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*Catalytic Z-Selective Cross-Metathesis with Secondary Silyl- and Benzyl-Protected Allylic Ethers: Mechanistic Aspects and Applications to Natural Product Synthesis*

# Catalytic *Z*-Selective Cross-Metathesis with Secondary Silyl- and Benzyl-Protected Allylic Ethers: Mechanistic Aspects and Applications to Natural Product Synthesis**

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Catalytic cross-metathesis (CM)[1] offers a concise and broadly applicable approach to synthesis of a large variety of alkenes.[2] One of the special attributes of CM is that, with an appropriate catalyst class, it can deliver a new C=C bond while generating high stereoselectivity; this is contrary to catalytic cross-coupling with vinylboronates, vinyl halides or related entities, where the stereochemical identity of a substrate must initially be established by a separate process.[3] In 2011, we reported that stereoselective CM reactions of enol ethers or allylic amides with terminal alkenes can be effected by a Mo-based monoalkoxide pyrrolide (MAP) complex to afford the higher-energy *Z* isomers.[4] We have subsequently examined the

possibility of catalytic *Z*-selective CM reactions with secondary allylic ethers, an important class of starting materials that, due to steric factors, represent a reactivity challenge. Another area of recent activity corresponds to reactions with alkyne-containing olefin cross partners. Our interest in this set of substrates is for two reasons: (1) Alkyne-containing *Z*-alkenes cannot be easily accessed through the traditional partial hydrogenation protocols; (2) Catalytic CM of substrates that bear an acetylene unit can be problematic with high-oxidation state olefin metathesis catalysts.[5]

Herein, we outline the first examples of efficient and highly stereoselective catalytic CM processes that furnish *Z*-disubstituted olefins that bear a versatile secondary allylic silyl and benzyl ether site, including those that contain an alkyne group.[6] Reactions are promoted at ambient temperature by 1.5—6.0 mol % of a Mo-based MAP complex; products are obtained within eight hours in 39—87% yield and 78:22 to >98:2 *Z:E* ratio. The present studies reveal a number of mechanistic insights that should prove of value in the design of *Z*-selective CM processes that afford allylic ethers. Utility is demonstrated through applications to stereoselective synthesis of alkyne-containing natural products. It should be noted that *Z*-selective Ru-based carbenes, introduced more recently, have not yet been effectively employed with terminal alkenes that bear a substituent at their allylic position.[7]

Allylic alcohols and derivatives are commonly used as starting materials for stereoselective transformations where the identity of the reacting alkene isomer is critical: *E* and *Z* olefins typically deliver different product diastereomers and in many cases the *Z* isomers under reactions with higher stereoselectivity.[8] One instance relates to Cu–catalyzed enantioselective allylic substitutions that generate C—C or C—B bonds and involve the use of *Z* allylic phosphates[9] or halides,[10] entities typically prepared via the corresponding alcohols (Scheme 1). Another example pertains to diastereoselective Ti–mediated cross-coupling of allylic alcohols with imines or aldehydes (Scheme 1).[11] *Z*-Allylic alcohols reside in biologically active molecules as well; anti-fungal, anti-cancer, anti-oxidant and immunosuppressive agent falcarindiol[12] (**1**, Scheme 1) and a number of related naturally occurring derivatives (e.g., **2**,[13] Scheme 1) contain a *Z*-alkene with neighboring alkyne units. An efficient catalytic method for *Z*-selective synthesis of allylic ethers would constitute an important objective in chemical synthesis.

**As substrates in stereoselective reactions**   **As biologically active natural products**
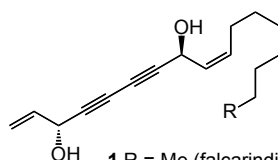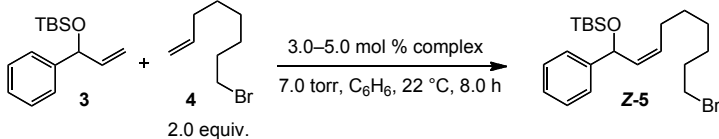


*Scheme 1.* *Z*-Allylic alcohols and their derivatives serve as substrates in stereoselective transformations and reside in biologically active molecules. Lg = leaving group.

