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Efficiency of a Ruthenium Catalyst in Metathesis Reactions of Sulfur-Containing Compounds

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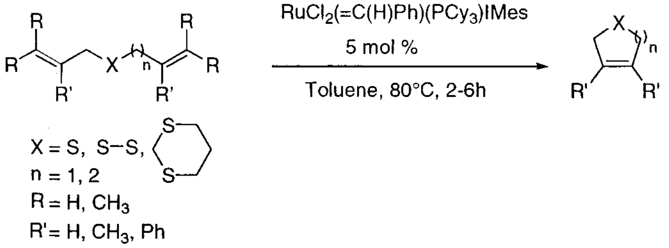
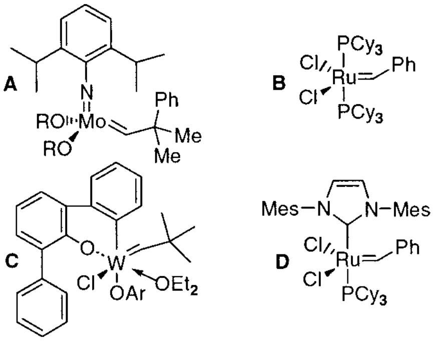
ABSTRACT



1,3-Dimesitylimidazol-2-ylidene ruthenium benzylidene catalyst ($RuCl_2(=C(H)Ph)(PCy_3)(IMes)$) has been successfully employed in ring-closing metathesis reactions of acyclic diene sulfides, disulfides, and dithianes and in self-cross metathesis reactions of ene-sulfides, thioethers, and thiols.

Over the past few years, olefin metathesis reactions catalyzed by well-defined alkylidene complexes have evolved into a widely applicable methodology in organic synthesis.[1] To date, molybdenum (**A**)[2] and ruthenium (**B**)[3] complexes (Figure 1) are the most routinely used catalysts for ring-closing metathesis (RCM), cross metathesis (CM), and other metathesis-type reactions. The commercial availability and effectiveness of these catalysts now allow olefin metathesis strategies to be viewed as practical methods for the synthesis



R= $CMe(CF_3)_2$, Mes=C_6H_2-2,4,6-$(CH_3)_3$

Figure 1. RCM catalysts.

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(1) For recent reviews, see: (a) Grubbs, R. H.; Chang S. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056. (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (e) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519−529.

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of medium size ring,[4] spiro, and polycyclic systems[5] and natural products.[6] Although Grubbs' catalyst (**B**) exhibits excellent functional group compatibility, Schrock's catalyst (**A**) displays higher reactivity toward a broad range of substrates.[7]

Metathesis reactions on substrates bearing a large range of functionalities and heteroatoms are fully documented in the literature, but astonishingly very few examples of substrates containing sulfur atoms have been so far reported. Tungsten (**C**)[8] and molybdenum (**A**)[9] catalysts (Figure 1) were until lately the only two known catalysts to display efficiency in metathesis reactions on substrates containing sulfur atoms. Very recently catalyst **B** was shown to perform enyne metathesis of sulfur-containing alkynes[10] and to promote RCM reactions of acyclic sulfones and α-thiophosphonate.[11]

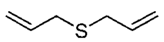
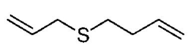
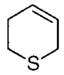
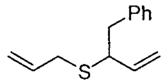
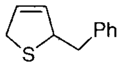
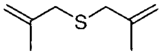
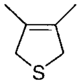
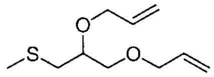
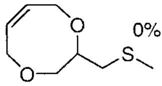
In fact, many failures in RCM-type reactions of sulfur compounds are reported in multistep synthesis and have compelled authors to revise their synthetic strategy.[12] To overcome this unsatisfactory situation and broaden the scope of metathesis reactions, we reinvestigated new conditions and catalysts in order to conduct RCM reactions on sulfur-containing compounds.

Replacement in catalyst **B** of one of the phosphine ligands by a strong electron-donating and sterically hindered *N*-heterocyclic carbene[13] (e.g., *N*,*N*-bis(mesityl)imidazol-2-ylidene, IMes) led to a new ruthenium catalyst **D**[14] (Figure 1). This catalyst and its saturated imidazol-2-ylidene analogue[15] have been reported to improve effectiveness in metathesis activity, thermal stability, and inertness toward oxygen and moisture.[16−17] Complex **D** bears the high reactivity of **A** while maintaining the functional group tolerance of **B**.

We investigated therefore the potential of **D** as catalyst in metathesis involving substrates containing sulfur atoms. Herein we report the first examples of RCM and self-CM reactions of a series of acyclic diene sulfur species (sulfides, disulfides, thioethers) catalyzed by **D**. We intended to evaluate its compatibility and effectiveness compared to that of parent complex **B** and to performances reported for catalysts **A** and **C**.

