Z-SELECTIVE ALKENE CROSS- AND RING-CLOSING METATHESIS

Reported by Hyung Min Chi November 28, 2011

INTRODUCTION

Many natural products contain *Z* alkene moieties and the stereochemical identity of these alkenes can significantly impact their respective biological activities.[1] Several synthetic approaches to generate disubstituted *Z* alkenes exist, such as the Wittig reaction, catalytic hydrogenation, and transition metal catalyzed cross-coupling reactions. However, each approach has limitations and drawbacks. As a result, an efficient and general route to selectively generate *Z* alkenes would be synthetically useful.

DEVELOPMENT OF MONOARYLOXIDE-PYRROLIDE (MAP) CATALYST

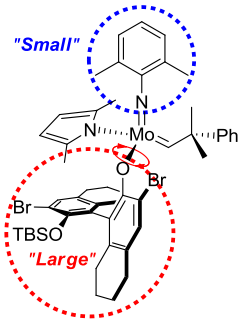

Figure 1. MAP Mo catalyst

There have been a number of preliminary studies preceding the development of the *Z*-selective cross-metathesis. In the past five years, the monoaryloxide-pyrrolide (MAP) molybdenum catalyst (Figure 1) has been developed by Schrock and Hoveyda to achieve enantioselective metathesis.[2] With mechanistic understanding of enantioselective metathesis, they recognized that they could achieve better objective – *Z* selectivity in alkene metathesis reactions. As a result, Z-selective and enantioselective ring-opening/cross-metathesis (ROCM) was developed.[3] Mechanistic studies on the relationship of catalyst structure with high selectivity in *Z* alkene formation proved that the flexibility of the bulky monoaryloxide ligand was critical.[4,5] *Z*-Selective homocoupling was achieved through variation of MAP ligands.[6]

Z-SELECTIVE CROSS-METATHESIS

A major challenge in alkene cross-metathesis is that six distinct products are possible (Figure 2). To overcome this challenge, Grubbs and coworkers have employed an excess of one of the cross-coupling substrates to achieve high efficiency.[7,8] Under this condition, metathesis is highly *E*-selective due to thermodynamic control. Additional limitation about this approach is when a valuable substrate is employed.

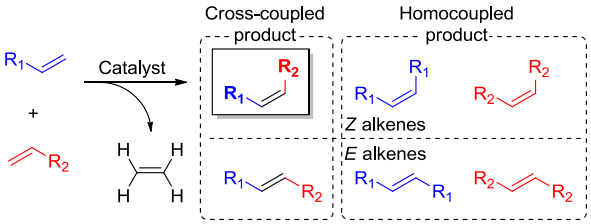

Figure 2. Possible outcomes of a cross-metathesis (CM) and the desired product.

Schrock and Hoveyda demonstrated the first highly *Z*-selective alkene cross-metathesis of aliphatic alkenes with use of an excess of enol ethers or allylic amides.[9] Due to electronic factors, the

homocoupling of enol ether was disfavored.[10] Interestingly, high yields and selectivities with an equal amount of substrates were observed for reactions performed under reduced pressure to remove ethylene as it was formed (Figure 3). Removal of ethylene was critical because it was not only detrimental to the rate of cross-metathesis but its presence was the main contributor to alkene isomerization.

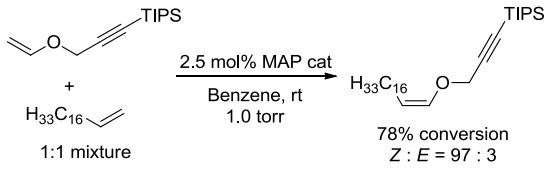

Figure 3. *Z*-Selective CM of C18 (plasm)-16:0 (PC) intermediate.

Z-SELECTIVE MACROCYCLIC RING-CLOSING METATHESIS

Another major advance in this field is the development of *Z*-selective macrocyclic ring-closing metathesis.[11] While formation of *Z* alkenes is exclusive with small or medium sized rings, it is very difficult to generate *Z* alkenes for larger rings due to a much diminished thermodynamic preference. Because ring-closure is intramolecular, the employment of excess amount of one substrate could not be applied toward increased selectivity. Conventional approaches to the macrocyclic ring-closing metathesis are run at very dilute concentrations. However, by employing the attenuated derivative of W-based MAP catalyst, *Z*-selective 15- and 16-membered ring closures of up to 0.1 M solutions were accomplished (Figure 4).

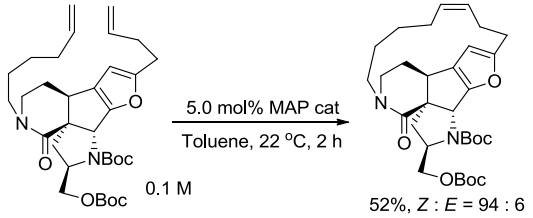

Figure 4. *Z*-Selective catalytic RCM of nakadomarin A intermediate

CONCLUSION

Recent developments from Schrock and Hoveyda's collaboration provide a unique solution to the Holy Grail in the field of alkene metathesis. These metathesis reactions were possible with the development of MAP catalysts. Mechanistic analysis of the catalyst-substrate transition state structure was vital toward the development of *Z* alkene selective reaction systems. Because a large number of biologically active compounds have macrocyclic *Z* alkene or moieties that can be obtained from stereoselective transformation of a *Z* alkene, the ability to selectively form *Z* alkene is sure to be a powerful tool to synthetic chemists.

REFERENCES

(1) Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086.
(2) Malcolson, S. J.; Meek, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933.
(3) Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3844.
(4) Flook, M. M.; Jiang, A. J.; Schrock, R. R.; Muller, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7962.
(5) Solans-Monfort, X.; Copéret, C.; Eisenstein, O. *J. Am. Chem. Soc.* **2010**, *132*, 7750.
(6) Jiang, A. J.; Zhao, Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 11630.
(7) Choi, T.-L.; Lee, C. W.; Chatterjee, A. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 10417.
(8) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
(9) Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461.
(10) Grubbs, R. H., Ed. *Handbook of Metathesis*; Wiley-VCH: Weinheim, 2003; Vol. 1, 246-295.
(11) Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88.