We first probed the CM of sterically demanding silyl ether **3** and bromo–alkene **4** in the presence of different catalyst

systems at 22 °C and under 7.0 torr of vacuum to minimize post-CM

isomerization as well as increase reaction rate.[4a]  Contrary to

Mo bis-alkoxide **6** and Ru carbene **7** (5.0 mol %; Scheme 2), which

generate **5** with a strong preference for the *E* isomer (5% *Z*, 76—

80% yield; entries 1—2, Table 1), reaction with MAP complex **8**

(3.0 mol %) furnishes *Z*–**5** in 95:5 *Z*:*E* selectivity (69% yield;

**Table 1:** Initial evaluation of catalysts for stereoselective synthesis of *Z*-**5**.[a]



| Entry | Complex; Mol %[b] | Conv. [%][c] | Yield [%][d] | *Z*:*E* (**5**)[c] |
|-------|-------------------|--------------|--------------|--------------------|
| 1 | **6**; 5.0 | 95 | 80 | 5:95 |
| 2 | **7**; 5.0 | 98 | 76 | 5:95 |
| 3 | **8**; 3.0 | 79 | 69 | 95:5 |
| 4 | **9**; 5.0 | 64 | 62 | 81:19 |
| 5 | **10**; 5.0 | 25 | 20 | >95:5 |

[a] Performed under $N_2$ atm.  [b] Complexes **6**-**7** and **10** were prepared separately before use, whereas **8**-**9** were synthesized and used in situ from reactions of the corresponding bis-pyrrolide and the chiral aryl alcohol (5.0 mol % each); since generation of **8** leads to ~30% bis-aryloxide (inactive), 3.0 mol % of the MAP complex is available to catalyzed reaction. [c] Determined by analysis of ^{1}H NMR spectra of unpurified mixtures; conversion values refer to consumption of the substrate (±2%). [d] Yield of isolated and purified products.  See the Supporting Information for details.
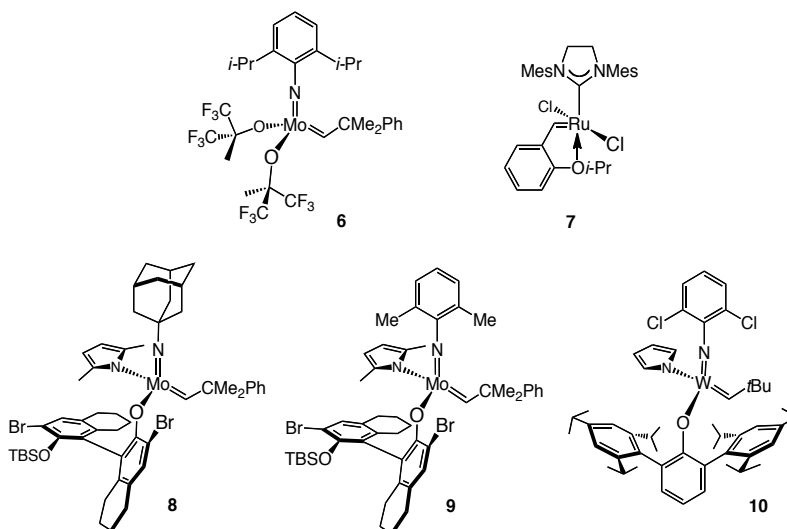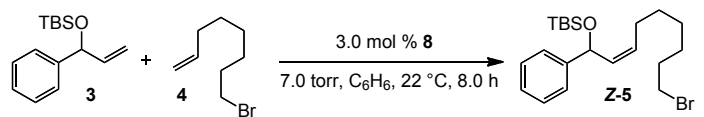


**Scheme 2.** Various complexes used in the initial screening shown in Table 1.

entry 3, Table 1).   Although conversion is lower with the MAP complex compared to **6** or **7** (79% vs. 95—98% conv.), the desired allylic ether is isolated in a similar yield, indicating diminished byproduct generation with the stereogenic-at-Mo catalyst.[14] Catalytic CM with the more sizeable arylimido **9** is less efficient (64% conv. vs. 79% conv. for **8**; entry 4) and 19% of the undesired *E* alkene is formed, likely due to a smaller size difference between the arylimido and aryloxide ligands (vs. in **8**).[4a]   The less active W alkylidene **10**[15] delivers the highest *Z:E* ratio (>95:5), albeit in 20% yield (entry 5, Table 1).

