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Endo-Selective Enyne Ring-Closing Metathesis Promoted by Stereogenic-at-W Mono-Pyrrolide Complexes

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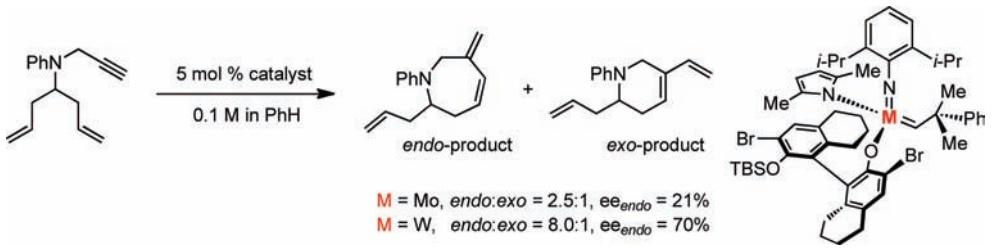
ABSTRACT



The utility of W-alkylidene complexes for enyne ring-closing metathesis is demonstrated in a direct comparison with Mo-based analogs. Tungsten complexes lead to less alkyne oligomerization and higher levels of *endo*-selectivity and enantioselectivity.

Although high oxidation state W-based imido alkylidene bis-alkoxide complexes were the first well-defined olefin metathesis catalysts to be developed,[1] they have not been explored in chemical synthesis as extensively as related Mo catalysts.[2] Among the reasons for Mo catalysts being preferred are the relatively high stability of tungstacyclobutane intermediates toward loss of olefin, a perceived higher sensitivity of tungsten complexes to certain functional groups, and commercial availability of some Mo complexes. In virtually no olefin metathesis reactions have activities and selectivities of tungsten and molybdenum catalysts been compared directly in more than a cursory manner.

Recently, we have turned to an exploration of monoaryloxide pyrrolide (MAP) imido alkylidene catalysts,[3] which are highly reactive and selective for a variety of olefin metathesis processes.[4] In the process, we discovered that W-based catalysts can be dramatically more selective than Mo-based catalysts, for example, for homocoupling of terminal olefins to generate *Z* internal olefins with high selectivity.[5] Structural and kinetic studies of tungsten and

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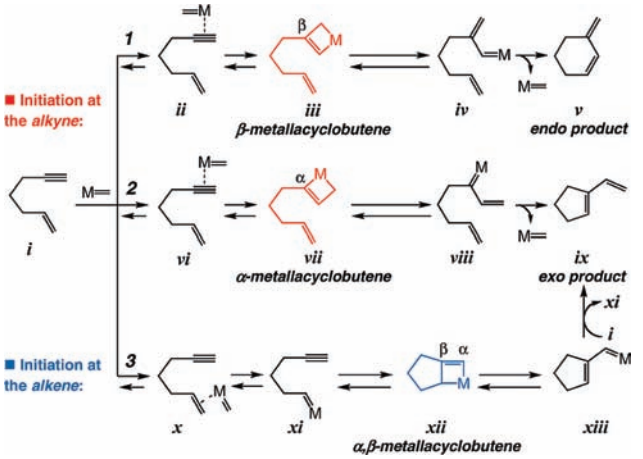
molybdenum MAP complexes suggest that methylidene intermediates can be relatively stable and long-lived.[6] Accordingly, if both Mo and W MAP methylidene species are long-lived in the appropriate circumstances, higher turnover numbers should be obtained.

Scheme 1. Various Modes of Reaction in Enyne RCM



One property of Mo-MAP complexes is their ability to catalyze enyne metathesis reactions to give *endo* products preferentially (Scheme 1);[7] such cyclic dienes are virtually inaccessible through enyne reactions catalyzed by Ru carbenes.[8] Although some enyne reactions catalyzed by Ru complexes have been proposed to follow a mechanism in which the olefin binds to the metal first (Scheme 1), we have suggested that the *endo* product *v* is generated when the terminal alkyne binds initially to Mo, affording a *β*-metallacyclobutane intermediate *iii*. Conversely, the *exo* product *ix* is formed through the intermediate α-metallacyclobutane *vii*. Mixtures of *endo*- and *exo*-products form through the competitive reaction pathways shown in Scheme 1. One of the limitations in enyne metathesis by Mo-based MAP complexes might arise from multiple reactions that involve a terminal acetylene (i.e., oligomerization or polymerization).[9] The yields and purity of enyne metathesis products prepared through the use of Mo catalysts therefore can be limited. As a consequence of the superior selectivity of tungsten catalysts for *Z*-selective homocoupling of terminal olefins, presumably as a result of the better-controlled reactivity of W-complexes,[5] we felt compelled to explore the ability of such complexes in promoting enyne RCM reactions.

