Cross-Metathesis

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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**

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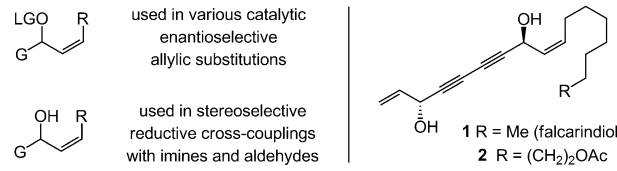
Allylic alcohols and derivatives are used regularly in stereoselective transformations, where the derived *E* and *Z* alkenes typically deliver different diastereomers and one geometric form reacts with higher stereoselectivity.[1] Some recently developed Cu-catalyzed enantioselective allylic substitutions require *Z*-allylic phosphates[2] or halides,[3] entities typically prepared via the corresponding alcohols (Scheme 1). Another



Scheme 1. *Z*-Allylic alcohols and their derivatives serve as substrates in stereoselective transformations (left), and reside in biologically active molecules (right). G = functional group, LG = leaving group.

example pertains to diastereoselective Ti-mediated cross-coupling of allylic alcohols with imines or aldehydes.[4] Biologically active molecules can contain *Z*-allylic alcohols as well; anti-cancer and immunosuppressive agent falcarindiol[5] (**1**, Scheme 1) and related derivatives (e.g., **2**)[6] contain a *Z* alkene and neighboring alkyne units. Development of efficient catalytic methods for *Z*-selective synthesis of allylic ethers/alcohols is therefore a compelling objective.

Catalytic cross-metathesis (CM)[7] offers a broadly applicable approach to olefin synthesis.[8] We have reported that stereoselective CM of enol ethers or allylic amides with terminal alkenes can be effected by Mo-based monoalkoxide pyrrolide (MAP) complexes to afford the higher-energy *Z* isomers.[9] Catalytic *Z*-selective CM with secondary allylic ethers, starting materials that present a reactivity challenge because of steric factors, has not been disclosed. Also unexplored are related transformations that generate alkyne-bearing products (cf. **1** and **2**, Scheme 1). The importance of the latter processes is twofold: 1) Catalytic CM of acetylene-containing substrates is vulnerable to catalyst deactivation. 2) Synthesis of alkyne-containing *Z* alkenes by catalytic partial hydrogenation may be hampered by issues of chemoselectivity and inseparable by-products.

Herein, we outline the first examples of efficient catalytic CM processes that furnish *Z*-disubstituted allylic silyl or benzyl ethers, many of which contain an alkyne group.[10] Reactions are promoted at ambient temperature by 1.5–6.0 mol% of a Mo-based MAP complex; *Z* alkenes are obtained in eight hours in 39–87% yield and 78:22 to greater than 98:2 *Z*:*E* ratio. The present studies reveal a number of mechanistic insights regarding the influence of substrate structure on CM efficiency and selectivity. Utility is demonstrated through applications to stereoselective synthesis of alkyne-containing natural products. It merits mention that the more recently introduced *Z*-selective Ru-based catalysts are yet to be employed effectively with alkenes that bear a secondary allylic substituent.[11]

We first probed the CM of sterically demanding silyl ether **3** and bromo alkene **4** in the presence of different catalysts at 22 °C and under a vacuum of 7.0 torr (930 Pascal) to minimize post-CM isomerization and increase the reaction rate.[9a] 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[12] (5% *Z* isomer, 76–80% yield; Table 1, entries 1 and 2, respectively), reaction with MAP complex **8** (3.0 mol%) furnishes *Z*-**5** in 95:5 *Z*:*E* selectivity (69% yield; Table 1, entry 3). 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 by-product generation with the stereogenic-at-Mo catalyst.[13] Catalytic CM with the more sizeable arylimido-substituted complex **9** is less efficient (64% conv. vs. 79% conv. for **8**; Table 1, entry 4 vs. entry 3) and 19% of the undesired *E* alkene is formed, likely because of a smaller size difference between the arylimido and aryloxide ligands (vs. in **8**).[9a] The less active W–alkylidene **10**[14] delivers **5** with the highest *Z*:*E* ratio (> 95:5), albeit in 20% yield (Table 1, entry 5).

