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Mo-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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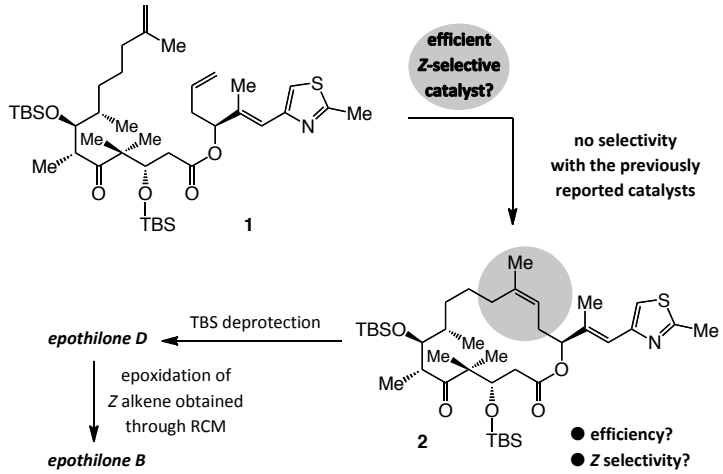
Macrocyclic ring-closing metathesis (RCM) has had an enormous impact on organic chemistry;[i,ii] such influence has been in spite of the absence of reliable stereoselective catalyst-controlled protocols. High stereoselectivity is crucial to applications in complex molecule synthesis: a non-discriminating RCM, often performed late stage in a multi-step route, can be costly (overall yield reduction by ≥50%). We have reported that with Mo- or W-based mono-aryloxide pyrrolide (MAP) complexes, macrocyclic disubstituted *Z* olefins can be obtained efficiently and stereoselectively.[iii] Another problem, more challenging and

strategically distinct, relates to synthesis of macrocyclic *trisubstituted* alkenes;[ii] re-routing through diyne RCM[iv]/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.[v] On occasions when there is stereochemical control, what is generated might be the preferred form[vi] or, frequently, one that is undesired,[vii] 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.[viii] 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, regenerating the monomeric species and the cyclic trisubstituted alkene.[ix] In contrast to reactions that yield disubstituted olefins,[iii] however, post-RCM isomerization is generally a less 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

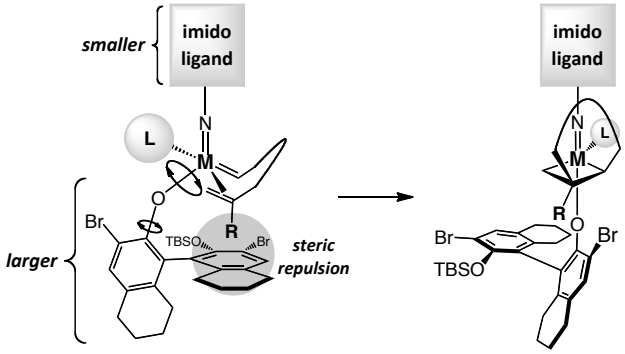
anti-cancer natural products epothilones B and D (Scheme 1).[x] We document the unexpected finding that Mo complexes bearing two sizeable F-substituted aryloxides and a pentafluorophenylimido group deliver the desired olefin in 73–82% yield and 91% *Z* selectivity (7.5–10 mol %, 22 °C, 2.5–6.0 h). Mo complexes are prepared by reaction of a bis-pyrrolides[xi] with two equivalents of an appropriate aryl alcohol. A rationale for the high activity of the sterically demanding catalysts is presented.



Scheme 1. Catalytic RCM of triene **1** to afford macrocyclic lactone **2**, a key intermediate in the total synthesis of anti-cancer agents epothilones D and B.

The difficulty of designing an efficient olefin metathesis catalysts that afford highly substituted macrocyclic alkenes with high *Z* selectivity become evident through complexes in Scheme 2. Unlike the reactions leading to disubstituted olefins where H atoms are oriented towards the sizeable aryloxide,[xii] 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,[xiii] which has branching in the form of a methyl group at a distal (δ) carbon.