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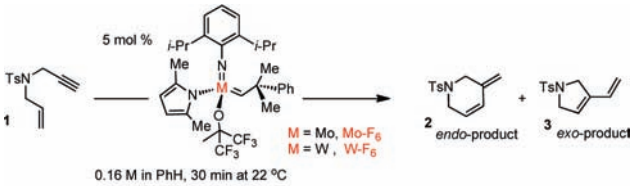
Table 1. Enyne Metathesis of **1** with Mo- and W-based MAP Catalysts[a]



entry	catalyst	conv (%)[b]	yield (%)	endo:exo[c]
1	Mo-F_6	>98	88	>20:1
2	W-F_6	>98	94	>20:1

[a] Reactions were performed under N_2 atmosphere with 5 mol % catalyst in C_6H_6 at 22 °C. [b] Conv was based on consumption of substrate. [c] Ratios were determined by analysis of 1H NMR spectra of unpurified reaction mixtures.

We began by examining enyne metathesis by Mo- and W-catalysts of tosylamide **1** (Table 1). We found that a W-based catalyst provides levels of selectivity and reactivity at least as high as the analogous Mo-based variant.

Table 2. More Efficient and Selective Enyne Metathesis with W-based Catalysts[a]

substrate	product	catalyst	concn	time	conv (%)[b]	endo:exo[c]	yield (%)
4	5	Mo-F_6	0.05 M	15 min	>98	>20:1	<40
			0.01 M	15 min	>98	>20:1	<50
		W-F_6	0.05 M	15 min	>98	>20:1	71
			0.01 M	15 min	>98	>20:1	92
6	7	Mo-F_6	0.05 M	15 min	>98	20:1	<40
			0.01 M	15 min	>98	>20:1	<40
		W-F_6	0.05 M	15 min	>98	>20:1	71
			0.01 M	15 min	>98	>20:1	92
8	9	Mo-F_6	0.16 M	1 h	>98	>20:1	68
		W-F_6	0.16 M	1 h	>98	>20:1	80
10	11	Mo-F_6	0.10 M	1 h	>98	>20:1	<60
		W-F_6	0.10 M	1 h	>98	>20:1	95
12	13	Mo-F_6	0.10 M	1 h	>98	>20:1	60
		W-F_6	0.10 M	1 h	>98	>20:1	90
14	15	Mo-F_6	0.10 M	10 min	>98	>20:1	70
		W-F_6	0.10 M	10 min	>98	>20:1	90

[a–c] See Table 1.

Encouraged by these results, we turned to substrates that undergo facile oligomerization in the presence of Mo-catalysts. As the data in Table 2 illustrate, in the case of enyne metathesis of **4**, where a medium ring is generated, and of **6**, where the rate of ring-closure is slower, presumably as a consequence of increased substitution at the alkene, relatively high dilution conditions proved to be necessary for Mo-catalyzed processes (1×10^{-3} and 2×10^{-3} M, respectively).[7b] When the reactions were carried out at a concentration of 0.01 M, <40% enyne metathesis products were obtained with the Mo−F_6 complex (Table 1) and separation of the desired product from oligomeric side products proved difficult (Table 2).

In contrast, RCM performed in the presence of W−F_6 at a concentration of 0.05 M yielded *endo* products **5** and **7** in 60−70% isolated yield.[10] When the above transformations were carried out with W−F_6 at a concentration of 0.01 M, the yield was >90%. A similar trend was observed for other substrates, such as the aryl-substituted tosylamides **8** and **14**, as well as the anilines **10** and **12**; use of W−F_6 led to the enyne metathesis products in higher yields.

