press.
13. The structures of the products have been verified by satisfactory elemental analyses; by ^{1}H and ^{13}C NMR spectroscopy, and by MS and HRMS.
14. **Representative procedure for the Swern oxidation (3)**. A solution of DMSO (1.36 mmol) in CH_2Cl_2 (0.34 ml) was added to a solution of oxalyl chloride (0.68 mmol) in CH_2Cl_2 (1.80 ml) under argon at -60 °C. The mixture was stirred for 2 min before a solution of reactant **2** (0.68 mmol) in CH_2Cl_2 (1.5 ml) was added dropwise. The reaction mixture was stirred at -10 °C for 15 min, worked up in the standard manner and the product purified by flash chromatography.

15. **Representative procedure for the RCM reactions (4)**. Bis(tricyclohexylphosphine)benzylidene ruthenium dichloride (0.022 mmol, 2 mol%) in dry degassed 1,2-dichloroethane (1 ml) was added to a solution of the reactant **3a** (1.072 mmol) in dry degassed 1,2-dichlorethane (15 ml). The reaction mixture was stirred at 40 °C for 4 h before the solvent was evaporated and the residual material subjected to flash chromatography (hexane:EtOAc 4:1 or 9:1). The product was a colourless oil. **Spectroscopic data for product 4a**. $[\alpha]_D$= -21.7° (c = 0.70, $CHCl_3$). ^1H NMR (200 MHz): δ 0.62 (d, *J* 7 Hz, 3H, CH_3), 1.05 (d, *J* 7 Hz, 3H, CH_3), 1.90-2.63 (m, 5H, 2 x CH_2, CH), 3.60 (s, 3H, CH_3O), 3.67 (s, 3H, OCH_3), 4.30 (d, *J* 3 Hz, 1H, CH), 5.90 (m, 1H, CH=), 6.99-7.06 (m, 1H, CH=). ^{13}C NMR (50 MHz): δ 16.61 (CH_3), 19.30 (CH_3), 22.40 (CH_2), 30.57 (CH), 34.20 (CH_2) , 52.47 (CH_3O), 52.55 (CH_3O), 60.70 (C-2), 65.01 (C-5), 127.56 (CH=), 151.41 (CH=), 161.06 (C), 164.47 (C), 193.63 (C=O). MS(EI): 264 (8, M^+), 221 (100), 193 (17), 153 (35), 80 (29).

16. **Representative procedure for the preparation of cyclic α-amino acid esters (6)**. The spirane **4** (0.758 mmol) was added to a solution of trifluoracetic acid (38 ml, 0.2 M) in acetonitrile (38 ml) and the reaction mixture stirred at ambient temperature for 5 d. The reaction mixture was worked up according to our standard procedure,[9,10] and the product isolated after flash chromatography using 3% methanol in dichloromethane.
Spectroscopic data for product 6a. $[\alpha]_D$= -59.0° (c = 0.30, $CHCl_3$). ^1H NMR (300 MHz): δ 1.88-2.34 (m, 6H 2xCH_2, NH_2), 3.68 (s, 3H, CH_3O), 6.06 (m, 1H, CH=), 6.95 (m, 1H, CH=). ^{13}C NMR (75 MHz): δ 23.70 (CH_2), 33.69 (CH_2), 52.73 (CH_3O), 64.23 (C-1), 127.39 (CH=), 150.27 (CH=), 172.48 (C=O), 194.77 (C=O). MS(EI): 169 (10, M^+), 110 (100), 101 (63), 82 (37), 68 (33).

17. Goodman, M.; Shao, H. *Pure Appl. Chem.* **1996**, *68*, 1303-1308 and references therein.

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