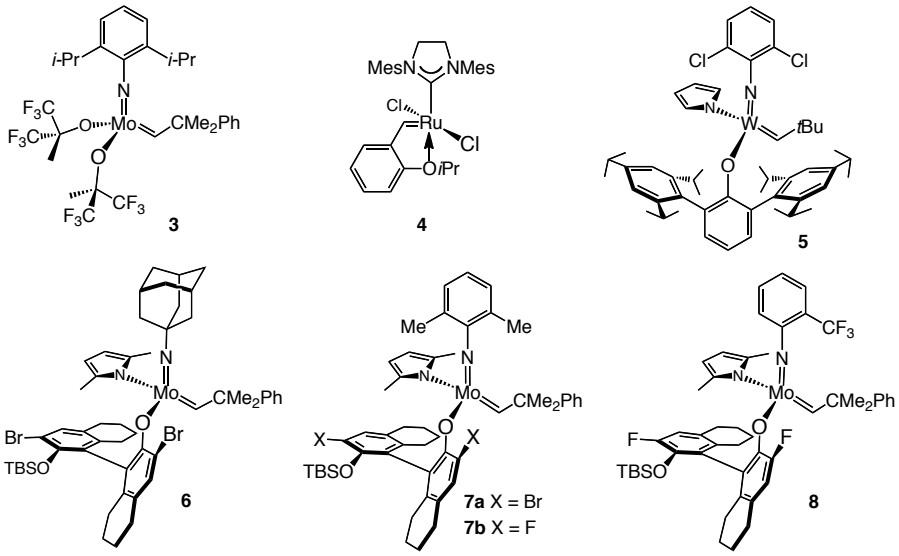
An alkyl substituent must point towards the larger aryloxide:
High efficiency and *Z*-selectivity more challenging to achieve (vs. disubstituted variants)

Scheme 2. The challenge of achieving high efficiency and stereoselectivity in a macrocyclic RCM reaction that affords a trisubstituted alkene. L = ligand; R = alkyl group.

We synthesized precursor **1** by a 17-step sequence based on previous disclosures.[xiv] Selection of **2** as the target (**2**) was because catalytic *Z*-selective RCM of the corresponding disubstituted alkenes had been investigated;[iii] the present study would therefore allow a comparison of the influence of the additional alkene substituent on the catalytic process. To ensure sufficient conversion to **2**, 20 mol % loading was employed in the initial screening along with a reaction time of 24 hours. We confirmed that Mo bis-alkoxide **3** and Ru carbene **4** (entries 1–2, Table 1) deliver minimal selectivity favoring the *E* isomer with the latter complex being less effective (59% conv., 50 °C, 48 h).[xv] None of the macrocycle is formed in the presence of the less active W-based alkylidene **5** (entry 3),[iiib] which is effective in the formation of the corresponding *Z* disubstituted macrocyclic alkenes.[iii] There is low conversion to **2** with Mo-based MAP complexes **6** and **7a** at 22 or 50 °C (<10–30% conv.;

entries 4–7, Table 1); RCM with **6** at a higher temperature leads to 17% conversion to a 75:25 mixture *Z*-**2**:*E*-**2** along with nearly equal amounts of the homocoupled product (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 (entry 7, vs. adamantylimido **6** and its more exposed Mo center in entry 5), and found the increase in conversion with F-substituted aryloxide **7b** intriguing (60% conv.

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



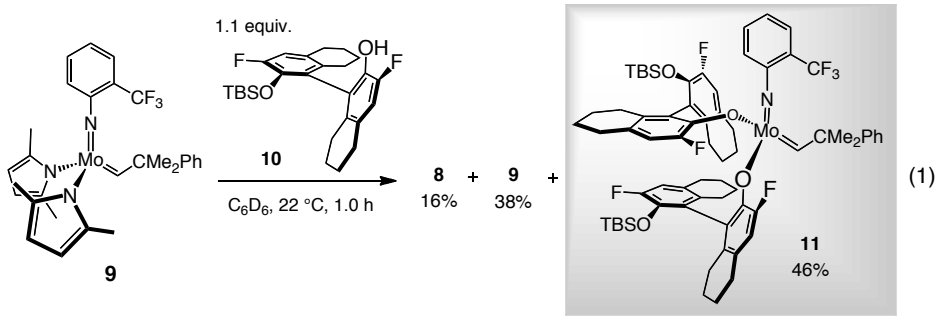
samples of **6**-**8** were prepared and used in situ (might contain other comlpexes)

