JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
Cite This: J. Am. Chem. Soc. XXXX, XXX, XXX-XXX
pubs.acs.org/JACS

Synthesis of *Z*- or *E*-Trisubstituted Allylic Alcohols and Ethers by Kinetically Controlled Cross-Metathesis with a Ru Catechothiolate Complex

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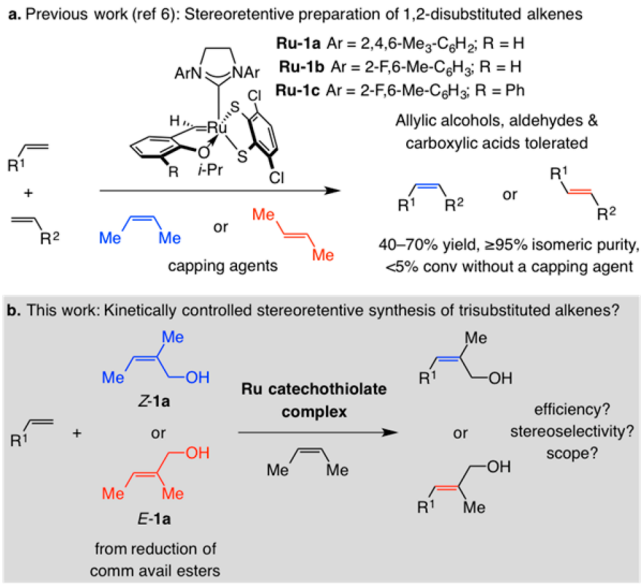
Supporting Information

ABSTRACT: The first examples of kinetically controlled cross-metathesis reactions that generate *Z*- or *E*-trisubstituted alkenes are disclosed. Transformations are catalyzed by ≤6.0 mol % of a Ru catechothiolate complex and afford trisubstituted allylic alcohols and ethers in up to 81% yield and >98% stereoisomeric purity. The method has considerable scope, as olefins containing an alcohol, an aldehyde, an epoxide, a carboxylic acid, or an alkenyl group may be used. Mechanistic models that account for the observed levels and trends in efficiency and stereochemical control are provided, based on DFT studies.

In 2013, we discovered that Ru catechothiolate complexes, prepared from readily accessible starting materials, can promote *Z*-selective ring-opening cross-metathesis (ROCM).[1,2] We subsequently demonstrated that yields, diastereoselectivities, and *Z* selectivities are higher when an allylic alcohol group is involved in ROCM[3] or cross-metathesis (CM),[4] and modification of the bidentate and/or the *N*-heterocyclic carbene (NHC) ligand can be beneficial (e.g., **Ru-1a**–**c**, Scheme 1a). Two features, the combination of which are unavailable in other stereoselective Ru- or Mo- and W-based catalyst systems,[4b,5] are notable: (1) The catalytic active Ru dithiolates are especially robust, and reactions may be performed in the presence of a Brønsted acid (e.g., a carboxylic acid), an electrophilic site (e.g., an aldehyde), a Lewis base (e.g., an amino acid), or a bulky allylic substituent.[4a,6] (2) Acyclic 1,2-disubstituted olefins may be used as substrates,[4a] a crucial attribute not shared by other Ru-based *Z*-selective catalysts,[4a] providing the opportunity for the development of efficient stereoretentive transformations. We recently demonstrated that with *Z*- or *E*-butene as capping agents,[6] the intermediacy of unstable methylidene complexes[4a,7] can be avoided and a considerable array of linear and macrocyclic *Z*- or *E*-alkenes, including those containing the aforementioned polar or hindered substituents, accessed efficiently and with high stereoisomeric purity.