Next, we probed the effect of cross partner concentration (Table 2). Because reactions are carried out under vacuum, excess amounts of a relatively volatile terminal alkene might be needed; otherwise, 2.0–3.0 equivalents suffice (Table 2), and the reaction proceeds efficiently with as little as 1.0–

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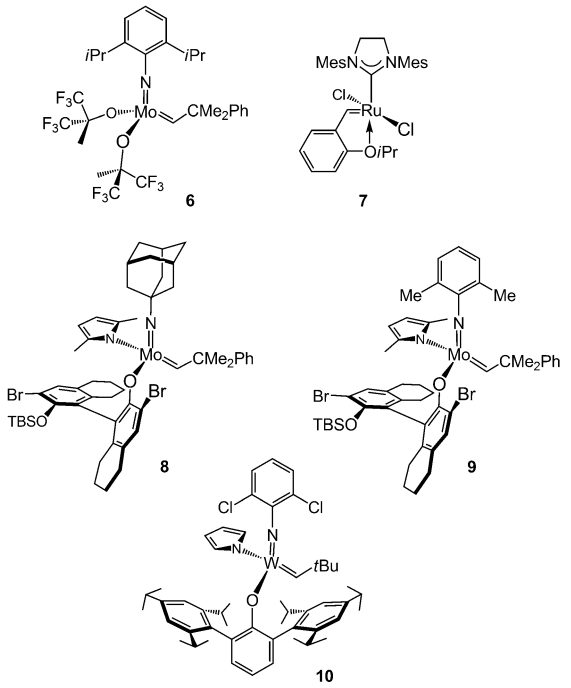
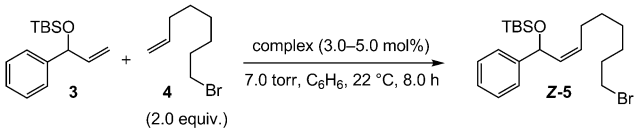


Scheme 2. Complexes used in the initial screening shown in Table 1. Mes = 2,4,6-trimethylphenyl.

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

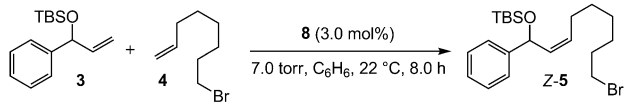


Entry	Complex; mol%[b]	Conv. [%][c,d]	Yield [%][e]	*Z*:*E* (**5**)[d]
1	**6**; 5.0	95	80	5:95
2	**7**; 5.0	98	76	5:95
3	**8**; 3.0	79	69	95:5
4	**9**; 5.0	64	62	81:19
5	**10**; 5.0	25	20	>95:5

[a] Reactions performed under N_2 atmosphere with a vacuum of 7.0 torr (930 Pascal). [b] Complexes **6**, **7**, and **10** were prepared separately before use, whereas **8** and **9** were synthesized from the corresponding bis(pyrrolide) and the chiral aryl alcohol (5.0 mol% each) and used in situ; 3.0 mol% of MAP complex **8** is available to catalyze the reaction because the generation of **8** leads to around 30% bis(aryloxide), which is significantly less active. [c] Conversions refer to consumption of the substrate (±2%). [d] Determined by ^{1}H NMR analysis of unpurified mixtures. [e] Yields of isolated and purified products. See the Supporting Information for details. TBS = *t*-butyl(dimethyl)silyl.

1.5 equivalent of alkene **4**. It is particularly noteworthy that *Z* selectivity is diminished when less **4** is present (Table 2, entries 1 and 2 vs. entries 3 and 4); 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 *Z* alkene product (**5**) to engender olefin isomerization. Another important point is

Table 2: Effect of cross partner concentration on efficiency of *Z*-selective CM.[a]



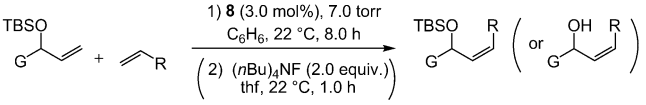
Entry	Equiv. of **4**	Conv. [%][b,c]	Yield [%][d]	*Z*:*E*[c]
1	1.0	56	45	91:9
2	1.5	67	65	90:10
3	2.0	79	69	95:5
4	3.0	72	65	95:5
5	10	<2	NA	NA

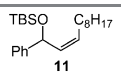
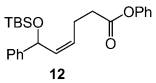
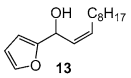
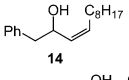
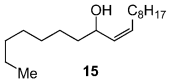
[a] Reactions performed under N_2 atmosphere with a vacuum of 7.0 torr (930 Pascal). [b] Conversions refer to consumption of the substrate (±2%). [c] Determined by ^{1}H NMR analysis of unpurified mixtures. [d] Yields of isolated and purified products. See the Supporting Information for details. NA = not applicable.

that a large excess of the less hindered alkene partner can be deleterious to CM efficiency (<2% **5** with 10 equiv **4**; Table 2, entry 5); rapid homodimerization of **4** probably leads to a burst of ethylene production and formation of a significant amount of the methylidene complex, which is exceptionally reactive and more prone to decomposition[15] (vs. alkylidenes derived from **3** or **4**).