Table 3. Enhanced *endo*-Selectivity by W-based Catalysts[a]

entry	catalyst	conv (%)[b]	*endo*:*exo*[c]
1	Mo-F_6	>98	5:1
2	W-F_6	60	10:1
3[d]	W-F_6	>98	10:1

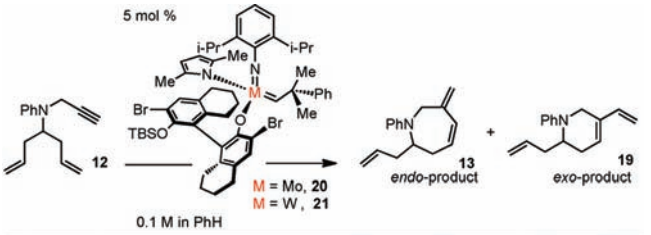
[a−c] See Table 1. [d] Catalyst (10 mol %) was used.

At least in certain cases, W-based catalysts are more *endo*-selective than Mo-based alkylidenes. As shown in Table 3, enyne metathesis of internal alkyne substrates **16** with Mo−F_6 yielded a mixture of *endo*- and *exo*-products in a ratio of 5:1. It is plausible that the sterically less accessible internal alkyne discourages Mo-alkylidene alkyne association as depicted in ***ii*** in Scheme 1, pathway 1, leading to partial reaction through pathway 3 and initiation at the alkene site. An indiscriminate α- and β-addition of the alkylidene to the internal alkyne may also be responsible for the low selectivity. The use of W−F_6 resulted in a much-improved *endo*-selectivity of 10:1, albeit with a lower reaction efficiency; a 10 mol % loading was necessary to achieve full conversion to the desired product.

We have previously reported examples of enantioselective enyne metathesis desymmetrization reactions performed under ethylene. Such processes likely involve cross-metathesis with ethylene, followed by enantioselective RCM of the tetraene intermediate.[7b] We report here that W-based catalysts provide enhanced *endo*- as well as enantioselectivity for desymmetrization of aniline dienyne **12**. As summarized in Table 4, under otherwise identical conditions, while Mo-based catalyst **20** provided a 2.5:1 mixture of **13** and **19**, with only 21% ee for the major isomer **13**, the corresponding W-catalyst **21** yielded a higher ratio (8:1 favoring **13**) with an ee of 70%. Both catalysts can be generated *in situ* from alcoholysis of the corresponding bis-pyrrolide complexes. We note that, unlike the reaction performed in the presence of W−F_6, which cleanly yielded the desired product, the reaction catalyzed by **20** and **21** led to a significant amount of oligomerization (20−30%). When the same transformations were carried out in the presence of ethylene, the *endo*- and enantioselectivities of the products remained the same, which implies that such reactions proceed through a true enyne metathesis pathway.

(10) See Supporting Information for a direct comparison of crude NMR spectra of reactions performed with Mo−F_6 and W−F_6 complexes.

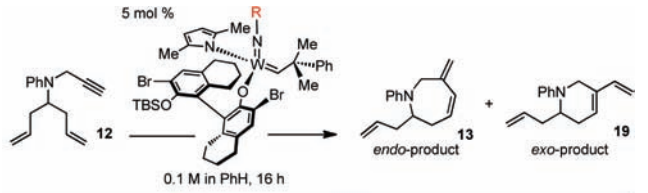
Table 4. Mo- and W-Catalyzed Enantioselective Ring-Closing Enyne Metathesis[a]



entry	atmosphere	catalyst	time (h)	conv (%)[b]	yield$_{13}$ (%)	*endo*:*exo*[c]	ee$_{13}$ (%)[d]
1	N_2	**20**	1	~60	\	2.5:1	21
2	N_2	**21**	1	~60	\	8.0:1	70
3	CH_2CH_2	**20**	16	>98	54	2.5:1	20
4	CH_2CH_2	**21**	1	~90	57	8.0:1	70

[a−c] See Table 1. [d] Determined by chiral HPLC analysis.