A compelling unaddressed question is whether, through bypassing unstable methylidene species by the capping strategy,[6] Ru catechothiolate catalysts can promote efficient stereoretentive CM to generate trisubstituted *Z*- or *E*-alkenes (Scheme 1b). Such transformations would be challenging for several reasons, including the intermediacy of more congested metallacyclobutane (mcb) intermediates. CM protocols designed for synthesis of trisubstituted olefins are indeed scarce,[8] and the few extant methods afford the lower energy *E* isomer only in up to 80% selectivity[8a,c] as the result of smaller energy gaps between stereoisomers (vs 1,2-disubstituted alkenes).[9] Herein, we disclose the first examples of kinetically controlled CM processes that furnish trisubstituted olefins efficiently and with high *Z*:*E* or *E*:*Z* ratios.

Scheme 1



We focused on synthesis of trisubstituted allylic alcohols because these moieties are found in many biologically active compounds and have considerable utility in chemical synthesis (e.g., directed reactions[10]). There are a limited number of approaches to stereoselective synthesis of trisubstituted allylic alcohols, such as those involving α-alkoxy ketones[11] or alkynes.[12] CM offers a distinct and important disconnection, with considerable versatility owing to the relative stability of alkenes in the presence of strongly nucleophilic or basic reagents.

We first examined representative CM with dichloro complex **Ru-2** (Scheme 2). Regardless of whether 1,1-disubstituted allylic alcohol **1a** or *Z*- or *E*-**1b**[13] was used, the thermodynamically favored *E*-**3a** was formed predominantly (61–71% yield and 87–91% *E* selectivity).

We then probed the ability of Ru catechothiolate complexes to serve as catalysts (Table 1); all reactions were carried out in a

Received: September 21, 2017

DOI: 10.1021/jacs.7b10010
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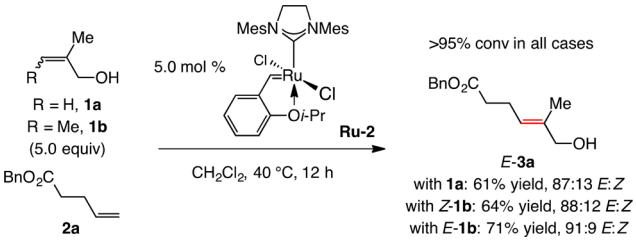
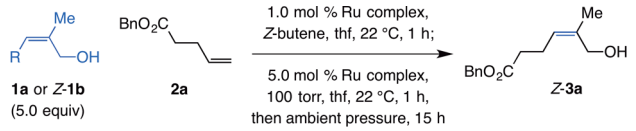
Scheme 2. Reactions with a Dichloro-Ru Complex[a]



[a]Conversion (loss of **2a**) determined by analysis of ^{1}H NMR spectra of unpurified mixtures. Yields correspond to purified products. See the Supporting Information for details.

single vessel. There was 82% consumption of the terminal alkene (**2a**) with 1,1-disubstituted olefin **1a** (entry 1). Analysis of the ^{1}H NMR spectrum of the product mixture indicated the major component to be derived from homometathesis of *Z*-methyl-substituted (capped)[6] **2a** (<5% **3a**). Reaction of *Z*-**1b** with **2a** in the presence of *Z*-butene (10 equiv) and 6.0 mol % **Ru-1a** afforded *Z*-**3a** in just 31% yield (81% conv) as a single stereoisomer (>98% *Z*; entry 2); thus, homometathesis of the capped terminal alkene derivative was again predominant. To increase CM efficiency, we turned to **Ru-1b**,[4c] a complex with a smaller NHC ligand (entry 3). Accordingly, under otherwise identical conditions, **3a** was isolated in 76% yield and >98% *Z*:*E* ratio. Further optimization (entries 4 and 5) revealed that with 5.0 equiv *Z*-**1b** and *Z*-butene, **3a** may be obtained in 74% yield, as pure *Z* isomers.[14] The data in entry 6 confirm the central role of the capping agent.[6] The transformation is scalable: 0.6 g **2a** was converted to 0.57g of *Z*-**3a** (77% yield, >98:2 *Z*:*E*).