Entry	Complex	*T* [°C]; Time [h]	Conv. to **2** [%][b]	Homocoupled Product [%][b]	*Z*:*E* (**2**)[b]
1	**3**	22; 24	81	≤10	45:55
2	**4**	50; 48	59	≤10	43:57
3	**5**	80; 24	<2	<2	na
4	**6**	22; 24	<10	≤10	nd
5	**6**	50; 24	17	18	75:25
6	**7a**	22; 24	<10	≤10	nd
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] Reactions 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. TBS = *t*butyl(dimethyl)silyl; na = not applicable; nd = not determined.

in 24 h at 22 °C; entry 8, Table 1). Based on the postulate that electron-withdrawing aryloxy ligands improve RCM efficiency, we prepared and evaluated the performance of *o*-trifluoromethylphenylimido mono-pyrrolide **8** (entry 9, Table 1): 73% conversion to **2** was observed within eight hours and *Z* selectivity improved to 74% (vs. 61:39 *Z*:*E* with **7b** in entry 8).

At this point, we considered the fact that reactions of bis-pyrrolides with an F-substituted (vs. Cl- or Br-) aryl alcohol generate significant amounts of the corresponding bis-aryloxide. For example, treatment of **9** with 1.1 equivalents of fluorinated carbinol **10**, as shown in Eq. (1), leads to the formation of only 16% of mono-pyrrolide **8** along with 46% bis-aryloxide **11** (38% **9** remains unreacted). The relatively efficient formation of the bis-aryloxide 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% bis-aryloxide with the Br-substituted alcohol).[xvi] Based on previous observations regarding the minimal efficiency exhibited by Mo bis-aryloxide alkylidenes bearing a 2,6-dialkylphenylimido[xvii] or adamantylimido ligand,[xvi] we presumed that such lack of reactivity extends to all complexes regardless of the imido group; 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**).

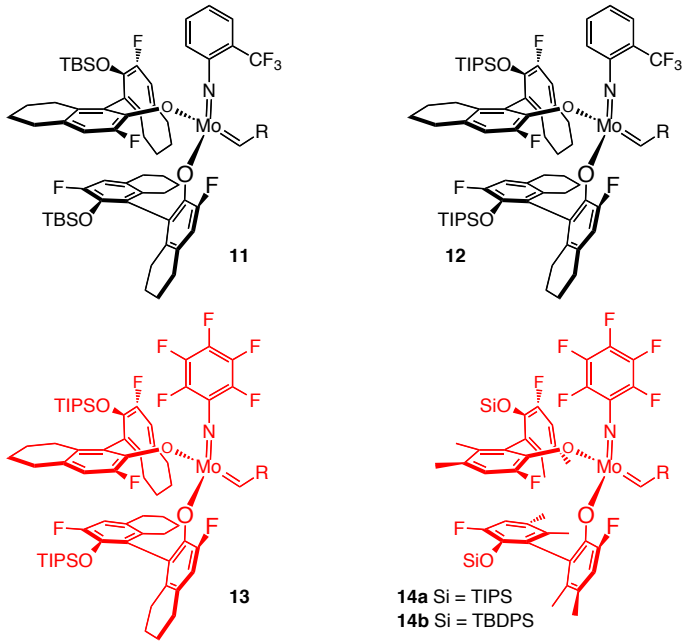


Only to confirm the aforementioned supposition, we prepared pure **11** by subjecting **9**[xviii] to *two* equivalents of **10** (1.0 h, 22 °C; >95% conv. to **11**; <2% byproduct formation), and probed its ability to facilitate the formation of **2**. To our surprise, we discovered that the majority — if not all — of the reactivity generated by the mixture resulting from treatment of bis-pyrrolide **9** with alcohol **10** arises from the corresponding bis-aryloxide complex. In the presence of pure **11** present (entry 1, Table 2), there is 84% conversion to **2** in seven hours with 77:23 *Z*:*E* selectivity (vs. 73% conv. in 8 h and 74:26 *Z*:*E* under the conditions in entry 9, Table 1).