Next, we examined the effect of cross partner concentration on CM efficiency (Table 2).  Since CM reactions are carried out under vacuum, excess amounts of a relatively volatile cross partner might be needed; otherwise, as illustrated in Tables 2, 2.0—3.0 equivalents suffice, and there is significant efficiency with as little as 1.0—1.5 equivalent of bromoalkene **4**.  It is particularly noteworthy that *Z* selectivity is diminished when less **4** is present (compare entries 1—2 vs. 3—4, Table 2); this may be attributed to the fact that, with lower amounts of the less hindered cross partner being available, the catalytically active alkylidene species react more frequently with the product *Z* alkene (**5**) to engender olefin isomerization. Another important point is that, as shown in entry 5 (Table 2), large excess of the less hindered alkene partner can be deleterious to CM efficiency (<2% **5** detected with 10 equiv. **4**); rapid homodimerization of **4** probably leads to a burst of ethylene

production and formation of a significant amount of the methylidene complex, which is highly reactive but also more prone to decomposition[16] (vs. alkylidenes derived from **3** or **4**).

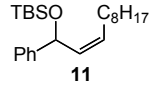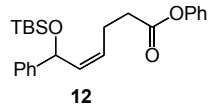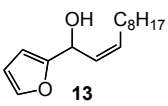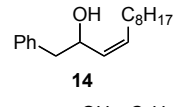***Table 2:*** Effect of cross partner concentration on efficiency of *Z*-selective CM.[a]
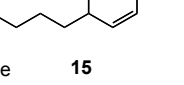
| Entry | Equiv. of **4** | Conv. [%][b] | Yield [%][c] | *Z:E*[b] |
|-------|-----------------|--------------|--------------|----------|
| 1 | 1.0 | 56 | 45 | 91:9 |
| 2 | 1.5 | 67 | 65 | 90:10 |
| 3 | 2.0 | 79 | 69 | 95:5 |
| 4 | 3.0 | 72 | 65 | 95:5 |
| 5 | 10 | <2 | na | na |

[a] Performed under $N_2$ atm.  [b] Determined by analysis of MHz $^1$H NMR spectra of unpurified mixtures and refer to consumption of the substrate (±2%). [c] Yield of isolated and purified products.  See the Supporting Information for details.  na = not applicable.

A range of *t*-butyl(dimethyl)silyl allyl ethers can be synthesized through Mo-catalyzed CM (Table 2).  The expected silyl ether, or the corresponding alcohols (after deprotection; entries 1—3 and 5, Table 3) can be isolated in 61—86% yield and 78:22—95:5 *Z*:*E*.  In one instance (entry 4), CM does not proceed further than 43% conversion; this might be due to unfavorable steric interactions between the benzyl group and the adamantylimido unit in the *syn*-substituted metallacyclobutane intermediate (see below for additional data).  Products bearing a relatively small (vs. entries 1-3, Table 3) *n*-alkyl substituent are isolated with lower *Z* selectivity (entries 4—5, Table 2).  Control experiments indicate that this is partly the result of post-CM isomerization, a process expected to be more facile with alkene products that carry smaller substituents and are thus more accessible.  As an example, after 2.5 h, **15** is

isolated as a 91:9 *Z:E* mixture (38% conv.), and after 36 hours, the *Z:E* ratio drops to 65:35 (81% conv.).[17]

**Table 3:** Synthesis of various allyl silyl ethers through *Z*-selective catalytic CM.[a]



| Entry | *Z* alkene product | Conv. [%][b] | Yield [%][c] | *Z:E*[b] |
|-------|--------------------|--------------|--------------|----------|
| 1 | **11** | 89 | 86 | 95:5 |
| 2 | **12** | 83 | 72 | 95:5 |
| 3 | **13** | 82 | 80[d] | 95:5 |
| 4 | **14** | 43 | 37[d] | 86:14 |
| 5 | **15** | 68 | 61[d] | 78:22 |