Table 1. Initial Evaluation with Ru Catechothiolate Complexes[a]

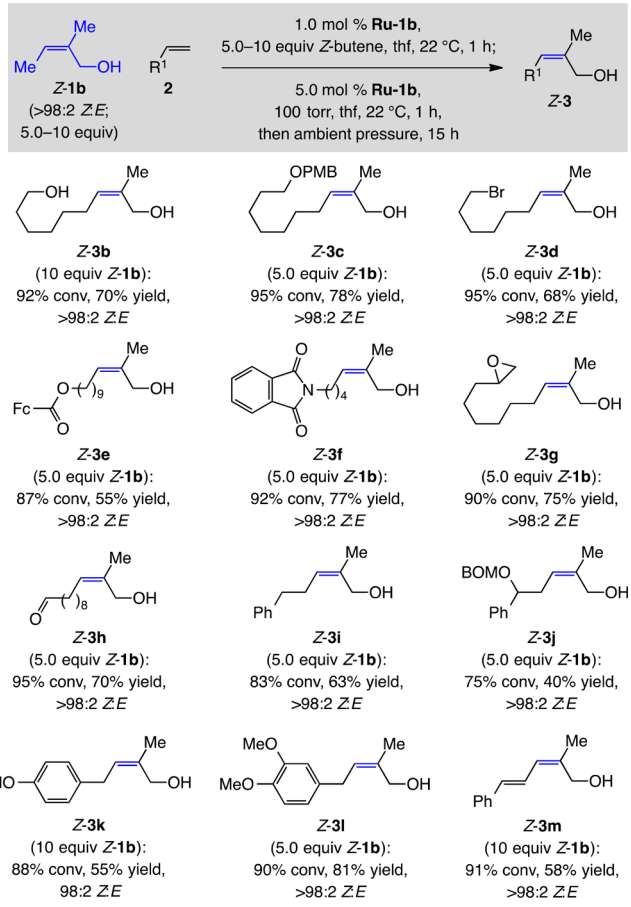


entry	Ru complex; allylic alcohol	equiv *Z*-**1b**; equiv *Z*-butene	conv (%);[b] yield (%)[c]	*Z*:*E*[b]
1	**Ru-1b**; **1a**	5.0; 5.0	82; <5	na
2	**Ru-1a**; *Z*-**1b**	5.0; 10	81; 31	>98:2
3	**Ru-1b**; *Z*-**1b**	5.0; 10	90; 76	>98:2
4	**Ru-1b**; *Z*-**1b**	3.0; 10	86; 65	>98:2
5	**Ru-1b**; *Z*-**1b**	5.0; 5.0	95; 74	>98:2
6	**Ru-1b**; *Z*-**1b**	5.0; none	21; 15	>98:2

[a]See the Supporting Information for details. [b]Conversion (loss of *Z*-Me-substituted alkene derived from **2a**) determined by analysis of ^{1}H NMR spectra of unpurified mixtures. [c]Yields correspond to purified products. na = not applicable.

Various *Z*-trisubstituted allylic alcohols were prepared in up to 81% yield and exceptional stereoisomeric purity (*Z*-**3b**-**3m**, Scheme 3). This included compounds with a hydroxy (*Z*-**3b**), a Lewis basic phthalimide (*Z*-**3f**), an epoxide (*Z*-**3g**), or an aldehyde (*Z*-**3h**). Comparison of the yields for *Z*-**3i** (63%) and *Z*-**3j** (40%) demonstrates that CM with *β*-branched alkenes can be more sluggish. Benzylic trisubstituted olefins *Z*-**3k** and *Z*-**3l** were isolated in 55% yield with 98:2 *Z*:*E* ratio and 81% yield and >98:2 *Z*:*E* ratio, respectively. The transformation leading to *Z*-**3k** was more efficient with 10 equiv *Z*-**1b** (vs 40% yield with 5.0 equiv).

