Published in final edited form as:

Angew Chem Int Ed Engl. 2013 August 5; 52(32): . doi:10.1002/anie.201302538.

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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Keywords

allylic ethers; cross-metathesis; olefin metathesis; molybdenum; synthesis; Zolefins

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 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 faltarindiol^[5] (**1**, Scheme 1) and related derivatives (e.g., **2**,^[6] Scheme 1) 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 due to steric factors present a reactivity challenge, have not been disclosed. Also unexplored are related transformations that generate alkyne bearing products (cf. **1–2**, 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

**Financial support was provided by the NIH (GM-59426).

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alkyne-containing *Z* alkenes by catalytic partial hydrogenation may be hampered by issues of chemoselectivity and inseparable byproducts.

Herein, we outline the first examples of efficient catalytic CM processes that furnish *Z*-disubstituted allylic silyl or benzyl ethers; many products 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 >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 7.0 torr (930 Pascal) of vacuum to minimize post-CM isomerization and increase 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*, 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; 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.^[13] 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 aryloxo ligands (vs. in **8**).^[9a] The less active W alkylidene **10**^[14] delivers the highest *Z:E* ratio (>95:5), albeit in 20% yield (entry 5, Table 1).

Next, we probed the effect of cross partner concentration (Table 2). Since reactions are carried out under vacuum, excess amounts of a relatively volatile terminal alkene 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 alkene **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** with 10 equiv. **4**); rapid homodimerization of **4** probably leads to a burst of ethylene production and formation of a significant amount of the methyldiene complex, which is exceptionally reactive and more prone to decomposition^[15] (vs. alkylidenes derived from **3** or **4**).

A range of *t*-butyl (dimethyl) silyl allyl ethers can be used (Table 3); the expected silyl ethers, or the corresponding alcohols (after deprotection; entries 1–3 and 5, Table 3) are 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 arising from the propinquity of the phenyl moiety of the benzyl group which happens to be positioned most proximally to adamantylimido unit in the *syn*-substituted metallacyclobutane intermediate; in contrast, a shorter phenyl or a longer and more flexible phenethyl 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 (entries 4–5 vs. entries 1–3, Table 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 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.); similarly, the selectivity with which **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 the less 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 stereoselectivity can be retained at high conversion (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, to our surprise, in 90:10 to >98:2 *Z:E* ratios. Thus, not only does high *Z*selectivity persist at late stages of CM, 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** (entries 1–3, Table 4) is consistent with the observation regarding the corresponding silyl ether (entry 4, Table 3).

Propargyl-allyl silyl ethers were the third substrate type examined, partly as a preamble to stereoselective synthesis of the class of natural products 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 >98:2 *Z:E* ratio (Table 5). Only in the case of alkyl-substituted alkyne in entry 5 of Table 5, is none of the desired product formed.

Several unexpected stereoselectivity variations have notable mechanistic implications. The first set of observations relate to reactions of substrates with more diminutive substituents delivering higher *Z:E* ratios (Tables 4–5 vs. Table 3); this is 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] Such 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) mono-substituted 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 1–3, generation of **B** is less facile (vs. **C** or **D**),^[18] the more reactive **A** is present at a higher concentration; as a result, a larger degree of stereoselectivity loss through reaction with the product *Z*alkene ensues.

Another set of observations relates to the effect of alkyne substituents 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) as opposed to 66–72% conversion to **22–24** with twice the catalyst amount and longer reaction times (8.0 h; entries 1–3, Table 5). What is more, allylic ether **26** is not generated (entry 5, Table 5). To establish if the above reactivity trends are due to 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. entry 1, Table 5), is subjected to the reaction conditions in the presence of **28**, disubstituted alkene **26** is, again, not formed and nor is any **22** detected (<2% conversion to any type of product by ¹H NMR analysis); 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 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 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 entries 1–3 versus 4 of Table 5 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 <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. entry 1, Table 5) is attempted with 5.0 mol % **7** (22 °C, 16 h).^[19] This is in contrast to the Ru-catalyzed CM with non-acetylenic substrates (e.g., entry 2 of Table 1).

Stereoselective syntheses of faltarindiol and derivatives **2** and **35** demonstrate utility (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. Subsequent Cu-catalyzed cross-coupling with alkynyl bromide **31** affords faltarindiol. Similarly, natural product **2** as well as its C16 epimer^[20,21] can be synthesized in 56% overall yield; the corresponding CM proceeds in 92% yield and 92:8 *Z:E* selectivity. That the related analogue **2** can be prepared by 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. The routes in Scheme 5 obviate the need for fragile *Z*-enals and/or the difficulties in site-selective partial hydrogenation of poly-alkynyl substrates.

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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13. Unlike reactions with Mo and W 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.
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16. 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.
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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, C₆D₆; by ¹H NMR analysis).

19. Catalyst deactivation 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. Due to 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.

21. Excess cross partner (10 equiv.) is used in CM leading to 30 due to relative volatility of 1-nonene.
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As substrates in stereoselective reactions

used in various catalytic
enantioselective
allylic substitutions

used in stereoselective
reductive cross-couplings
with imines and aldehydes

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.

Scheme 2.

Various complexes used in the initial screening shown in Table 1.

More reactive towards Z-disubstituted olefin product: more post-CM isomerization

Less reactive towards Z-disubstituted olefin product: less post-CM isomerization

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.

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.

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 anti-cancer, anti-fungal and immunosuppressive activity.

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

Entry	Complex; Mol % ^[b]	Conv. [%] ^[c]	Yield [%] ^[d]	<i>Z</i> : <i>E</i> (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

Entry	Complex; Mol % ^[b]	Conv. [%] ^[c]	Yield [%] ^[d]	<i>Z</i> : <i>E</i> (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]Set up under N₂ atm. and performed under 7.0 torr (930 Pascal).^[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 ¹H 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.

Table 2Effect 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

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]Set up under N₂ atm. and performed under 7.0 torr (930 Pascal).^[b]Determined by analysis of ¹H 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.

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

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

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

^[a]Set up under N₂ atm. and performed under 7.0 torr (930 Pascal) 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 ¹H 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.

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

Entry	Z alkene product	Conv. [%] ^[b]	Yield [%] ^[c]	Z:E ^[b]
1		90	85	>98:2
2		43	39 ^[d]	>98:2
3		66	60 ^[d]	>98:2
4		93	87 ^[d]	>98:2
5		82	70	92:8
6		89	87 ^[d]	90:10
7		91	72	92:8

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

^[a]Set up under N₂ atm. and performed under 7.0 torr (930 Pascal); 2.0–3.0 equiv. of the olefin partner was used.

^[b] Determined by analysis of ¹H 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 debenzylolation steps).

^[e] Overall yield (for CM and desilylation steps). See the Supporting Information for details.

TES = triethylsilyl.

Table 5Synthesis 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

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

^[a]Set up under N₂ atm. and performed under 7.0 torr (930 Pascal).^[b]Determined by analysis of ¹H 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.