[a] Performed under N$_2$ atm. with 2.0-3.0 equiv. cross partner and 3.0 mol % **8** (generated *in situ*).  [b] Conv. values correspond to the CM step; determined by analysis of $^1$H NMR spectra of unpurified mixtures and refer to substrate consumption in the CM step (±2%). [c] Yield of purified products. [d] Overall yield (for CM and desilylation). See the Supporting Information for details.

We then turned our attention to investigating CM reactions with the less sterically congested *p*-methoxybenzyl ethers. Based on the aforementioned findings regarding the susceptibility of the comparatively exposed *Z* alkene products to isomerization (e.g., entry 5, Table 2), we were concerned whether high *Z:E* ratios can be retained at relatively high conversion in such cases (vs. silyl ethers). Nevertheless, as shown in Table 4, *Z*-disubstituted allyl ethers, or alcohols after oxidative deprotection, are obtained in 39—87% yield (for two steps in entries 2—4 and 6) and, somewhat to our surprise,

in 90:10 to >98:2 *Z:E* ratios.  Thus, not only high *Z* selectivity
persists at late stages of the CM reactions (up to 93% conv.),
disubstituted alkenes are generally isolated with higher
stereoisomeric purity compared to the corresponding silyl ethers
(Table 2).  The lower efficiency with which **14** is generated
after PMB removal, versus **16** and **17** (entries 1–3, Table 4), is
consistent with the observation regarding the process with the
corresponding silyl ether substrate (entry 4, Table 3); similar
arguments as mentioned before are applicable here as well.
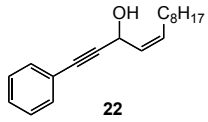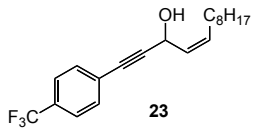
**Table 4:** Synthesis of various allyl *p*-methoxybenzyl ethers through *Z*-selective catalytic CM.[a]



| Entry | *Z* alkene product | Conv. [%][b] | Yield [%][c] | *Z:E*[b] |
|-------|-------------------|--------------|--------------|----------|
| 1 | **16** | 90 | 85 | >98:2 |
| 2 | **14** | 43 | 39[d] | >98:2 |
| 3 | **17** | 66 | 60[d] | >98:2 |
| 4 | **18** | 93 | 87[e] | >98:2 |
| 5 | **19** | 82 | 70 | 92:8 |
| 6 | **20** | 89 | 87[d] | 90:10 |
| 7 | **21** | 91 | 72 | 92:8 |

[a] Performed under N$_2$ atm; 2.0–3.0 equiv. of the olefin cross partner was used.  [b] Determined by analysis of $^1$H NMR spectra of unpurified mixtures; conversion values refer to consumption of the substrate in the CM step (±2%). [c] Yield of isolated and purified products.  [d] Overall yield (for CM and debenzylation steps). [e] Overall yield (for CM and desilylation steps).  See the Supporting Information for details. TES = triethylsilyl.

Propargyl-allyl silyl ethers were the third substrate type examined, partly as a preamble to stereoselective synthesis of the class of natural products represented in Scheme 1. The concern here was that, in spite of the presence of a *t*-butyldimethylsilyl ether, the relatively diminutive alkynyl substituent could expose the *Z* olefin product to post-metathesis isomerization. Again, as observed with the benzyl ethers in Table 4, in most instances, Mo-catalyzed CM proceeds readily and in 90:10 to >98:2 *Z:E* ratio (Table 5). Only in the case of alkyl-substituted alkyne in entry 5 of Table 5, none of the desired product is formed (see below for mechanistic rationale).
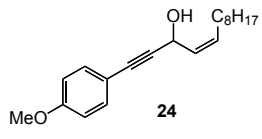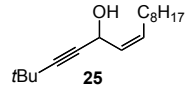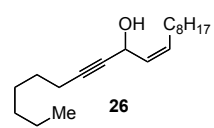
**Table 5:** Synthesis of various alkynyl silyl ethers through *Z*-selective catalytic CM.[a]