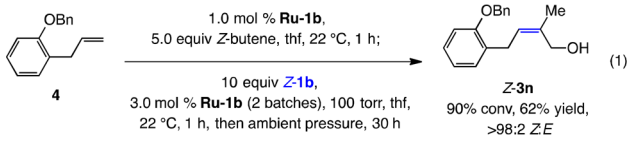
Scheme 3. Scope I: *Z*-Trisubstituted Allylic Alcohols[a]



[a]Same conditions as Table 1, except 10 equiv of *Z*-butene for *Z*-**3k**. Conversion (loss of *Z*-Me-substituted alkene from **2**) determined by analysis of ^{1}H NMR spectra of unpurified mixtures. Yields correspond to purified products. See the Supporting Information for details. Fc = ferrocenyl.

Chemoselective synthesis of *Z*,*E*-diene *Z*-**3m** further underscores utility.

The reaction leading to *o*-benzyloxy-substituted *Z*-**3n** (eq 1), recently used to prepare and ascertain the structure of naturally



occurring antiproliferative agent xiamenmycin A,[15] was challenging: use of 6.0 mol % **Ru-1b** in two equal portions was necessary. The *Z*-trisubstituted allylic alcohol was synthesized in 62% overall yield, compared to 67% reported before,[15] from a commercially available phenol (benzyl protection in 96% yield). This is more step-economical than the more traditional sequence (two vs four steps), as reduction of the enoate generated by a Horner–Wadsworth–Emmons reaction ($LiAlH_4$, thf, reflux) was not necessary.[15]

Another key attribute is showcased by reactions with *E*-**1b**.[13] The *E*-trisubstituted allylic alcohols were prepared with efficiency and stereoretention (Scheme 4) similar to those of the *Z* isomers (Scheme 3). Here too, the catalytic stereoretentive approach was broadly applicable.

DOI: 10.1021/jacs.7b10010
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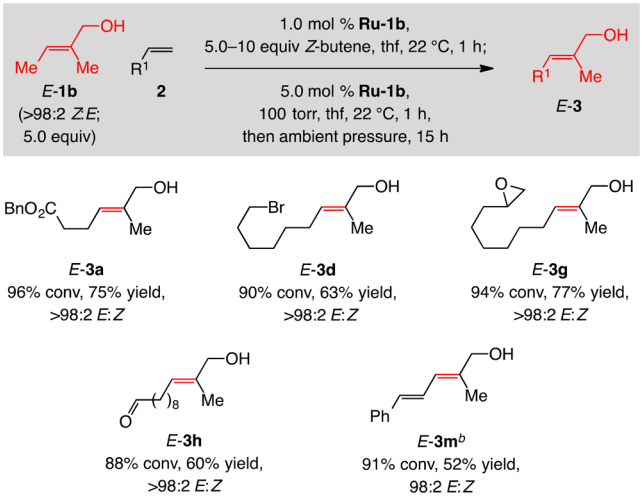
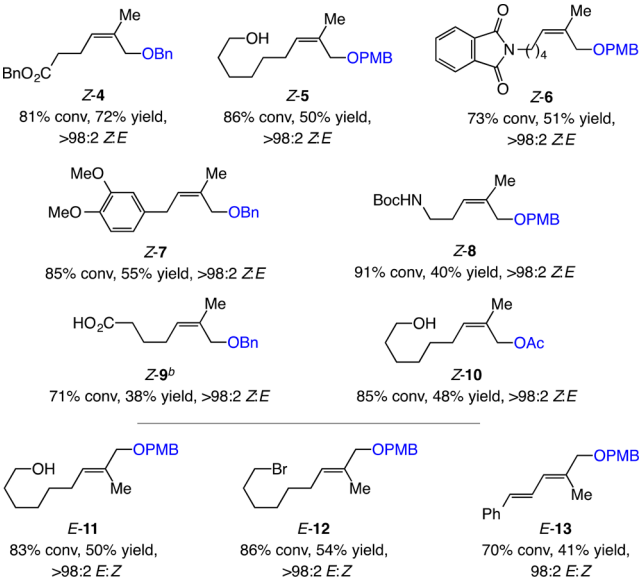
Scheme 4. Scope II: *E*-Trisubstituted Allylic Alcohols[a]



[a]Same conditions as Table 1; 5.0 equiv *Z*-butene used except for **3m** (10 equiv). Conversion (loss of *Z*-Me-substituted alkene derived from **2**) determined by analysis of ^{1}H NMR spectra of unpurified mixtures. Yields correspond to purified products. [b]10 equiv *E*-**1b** used. See the Supporting Information for details.

