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On the mechanism of a double ring-closing metathesis reaction

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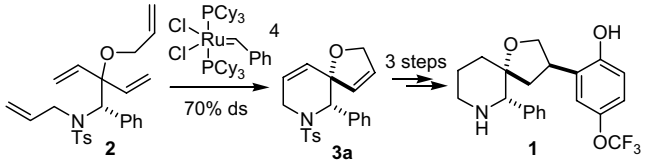
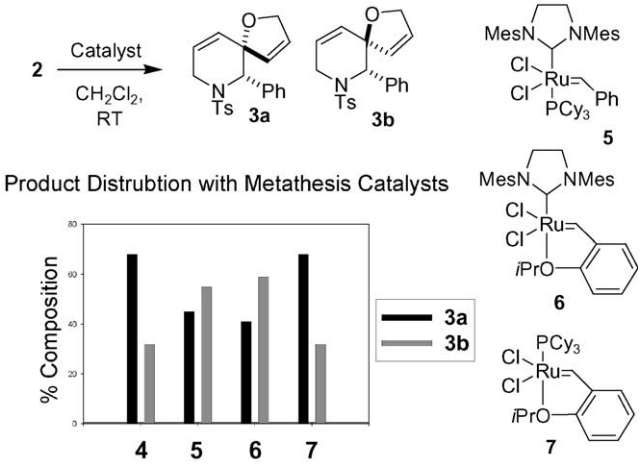
Abstract—A detailed study of the steps involved in the double ring-closing metathesis reaction of **2** to **3** has been carried out. Both the selectivity and mechanism were affected by choice of catalyst.

We have recently published the synthesis of the NK1 receptor antagonist **1**, which proceeds via a diastereoselective double ring-closing metathesis (RCM) reaction of tetraene **2** to afford **3a** as the major product in 70% selectivity (Scheme 1).[1,2] As part of our ongoing interest in these double RCM reactions a detailed study of the ring-closing step with a range of commercially available metathesis catalysts has been carried out.[3] In this letter the results of these studies are presented along with a model for when the choice of catalyst can influence the outcome of a diastereoselective RCM reaction.[4]

Molecular modeling studies on the diastereomeric compounds **3a** and **3b** indicated that **3a** should be preferred based on thermodynamic considerations.[1a] Although a modest preference for this compound was seen when employing catalyst **4**[5] the ratio was less than anticipated, and the non-equilibration of either isolated product isomer under the reaction conditions led us to propose that the reaction proceeded under kinetic control. In order to bias the stereochemical outcome in favor of the desired isomer other catalysts were screened. It was thought that use of the more reactive second generation catalyst **5**[6] would allow for thermodynamic control. However, the reaction of **2** with both this catalyst and with the Grubbs–Hoveyda catalyst **6**[7] proceeded in favor of the *other isomer* **3b**, albeit with low selectivity (Scheme 2). Reaction with catalyst **7**[8] gave a comparable result to that obtained with **4**. As with the first generation catalyst no equilibration of either isomer was seen under the reaction conditions and we again propose that this outcome is the result of a kinetic cyclization. Based on the different stereochemical outcome it seemed likely that a different mechanism would be operating and we sought to explore these differences and show the scope and limitations of trying to influence reaction outcome based on catalyst selection.



Scheme 1.



Scheme 2.

Keywords: Ring-closing metathesis; Spirocycles; Intermediates.
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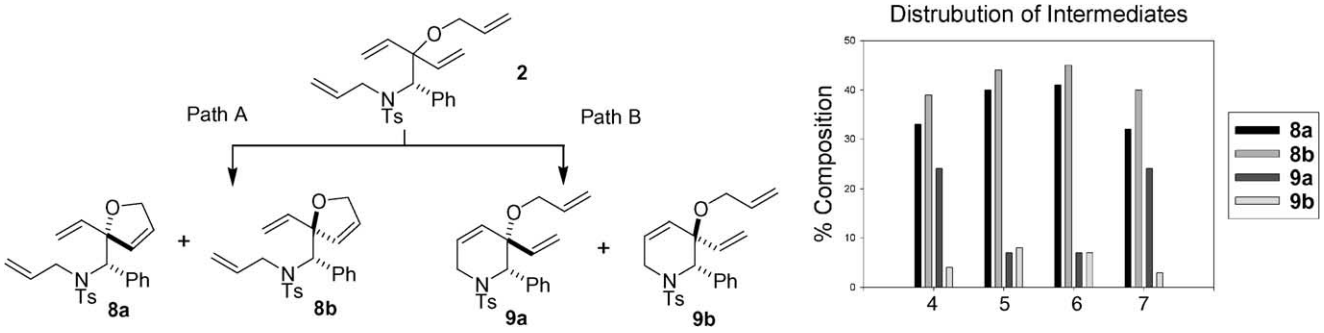