| Entry | Z alkene product | mol %; Conv. [%][b] | Yield of alcohol [%][c] | Z:E[b] |
|---|---|---|---|---|
| 1 | **22** | 3.0; 72 | 68 | >98:2 |
| 2 | **23** | 3.0; 73 | 64 | >98:2 |
| 3 | **24** | 3.0; 66 | 60 | >98:2 |
| 4 | **25** | 1.5; 84 | 76 | 90:10 |
| 5 | **26** | 3.0; <2 | na | na |

[a] Reactions performed under $N_2$ atm. [b] Determined by analysis of $^1$H NMR spectra of unpurified mixtures; conversion values refer to consumption of the substrate in the CM step (±2%). [c] Yield of isolated and purified products. See the Supporting Information for details. na = not applicable.

A number of unexpected variations in efficiency and stereoselectivity regarding the above-mentioned transformations have mechanistic implications and thus merit brief discussion. The first set of noteworthy findings relate to the changes in *Z* selectivity as a function of substrate structure in CM reactions in Tables 2—5. Such differences are probably connected to relative abundance of different alkylidenes derived from several cross partners. Unlike complexes originating from the less hindered mono-substituted olefins (cf. **I**, Scheme 3), those represented by **II-IV** are more sizeable and less prone to causing post-CM isomerization.[18] In the case of silyl ethers shown in Tables 1—3, generation of **II** is less facile (vs. **III** or **IV**);[19] accordingly, the more reactive **I** is present at a higher concentration, engendering stereoselectivity loss to a larger degree through reaction with the product *Z*-alkene.
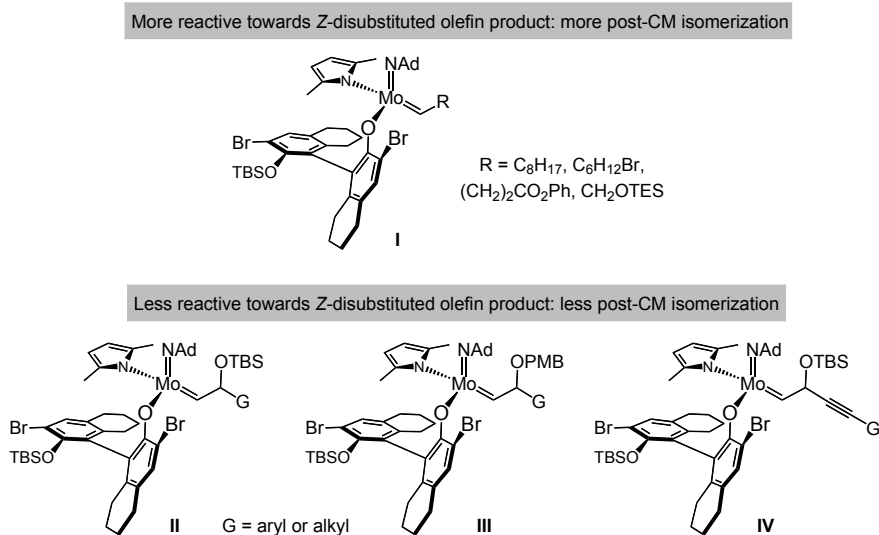


**Scheme 3.** Different Mo alkylidenes present in solution: their ease of formation and reactivity can influence the final *Z:E* ratios. Ad = adamantyl; TBS = *t*-butyl(dimethyl)silyl.