In *Z*-selective and diastereoselective ROCM with Ru catecholthiolate catalysts, unlike allylic alcohols, there is typically <5% conversion to the desired products when allylic ethers are used.[3a] This is however not the case here: CM under the same conditions used to obtain trisubstituted allylic alcohols afforded *Z*-**4** in 72% yield (81% conv) and >98:2 *Z*:*E* ratio (Scheme 5). Several other *Z*- or *E*-trisubstituted allylic ethers were accessed likewise, although yields were somewhat lower (vs allylic alcohols; Scheme 5). Carboxylic acid **9** and allylic acetate **10** were particularly difficult cases, and more of the trisubstituted allylic ether (10 and 20 equiv, respectively) was needed (38% and 48%, respectively). The high conversion implies that homometathesis of the *Z*-methyl-substituted olefin is facile but not the formation of the trisubstituted alkenes. The lower efficiency for *Z*-**9** may be attributed to competitive decomposition of the active Ru complex, a complication less problematic for reactions leading to 1,2-disubstituted alkenes.[4a] It should be emphasized that no other stereoselective catalyst class, Ru-based or otherwise, can be used for kinetically controlled synthesis of a stereoisomerically pure trisubstituted alkene that contains a carboxylic acid group.

Scheme 5. Scope III: *Z*- and *E*-Trisubstituted Allylic Ethers[a]



[a]Same conditions as in Table 1; 10 and 20 equiv allylic ether used for *Z*-**9** and *Z*-**10**, respectively. Conversion (loss of *Z*-Me-substituted alkene derived from α-olefin) determined by analysis of ^{1}H NMR spectra of unpurified mixtures. Yields correspond to purified products. [b]Same conditions as eq 1. See the Supporting Information for details.

Trisubstituted allylic ethers are formed more readily than their 1,2-disubstituted variants likely because in the corresponding mcb intermediates, the hydroxyl/alkoxy unit is attached to Cβ so that steric pressure is minimized (**II** vs Cα in **I**, Figure 1). There is accordingly lesser electron−electron repulsion between the heteroatom and the apical sulfide, dispensing with the need for H-bonding to counter unfavorable interactions.[3a]

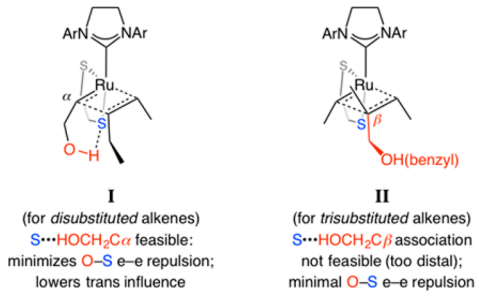
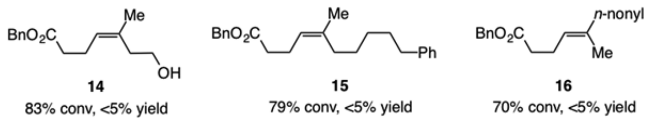


Figure 1. Unlike reactions leading to 1,2-disubstituted alkenes, H-bonding and e−e repulsion play less of a role en route to trisubstituted olefins.

CM between **2a** and some other trisubstituted olefins (Scheme 6) indicated that reactions involving the homoallylic alcohol derivative of *Z*-**1b** (cf. **16**) or those with an alkyl group give little of the desired products (<5% yield; 70−83% homometathesis). These findings, along with those in Table 1 and Schemes 3−5, show that an allylic heteroatom is needed for efficient transformation.

Scheme 6. Allylic Heteroatom Is Required for High Efficiency[a]



[a]Same conditions as Table 1. Conversion determined by analysis of ^{1}H NMR spectra of unpurified mixtures. See the Supporting Information for details.

