Ring-Closing Metathesis (RCM) for the Synthesis of Cyclic Sulfoximines

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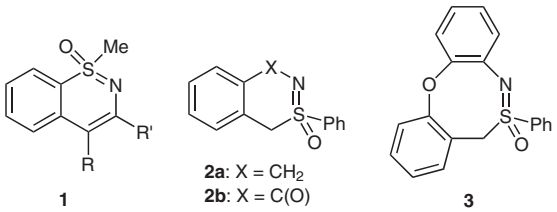
This paper is dedicated to Professor Dr. Bernd Giese on the occasion of his 65th anniversary

Abstract: Chiral heterocycles can be prepared starting from doubly unsaturated sulfoximine derivatives by ring-closing metathesis reaction in good yields.

Key words: catalysis, heterocycles, macrocycles, ring-closing metathesis, sulfoximines

Sulfoximines[1] are useful sulfur reagents in asymmetric synthesis[2] and biological chemistry.[3] Since their discovery in 1946,[4] cyclic sulfoximine derivatives have attracted particular attention,[5] and several methods have been devised for their synthesis. For example, Harmata and coworkers used annulation reactions of alkynes with sulfonimidoyl chlorides, and domino sequences involving palladium catalyses followed by ring closures for the preparation of benzothiazines **1**.[6] Palladium-catalyzed intramolecular α-arylations of sulfoximines affording heterocyclic products **2** and **3** were recently introduced by us[7] (Figure 1).

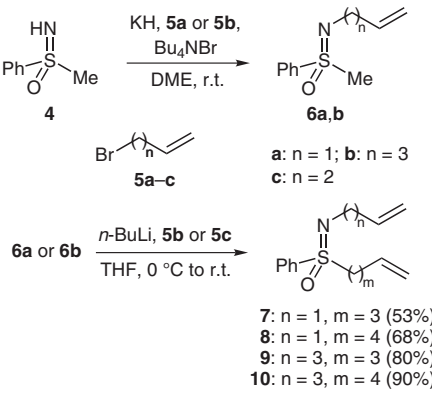


1 3

Figure 1 Cyclic sulfoximines obtained by palladium catalyses followed by ring formation (see text)

We wondered, if the recently developed ring-closing metathesis (RCM)[8] could also be used for the preparation of sulfoximine-containing heterocycles. With appropriately designed starting materials macrocyclic sulfoximine derivatives should result, which are difficult to prepare by other means.[9] To the best of our knowledge, RCM has only once been employed in sulfoximine chemistry,[3f] and there, its efficiency was used as indication for conformational issues of the cyclizing pseudopeptide.

Various routes were developed for the synthesis of the doubly unsaturated starting materials, which were required for the RCM. Initially, readily accessible racemic *S*-methyl-*S*-phenyl sulfoximine (**4**) served as the precursor.[10] Its deprotonation with KH in the presence of Bu_4NBr and subsequent treatment with allyl bromide (**5a**) or 5-bromopentene (**5b**) afforded N-substituted products **6a** (80%) and **6b** (71%), respectively, in good yields. A second deprotonation/alkylation sequence using *n*-BuLi as base and 5-bromopentene (**5b**) or 4-bromobutene (**5c**) gave **7**–**10** in yields up to 90% (Scheme 1).



Scheme 1 Synthesis of doubly unsaturated sulfoximines to be used as starting materials for RCM reactions

Oxidation of allyl phenyl sulfide (**11**) followed by standard imination of the resulting sulfoxide **12** with a mixture of NaN_3 and H_2SO_4 afforded the corresponding sulfoximine **13**. Attempts to allylate **13** selectively at the sulfoximine nitrogen to give **14** led to a mixture of **15** and **16**[11] (Figure 2).

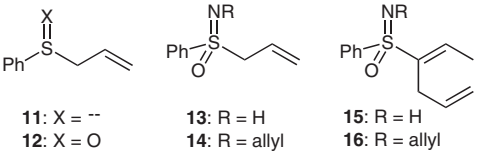


Figure 2 Attempted synthesis of **14** starting from allyl phenyl sulfide (**11**)

As depicted in Scheme 2, N-acylated sulfoximines **19**–**21** and N-allylated derivative **22** were prepared through the intermediacy of NH-sulfoximines **13**, **15**, and **18**. For the synthesis of the latter compound a standard MCPBA oxidation of sulfide **17** followed by rhodium-catalyzed imination[12] of the resulting sulfoxides (not shown) was applied. Treatment of **13**, **15**, and **18** with acryloyl chloride in the presence of a base afforded acylated products