Another significant observation is in connection with the influence of the alkyne substituent on catalytic CM (cf. Table 5). For instance, there is 84% conversion to *t*-butyl-substituted **25** with only 1.5 mol % **8** after 1.0 hour (entry 4, Table 5) versus 66—72% conversion to aryl-containing **22-24** with twice the catalyst amount and significantly longer reaction times (8.0 h; entries 1—3, Table 5); moreover, allylic ether **26** cannot be formed (entry 5, Table 5). To establish whether the above reactivity trends are due to partial or complete catalyst deactivation or lack of substrate reactivity, we performed the experiment depicted in Scheme 4. When silyl ether **27**, which undergoes catalytic CM to afford **22** (cf. entry 1, Table 5), is subjected to the same reaction conditions but in the presence of **28, 26** is, again, not formed, nor can any **22** be detected (<2% conversion to any type of product by ^{1}H NMR analysis). The latter finding illustrates that the presence of an uncongested internal alkyne results in catalyst deactivation.[20] The proposed scenario explains the need for lower catalyst loading and shorter reaction time with the larger *t*-butyl-substituted alkyne substrate used in entry 4 of Table 5 (1.5 mol % **8** in 1.0 h vs. 3.0 mol % in 8.0 h for aryl-substituted variants in
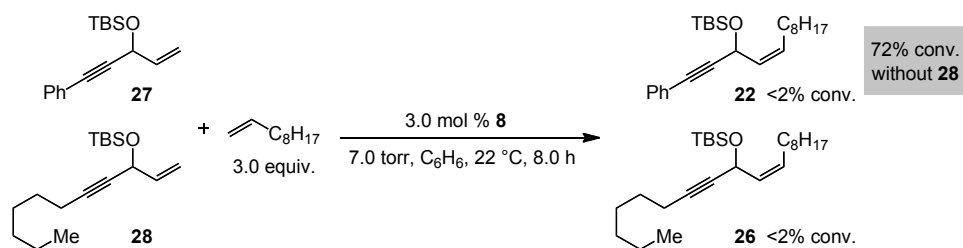


**Scheme 4.** An unhindered alkyne can lead to catalyst inhibition, as shown by complete lack of reactivity when allylic silyl ethers **27** and **28** are subjected to the reaction conditions simultaneously.

entries 1—3). The higher *Z* selectivity in the formation of aryl-substituted products **22**—**24** may be because there is still, in spite of the higher loading, less active catalyst available to prompt olefin isomerization. The lower conversion values in entries 1—3 versus 4 of Table 5 are consistent with the suggested scenario.

Stereoselective syntheses of falcarindiol and derivatives **2** and **35** underscore the substantial utility of the present stereoselective protocols (Scheme 5). Mo-catalyzed CM of silyl ether **29** with 1-nonene and deprotection furnishes propargyl alcohol **30** in 94% overall yield and 92:8 *Z:E* ratio. Subsequent Cu-catalyzed cross-coupling with alkynyl bromide **31** affords falcarindiol. Similarly, natural product **2** as well as its C16 epimer[21] are synthesized in 56% overall yield; the corresponding
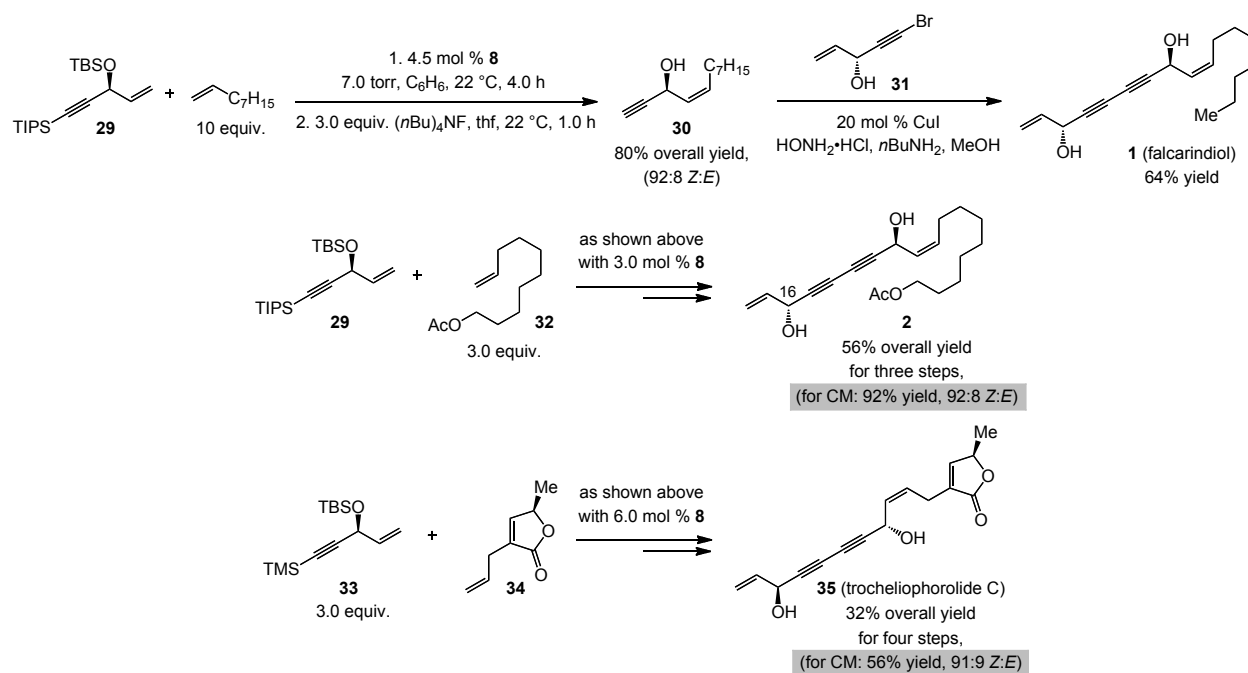