A range of *tert*-butyl(dimethyl)silyl allyl ethers can be used (Table 3); the expected silyl ethers, or the corresponding alcohols (after deprotection; Table 3, entries 1–3 and 5) are isolated in 61–86% yield and 78:22–95:5 *Z*:*E* ratio. In one

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



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

[a] Reactions performed under N_2 atmosphere with a vacuum of 7.0 torr (930 Pascal) with 2.0–3.0 equiv. of the cross partner and 3.0 mol% of **8** (generated in situ). [b] Conversions refer to substrate consumption in the CM step (±2%). [c] Determined by ^{1}H NMR analysis of unpurified mixtures. [d] Yields of purified products. [e] Overall yield (for CM and desilylation). See the Supporting Information for details.

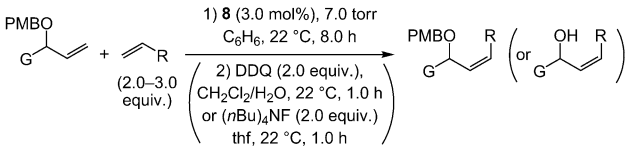
instance (Table 3, entry 4), CM does not proceed further than 43% conversion; this result might be due to unfavorable steric interactions arising from the propinquity of the phenyl moiety of the benzyl group, which happens to be positioned most proximally to the adamantylimido unit in the *syn*-substituted metallacyclobutane intermediate. In contrast, a shorter phenyl or a longer and more flexible phen-ethyl unit might engender a lower degree of steric repulsion with the aforementioned catalyst moiety (see below for additional data). Products bearing a relatively small *n*-alkyl substituent are isolated with lower *Z* selectivity (Table 3, entries 4 and 5 vs. 1–3). 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 groups. For example, after 4.0 h, **14** is isolated as an 85.15 *Z*:*E* mixture (38% conv.), and after 36 h, the *Z*:*E* ratio drops to 69:31 (81% conv.); similarly, the selectivity with which the TBS ether of **17** is generated is diminished significantly (from 82:18 in 4.0 h to 65:35 *Z*:*E* in 36 h).[16]

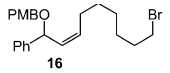
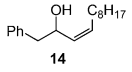
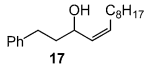
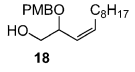
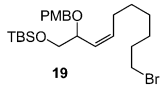
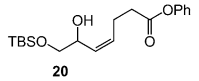
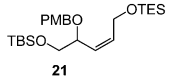
We then turned to CM of less congested *p*-methoxybenzyl ethers. Based on the aforementioned findings regarding the susceptibility of the comparatively exposed *Z* alkene products to isomerization (e.g., Table 2, entry 5), we were concerned whether high stereoselectivity can be retained at high conversion (vs. silyl ethers). Nevertheless, *Z*-disubstituted allyl ethers, or alcohols after oxidative deprotection, are obtained in 39–87% yield (over two steps; Table 4, entries 2–4 and 6) and, to our surprise, in 90:10 to greater than 98:2 *Z*:*E* ratios. Thus, high *Z* selectivity persists at late stages of CM, and disubstituted alkenes are isolated with generally higher stereoisomeric purity compared to silyl ethers (Table 3). The lower efficiency with which **14** is generated versus **16** and **17** (Table 4, entries 1–3) is consistent with the observation regarding the corresponding silyl ether (Table 3, entry 4).

Propargyl allyl silyl ethers were the third type of substrates examined, partly as a preamble to the stereoselective synthesis of the class of natural products shown in Scheme 1. The concern here was that, in spite of the presence of a silyl ether, the relatively small alkynyl substituent might expose the *Z* olefin product to post-metathesis isomerization. Again, as with the benzyl ethers in Table 4, in most instances, Mo-catalyzed CM proceeds readily and in 90:10 to greater than 98:2 *Z*:*E* ratio (Table 5). Only in the case of alkyl-substituted alkyne is none of the desired products formed (Table 5, entry 5).