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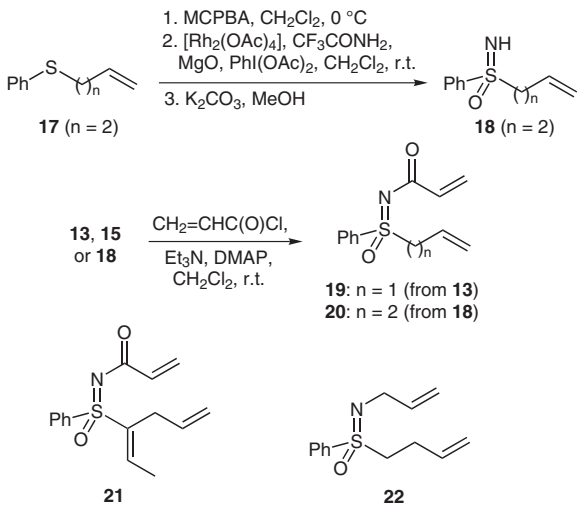
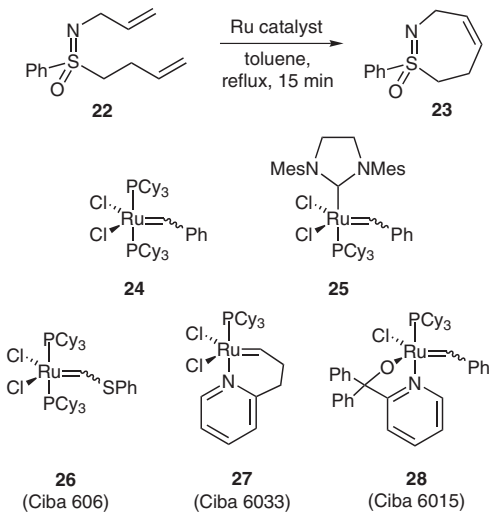


Scheme 2 Reaction sequence for the preparation of unsaturated sulfoximines

19–**21**.[13] N-Allylated **22** was obtained by allylation of **18** with allyl bromide (**5a**).

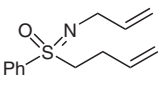
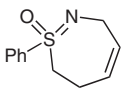
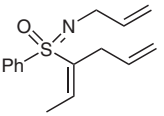
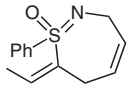
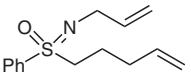
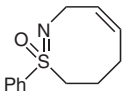
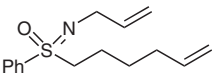
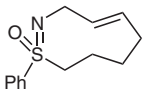
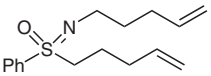
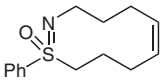
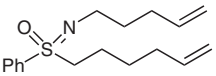
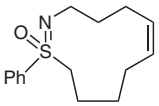
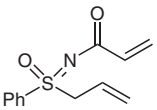
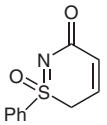
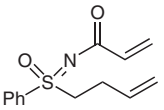
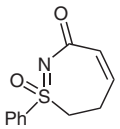
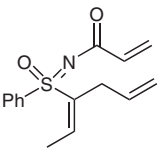
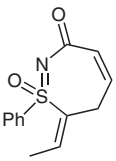
The investigation of the RCM reaction began with a catalyst screening using sulfoximine **22** as test substrate. To our surprise we found that only one (**25**, '2nd generation Grubbs') out of the five tested ruthenium carben complexes **24**–**28** was catalytically active affording 7-membered cyclic sulfoximine **23** in reasonable yield. Thus, with 20 mol% of **25**, product **23** was obtained in 65% yield. Gratifyingly, the catalyst loading could be reduced to 10 and even 5 mol% affording sulfoximine **23** in 97 and 85% yield, respectively (Scheme 3). Toluene was the solvent of choice, and under reflux full conversion was achieved within 15 minutes. Use of dichloromethane proved to be unsuitable for this catalysis.

Next, the substrate scope was evaluated. To our delight a variety of cyclic sulfoximines could be prepared by the RCM reaction (Table 1). The best results were achieved with 20 mol% of **25**, which generally led to sulfoximine-



Scheme 3 RCM reaction of **22** to give heterocyclic sulfoximine **23** catalyzed by ruthenium carben complexes **24**–**28**

Table 1 RCM of Unsaturated Sulfoximines Catalyzed by **25**

Entry	Starting Material	Product	Yield (%)[a]
1	 **22**	 **23**	97
2	 **15**	 **29**	75
3	 **7**	 **30**	90
4	 **8**	 **31**	57
5	 **9**	 **32**	48
6	 **10**	 **33**	61
7	 **19**	 **34**	95
8	 **20**	 **35**	86
9	 **21**	 **36**	75

[a] The yield refers to the amount of heterocycle obtained after column chromatography. At that stage, the product still contained traces of the metal catalyst, which could not be removed in this manner.

based heterocycles in good to excellent yields. For example, 8- and 11-membered cyclic products **30** and **33** were obtained in 90 and 61% yield, respectively (Table 1, entries 3 and 6). Also, acryloated sulfoximines **19**–**21** reacted well affording the corresponding cyclic products **34**–**36** in high yields (entries 7–9).