The activity of ruthenium complex **D** in RCM of acyclic diene sulfides[18] was initially investigated. The results are reported in Table 1.[19]

Table 1. RCM of Sulfides

entry	substrate	product	catalysts		
			D	B	A-C
1			100%[a]	12%[b]	A: 99%[c] C:100%[d]
2			100%[a]	0%[b]	nd
3			0%[a]	0%[b]	nd
4			0%[a]	0%[b]	C: 0%[d]
5			0%[e]	0%	nd

[a] 0.1 M C_7D_8, 5 mol % **D**, 80 °C, 1 h. [b] 0.1 M C_6D_6, 5 mol % **B**, rt, 20 h. [c] Reference 9a and b. [d] Reference 8b. [e] 0.005 M C_7H_8, 5-10 mol % **D**, 80 °C, 30 h. nd = not determined.

First, we studied substituted diallyl sulfides (entries 1, 3, 4) and allyl-homoallyl sulfide (entry 2) in the presence of 5

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mol % of catalyst **D**. Diallyl sulfide led quantitatively to 2,5-dihydrothiophene as catalysts **A** and **C** do (entry 1). Grubbs' complex **B** performed the cyclization in only 12% yield.

Under similar reaction conditions, RCM reaction of one carbon homologated sulfide furnished 3,6-dihydro-2*H*-thiopyrane in 100% yield, whereas catalyst **B** failed totally (entry 2).

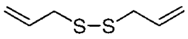
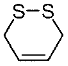
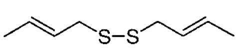
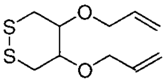
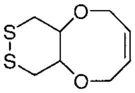
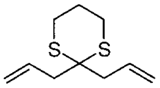
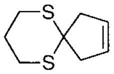
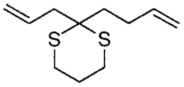
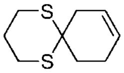
α-Benzyl diallyl sulfide (entry 3) or dimethallyl sulfide (entry 4) does not lead to the formation of RCM product. These results highlight the influence of substituents that slow the RCM and deactivate the catalyst by complexation of the metal by heteroatoms, especially by sulfur atoms.[7,8b]

Moreover, cyclization of an eight-membered ring bearing a methyl sulfide moiety failed with both catalysts **B** and **D** even under high dilution conditions (entry 5).[20]

These examples show the efficiency of catalyst **D** compared to that of catalysts **A** or **C** and the low efficacy of catalyst **B** in RCM reactions of substrates containing sulfide functionalities.

Next we investigated RCM reactions involving disulfide compounds (Table 2).[18,21]

Table 2. RCM of Disulfides

entry	substrate	product	catalysts D	 B	 A
1			60%[a] 100%[b]	15%[c]	77%[d]
2			6%[b,e]	0%[c]	54%[d]
3			80%[f]	0%[g]	nd
4			0%[a,b]	0%[c]	nd
5			63%[h] 25%[b]	0%[c]	nd

[a] 0.1 M C_7D_8, 5 mol % **D**, 80 °C, 2 h. [b] 0.1 M CD_2Cl_2, 5 mol % **D**, reflux, 4 h. [c] 0.1 M C_6D_6, rt, 24 h or 0.1 M CD_2Cl_2, 5 mol % **B**, reflux, 12 h. [d] Reference 9b. [e] Plus 40% dimerization product. [f] 0.005 M C_7H_8, 10 mol % **D**, 80 °C, 4 h, isolated yield. [g] No RCM in standard concentration or 0.005 M. [h] 0.1 M C_7D_8, 5 mol % **D**, 80 °C, 6 h, isolated yield. nd = not determined.

Allyl disulfide and 5 mol % of **D**, refluxed for 4 h in CD_2Cl_2 gave quantitatively 3,6-dihydro-[1,2]dithiine and a 60% yield when the reaction was conducted in toluene.[22] Under similar conditions catalyst **B** led to a 15% yield of the desired product (entry 1). Schrock's catalyst **A**, used in 10 mol % for 1 h in benzene at 20 °C, afforded the cyclic product in 77% yield (entry 1).

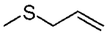
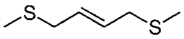
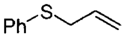
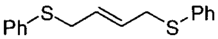
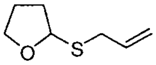
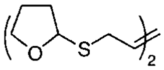
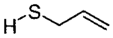
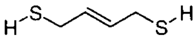
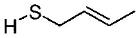
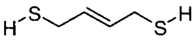
Introduction of two methyl groups on the terminal double bonds (entry 2) led (under standard conditions) to a dramatic decrease in the formation of RCM product (6% yield), while dimerization product was observed in 40% yield. Under these conditions, catalyst **B** proved to be totally ineffective in contrast to catalyst **A**, which gave a 54% yield. These results clearly show the Schrock catalyst **A** to be more efficient for RCM of substituted olefins in this substrate family.

Interestingly, a bicyclic compound obtained by RCM of an eight-membered ring could be isolated with catalyst **D**, whereas catalyst **B** was totally inefficient under similar conditions (entry 3).