Scheme 3.

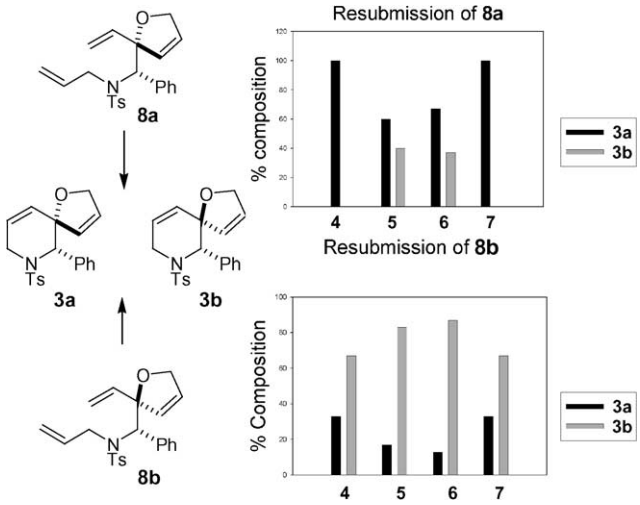
The double RCM reaction could proceed through the intermediacy of four monocyclic intermediates **8a**, **8b**, **9a**, and **9b**, resulting from the initial formation of a five membered ring (path A to give **8a** and **8b**) or a six membered ring (path B to give **9a** and **9b**) (Scheme 3). Under the reaction conditions these monocycles would in turn be expected to react further to afford the observed spirocyclic products. To explain the selectivity observed in these reactions, both the relative ratios and the subsequent reactions of these intermediates were of interest.

The reaction of alkene **2** with the 'first generation' type catalysts **4** and **7** gave no selectivity for formation of **8a** over **8b** but led to a high preference for the formation of **9a** over **9b** (ca. 90:10 ratio).[9] Path A, leading to formation of **8**, was seen to be the major pathway accounting for over 70% of the reaction intermediates.[10] The use of the 'second generation' type catalysts **5** and **6** also favored path A over path B with five membered rings accounting for 90% of intermediates.[11] As with the previous catalysts, no selectivity for formation of **8a** over **8b** was seen, however in this case **9a** and **9b** were also formed in equimolar amounts. Hence, for these cyclizations the two diastereomeric five membered rings are formed in the same relative ratio independent of catalyst, but different relative ratios of six membered rings were obtained when switching from first to second generation catalysts.[12] The rate determining step for these reactions is expected to be the intermolecular reaction of the catalyst with one of the allyl groups, with the subsequent intramolecular cyclization being rapid.[13] As such, the dominance of path A is due to a preferential interaction of catalyst with the oxygen bound allyl group, rather than a kinetic preference for formation of five membered rings per se. However, the lack of selectivity or catalyst dependence in this step (as opposed to that seen operating in path B) may be due to the subsequent intramolecular cyclization being particularly rapid for formation of five membered rings.