Several unexpected stereoselectivity variations have notable mechanistic implications. The first set of observations relate to reactions of substrates that have smaller substituents and deliver higher *Z*:*E* ratios (Tables 4 and 5 vs. Table 3). The latter findings are in spite of the more hindered alkenes being expected to furnish alkene products that are better protected from post-CM isomerization and with higher kinetic *Z* selectivities.[9] The observed differences are probably tied to the relative abundance and reactivity of alkylidenes derived from various cross partners. Unlike complexes originating from the less hindered (non-allylic ether) monosubstituted olefins (cf. **A**, Scheme 3), those represented by **B**–**D** are more sizeable and less prone to causing post-CM isomerization.[17] With silyl ethers in Tables 1, 2, and 3, generation of **B** is less facile (vs. **C** or **D**),[18] and the more reactive **A** is present at a higher concentration. As a result, there is more extensive loss of stereoselectivity through reaction with the *Z* alkene product.

Table 4: Synthesis of various allyl *p*-methoxybenzyl (PMB) ethers through *Z*-selective catalytic CM.[a]

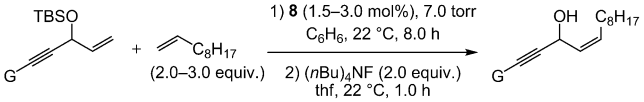


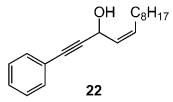
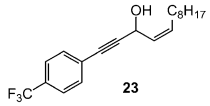
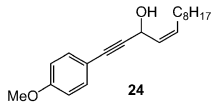
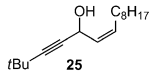
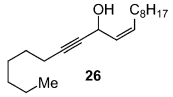
Entry	*Z* Alkene Product	Conv. [%][b,c]	Yield [%][d]	*Z*:*E*[c]
1	 **16**	90	85	>98:2
2	 **14**	43	39[e]	>98:2
3	 **17**	66	60[e]	>98:2
4	 **18**	93	87[f]	>98:2
5	 **19**	82	70	92:8
6	 **20**	89	87[e]	90:10
7	 **21**	91	72	92:8

[a] Reactions performed under N_2 atmosphere with a vacuum of 7.0 torr (930 Pascal) with 2.0–3.0 equiv. of the olefin cross partner. [b] Conversions refer to consumption of the substrate in the CM step (±2%). [c] Determined by ^{1}H NMR analysis of unpurified mixtures. [d] Yields of isolated and purified products. [e] Overall yields (for CM and debenzylation steps). [f] Overall yield (for CM and desilylation steps). See the Supporting Information for details. TES = triethylsilyl.

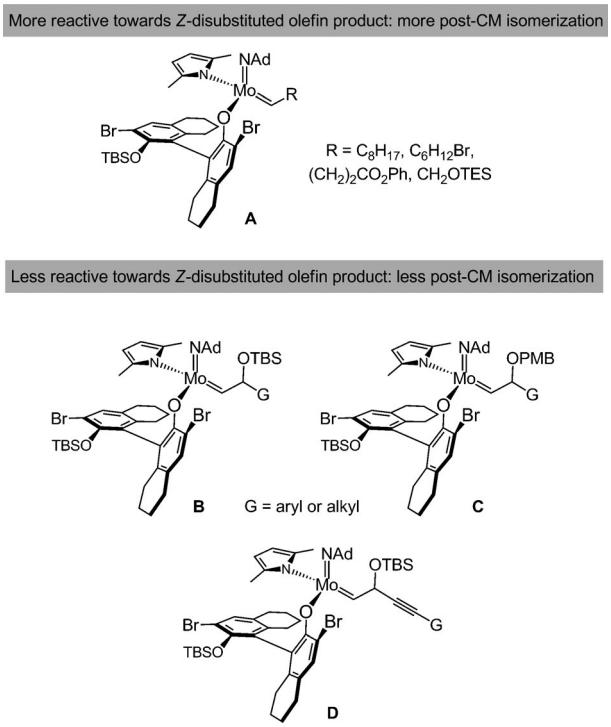
Another set of observations relates to the effect of alkyne substituents on catalytic CM (cf. Table 5). For instance, there is 84% conversion to *tert*-butyl-substituted **25** with only 1.5 mol% **8** after 1.0 h (Table 5, entry 4) as opposed to 66–72% conversion to **22**–**24** with twice the catalyst amount and longer reaction times (8.0 h; Table 5, entries 1–3). What is more, allylic ether **26** is not generated (Table 5, entry 5). To establish if the above reactivity trends are a result of catalyst deactivation or originate from lack of substrate reactivity, we performed the experiment shown in Scheme 4. When silyl ether **27**, which undergoes catalytic CM to afford **22** (cf. Table 5, entry 1), is subjected to the reaction conditions in the presence of **28**, disubstituted alkene **26** is, again, not formed and nor is any **22** detected (according to ^{1}H NMR analysis <2% conversion to any type of product). This finding illustrates that an uncongested internal alkyne can result in catalyst deactivation.[19] The proposed scenario explains the lower catalyst loading and shorter reaction time required for the larger *tert*-butyl-substituted alkyne substrate used in Table 5, entry 4 (1.5 mol% **8** in 1.0 h vs. 3.0 mol% in 8.0 h