RCM reaction performed on diallyl [1,3]dithiane failed completely even under drastic conditions (entry 4), while the corresponding allyl homoallyl [1,3]dithiane gave the desired spiro compound in 63% isolated yield by performing the RCM with catalyst **D** in toluene (entry 5). Catalyst **B** proved to be totally ineffective for substrates bearing dithioacetal functionalities (entries 4 and 5).

Finally, we investigated self-cross metathesis (CM) of various acyclic allyl thioethers and thiols to examine the influence of the substituents on the sulfur atom during metathesis reactions.[23] The results are reported in Table 3.

Table 3. Self-Cross Metathesis

entry	substrate	product	catalysts D	 B	 C
1			48%[a]	20%[b]	20%[c]
2			100%[a]	30%[b]	nd
3			100%[a] 89%[d]	11%[e]	nd
4			45%[a]	0%[b]	nd
5			38%[a]	0%[b]	nd

[a] 0.1 M C_7D_8, 5 mol % **D**, 80 °C, 2 h. [b] 0.1 M C_6D_6, 5 mol % **B**, rt, 20 h. [c] Reference 8c. [d] 0.1 M C_7H_8, 5 mol % **D**, 80 °C, 2 h, isolated yield. [e] 0.1 M C_6H_6, 5 mol % **B**, rt, 24 h. nd = not determined.

When allyl methyl sulfide was reacted under standard metathesis conditions with catalysts **D** or **B**, the resulting dimer was obtained in 48% and 20% yields, respectively

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(18) When not commercially available, the diene sulfides were synthesized following the reported procedure: Bastien, G.; Surzur, J.-M. *Bull. Soc. Chim. Fr.* **1982**, *II*, 84–88.

(19) **Representative Procedure.** The metathesis reactions of volatile compounds were run in deuterated solvent. In a typical reaction, a solution of acyclic diene sulfide (typical concentration 0.1 M) in dry solvent (toluene-d_8 or CD_2Cl_2 or CH_2Cl_2) with a catalytic amount of ruthenium benzylidene (5 mol %) was weighed in a flask or in a NMR tube and heated to 80 °C or refluxed (CD_2Cl_2). Product formation and diene disappearance were monitored by integration of the allylic methylene picks. The formation of known cyclic product was confirmed by comparison with literature data. McIntosh, J. M. *Can. J. Chem.* **1978**, 131–134. McIntosh, J. M.; Siddiqui, M. A. *Can. J. Chem.* **1983**, *61*, 1872–1875. Lozac'h, R.; Braillon, B. *J. Magn. Reson.* **1973**, *12*, 244–260.

(20) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108–2109.

(entry 1). Despite longer reaction time and catalyst additions, the yields could not be increased. Schrock's catalyst **A** was reported to lead to a 20% yield.

Allyl phenyl sulfide treated with **D** or **B** allowed yields higher than those observed with allyl methyl sulfide (entry 2 vs entry 1). Complex **D** performed the CM reaction in quantitative yield, whereas **B** only afforded 30% yield.

A cross metathesis reaction was then carried out on a sulfur-protected (as the THF derivative) allylthiol (entry 3). Dimerization occurs with a 89% yield when using catalyst **D**, but the desired product was obtained in 11% yield with catalyst **B**.

Finally free allyl thiols were tested in CM reaction (entries 4 and 5). Dimerization was observed for the first time for this class of compound by using **D** as a catalyst. Noteworthy, a drop in yield was observed for CM of crotyl (38% yield, entry 5) compared to that of the corresponding allyl derivative (45% yield, entry 4). Under similar conditions, catalyst **B** proved ineffective (entries 4 and 5).

In conclusion, 1,3-dimesitylimidazol-2- ylidene ruthenium benzylidene complex **D** was shown to display catalytic efficiency similar to that of Schrock's catalyst **A** in RCM and CM reactions of sulfide and disulfide functions.

A RCM reaction of a diene bearing a dithioacetal was observed for the first time by using catalyst **D**. In addition, **D** was successfully employed in the first cross metathesis reaction of olefins bearing free thiols. This reactive profile, combined with a remarkable stability displayed toward oxygen, moisture, and heat, make catalyst **D** a very attractive complex in organic synthesis for substrates containing sulfur atoms, especially in the construction of structures bearing dithiane as protective groups.

However, limitations in RCM reactions of sterically hindered substrates require further investigations with new catalysts to enlarge the scope of metathesis reactions on sulfur-containing substrates.

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Supporting Information Available: Experimental procedure and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Disulfides were commercially available or were synthesized following the reported procedure: Moore, G. C.; Trego, B. R. *Tetrahedron* **1962**, *18*, 205−218.

(22) NMR yield, 40% of starting substrate was recovered.

(23) The unsaturated sulfide substrates were commercially available or were obtained after allylation of the corresponding thiols or following ref 21.