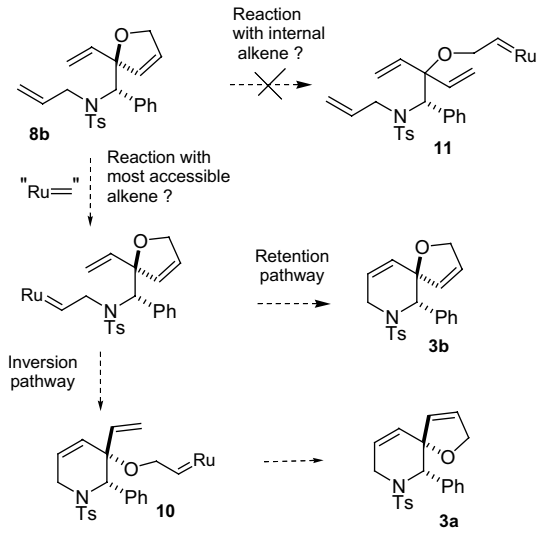
For all catalysts the relative ratios of the four intermediates to each other remained essentially constant throughout the course of the reaction, indicating similar rates of further conversion for these isomers. However, the observed ratios of **8a** and **9a** to **8b** and **9b** at this stage of the reaction does not account for the final product distribution, leading to the proposal that some scrambling of the initial stereochemistry must result during the second ring closing step.

Conversion of the isolated intermediates to products was then studied by resubjection of the purified isomers to reaction conditions. The reaction of compounds **8a** and **8b** with all four catalysts gave different results depending on the choice of catalyst. Reaction of **8a** with 'first generation' catalysts gave **3a** as the sole product (Scheme 4). However use of the second generation catalysts with **8a** gave 36% of the unexpected **3b** along with **3a** indicating that a competing pathway was operating as well as direct cyclization. In contrast, for **8b** the inversion pathway was more significant with first generation catalysts (30% of **3a** formed), but only accounted for 13% of the mixture with the second generation catalysts. While the exact factors underlying the partitioning of pathways for this particular step are not obvious, it can be concluded that for formation of these six membered rings significantly different results are obtained with first versus second generation catalysts.

We propose that the inversion pathway occurs via a ring closing/intramolecular ring opening mechanism (Scheme 5). For example, initial reaction of the catalyst with the free allyl group in **8b** could be followed by direct cyclization to give **3b** (retention of stereochemistry) or ring opening in an intramolecular sense to give **10** (inversion of stereochemistry) followed by rapid ring closing to give **3a**. Initial ring opening of the hindered internal olefin in the five membered ring seemed unlikely and com-



Scheme 4.

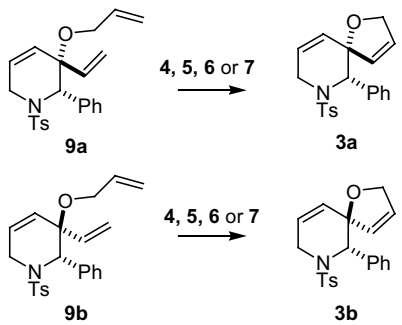


Scheme 5.

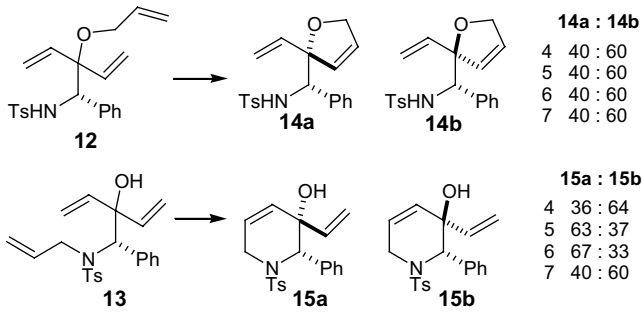
pound **11** would be expected to lead to other reaction intermediates, which were not observed during these reactions.

The formation of products from **9a** and **9b** was also studied. With all four catalysts **9a** afforded solely **3a**, and **9b** afforded solely **3b**, no equilibration or inversion was seen, indicating that the choice of catalyst does not affect formation of these five membered rings (Scheme 6). Notably the relative ratios of the four intermediates combined with a knowledge of how each compound is then converted to one or both products accounts for the stereochemical outcome of each of the reactions.