**Scheme 5.** Application of *Z*-selective cross-metathesis of allylic ethers to the preparation of natural products falcarindiol (**1**) and derivatives **2** and **35** (proposed structure) which possess anti-cancer, anti-fungal and immunosuppressive activity. See the Supporting Information for details.

CM proceeds in 92% yield and 92:8 *Z:E* selectivity. That the related analogue **2** can be prepared by simply altering the structure of the cross partner as well as synthesis of trocheliophorolide C (**35**)[22,23] further underscore the power of catalytic CM as a stereoselective coupling strategy.[24] The routes outlined in Scheme 5 obviate the need for fragile *Z*-enals and/or the difficulties in site-selective partial hydrogenation of poly-alkynyl substrates.

The catalytic *Z*-selective CM strategies described herein constitute a notable addition to an already significant set of transformations. Mo-based MAP complexes promote the coupling of sterically congested allylic silyl ethers or of less sizeable benzyl or alkyne-substituted variants without a significant penalty in the form of post-CM isomerization. We elucidate several mechanistic nuances, including the significant influence of internal alkynes and that of the size of cross partners on reactivity and selectivity; such understanding is crucial in successful planning of synthesis schemes involving *Z*-selective CM reactions. Development of additional catalysts and methods for stereoselective CM are in progress.

**Keywords:** cross-metathesis, olefins, olefin metathesis, molybdenum, *Z* alkenes

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[11] a) M. Takahashi, M. McLaughlin, G. C. Micalizio, *Angew. Chem. Int. Ed.* **2009**, *48*, 3648–3652; b) M. Z. Chen, M. McLaughlin, M. Takahashi, M. A. Tarselli, D. Yang, S. Umemura, G. C. Micalizio, *J. Org. Chem.* **2010**, *75*, 8048–8059; c) D. Yang, G. C. Micalizio, *J. Am. Chem. Soc.* **2011**, *133*, 9216–9219; d) D. Yang, G. C. Micalizio, *J. Am. Chem. Soc.* **2012**, *134*, 15237–15240.

[12] For studies regarding isolation and biological activity of falcarindiol, see: a) S. Mitsui, K. Torii, H. Fukui, K. Tsujimura, A. Maeda, M. Nose, A. Nagatsu, H. Mizukami, A. Morita, *J. Pharm. Exp. Therap.* **2010**, *333*, 954–960; b) P. Wyrembek, R. Negri, P. Kaczor, M. Czyzewska, G. Appendino, J. W. Mozrzymas, *J. Nat. Prod.* **2012**, *75*, 610–616. For determination of absolute stereochemistry (through Ru-catalyzed ethenolysis of the *Z* alkene), see: c) A. S. Ratnayake, T. Hemscheidt, *Org. Lett.* **2002**, *4*, 4667–4669; d) S. Tamura, T. Ohno, Y. Hattori, N. Murakami, *Tetrahedron Lett.* **2010**, *51*, 1523–1525.

