**2. Olefin Metathesis in Organic Synthesis (in collaboration with A. H. Hoveyda)**

The greatest improvement in the synthesis of C=C bonds in the last few years has been the ability to prepare disubstituted olefins that have the *Z* configuration from two terminal olefins employing a MAP (MonoAryloxide Pyrrolide) catalysts. The intermediate metallacyclobutane complexes in these reactions contain the phenoxide and imido ligands in apical positions. The terphenoxide ligand forces all substituents on the metallacyclobutane rings to lie on one side of the ring, thereby ensuring formation of *Z* olefins in metathesis reactions. These results are part of the continuing search for chemoselectivity in various olefin metathesis reactions (terminal, disubstituted *cis*- and *trans*-internal, 1,1-disubstituted, etc.). Some representative Mo- and W-based MAP catalysts are shown in Scheme 1.





Because *Z* olefins can be made selectively, they also can be consumed selectively. For example, we demonstrated that the *Z* isomer of an easily accessible *E/Z* mixture can be destroyed selectively in the presence of ethylene and the *E* alkene thereby isolated readily in high yield and purity. Therefore, it is now possible to prepare *E* olefins indirectly through selective ethenolysis of the *Z* olefin (usually ~20%) in an *E/Z* mixture.

Both electron-withdrawing imido ligands and tungsten complexes have been most desirable in several applications recently. We have found that tungsten NArR alkylidene complexes can be prepared that contain the electron-withdrawing ArR groups 2,4,6-X3C6H2 (ArX3, X = Cl, Br), 2,6-Cl2-4-CF3C6H2 (ArCl2CF3), and 3,5-(CF3)2C6H3 (Ar(CF3)2). Reported complexes include W(NArR)2Cl2(dme) (dme = 1,2-dimethoxyethane), W(NArR)2(CH2CMe3)2, W(NArR)(CHCMe3)(OTf)2(dme), and W(NArR)(CHCMe3)(ODBMP)2 (DBMP= 4-Me-2,6-(CHPh2)C6H2. The bisimido intermediates were prepared in good yields through addition of RNHTMS to WCl6, a route which avoids the potentially problematic replacement of W=O with W=NR constructs. Addition of two neopentyl groups followed by addition of triflic acid yields the W(NArR)(CH2CMe3)(OTf)2(1,2-dimethoxyethane) starting materials.



MonoAlkoxide Pyrrolide (MAP) complexes that contain a 2,6-dimesitylphenylimido (NAr\*) ligand react with ethylene to yield unsubstituted metallacyclobutanes that are in equilibrium with methylidene complexes, W(NAr\*)(CH2)(Me2Pyr)(OR) (R = *t*-Bu, OCMe(CF3)2, SiPh3, or 2,6-Me2C6H3). W(NAr\*)(CH2)(Me2Pyr)(OR) (R = SiPh3 or 2,6-dimethylphenoxide) complexes react readily with one equivalent of DCMNBD (2,3-dicarbomethoxynorbornadiene) to give only a monoinsertion product. The facile reaction between the monoinsertion product and ethylene then allows these complexes to be catalyts for the ring-opening cross-metathesis (ethenolysis) of DCMNBD and DCMNBE (2,3-dicarbomethoxynorbornene) with minimal formation of polymer.



Structure of W(NAr\*)(CH2)(Me2Pyr)(OSiPh3)

A reliable, practical and general approach for the efficient and highly stereoselective synthesis of macrocyclic alkenes by catalytic RCM have been reported that deliver up to 97% of the Z isomer owing to control induced by a tungsten-based alkylidene. Utility is demonstrated through the stereoselective preparation of epothilone C and nakadomarin A, the previously reported syntheses of which have been marred by late-stage, nonselective RCM. The tungsten alkylidene can be manipulated in air, delivering the products in useful yields with high stereoselectivity. As a result of efficient RCM and re-incorporation of side products into the catalytic cycle with minimal alkene isomerization, desired cyclizations proceed in preference to alternative pathways, even under relatively high substrate concentration.



A concise diastereo- and enantioselective route that furnishes the anti-proliferative natural product neopeltolide has been completed. Catalytic transformations are employed to address every stereochemical issue. Among them are an enantioselective ring-opening/cross-metathesis promoted by a Mo monopyrrolide aryloxide (MAP) complex and a macrocyclic ring-closing metathesis that affords a trisubstituted alkene catalyzed by a Mo bis-aryloxide species. Furthermore, *Z*-selective cross-metathesis reactions were employed in stereoselective synthesis of the acyclic dienyl moiety of the target molecule. **(**M. Yu, R. R. Schrock, A. H. Hoveyda, *Angew. Chem., Int. Ed.* **2014**, in press.)

A convergent diastereo- and enantioselective total synthesis of anticancer and antifungal macrocyclic natural product disorazole C1 has been completed. The central feature of the route is the application of catalytic *Z*-selective cross-metathesis (CM). Specifically, we have been able to show that catalyst-controlled stereoselective CM can be performed to afford structurally complex *Z* alkenyl–B(pin) (pin = pinacolato) as well as *Z* alkenyl iodide compounds reliably, efficiently, and with high selectivity. The resulting intermediates are then joined in a single-step operation through catalytic inter- and intramolecular cross-coupling to furnish the desired 30-membered ring macrocycle containing the critical (*Z*,*Z,E*)-triene moieties. (A. W. H. Speed, T. J. Mann, R. V. O’Brien, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2014**, in press.)



The following selected and recent papers are relevant to this area of chemistry (see the complete publication list for others): 525, 528, 532, 533, 534, 535, 536, 537, 538, 539, 542, 546, 547, 559, 560, 562