As indicated by the ^{13}C NMR spectra, the 9- to 11-membered ring products **31**–**33** were obtained as *E*/*Z* mixtures, and we are currently exploring the selective formation of those compounds as well as derivatives thereof.

In summary, we investigated the RCM reactions of doubly unsaturated sulfoximines and prepared novel heterocycles in this manner. Ruthenium-benzylidene complex **25** proved to be the most active catalyst for the ring closure providing cyclic sulfoximines in good to excellent yields.

All reactions were carried out under argon using standard Schlenk techniques. Toluene was distilled over sodium/benzophenone and stored under argon. NH-Sulfoximines were prepared according to the literature. All other starting materials were obtained from commercial suppliers and used without further purification. NMR spectra were recorded in $CDCl_3$ with TMS as internal standard on a Varian Gemini 300 spectrometer (300 and 75 MHz for ^1H and ^{13}C NMR spectra, respectively) or an Innova 400 spectrometer (400 and 100 MHz for ^1H and ^{13}C NMR spectra, respectively), FTIR spectra on a Perkin-Elmer PE-1760 FT apparatus and MS spectra on a Varian MAT 212 using chemical ionization technique.

Compound **22** was obtained by allylation of **18** with allyl bromide (**5a**).

_N_-Allyl-_S_-but-3-enyl-_S_-phenylsulfoximine (22)
Yield: 80%.

IR ($CHCl_3$): 3075, 1642, 1444, 1412, 1266, 1222, 1139, 1086, 997, 917, 747, 692 cm^{-1}.

^1H NMR: δ = 7.92–7.88 (m, 2 H_{arom}), 7.67–7.55 (m, 3 H_{arom}), 6.01–5.90 (m, 1 H), 5.77–5.66 (m, 1 H), 5.32–5.25 (md, 1 H, *J* = 16.8 Hz), 5.10–4.98 (m, 3 H), 3.70–3.62 (md, 1 H, *J* = 15.4 Hz), 3.54–3.46 (md, 1 H, *J* = 15.4 Hz), 3.36–3.18 (m, 2 H), 2.62–2.49 (m, 1 H), 2.47–2.35 (m, 1 H).

^{13}C NMR: δ = 137.9, 137.8, 134.0, 132.9, 129.4, 129.3, 116.9, 114.5, 55.8, 46.1, 27.1.

MS: *m*/*z* = 234.2 (M^+, 3%).

Anal. Calcd for $C_{13}H_{17}NOS$: C, 66.34; H, 7.28; N, 5.95. Found: C, 66.11; H, 7.70; N, 5.61.

Ring-Closing Metathesis Reactions; 1-Phenyl-1λ⁴-[1,2]thiazepine-1-oxide (23); Typical Procedure
To refluxing toluene (200 mL) was rapidly added the doubly unsaturated sulfoximine **22** (0.1 mmol), followed by the ruthenium catalyst **25** (5 mol%). After 15 min at reflux, the mixture was cooled to r.t. and concentrated in vacuo. Column chromatography (silica gel, pentane–EtOAc, 1:1) afforded the **23** as a brown oil. NMR spectroscopy indicated the presence of traces of remaining catalyst, which could not be removed by chromatographical means; yield: 97%. Commonly, 20 mol% of the catalyst were used. In this case, **23** was obtained in 65% yield.

IR ($CHCl_3$): 3016, 2962, 2927, 1264, 1219, 1145, 1122, 760 cm^{-1}.

^1H NMR: δ = 8.06–8.03 (m, 2 H_{arom}), 7.58–7.46 (m, 3 H_{arom}), 5.83–5.77 (m, 1 H), 5.732–5.66 (m, 1 H), 4.31–4.23 (md, 1 H, *J* = 17.9 Hz), 3.81 (ddd, 1 H, *J* = 17.9, 5.8, 1.9 Hz), 3.70 (ddd, 1 H, *J* = 14.3, 11.2, 2.2 Hz), 3.27 (ddd, 1 H, *J* = 14.3, 7.7, 2.2 Hz), 2.54–2.43 (m, 1 H), 2.37–2.27 (m, 1 H).

^{13}C NMR: δ = 137.6, 132.3, 131.9, 127.9, 127.2, 126.2, 57.1, 41.5, 21.4.

MS: *m*/*z* (%) = 207.9 ($[M + H]^+$, 4), 206.8 ($[M]^+$, 2).

HRMS (EI): *m*/*z* cald for $C_{11}H_{13}NOS$: 207.0718; found: 207.0718.

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