Ring-Closing Metathesis

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Molybdenum-Based Complexes with Two Aryloxides and a Pentafluoroimido Ligand: Catalysts for Efficient *Z*-Selective Synthesis of a Macrocyclic Trisubstituted Alkene by Ring-Closing Metathesis**

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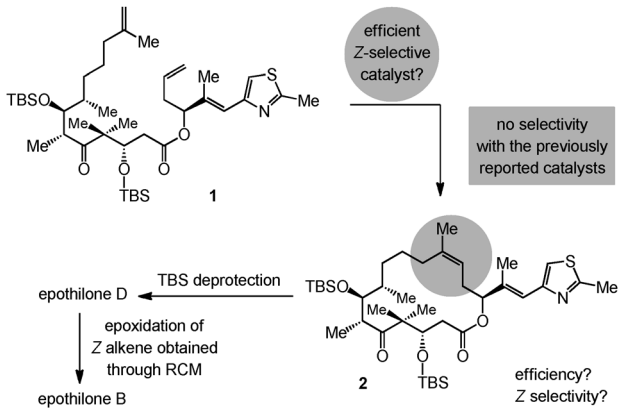
Macrocyclic ring-closing metathesis (RCM) has had an enormous impact on organic chemistry;[1,2] such influence has been in spite of the absence of reliable stereoselective catalyst-controlled protocols. High stereoselectivity is crucial to applications in complex molecule synthesis: a nondiscriminating RCM, often performed late stage in a multi-step route, can be costly (overall yield reduction by 50%). We have reported that with molybdenum- or tungsten-based monoaryloxide pyrrolide (MAP) complexes, macrocyclic disubstituted *Z* olefins can be obtained efficiently and stereoselectively.[3] Another problem, more challenging and strategically distinct, relates to the synthesis of macrocyclic trisubstituted alkenes;[2] rerouting through diyne RCM[4]/alkyne functionalization is not an attractive option in such instances.

Little or no stereoselectivity has hitherto been observed in most catalytic RCM reactions that produce a trisubstituted olefin within a large ring.[5] On occasions when there is stereochemical control, the isomer generated might be the preferred form[6] or, frequently, one that is undesired,[7] depending on the energy differential between the possible isomers (substrate control). There are numerous challenges to be overcome in designing an olefin metathesis catalyst that stereoselectively delivers trisubstituted macrocyclic alkenes. First, the catalyst must efficiently and stereoselectively promote olefin formation, while avoiding adventitious isomerization that can accompany reactions of slower reacting alkene substrates.[8] Second, RCM needs to occur in preference to the intermolecular homocoupling of two terminal olefins; the catalyst must also be sufficiently active and long-lived to be able to reverse the undesired side reaction, to regenerate the monomeric species and the cyclic trisubstituted alkene.[9] In contrast to reactions that yield disubstituted olefins,[3] however, post-RCM isomerization is generally not a significant complication and loss of kinetic selectivity is usually less likely.

Herein, we introduce a new class of catalysts for efficient and *Z*-selective formation of trisubstituted macrocyclic olefins, developed in the context of the synthesis of a precursor to anticancer natural products epothilones B and D (Scheme 1).[10] We document the unexpected finding that



Scheme 1. Catalytic RCM of triene **1** to afford macrocyclic lactone **2**, a key intermediate in the total synthesis of anticancer agents epothilones D and B. TBS = *tert*-butyl(dimethyl)silyl.

Mo complexes bearing two sizeable fluoro-substituted aryloxides and a pentafluorophenylimido group deliver the desired olefin in 73–82% yield and 91% *Z* selectivity (7.5–10 mol% of catalyst, 22 °C, 2.5–6.0 h). Mo complexes are prepared by reaction of bispyrrolides[11] with two equivalents of an appropriate aryl alcohol. A rationale for the high activity of the sterically demanding catalysts is presented.

The difficulty of designing efficient olefin metathesis catalysts that afford highly substituted macrocyclic alkenes with high *Z* selectivity is evident from the complexes shown in Scheme 2. Unlike the reactions leading to disubstituted olefins where H atoms are oriented towards the sizeable aryloxide,[12] in the transformations leading to a trisubstituted olefin, an alkyl unit must point in the direction of the large ligand. In the case of **1**, there exists a relatively small size difference between the methyl group and the aliphatic side chain of the same alkene,[13] which has branching in the form of a methyl group at a distal (δ) carbon.