The related cyclization of compounds **12** and **13** have also been studied and results are in line with expectation based on the intermediates obtained from **2** (Scheme 7). The reaction of **12**—to form a five membered ring—was independent of catalyst; in all cases a near non-selective cyclization to give a ca. 40:60 mixture of **14a** and **14b** was obtained.[14] However reaction of **13** to from the six membered rings **15a** and **15b** did depend on the choice of catalyst. Although the reactions showed only modest selectivity, a different major product was seen when switching from first to second generation catalysts.



Scheme 6.



Scheme 7.

The major isomer from reactions with the first generation catalysts had the opposite chirality at the newly formed stereocenter to that obtained when the hydroxyl group was protected as the allyl ether as in **2**.

In conclusion, a detailed study of different RCM reactions in the phenyl glycine derived system has been carried out. In these substrates the formation of five membered rings was shown to be independent of the choice of catalyst. Where this cyclization defined a stereocenter (i.e., **2** to **8a** and **8b**, and **12** to **14a** and **14b**) reactions proceed with low selectivity. In the cases where the stereocenter has been previously set (i.e cyclization of **9a** and **9b**) no equilibration was seen and rapid formation of a single product was observed. In contrast, the formation of six membered rings can be influenced by catalyst choice, with different selectivities for formation of **9a** and **15a** being achieved with first and second generation catalysts. Where the stereocenter has previously been set as in **8a** and **8b** inversion mechanisms can operate during the formation of the six membered rings, with different product ratios resulting from different catalysts. These results can probably be attributed to the kinetic ease of formation of five membered rings, in these fast cyclizations selectivity is less likely and inversion does not play a role. The formation of six membered rings is expected to be slower allowing for some selectivity in cyclizations or for inversion mechanisms to complete. A knowledge of the intermediates formed during the double RCM reactions along with their further reactions accounts for the stereochemical outcome with all catalysts studied to date.

Acknowledgements

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9. Reactions were run in 0.1 M dichloromethane at room temperature using 5 mol % catalyst, additional catalyst was sometimes added.
10. A different ratio of intermediates was observed when the reaction was carried out using the original solvent of chloroform.
11. Compounds **8a**, **8b**, and **9a** have been previously characterized, see Ref. 1a. Key data for **9b**: Rotation α_D −148 (*c* 1.6, $CHCl_3$): ^1H (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.1 Hz, 2H), 7.19 (m, 5H), 7.10 (d, J = 8.1 Hz, 2H), 6.20–6.16 (m, 1H), 6.10–6.06 (m, 1H), 5.80 (ddt, J = 15.7, 10.5, 5.3 Hz, 1H), 5.46 (dd, J = 10.8, 17.5 Hz, 1H), 5.30 (s, 1H), 5.23 (dq, J = 17.2, 1.8 Hz, 1H), 5.21 (dd, J = 17.4, 1.0 Hz, 1H), 5.11 (dq, J = 10.4, 1.6 Hz, 1H), 5.08 (dd, J = 10.8, 1.0 Hz, 1H), 4.00 (ddd, J = 18.4, 3.5, 2.5 Hz, 1H), 3.88 (ddt, J = 12.3, 5.2, 1.5 Hz, 1H), 3.84 (ddt, J = 12.3, 5.4, 1.5 Hz, 1H), 3.60 (dt, J = 18.4, 2.3 Hz, 1H), 2.34 (s, 3H): ^{13}C (100.6 MHz, $CDCl_3$) δ 142.7, 138.0, 137.3, 136.8, 135.6, 129.1, 129.0, 128.1, 127.7, 127.6, 126.2, 116.8, 115.6, 75.3, 64.2, 64.1, 41.7, 21.4: LCMS 418.1 (M = Na, 10), 338 (MH+−AllOH, 10), 182 (100): HRMS calcd for $C_{23}H_{26}NO_3S$ (M+H) 396.1633, found 396.1635.
12. In this letter we use the term 'first generation catalyst' to cover those laking the dihydroimidazole ligand, that is, **4** and **7** and 'second generation catalyst' to cover those with the dihydroimidazole ligand, that is, **5** and **6**.
13. (a) Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484; (b) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123.
14. The stereochemical outcome of this reaction was determined by conversion of the mixtures of **14a** and **b**, or **15a** and **b** to the known compounds **8** and **9**.