With the source of high reactivity elucidated, we set out to improve efficiency and stereoselectivity through study of various bis-aryloxide alkylidenes (entries 2–8 of Table 2). As noted above (cf. 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 (entry 2, Table 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[xix] (cf. **13**) since we

envisioned that the stronger electron-withdrawing ability of the poly-halogenated 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

Table 2: Evaluation of Mo bis-aryloxides for conversion of **1** to **2**.[a]



11-**14** were prepared and used in situ; R = CMe_2Ph

Entry	Complex; Mol %	*T* [°C]; Time [h]	Pressure	Conv. to **2** [%];[b] Yield [%][c]	*Z*:*E*[b]
1	**11**; 20	22; 7.0	ambient	84; nd	77:23
2	**12**; 20	22; 9.0	ambient	61; nd	81:19
3	**13**; 20	22; 8.0	ambient	84; nd	86:14
4	**14a**; 20	22; 5.0	ambient	92; nd	85:15
5	**14a**; 10	22; 24	ambient	46; nd	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] Reactions 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. TIPS = (*i*Pr)$_3$Si; TBDPS = (*t*Bu)Ph_2Si. nd = not determined.

selectivity furnished by **13** are higher than that delivered by *o*-trifluoromethylphenylimido alkylidene **12** (84% conv. in 8.0 h and

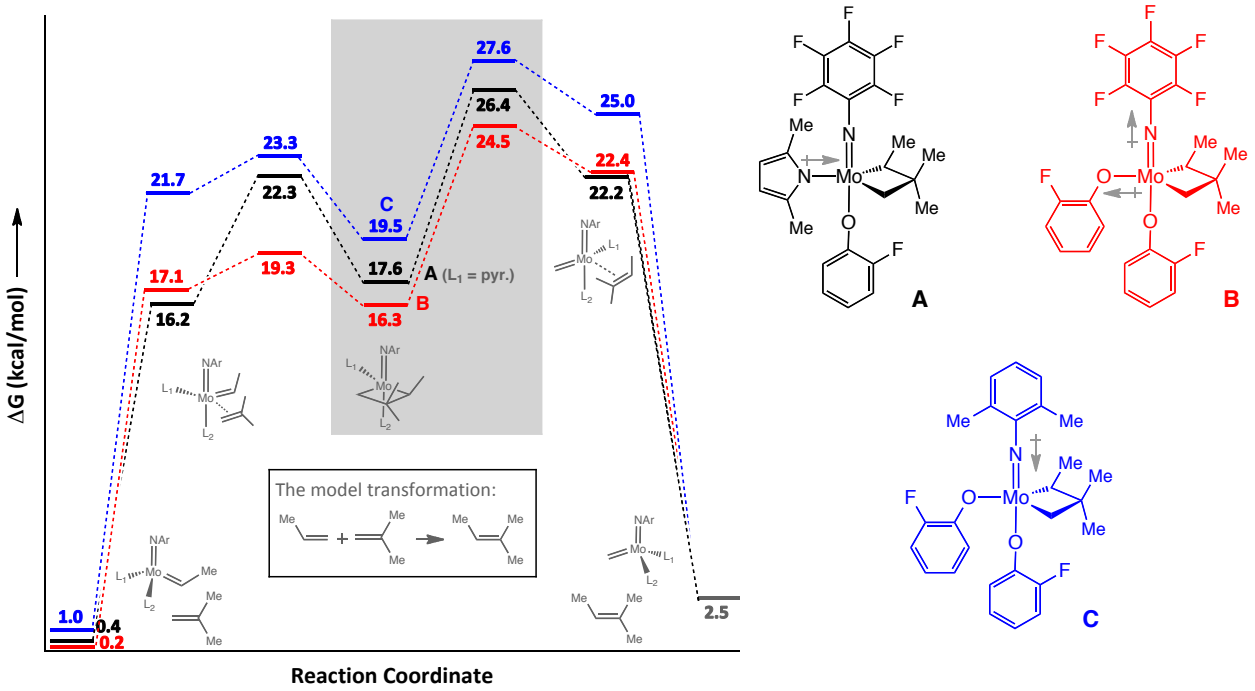
86% *Z* vs. 61% conv. in 9.0 h and 81% *Z*, respectively). We subsequently investigated a number of bis-biphenoxy derivatives, based on the hypothesis that the smaller aryloxide ligands might allow for improved activity without a significant drop in stereoselectivity. With 20 mol % bis-phenoxide **14a**, 92% of **1** is converted to cyclic alkene **2** within five hours to produce a 85:15 *Z*:*E* mixture (entry 4, Table 2). When 10 mol % **14a** is used, **2** is formed with 87:13 *Z*:*E* selectivity (entry 5, Table 2), 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 (formation of the relatively stable unsubstituted metallacyclobutane). Thus, as illustrated in entry 6 of Table 2, we established that when the RCM is carried out with 10 mol % **14a** under 1.0 torr of vacuum, there is 88-89% conversion to **2** within only 2.5 hours, 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 % **14b** or **14b** (100 torr); the desired macrocyclic alkene is obtained in 73% yield and 91:9 *Z*:*E* ratio. To minimize the amount of solvent used, catalytic RCM reactions with **14b** were performed at 2.0 mM concentration (entries 7–8, Table 2 vs. 1.0 mM otherwise).