We synthesized precursor **1** by a 17-step sequence based on previous disclosures.[14] Compound **2** was selected as the

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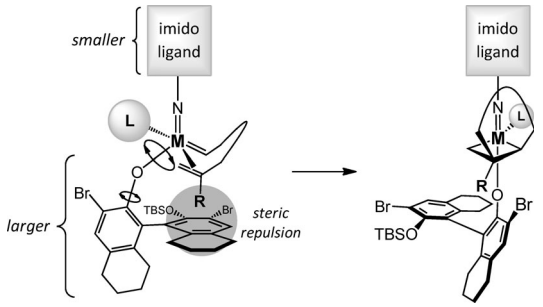
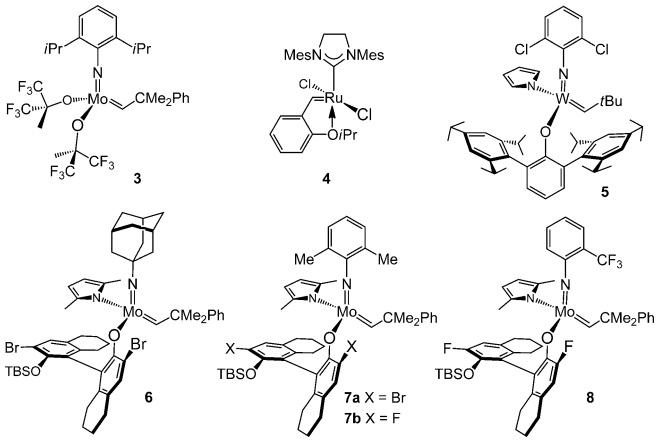


Scheme 2. The challenge of achieving high efficiency and stereoselectivity in a macrocyclic RCM reaction that affords a trisubstituted alkene. In such cases, an alkyl substituent must be oriented towards the larger aryloxide ligand, rendering high efficiency and *Z* selectivity more challenging. L = ligand, R = alkyl group.

target because catalytic *Z*-selective RCM of the corresponding disubstituted alkenes had been investigated;[3] the present study would therefore allow comparative evaluation of the influence of the additional alkene substituent on the catalytic process. To ensure sufficient conversion into **2**, 20 mol% loading was employed in the initial screening along with a reaction time of 24 h. We confirmed that Mo bisalkoxide **3** and Ru carbene **4** (Table 1, entries 1–2) deliver minimal

Table 1: Initial evaluation of various complexes for conversion of **1** into **2**.[a]

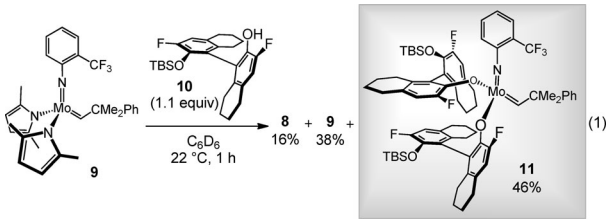


Entry	Complex	*T* [°C]	*t* [h]	Conv. to **2** [%][b]	Homocoupled Product [%][b]	*Z*/*E*[b]
1	**3**	22	24	81	≤10	45:55
2	**4**	50	48	59	≤10	43:57
3	**5**	80	24	<2	<2	n.a.
4	**6**	22	24	<10	≤10	n.d.
5	**6**	50	24	17	18	75:25
6	**7a**	22	24	<10	≤10	n.d.
7	**7a**	50	24	30	≤5	68:32
8	**7b**	22	24	60	≤5	61:39
9	**8**	22	8	73	11	74:26

[a] Samples of **6**–**8** were prepared and used in situ (therefore they might contain other complexes). Reactions were performed with 20 mol% of the complex in C_6H_6 (1.0 mM) under N_2 atm. [b] Determined by analysis of 500 MHz ^{1}H NMR spectra of unpurified mixtures and refers to consumption of the substrate (±2%). See the Supporting Information for details. Mes = mesityl, n.a. = not applicable, n.d. = not determined.

selectivity, favoring the *E* isomer, with the latter complex being less effective (59% conv., 50°C, 48 h).[15] None of the macrocycle is formed in the presence of the less active W-based alkylidene **5** (Table 1, entry 3),[3b] which is effective in the formation of the corresponding *Z* disubstituted macrocyclic alkenes.[3] There is low conversion into **2** with Mo-based MAP complexes **6** and **7a** at 22 or 50°C (<10–30% conv.; Table 1, entries 4–7); RCM with **6** at a higher temperature leads to 17% conversion into a 75:25 mixture (*Z*)-**2**/(*E*)-**2** along with nearly equal amounts of the homocoupled product (Table 1, entry 5). We were heartened by the observation that dimethylphenylimido complex **7a** delivers 30% conversion at 50°C, likely as a consequence of its relative stability (Table 1, entry 7, versus adamantylimido **6**, which posesses a more exposed Mo center, in entry 5), and found the increase in conversion with fluoro-substituted aryloxide complex **7b** intriguing (60% conv. in 24 h at 22°C; Table 1, entry 8). Based on the postulate that electron-withdrawing aryloxy ligands improve RCM efficiency, we prepared and evaluated the performance of *o*-trifluoromethylphenylimido monopyrrolide **8** (Table 1, entry 9): 73% conversion into **2** was observed within eight hours and *Z* selectivity improved to 74% (versus 61:39 *Z*/*E* with **7b** in entry 8 in Table 1).

At this point, we considered the fact that reactions of bispyrrolide alkylidenes with a fluoro-substituted (versus chloro- or bromo-) aryl alcohol generate significant amounts of the corresponding bisaryloxide complex. For example, treatment of **9** with 1.1 equivalents of fluorinated carbinol **10**, as shown in Equation (1), leads to the formation of only 16%



(1)

of monopyrrolide **8** along with 46% of bisaryloxide **11** (38% of **9** remains unreacted). The relatively efficient formation of the bisaryloxide complex is likely because the smaller size of the halide substituent and the higher acidity of the aryl alcohol facilitates protonation of a second pyrrolide ligand (e.g., <5% bisaryloxide with the Br-substituted alcohol).[16] Based on previous observations regarding the minimal efficiency exhibited by Mo bisaryloxide alkylidenes bearing a 2,6-dialkylphenylimido[17] or adamantylimido ligand,[16] we presumed that such lack of reactivity extends to all complexes regardless of the imido group; therefore, we initially assumed that the observed reactivity shown in entry 9 of Table 1, is largely derived from the minor amount of the MAP species (**8**).

To confirm the aforementioned supposition, we prepared pure **11** by subjecting **9**[18] to two equivalents of **10** (1 h, 22°C; >95% conv. to **11**; <2% byproduct formation), and probed its ability to facilitate the formation of **2**. To our surprise, we discovered that the majority—if not all—of the reactivity

generated by the mixture resulting from treatment of bispyrrolide **9** with alcohol **10** arises from the corresponding bisaryloxide complex (i.e. **11**). In the presence of pure **11** (entry 1, Table 2), there is 84% conversion into **2** in seven hours with 77:23 *Z*/*E* selectivity (versus 73% conv. in 8 h and 74:26 *Z*/*E* under the conditions in entry 9 of Table 1).

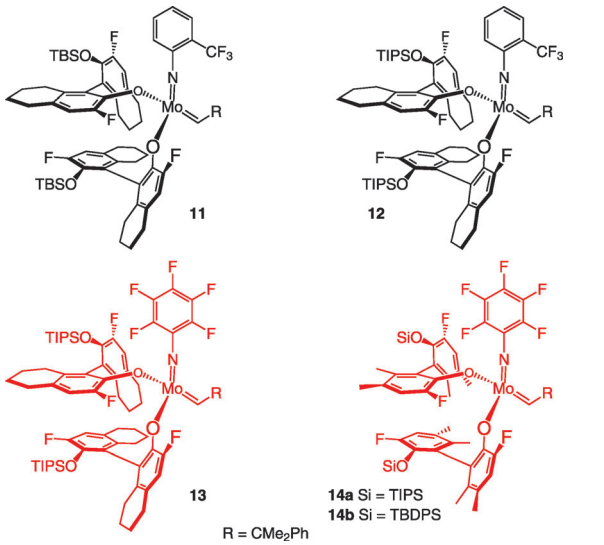
With the source of high reactivity elucidated, we set out to improve efficiency and stereoselectivity through study of various bisaryloxide alkylidene complexes (Table 2, entries 2–8). As noted above (see Scheme 2), a significant size difference between the aryloxide and imido ligands should lead to high *Z* selectivity. We therefore synthesized **12**, which bears large silyl units (Table 2, entry 2); such modification led to a slight increase in stereoselectivity and a less efficient cyclization (61% conv. in 9 h; 81:19 *Z*/*E*). We subsequently installed a pentafluorophenyl imido group[19] (see **13**) since we envisioned that the stronger electron-withdrawing ability of the polyhalogenated moiety could enhance activity (see above) while the smaller halogen units improve the *Z*/*E* ratio (vs. an *ortho*-CF_3 unit in **11**–**12**). Indeed, as shown in entry 3 of Table 2, the efficiency and selectivity furnished by **13** are higher than that delivered by *o*-trifluoromethylphenylimido alkylidene complex **12** (84% conv. in 8 h and 86% *Z* versus 61% conv. in 9 h and 81% *Z*, respectively). We subsequently investigated a number of bis(biphenoxy) derivatives, based on the hypothesis that the smaller aryloxide ligands might allow for improved activity without a significant drop in stereoselectivity. With 20 mol% of bisphenoxide complex **14a**, 92% of **1** is converted into cyclic alkene **2** within five hours to produce a 85:15 *Z*/*E* mixture (Table 2, entry 4). When 10 mol% of **14a** is used, **2** is formed with 87:13 *Z*/*E* selectivity (Table 2, entry 5), but efficiency suffers considerably (46% conv. in 24 h).

At this juncture, we contemplated the possibility that formation of the comparatively stable unsubstituted metallacyclobutane, derived from reaction with ethylene and released as the byproduct, might be diminishing reaction rates. Thus, as illustrated in entries 6 and 7 of Table 2, we established that when the RCM is carried out with 10 mol% of either **14a** or **14b** under 1.0 torr of vacuum, there is 88% and 89% conversion into **2** within only 2.5 h, and the desired macrocycle is isolated in 76% and 82% yield and 90% and 91% *Z* selectivity, respectively. Catalytic RCM is similarly efficient and *Z* selective with 7.5 mol% of **14b** (100 torr); the desired macrocyclic alkene is obtained in 73% yield and 91:9 *Z*:*E* ratio (Table 2; entry 8). To minimize the amount of solvent used, catalytic RCM reactions with **14b** were performed at 2.0 mM concentration (Table 2, entries 7 and 8 vs. 1.0 mM otherwise).

The basis for high *Z* selectivity has already been provided (see Scheme 2); the proposed scenario is congruent with the improved stereodifferentiation furnished by the smaller perfluorophenylimido-bearing complex (versus *o*-trifluoromethylphenyl; Table 2, entries 2 and 3). However, rationalization of the finding that the larger bisaryloxide complexes are more effective than MAP alkylidenes is less straightforward. Since complexes with sterically demanding ligands are unlikely candidates for effective catalysis, particularly for the preparation of more-congested olefins, we surmised that electronic effects must play a role in delivering the surprising reactivity.

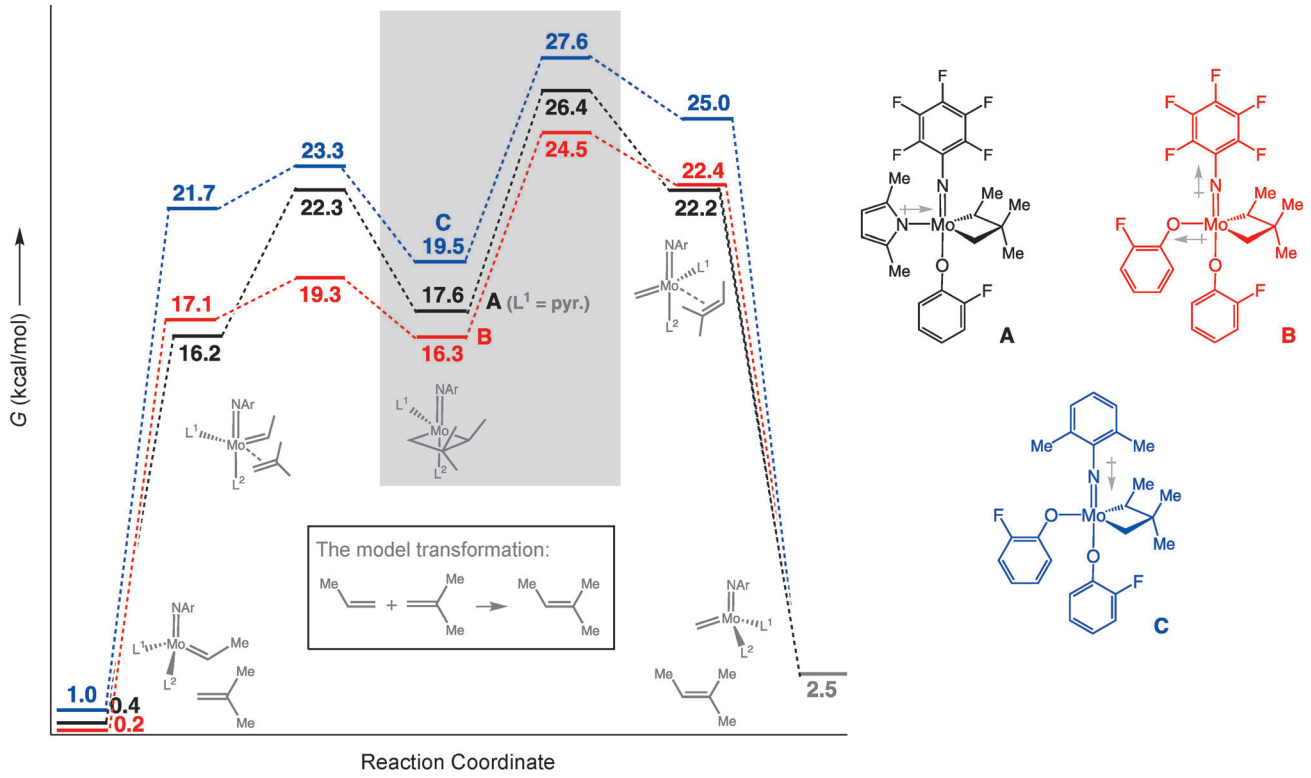
To address the latter reactivity question vis-à-vis the effectiveness of complexes such as **14a** and **14b**, we carried out DFT calculations with three representative systems (Scheme 3).[20] We probed the energetics associated with a model cross-metathesis reaction to afford a trisubstituted olefin via metallacyclobutane **A**, a monopyrrolide containing an *o*-fluorophenoxy ligand, or through the corresponding bisaryloxide metallacyclobutane **B**; both systems carry a pentafluorophenylimido ligand. We also examined the energetics of the same process with an alkylidene complex that furnishes **C**, which is a 2,6-dimethylphenylimido bisaryloxide complex [versus Mo=N(C_6F_5)]. As the results in Scheme 3 indicate,[21] metallacyclobutane **B** is lower in energy (versus **A** or **C**); this translates to a more accessible transition state for the metallacycle's productive cyclo-reversion, which is the highest point in the overall catalytic cycle, and a more facile macrocyclic RCM. The energy values for the route involving **C** support the experimental findings regarding the importance of the more electron-withdrawing and smaller pentafluoro-

Table 2: Evaluation of molybdenum bisaryloxides for conversion of **1** into **2**.[a]



Entry	Complex (mol%)	*T* [°C]	*t* [h]	Pressure	Conv. to **2** [%][b]	Yield [%][c]	*Z*/*E*[b]
1	**11** (20)	22	7	ambient	84	n.d.	77:23
2	**12** (20)	22	9	ambient	61	n.d.	81:19
3	**13** (20)	22	8	ambient	84	n.d.	86:14
4	**14a** (20)	22	5	ambient	92	n.d.	85:15
5	**14a** (10)	22	24	ambient	46	n.d.	87:13
6	**14a** (10)	22	2.5	1.0 torr	89	76	90:10
7	**14b** (10)	22	2.5	1.0 torr	88	82	91:9
8	**14b** (7.5)	22	6.0	100 torr	77	73	91:9