Table 5. Investigation of Imido Groups for Enantioselective Ring-Closing Enyne Metathesis[a]

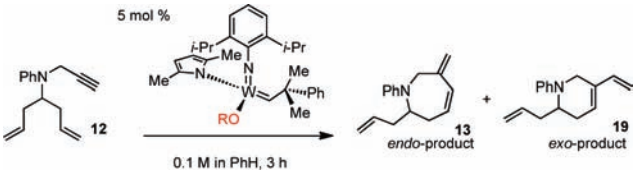


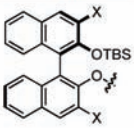
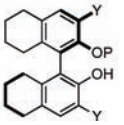
entry	imido group (R)	time (h)	conv (%)[b]	yield$_{13}$ (%)	*endo*:*exo*[c]	ee$_{13}$ (%)[d]
1	2,6-diisopropylphenyl	1	>98	57	8.0:1	70
2	2,6-dimethylphenyl	1	>98	74	3.4:1	44
3	2,6-dichlorophenyl	1	>98	70	4.6:1	49
4	2-*tert*-butylphenyl	1	>98	60	10.0:1	46

[a−d] See Table 4.

We carried out further structural optimization of the W-based MAP catalysts for enyne metathesis of **12**. Initial efforts focused on screening of various imido groups (Table 5). Out of four aryl imido groups investigated, the original 2,6-di-*iso*-propylphenylimido complexes (as in **21**) emerged as optimal, especially in terms of enantioselectivity. The effect of different chiral phenoxides derived from monoprotected BINOL or octahydro-BINOLs were examined next (Table 6). Whereas incorporation of different substitution at the 3,3′ positions of the chiral diols (different halides in entries 1, 2, 4 and 5, as well as Me in entry 3 in Table 6) resulted in less enantioselective reactions, catalyst **22** with a methyl ether unit on the chiral aryloxide was more reactive and promoted more selective reactions; cyclic diene **13** was formed in 60% isolated yield and 81% ee (entry 6, Table 6).[11] Further solvent screening (Table 7) identified diethyl ether as the optimal solvent in terms of *endo*-selectivity and enantioselectivity (91% ee), although the yield of the isolated product was only 35% as a consequence of significant competitive oligomerization.

Table 6. Investigation of Aryloxide Groups for Enantioselective Ring-Closing Enyne Metathesis[a]



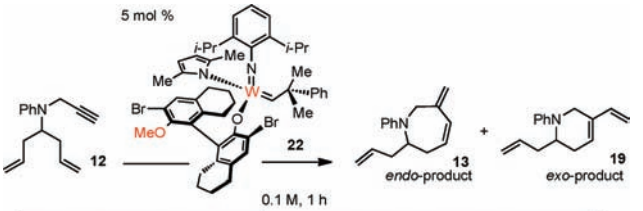
entry	OR ligand		conv (%)[b]	*endo*:*exo*[c]	ee_{13} (%)[d]
1		X = Br	38	>20:1	17
2		X = I	>98	10:1	30
3		X = Me	>98	10:1	30
4		X = Cl, P = TBS	37	5:1	65
5		X = I, P = TBS	36	10:1	38
6		X = Br, P = Me	>98	8:1	81

[a–d] See Table 4.

In conclusion, we have demonstrated that W-based MAP complexes promote more efficient and *endo*-selective enyne RCM than the corresponding Mo-based variants; the most notable distinction is fewer side reactions with W-based system. The observations described above, along with the findings concerning *Z*-selective homocoupling of terminal olefins,[5] underline the importance of examining W-based catalysts along with Mo-based catalysts in the context of various applications. The strategies outlined above, involving Mo- as well as W-based catalysts for olefin metathesis, will constitute a critical and unique attribute of the future studies in these laboratories.

(11) Other catalysts possessing a methyl ether of the other chiral diols were also tested; metathesis reactions with such complexes proved to be less enantioselective. See the Supporting Information for more screening data.

Table 7. Solvent Effect in W-Catalyzed Enantioselective Ring-Closing Enyne Metathesis[a]



entry	Solvent	conv (%)[b]	$yield_{13}$ (%)	*endo*:*exo*[c]	ee_{13} (%)[d]
1	benzene	>98	60	10:1	81
2	toluene	>98	\	10:1	85
3	THF	>98	\	10:1	75
4	Et_2O	>98	35	10:1	91
5	CH_2Cl_2	>98	\	10:1	61
6	pentane	>98	\	10:1	88

[a–d] See Table 4.

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Supporting Information Available. Experimental procedures and spectral data for products. This material is available free of charge via the Internet at http://pubs.acs.org.