Table 5: Synthesis of various alkynyl silyl ethers through *Z*-selective catalytic CM.[a]

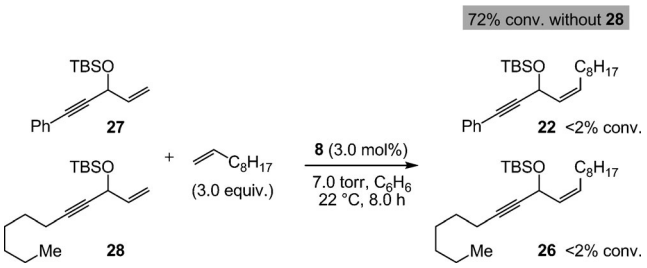


Entry	*Z* Alkene Product	Mol%; Conv. [%][b,c]	Yield [%][d]	*Z*:*E*[c]
1	 **22**	3.0; 72	68	>98:2
2	 **23**	3.0; 73	64	>98:2
3	 **24**	3.0; 66	60	>98:2
4	 **25**	1.5; 84	76	90:10
5	 **26**	3.0; <2	NA	NA

[a] Reactions performed under N_2 atmosphere with a vacuum of 7.0 torr (930 Pascal). [b] Conversions refer to consumption of the substrate in the CM step (±2%). [c] Determined by ^{1}H NMR analysis of unpurified mixtures. [d] Yields of isolated and purified products. See the Supporting Information for details.



Scheme 3. Different Mo–alkylidenes present in solution: their ease of formation and reactivity can influence the final *Z*:*E* ratios. Ad = adamantyl.



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.

for aryl-substituted variants in entries 1–3). The improved *Z* selectivity with aryl-substituted products **22**–**24** may be because there is, in spite of the higher loading, less active catalyst available to prompt olefin isomerization. The lower conversion in Table 5, entries 1–3 versus 4, are consistent with the suggested scenario. It is especially noteworthy that CM of alkyne-containing olefins cannot be efficiently promoted by Ru-based complexes such as **7**. For example, there is less than 2% conversion to any olefin metathesis products, including no detectable homodimerization of 1-decene, when the reaction involving a phenyl-substituted propargyl silyl ether (cf. Table 5, entry 1) is attempted with 5.0 mol% **7** (22°C, 16 h);[19] this observation is in contrast to the Ru-catalyzed CM with non-acetylenic substrates (e.g., Table 1, entry 2).

Stereoselective syntheses of falcarindiol and derivatives **2** and **35** demonstrate the utility of the *Z*-selective cross-metathesis (Scheme 5). CM of silyl ether **29** with 1-nonene and deprotection furnishes propargyl alcohol **30** in 94% overall yield and 92:8 *Z*:*E* ratio.[20] Subsequent Cu-catalyzed cross-coupling with alkynyl bromide **31** affords falcarindiol. Similarly, natural product **2** as well as its C16 epimer[21] can be synthesized in 56% overall yield; the corresponding CM proceeds in 92% yield and 92:8 *Z*:*E* selectivity. The preparation of the related analogue **2** by altering the structure of the cross partner, as well as synthesis of trocheliophorolide C (**35**)[22,23] further underscore the power of the catalytic CM as a stereoselective coupling strategy. The routes in Scheme 5 obviate the need for fragile *Z* enals and/or the difficulties in site-selective partial hydrogenation of polyalkynyl substrates.

Development of additional catalysts and methods for stereoselective olefin metathesis are in progress.

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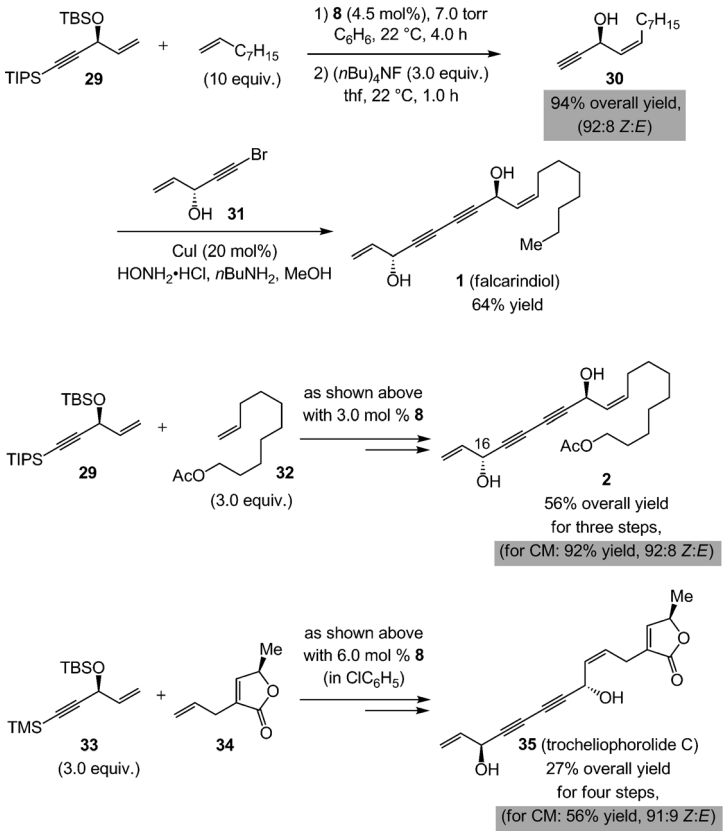

Scheme 5. Application of *Z*-selective CM of allylic ethers to the preparation of falcarindiol (**1**) and derivatives **2** and **35** (proposed structure), which possess anticancer, antifungal, and immunosuppressive activity. TIPS = triisopropylsilyl, TMS = trimethylsilyl.

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[9] Previously proposed models suggest that larger metallacyclobutane substituents engender increased steric repulsion with sizeable aryloxide ligand and thus cause higher *Z* selectivity. See: a) S. J. Meek, R. V. O'Brien, J. Llaveria, R. R. Schrock, A. H. Hoveyda, *Nature* **2011**, *471*, 461 – 466; for related studies, see: b) I. Ibrahem, M. Yu, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 3844 – 3845; c) M. Yu, I. Ibrahem, M. Hasegawa, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2012**, *134*, 2788 – 2799; d) E. T. Kiesewetter, R. V. O'Brien, E. C. Yu, S. J. Meek, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2013**, *135*, 6026.

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[12] Control experiments indicate that reactions with **6** and **7** are kinetically *E*-selective.

[13] Unlike reactions with Mo and W complexes **6** and **8**–**10**, around 10% of an isomeric 1,2-disubstituted product are derived from olefin-metathesis-based alkene isomerization/CM when Ru–carbene **7** is used.

[14] 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.

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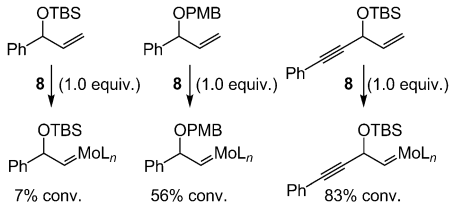
[16] The conversions indicated throughout this report correspond to the best balance between yield and *Z* selectivity, as further reaction can lead to *Z*-to-*E* isomerization.

[17] In complexes represented by **B** – **D**, the electron density at the alkylidene **C** is stabilized by the adjacent electron-withdrawing C–O bond, which lowers the 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.

[18] 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; by ^{1}H NMR analysis).



[19] Diminished catalyst activity might be due to deactivation of the resulting alkylidene by the sterically accessible alkyne, generation of a stable metallacyclobutene and/or its subsequent cleavage to afford a relatively unreactive disubstituted alkylidene. Detailed studies are in progress.

[20] An excess amount of the cross partner (10 equiv) is used in CM leading to **30** due to the relative volatility 1-nonene.

[21] Because of the distal relationship between the stereogenic centers in **2**, the precise stereochemical identity of the natural product is yet to be determined rigorously. Catalytic CM allows access to either isomer through the use of the enantiomerically pure alcohols. Control experiments indicate that there is no influence on the efficiency or *Z* selectivity of CM if enantiomerically pure catalyst/substrates are used in either isomeric form.

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[23] 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. For similar issues regarding the other members of this family of compounds, 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.