[a] **11**–**14** were prepared and used in situ. Reactions were performed in C_6H_6 (1.0 mM; except for entries 7–8: 2.0 mM) under N_2 atm, unless otherwise noted (vacuum); <10% homocoupled products observed in all cases. [b] Determined by analysis of 500 MHz ^{1}H NMR spectra of unpurified mixtures and refers to consumption of the substrate (±2%). [c] Yield of isolated and purified macrocyclic product (**2**). See the Supporting Information for details. R = CMe_2Ph, TBDPS = *tert*-butyldiphenylsilyl, TIPS = triisopropylsilyl.



Scheme 3. DFT calculations [B3LYP, BP86 (shown), B3PW91, M06] underscore the significance of the energy of the final metallacyclobutane intermediates (shown) and the facility of their cycloreversion to the overall rate of the macrocyclic RCM. See the Supporting Information for details.

phenylimido unit (e.g., versus *o*-trifluoromethylphenylimido). The favorable pathway via **B** might be partly rooted in the lowering of electronic repulsion that arises when the electron-donating alkyl ligands within the metallacyclobutane reside opposite to a more electron-deficient aryloxide (i.e., better dipole–dipole minimization with $L^1 = o\text{-}FC_6H_4O$ versus 2,5-dimethylpyrrolide in **A**).[22] For similar reasons, a metallacyclobutane with apically trans 2,6-dimethylphenylimido and aryloxide groups (**C**) should be higher in energy, thus leading to a less facile RCM, compared to one that carries a pentafluorophenyl unit (**B**). Diminished steric repulsion is crucial to stabilization of the metallacyclobutane and the rate of its turnover-limiting decomposition as well. A pentafluorophenylimido group, while offering electronic stabilization (see above), better accommodates the formation of a trisubstituted metallacyclobutane by the virtue of being smaller than a 2,6-dimethylphenylimido or an *o*-trifluoromethylphenylimido ligand.

The present findings imply that, although Mo-based MAP species promote olefin metathesis more efficiently than complexes containing the comparatively rigid bidentate diolates,[11b] they are less active—but more robust and longer living[23]—than alkylidenes that contain two monodentate alkoxide or aryloxide moieties, especially when an electron-deficient imido group is present. For applications where high reactivity and *Z* selectivity is required and post-RCM isomerization is less of a concern (e.g., synthesis of trisubstituted alkenes), the latter set of complexes should prove to be the superior choice.

Applications to highly stereoselective syntheses of other complex molecule natural products as well as design of additional catalysts are in progress. The origins of catalytic activity and selectivity outlined above will provide a mechanism-based platform for such initiatives.

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[18] Macrocyclic RCM was not observed with 20 mol% of bispyrrolide complex **9** (<2%).

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[20] To avoid costly calculations and substantial uncertainty owing to the size of the Mo bisaryloxides and diene **1**, a simpler cross-metathesis reaction was selected as the model transformation to elucidate the basis of catalyst activity levels. See the Supporting Information for details.

[21] For clarity, only the extrema for the formation and cleavage of the trisubstituted metallacyclobutanes are shown. Calculations indicate that none of the extrema en route to the starting alkylidene complex are outside the energy limits illustrated in Scheme 3; it is thus the largest energy gap shown that constitutes the required energy barrier.

[22] The energies presented for metallacyclobutanes here are higher than those previously calculated, likely because the less substituted metallacycles carrying the smaller methyl-substituted imido and methoxy ligands were examined (cf. ΔG for unsubstituted metallacylobutane related to **B** = ca. $-2.0\ \mathrm{kcal\,mol^{-1}}$); see: A. Poater, X. Solans-Monfort, E. Clot, C. Copéret, O. Eisenstein, *J. Am. Chem. Soc.* **2007**, *129*, 8207. The higher stability of the unsubstituted metallacyclobutanes accounts for the increased efficiency when ethylene is removed under vacuum (cf. entries 5–6, Table 2).

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