The basis for high *Z* selectivity has already been provided (cf. Scheme 2); the proposed scenario is congruent with the improved stereodifferentiation furnished by the smaller perfluorophenylimido-bearing complex (vs. *o*-trifluoromethylphenyl; entries 2–3, Table 2). However, rationalization of the finding that the *larger* bis-aryloxide 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 the 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-b**, we carried out DFT calculations with three representative systems (Scheme 3).[xx] We probed the energetics associated with a model cross-metathesis reaction to afford a trisubstituted olefin via metallacyclobutane **A**, a mono-pyrrolide containing an *o*-fluorophenoxy ligand, and its corresponding bis-aryloxide, proceeding through **B**; both systems carry a pentafluorophenylimido ligand. We also examined the energetics of the same process with an alkylidene that furnishes **C**, which is a 2,6-dimethylphenylimido bis-aryloxide [vs. Mo=N(C_6F_5)]. As the results in Scheme 3 indicate,[xxi] metallacyclobutane **B** is lower in energy (vs. **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 pentafluorophenylimido unit (e.g., vs. *o*- trifluoromethylphenylimido). The favorable pathway via **B** might be partly rooted in the lowering of electronic repulsion that arises when the donating alkyl ligands within the metallacyclobutane reside opposite to a more electron-deficient aryloxide (i.e., better dipole–dipole minimization with L_1 = *o*-FC_6H_4O vs. 2,5-dimethylpyrrolide in **A**).[xxii] For similar reasons,



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.

a metallacyclobutane with apically trans 2,6-dimethylphenylimido and aryloxide groups (**C**) should be higher in energy, 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 pentafluorophenyl imido group, while offering electronic stabilization (see above), by the virtue of being smaller than a 2,6-dimethylphenylimido or an *o*-trifluoromethylphenylimido ligand, better accommodates the formation of a trisubstituted metallacyclobutane.

The present findings imply that, although Mo-based MAP complexes promote olefin metathesis more efficiently than the comparatively rigid bidentate diolates,[xib] they are less active — but more robust and longer living[xxiii] — 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 the mechanism-based platform for such initiatives.

Keywords: catalysis, olefin metathesis, ring-closing metathesis, macrocyclic alkenes, trisubstituted olefins, *Z* olefins

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[xviii] Macrocyclic RCM was not observed with 20 mol % bis-pyrrolide **9** (<2%).

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[xx] To avoid costly calculations and substantial uncertainty due to the size of the Mo bis-aryloxides 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.

[xxi] 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 outside the energy limits illustrated in Scheme 3; it is thus the largest energy gap shown that constitutes the required energy barrier.

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

[xxiii] Such relative stability is likely due to an increase in the energy of the square-based pyramidal complexes, supposedly involved in catalyst decomposition pathways, by the donor pyrrolide ligand. See: X. Solans-Monfort, C. Copéret, O. Eisenstein, *J. Am. Chem. Soc.* **2010**, *132*, 7750.