[13] a) M. Kobaisy, Z. Abramowitz, L. Lermer, G. Saxena, R. E. W. Hancock, G. H. N. Towers, D. Doxsee, R. W. Stokes, *J. Nat. Prod.* **1997**, *60*, 1210–1213; b) J-H. Liu, S. Zschocke, R. Bauer, *Phytochem.* **1998**, *49*, 211–213; c) V. M. Dembitsky, *Lipids* **2006**, *41*, 883–924.

[14] Unlike reactions with Mo- and W-based complexes **6** and **8–10,** there is ~10% of an isomeric 1,2-disubstituted product derived from olefin metathesis-based alkene isomerization/CM when Ru carbene **7** is used. The absence of such byproducts, separation of which from the desired alkenes is challenging, is an important but overlooked attribute of high oxidation-state catalysts.

[15] For use of W complex **10** in *Z*-selective macrocyclic RCM reactions, see: a) M. Yu, C. Wang, A. F. Kyle, P. Jakubec, D. J. Dixon, R. R. Schrock, A. H. Hoveyda, *Nature* **2011**, *479*, 88–93; b) C. Wang, M. Yu, A. F. Kyle, P. Jakubec, D. J. Dixon, R. R. Schrock, A. H. Hoveyda, *Chem. Eur. J.* **2013**, *19*, 2726–2740.

[16] R. R. Schrock, *Chem. Rev.* **2009**, *109*, 3211–3226.

[17] The conversion values indicated throughout this report correspond to those that allow for the best balance between yield and *Z* selectivity, as further reaction can lead to *Z*-to-*E* isomerization.

[18] In complexes represented by **II–IV**, the electron density at the alkylidene C is stabilized by the adjacent electron-withdrawing C—O bond, lowering catalytic activity; see: D. S. La, E. S. Sattely, J. G. Ford, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2001**, *123*, 7767—7778.

[19] Accordingly, treatment of MAP complex **8** with 1.0 equiv. of the three allylic ethers shown below affords the derived alkylidenes with varying degrees of efficiency (2.0 h, 22 °C, $C_6D_6$; determined by ^{1}H NMR analysis).
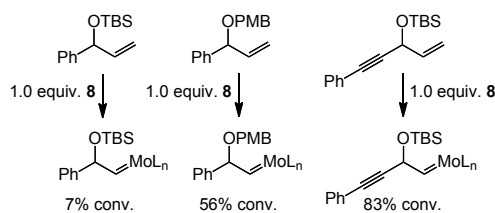


[20] Catalyst deactivation might be due to deactivation of the resulting alkylidene by the neighboring sterically accessible alkyne and/or generation of a stable metallacyclobutene. Studies to address such mechanistic issues are in progress.

[21] Because of the distal relationship between the stereogenic centers in **2**, the precise relative stereochemistry of the natural product is yet to be determined rigorously.  The catalytic CM allows access to either isomer through the use of the enantiomerically pure alcohol substrates.  It should be noted that control experiments indicate that there is no influence on the efficiency or *Z* selectivity of CM reactions if enantiomerically pure catalyst or substrates are used in either isomeric form.

[22] T. Rezanka, V. M. Dembitsky, *Tetrahedron* **2001**, *57*, 8743—8749.

[23] Excess (10 equiv.) is used in CM leading to **35** due to relative volatility of 1-nonene.

[24] The structure shown for **35** is that proposed for the isolated natural product; see ref. 22.  However, spectroscopic analysis indicates that the suggested structure might require revision.  Similar issues regarding the other members in this family of compounds have been recently reported; see: a) S. Hwang, J. H. Kim, H. S. Kim, S. Kim, *Eur. J. Org. Chem.* **2011**, 7414—7418; b) B. M. Trost, A. Quintard, *Org. Lett.* **2012**, *14*, 4698—4700.  Further details are provided in the Supporting Information.