To understand better why an allylic heteroatom is crucial to efficiency, DFT calculations were carried out.[16] We investigated the model reactions represented as **A**−**C** (Figure 2a). Congruent with the experimental results, the overall barriers for modes **A** and **C** (16.3 and 15.8 kcal/mol) were found to be lower than for **B** (17.9 kcal/mol).[17]

Transition-state analysis points to a rationale regarding the origin of the observed reactivity trends (Figure 2b). We propose that **ts1**$_B$ is higher in energy due to A(1,2) involving (C3−C4 and C2′−C3′) and A(1,3) strain[18] (involving C2−C3 and C2′−

DOI: 10.1021/jacs.7b10010
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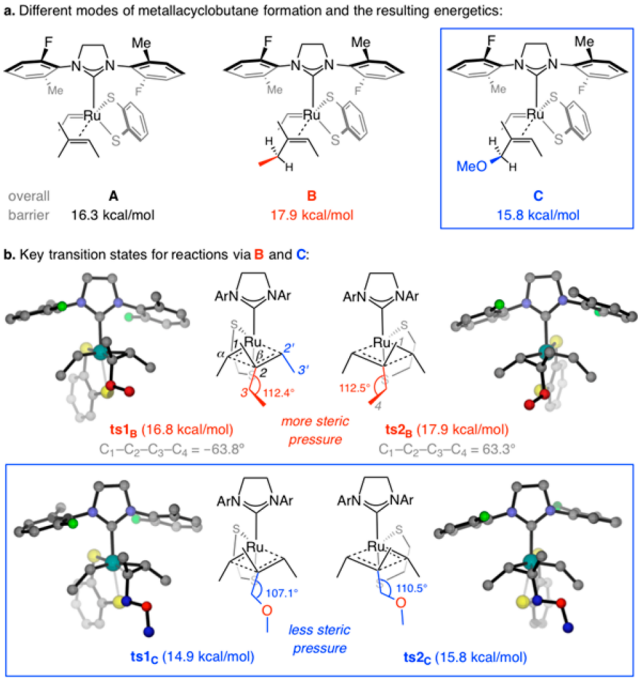

Figure 2. (a) Mechanistic analysis with model reactions that proceed via **A**–**C**. (b) Selected transition states with free energy values (PBE0-D3BJ/Def2TZVPP$_{thf(SMD)}$). See the Supporting Information for details. Ar = 2-F,6-MeC_6H_3; **ts** = transition state; SMD = solvation model based on density.

C3′); these unfavorable interactions are exacerbated as the mcb forms (namely, as sp^2-to-sp^3 rehybridization occurs). With the smaller methoxy group in **C**, steric pressure is diminished (Figure 1b); this is reflected in the smaller C^2–C^3–O bond angles, compared to those in **ts1**$_B$ and **ts2**$_B$ (107.1° and 110.5° vs 112.4° and 112.5°, respectively), which alleviate most of the strain.[16,19]

Development of additional Ru-based olefin metathesis catalysts and studies of their applications in stereoselective chemical synthesis are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b10010.

Experimental procedures, spectral and analytical data for all products, and calculations (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work is dedicated to Prof. Richard R. Schrock. Financial support was provided by the NSF (CHE-1362763). D.X. is a Kozarich Undergraduate Fellow. We thank M. S. Mikus and F. Romiti for insightful discussions.

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(13) Stereoisomerically pure *Z*- and *E*-**1b** can be easily prepared by reduction of commercially available carboxylic esters.

(14) Reaction with the corresponding enoate (precursor to *Z*-**1b**) leads to <2% conversion, probably due to low reactivity of the electron-deficient alkene and perhaps internal chelation within the derived Ru carbene. Studies to address this and related issues are in progress.

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(19) The *A* value for a methyl or an ethyl group is ~1.7–1.8, whereas it is ~0.6–0.7 for a hydroxy or methoxy group. The Charton values for the latter two units are not known. See: (a) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley Interscience: New York, 1994; pp 696–697. (b) Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 1552.

DOI: 10.1021/jacs.7b10010
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX