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Catalytic Cross-Metathesis Reactions That Afford *E*- and *Z*-Trisubstituted Alkenyl Bromides: Scope, Applications, and Mechanistic Insights

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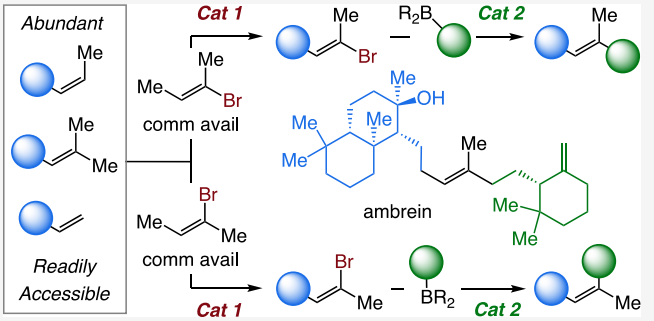
ABSTRACT: Stereochemically defined trisubstituted alkenes with a bromide and a methyl group at a terminus can be readily and stereoretentively derivatized through catalytic cross-coupling, affording unsaturated fragments found in many bioactive natural products. A direct method for generating such entities would be by stereocontrolled catalytic cross-metathesis (CM). Such methods are scarce however. Here, we present a stereoretentive strategy for CM between tri-, *Z*- or *E*-di, or monosubstituted olefins and *Z*- or *E*-2-bromo-2-butene, affording an assortment of *E*- or *Z*-trisubstituted alkenyl bromides. The majority of the transformations were catalyzed by two Mo monoaryloxide pyrrolide (MAP) complexes, one purchasable and the other accessible by well-established protocols. Substrates, such as feedstock trisubstituted olefins, can be purchased; the alkenyl bromide reagents are commercially available or can be prepared in two steps in a multigram scale. The catalytic process can be used to generate products that contain polar moieties, such as an amine or an alcohol, or sterically hindered alkenes that are α- or β-branched. The utility of the approach is highlighted by a brief and stereocontrolled synthesis of an unsaturated fragment of phomactin A and a concise total synthesis of ambrein. An unexpected outcome of these investigations was the discovery of a new role for the presence of a small-molecule alkene in an olefin metathesis reaction. DFT studies indicate that this additive swiftly reacts with a short-lived Mo alkylidene and probably helps circumvent the formation of catalytically inactive square pyramidal metallacyclobutanes, enhancing the efficiency of a transformation.



1. INTRODUCTION

Trisubstituted alkenes that contain a methyl and two *n*-alkyl groups but lack an allylic or a homoallylic polar group can be found within the framework of many bioactive compounds. Examples include sponalisolide B (bacteria quorum sensing inhibitor; Scheme 1a),[1] aplysinoplide C (antileukemic),[2] muqubilin (antibacterial),[3] phomactin A (PAF antagonist),[4] and ambrein (prized fragrant).[5] While most contain an *E* olefin, others, such as anticancer agent peloruside A,[6] bear a *Z*-trisubstituted alkene. Preparation of these olefins typically entails the pre-installment and removal of an activating group that might necessitate the use of strongly basic or forcing conditions (e.g., use of LDA or HMPA). Representative cases may be found in the reported total syntheses of ambrein (Scheme 1b).[7] In some instances,[5d,e] deletion of a secondary alcohol or a sulfone required several additional transformations, respectively, at times affording alkene regioisomers. In another case,[5f] a secondary heteroaryl sulfone and an aldehyde were condensed, affording (after deprotection) the target molecule as a stereoisomeric mixture.

An alternative strategy could involve catalytic olefin metathesis, but direct cross-metathesis (CM), that is, reaction between a mono- or disubstituted olefin and a 1,1-disubstituted or trisubstituted alkene, would be fraught with complications (Scheme 1c). Homo-metathesis (HM) of the less substituted alkene would be dominant and in the case of a monosubstituted olefin (G and/or G^1 = H) formation of a short-lived methylidene complex would lead to low efficiency.[8] A possibly more effective option would entail catalytic cross-coupling (CC), typically a stereoretentive process, between a stereo-defined trisubstituted alkenyl halide (Scheme 1d) and a monosubstituted alkyl-boron compound, which can be obtained by boron−hydride addition to a monosubstituted

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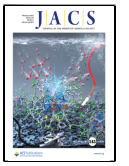

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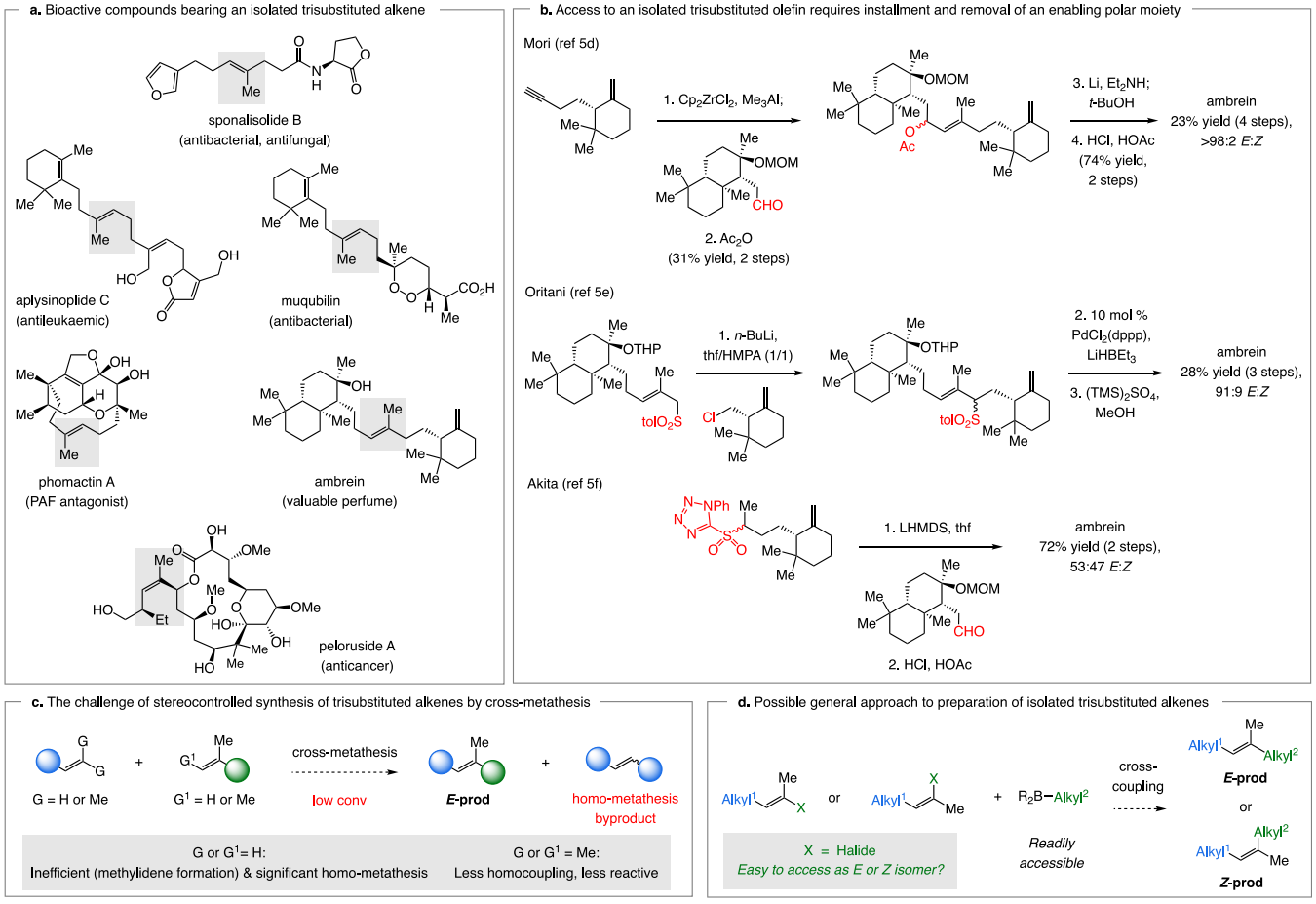
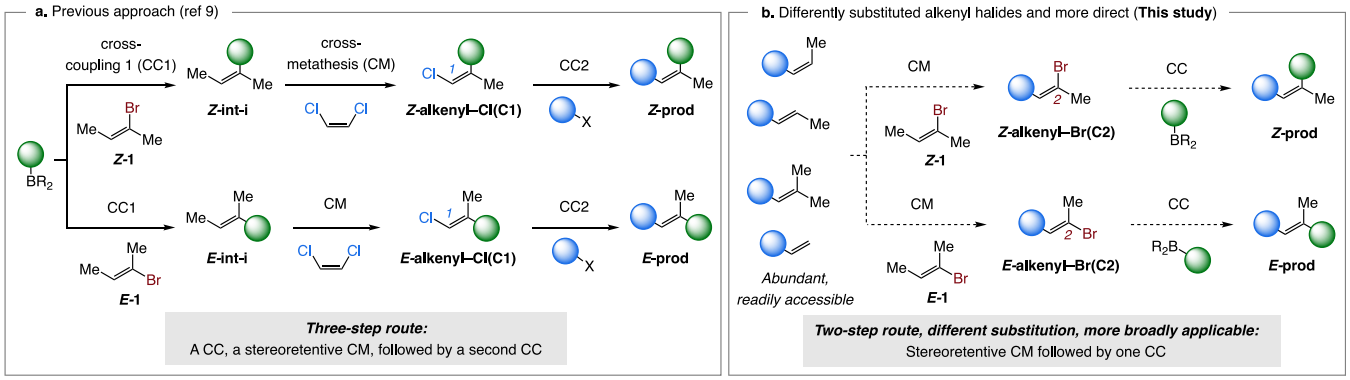
Scheme 1. Bioactive Compounds Containing All-Alkyl Trisubstituted Olefins: State-of-the-Art and Possible General Approach for Their Stereocontrolled Synthesis



Scheme 2. State-of-the-Art in Applying CM to Unfuctionalized Trisubstituted Alkene Synthesis and the Aim of This Study



olefin. The question then becomes: how might the requisite trisubstituted alkenyl halides be generated?

In search of a better way of accessing the above types of trisubstituted alkenes, we revisited a previous approach, one that comprises three reactions (Scheme 2a).[9] The first step is CC of an alkyl-boronate with *Z*- or *E*-2-bromo-2-butene (**Z**- or ***E*-1**), affording a trisubstituted *Z*- or *E*-trisubstituted alkene (**Z**- and ***E*-int-i**) with a methyl group at the less substituted carbon. This is followed by stereoretentive cross-metathesis (CM) with *Z*-1,2-dichloroethene to access *Z*- and *E*-trisubstituted alkenyl chlorides **Z**- and ***E*-alkenyl-Cl(C1)**. The final step is another CC, delivering the *Z*- or *E*-trisubstituted alkene products (**Z**- and ***E*-prod**).

A more concise alternative would entail CM between a tri-, di-, or monosubstituted alkene and **Z**- or ***E*-1** to afford **Z**- or ***E*-alkenyl−Br(C2)** (Scheme 2b); this time, the halogen would be connected to the more substituted C2 (vs C1 in **Z**- or ***E*-alkenyl−Cl(C1)**, Scheme 2a). The final trisubstituted alkenes would then be accessed by CC, completing a sequence that would probably be applicable to a wider range of alkenes. Not only a monosubstituted alkene (without the need for a priori formation of a C−B bond) but also a di- or trisubstituted alkene, several of which are renewable feedstock compounds,

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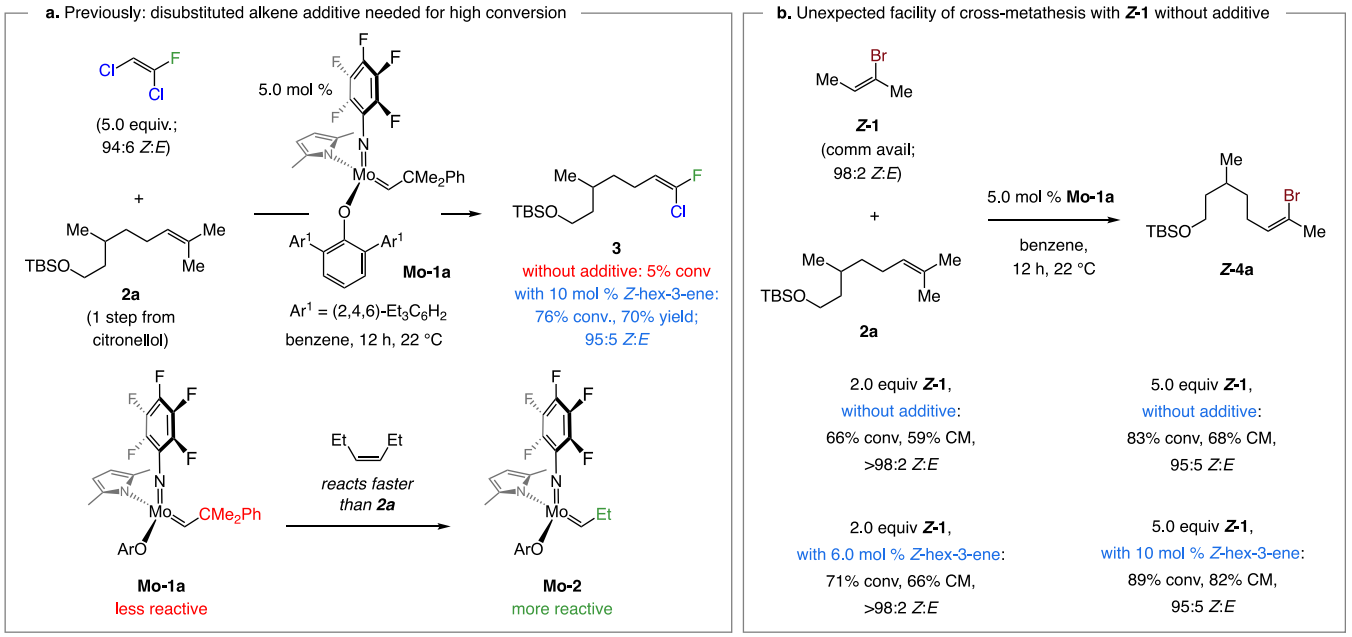
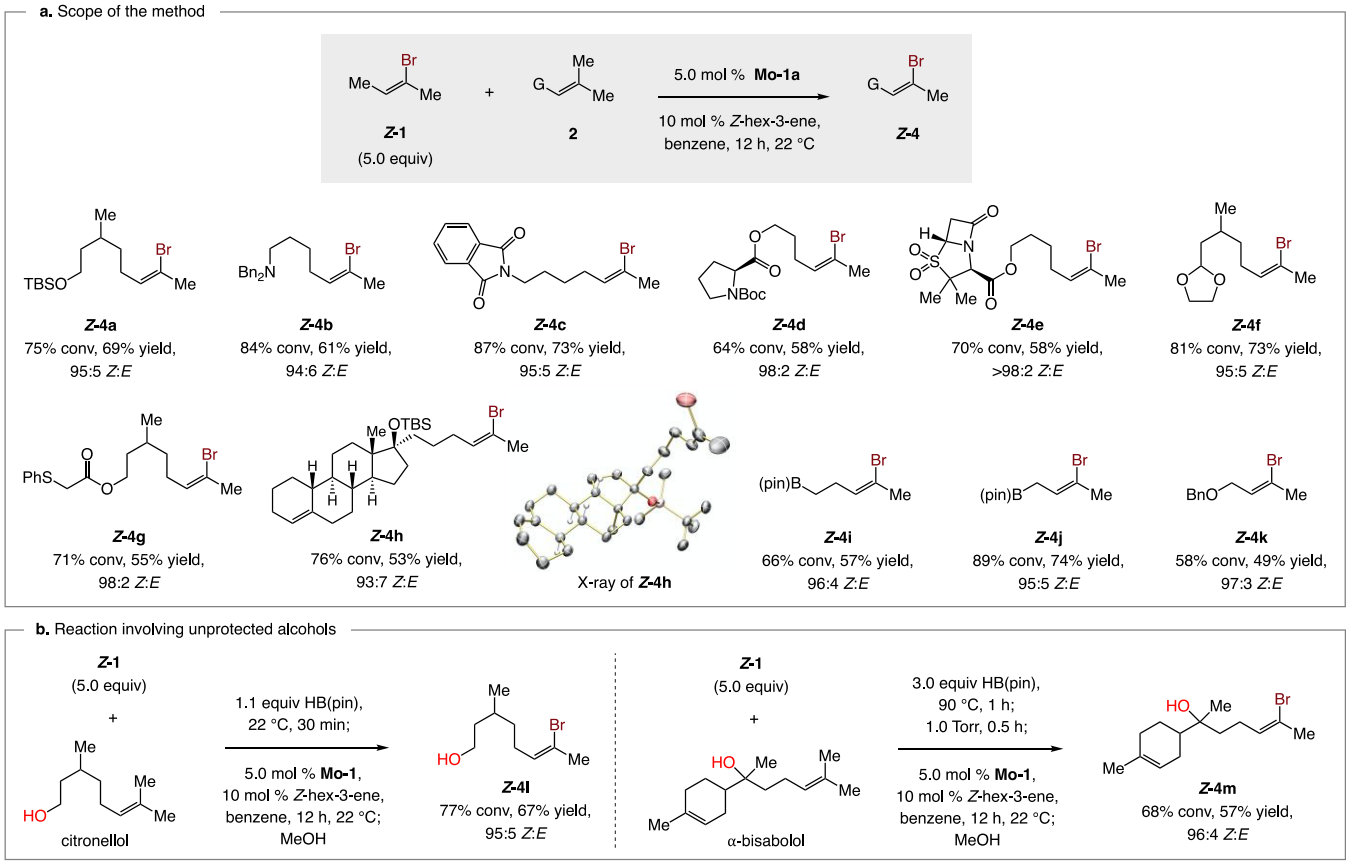
Scheme 3. Extant Data Regarding the Need for a Disubstituted Alkene Additive and Unanticipated Findings[a]



[a]Reactions performed under N_2 atm. Conversion (loss of **2a**) determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). See the Supporting Information for details. CM, cross-metathesis.

Scheme 4. Catalytic CM Reactions Involving *Z*-1 and a Trisubstituted Alkene[a]



[a]Reactions performed under N_2 atm. Conversion (loss of **2**) determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). See the Supporting Information for details. CM, cross-metathesis.

could then be used. Moreover, the ability to generate a trisubstituted olefin in either stereoisomeric form by altering the alkenyl bromide reagent enables efficient synthesis of a target compound as well as analogs with distinct shapes,

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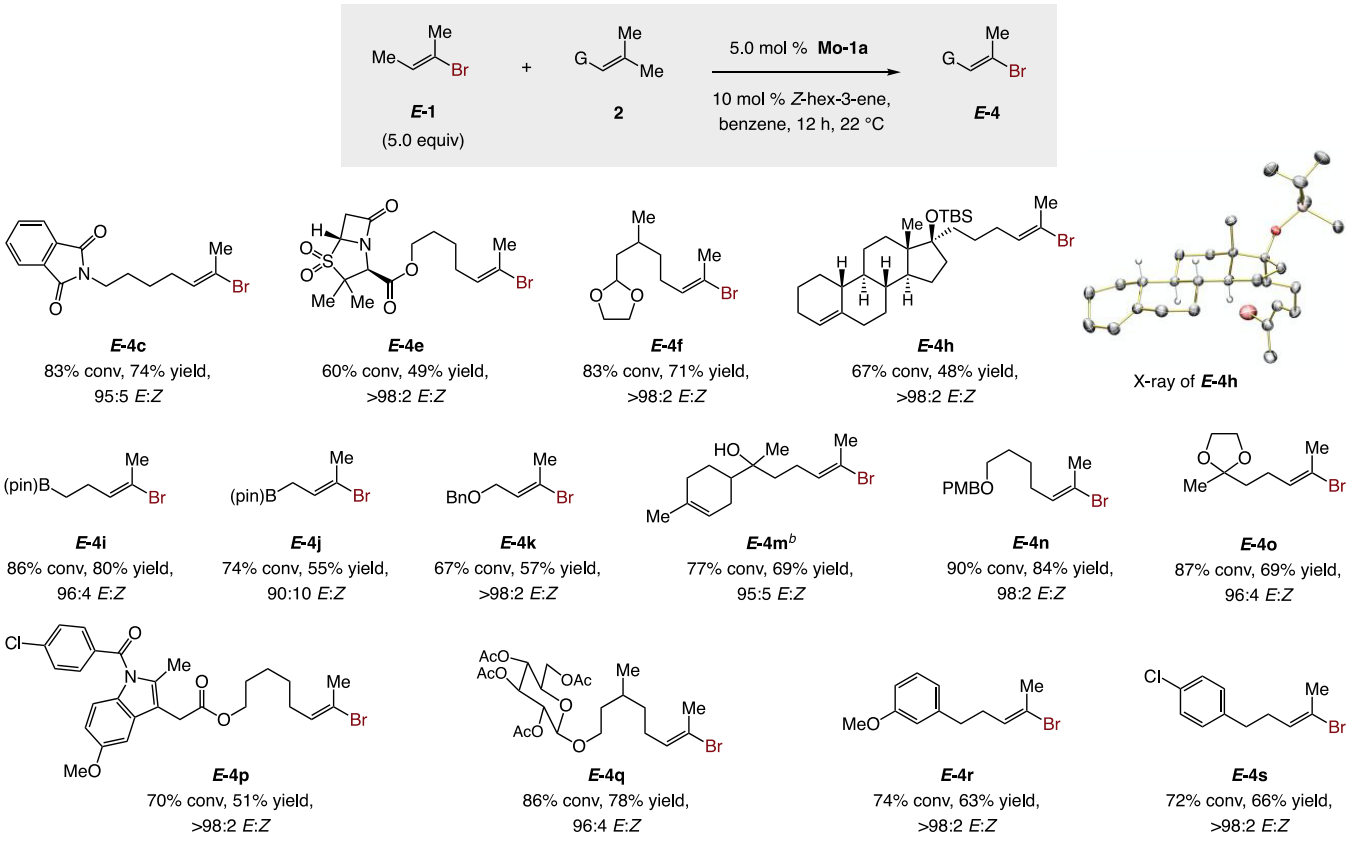
Scheme 5. Stereoretentive CM Involving a Trisubstituted Alkene and *E*-1[a]



[a]Reactions performed under N_2 atm. Conversion (loss of **2**) determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). [b]Traceless masking procedure applied (see Scheme 4b). See the Supporting Information for details.

capable of exhibiting a unique bioactivity profile.[10] An account of investigations designed to realize such a plan is provided below.

2. RESULTS AND DISCUSSION

2.1. Method Development. *2.1.1. Selecting the Alkene Type and an Unexpected Mechanistic Twist.* We began our studies with exploring the CM reactions of trisubstituted alkenes that contain a dimethyl terminus. These fragments can be found in a myriad of natural products, some are feedstock (e.g., citronellol) compounds and others have notable bioactivity (e.g., antidepressant/antibacterial/antimalarial hyperforin or antibacterial/antioxidant nemorosone).[11] What was appealing was the possibility of transforming these structures, by a single catalytic process, to an *E*- or *Z*-trisubstituted alkenyl bromide, which could in turn be used for analog generation. As represented by CM between citronellol-derived **2a** and *Z*- or *E*-1,2-dichloro-1-fluoroethene (Scheme 3a), recent studies had shown that transformations involving two trisubstituted olefins are possible if an appropriate small alkene additive were to be present (<5% conv otherwise).[12] The positive impact of the additive was attributed to rapid formation of the more reactive **Mo-2** (Scheme 3a).

As a control experiment, we subjected **Z-1** and **2a** to 5.0 mol % **Mo-1a** in the absence of an alkene additive. We expected minimal transformation. Surprisingly, however, there was 59% conversion to **Z-4a**, which was formed as a single stereoisomer (>98:2 *Z*:*E*). With more **Z-1** (5.0 equiv), the CM was somewhat more efficient (68% conv to **4a**) but less stereoretentive (95:5 *Z*:*E*). Efficiency increased only slightly when 6.0−10 mol % *Z*-hex-3-ene was added (for 2.0 and 5.0 equiv **Z-1**: 66% and 82% conv to **4a** and >98:2 and 95:5 *Z*:*E*, respectively). The additive effect was therefore not nearly as dramatic as was the case with trihalo alkenes.[12] These findings revealed two points: (1) Stereoretentive CM can be used to obtain trisubstituted alkenyl bromides efficiently (at least to generate a *Z* isomer). (2) In contrast to what we had originally proposed,[12] the origins of the considerable impact of an additive in CM reactions with *Z*- or *E*-1,2-dichloro-1-fluoroethene (Scheme 3a) are not only because of the formation of a more reactive alkylidene and faster catalyst initiation (see Section 2.3 for further analysis).

2.1.2. CM between Two Trisubstituted Alkenes, Generating Z-Trisubstituted Alkenyl Bromides. Reactions with various trisubstituted alkenes, bearing different heteroatomic substituents, afforded the desired *Z*-alkenyl bromides in 49−74% yield and 93:7 to >98:2 *Z*:*E* ratio (see **Z-4a−k**, Scheme 4a). Tertiary amines (e.g., **Z-4b**), imides and amides (e.g., **Z-4c** and **Z-4e**), sulfones (e.g., **Z-4e**), acetals (e.g., **Z-4f**), and sulfides (e.g., **Z-4g**) reacted readily and stereoretentively. When a substrate contained two trisubstituted alkenes, the less sterically hindered site reacted preferentially (e.g., **Z-4h**). Organoboron products **Z-4i** and **Z-4j** may be used in further C−C bond forming reactions.[13] Although somewhat less efficient, synthesis of **Z-4k** showed that trisubstituted alkenes bearing an allylic ether are suitable substrates. Feedstock trisubstituted alkenes were used directly: in situ protection of citronellol and α-bisabolol (Scheme 4b), effected through

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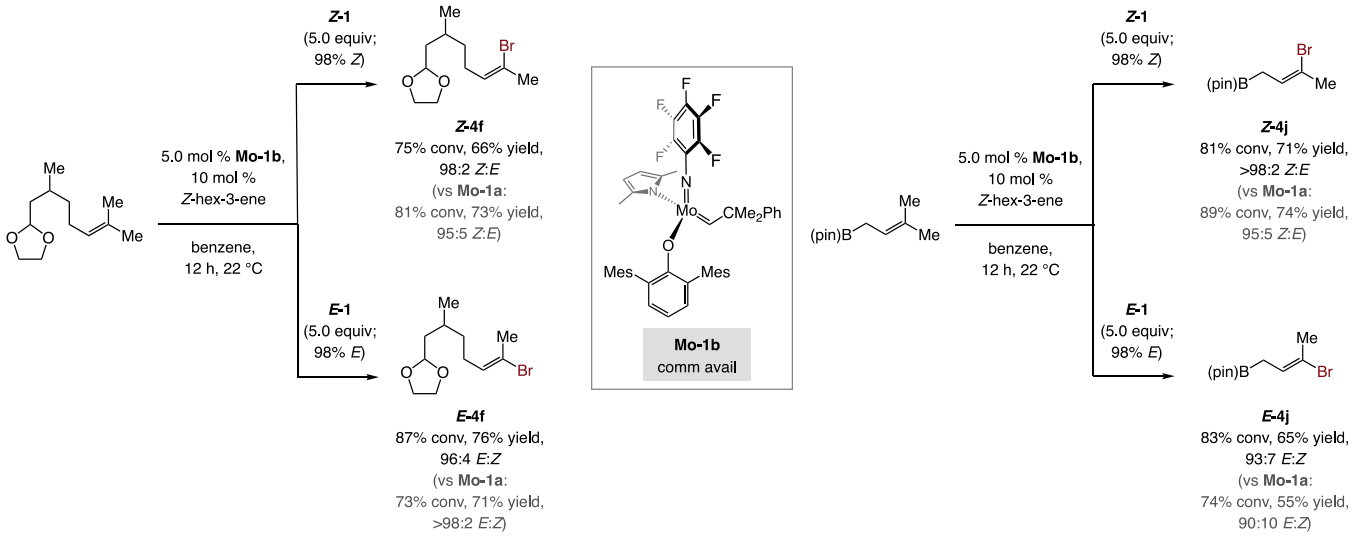
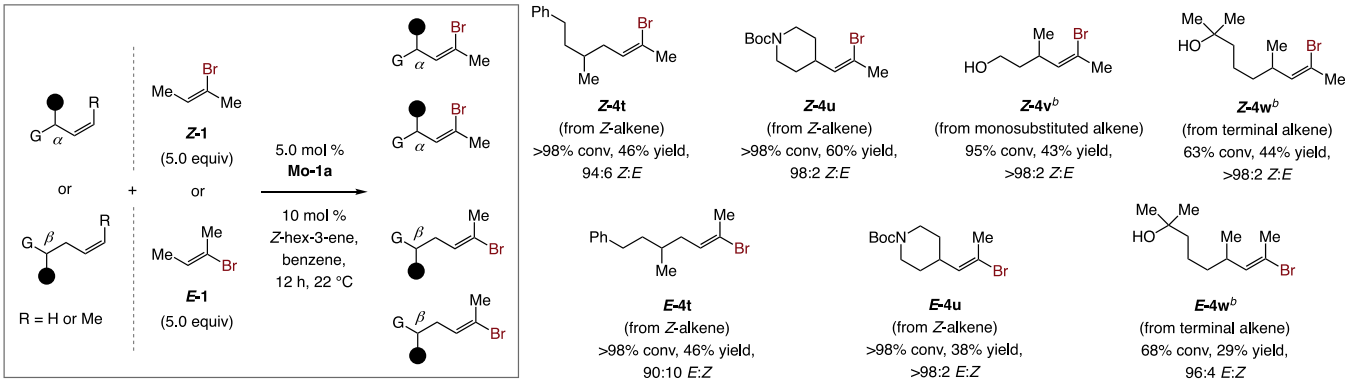
Scheme 6. Purchasable Mo Complex Gives Similar Results[a]



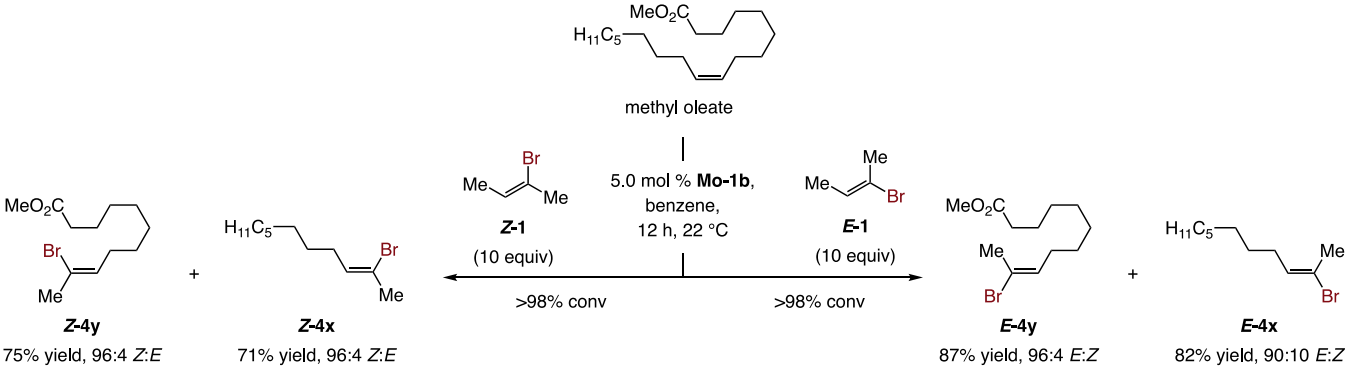
[a]Reactions performed under N_2 atm. Conversion (loss of trisubstituted olefin) determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). See the Supporting Information for details.

Scheme 7. CM of Sterically Demanding Alkenes[a]



[a]Reactions performed under N_2 atm. Conversion (loss of non-halogen-containing olefin) determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). [b]Traceless masking procedure was applied (see Scheme 4b). See the Supporting Information for details. CM, cross-metathesis.

Scheme 8. Conversion of a Feedstock Disubstituted Alkene to *E*- and *Z*-Trisubstituted Alkenyl Bromides[a]



[a]Reactions performed under N_2 atm. Conversion (loss of methyl oleate) determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). See the Supporting Information for details.

treatment with commercially available HB(pin),[14] was followed by CM and unmasking during workup (MeOH). We were accordingly able to access alkenyl bromides **Z-4l** and **Z-4m** in 67% and 57% yield and 95:5 and 96:4 *Z*:*E* ratio, respectively.

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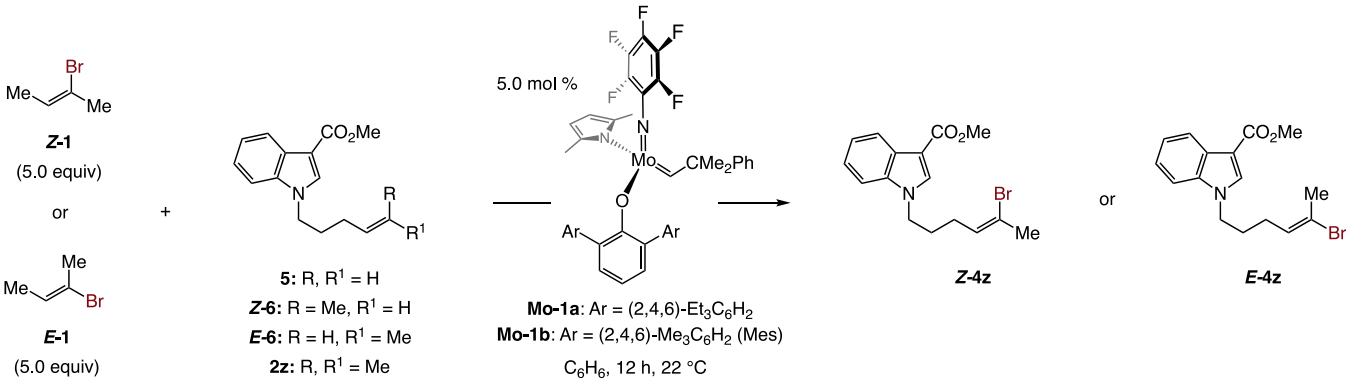
Table 1. CM Involving Trisubstituted Alkenyl Bromides *Z*- and *E*- and Different Types of Alkenes[a]



entry	alkenyl–Br	alkene	complex	major product	conv (%);[b] conv to **4z** (%)[b]	selectivity[b]	yield (%)[c]
1	***Z*-1**	**5**	**Mo-1a**	***Z*-4z**	89; 52	>98:2 *Z*:*E*	54
2	***Z*-1**	***Z*-6**	**Mo-1a**	***Z*-4z**	>98; 77	97:3 *Z*:*E*	80
3	***Z*-1**	***E*-6**	**Mo-1a**	***Z*-4z**	>98; 62	98:2 *Z*:*E*	64
4	***Z*-1**	**2z**[d]	**Mo-1a**	***Z*-4z**	66; 61	98:2 *Z*:*E*	62
5	***E*-1**	**5**	**Mo-1b**	***E*-4z**	93; 60	94:6 *E*:*Z*	58
6	***E*-1**	***Z*-6**	**Mo-1b**	***E*-4z**	>98; 76	95:5 *E*:*Z*	81
7	***E*-1**	***E*-6**	**Mo-1b**	***E*-4z**	>98; 79	95:5 *E*:*Z*	81
8	***E*-1**	**2z**[d]	**Mo-1a**	***E*-4z**	67; 63	95:5 *E*:*Z*	52

[a]Reactions performed under N_2 atm. [b]Conversion (loss of non-halogen-containing alkene) and selectivities determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). [c]Yields of purified products (±5%). [d]*Z*-hex-3-ene (6.0 mol %) used as an additive. See the Supporting Information for details.

2.1.3. CM between Two Trisubstituted Alkenes, Generating E-Trisubstituted Alkenyl Bromides. CM was similarly efficient and stereoretentive when ***E*-1** was used under otherwise identical conditions (Scheme 5). An assortment of *E*-trisubstituted alkenyl bromides was thus prepared directly in 48–84% yield and 90:10 to >98:2 *E*:*Z* selectivity.

2.1.4. Similar Results Can be Obtained with Two Different Complexes. Whereas, as noted above, **Mo-1a** typically affords the highest yields and stereoretentivities, use of a closely related complex, **Mo-1b**, which is commercially available, can lead to results that are similar (Scheme 6). A purchasable Mo complex can therefore be used for the large majority of transformations of this class.

2.1.5. CM with a Mono- or a 1,2-Disubstituted Alkene to Generate a Z- or E-Trisubstituted Alkenyl Bromide. Although we were able to convert trisubstituted olefins with a relatively sizeable moiety, such as an allyl–B(pin) (see ***Z*-** and ***E*-4j**), to the derived alkenyl bromides with reasonable efficiency, hardly any reaction was observed with an α- or a β-branched olefin (<5% conv). In these instances, a 1,2-disubstituted or a monosubstituted olefin should be used, as illustrated by stereoretentive synthesis of ***Z*-4t** and ***Z*-4u-w** as well as ***E*-4t**, ***E*-4u**, and ***E*-4w** (Scheme 7). The most challenging transformations were those affording products wherein certain conformations would be destabilized by A(1,3)-allylic strain (i.e., ***E*-4u** and ***E*-4w**).

Another notable class of disubstituted alkene substrates is the naturally occurring unsaturated fatty acids. Stereocontrolled transformation of these feedstock compounds, performed with purchasable **Mo-1b**, can lead to access stereodefined and readily modifiable *E*- or *Z*-trisubstituted alkenyl bromides. The examples regarding stereoretentive CM of methyl oleate to ***E*-4x** and ***Z*-4x** and ***E*-4y** and ***Z*-4y** are illustrative (Scheme 8).

2.1.6. CM Reactions with Differently Substituted Olefins. For a systematic comparison of the effectiveness of different types of olefin substrates, processes involving monosubstituted olefin **5**, 1,2-disubstituted alkenes ***Z*-** and ***E*-6** and trisubstituted olefin **2z** were investigated (Table 1). The desired products were obtained in highly enriched forms as either stereoisomer (97:3–98:2 *Z*:*E* and 94:6–95:5 *E*:*Z*) and in 52–81% yield, regardless of alkene substitution. Similar to the case of methyl oleate (see Scheme 8), CM with either **Mo-1a** or **Mo-1b** was effective. A larger gap between total conversion (disappearance of the limiting agent, the non-halogen-containing alkene) and conversion to ***Z*-** or ***E*-4z** for the monosubstituted olefin is on account of differing degrees of HM (entries 1 and 5, Table 1). In contrast, the values are more similar for reactions with trisubstituted alkene **2z** (entries 4 and 8). Therefore, the middle ground, namely, transformations with 1,2-disubstituted alkenes, proved to be the most efficient. Viewed from another angle, total conversion is highest for 1,2-disubstituted olefins, probably because these compounds inherently react faster than trisubstituted olefins and, unlike when terminal alkenes are involved, there is no methylidene complex (unstable) formation.[8] Moreover, while a 1,2-disubstituted olefin, which may be used as a *Z* or an *E* isomer, is less reactive than a monosubstituted alkene, it is also less prone to HM, and although more susceptible to HM compared to a trisubstituted olefin, it can re-enter the catalytic cycle and be converted to the CM product. Overall, depending on the type of alkene being used, efficient and stereoretentive CM can be performed with the necessary condition variations so that a desired outcome can be reached.

2.2. Demonstration of Utility. *2.2.1. Application to the Phomactin A Fragment.* We first focused on demonstrating how the catalytic method can facilitate access to the sparsely functionalized fragment of phomactin A. Previously (Scheme 9a),[15] alkenyl bromide ***E*,*E*-10**, an intermediate in phomactin A

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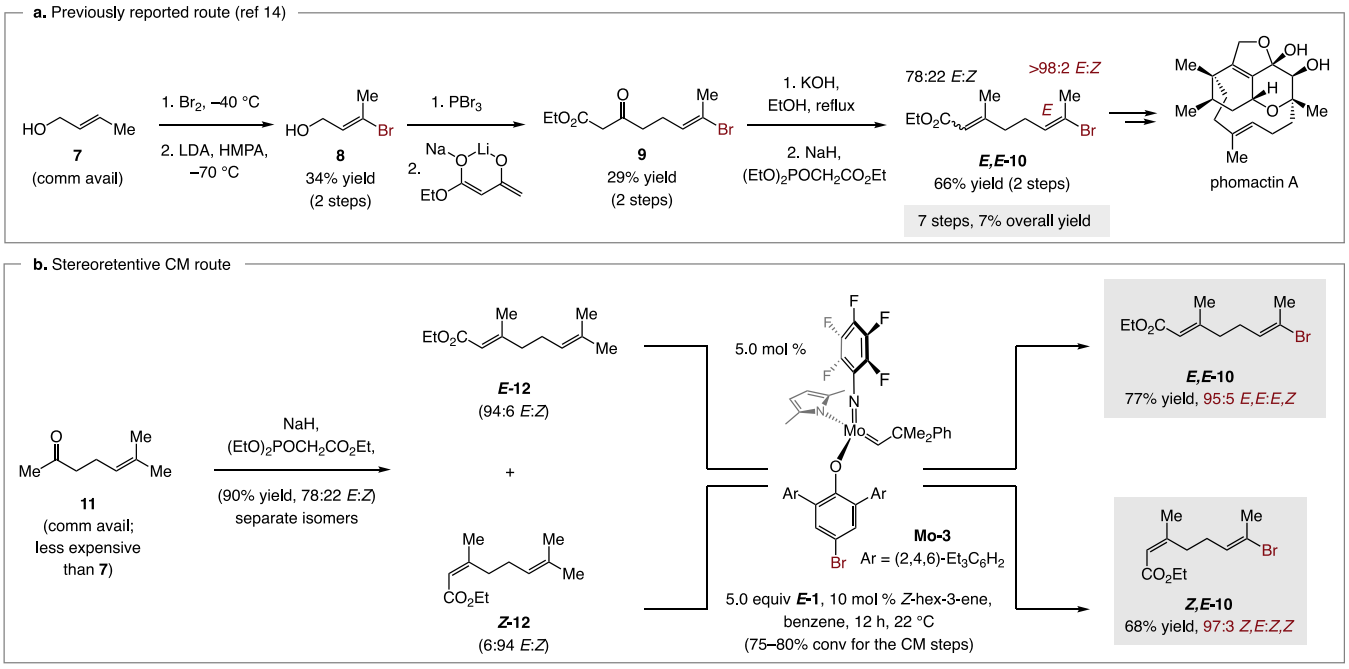
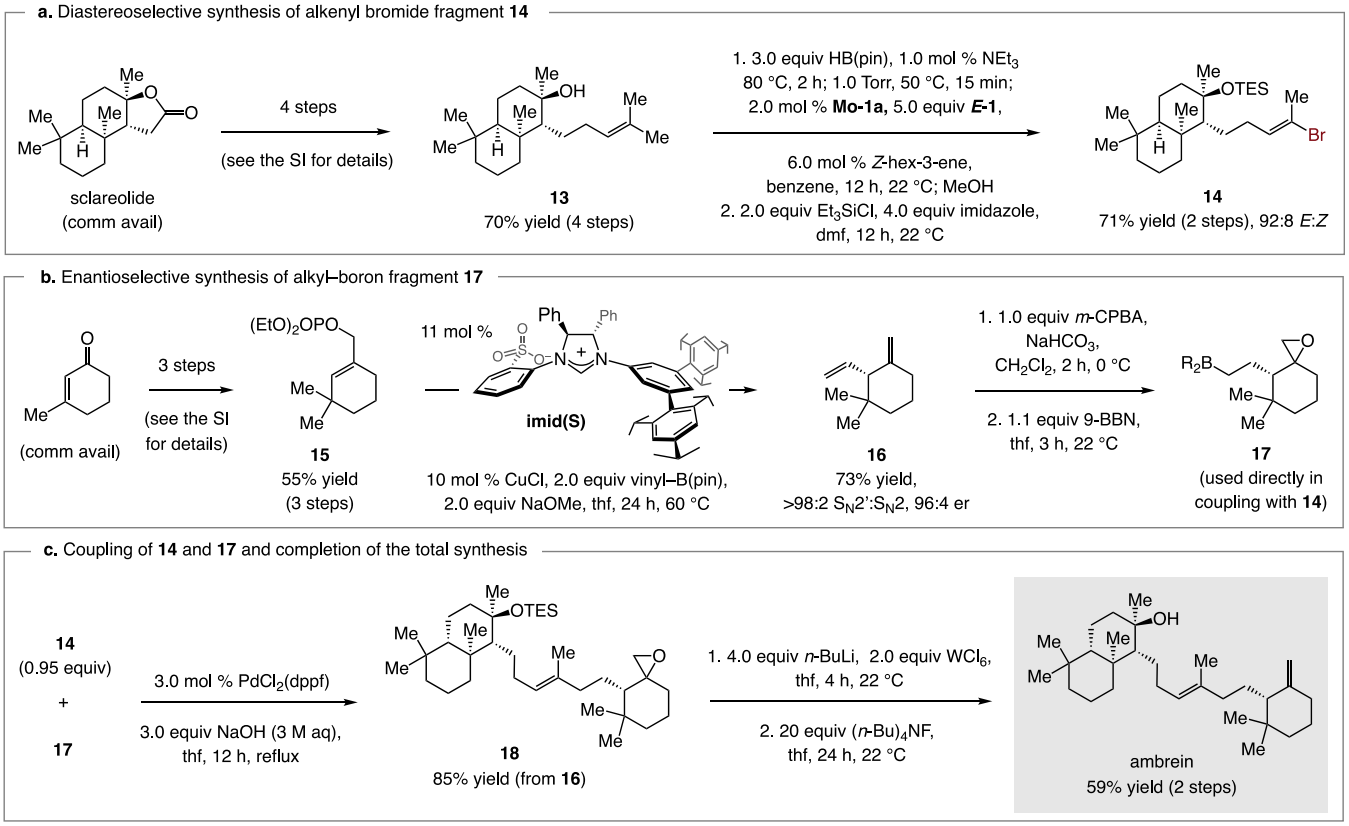
Scheme 9. Application to Stereoselective Synthesis of a Fragment of Phomactin A[a]



[a]Reactions performed under N_2 atm. For the CM steps, conversion (loss of non-halogen-containing alkene) and selectivities determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). See the Supporting Information for details.

Scheme 10. Application to a Convergent Total Synthesis of Ambrein[a]



[a]Reactions performed under N_2 atm. Stereoisomeric purity determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). See the Supporting Information for details.

total synthesis, was prepared in ~7% overall yield by a seven-step route starting with commercially available allylic alcohol **7**. Although the alkenyl bromide moiety was generated as a single isomer (>98:2 *E*:*Z*), the trisubstituted enoate moiety consisted

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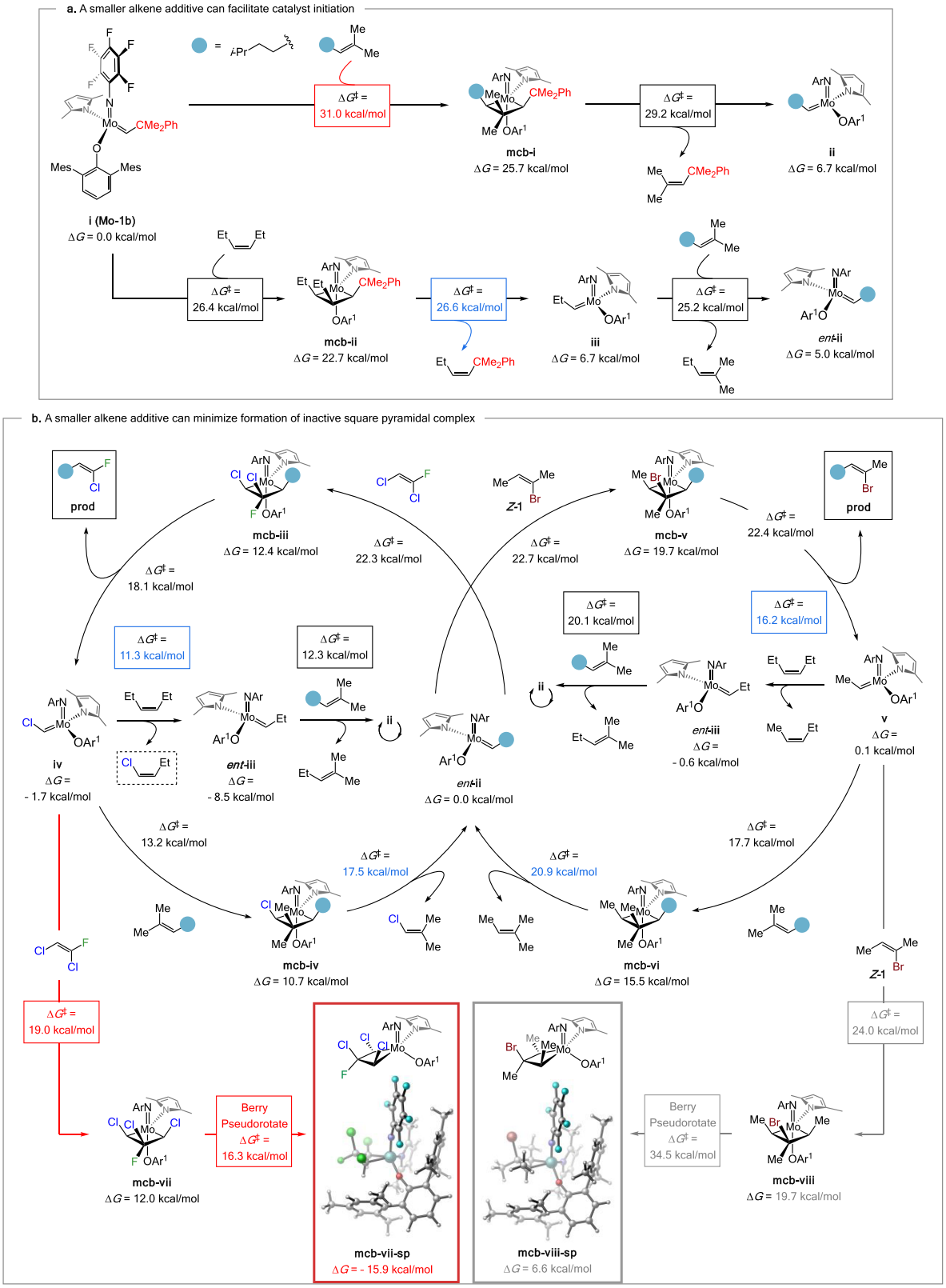
Scheme 11. Small-Alkene Additive Can Improve CM Efficiency by Minimizing Formation of Inactive Square Pyramidal Complexes[a]



[a]Computational studies were performed with M06/SDD(Mo)-6-311+G(d,p)/SMD(C_6H_6)//B3LYP-D3/SDD(Mo)-6-31G(d). Similar data were obtained with the ωB97X-D functional and DLPNO-CCSD(T) level of theory. Energy values in sections (a) and (b) are with respect to complexes **i** and ***ent*-ii**, respectively. The energy values in sections (a) and (b) are with respect to a tri- or disubsituted alkene alkene substrate and complexes **i** and ***ent*-ii**, respectively. See the Supporting Information for details. sp, square pyramid.

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of a 78:22 *E*:*Z* mixture, which was inconsequential in this application.

The CM route (Scheme 9b) began by the conversion of keto-alkene **11**, which is also purchasable and less costly than 7, to the corresponding enoate by a standard Horner−Wadsworth−Emmons reaction (90% yield and 78:22 *E*:*Z*). The stereoisomers were separated, and each isomer (i.e., ***E***- and ***Z*-12**) was subjected to the CM conditions. However, when **Mo-1a** was used, CM afforded only ∼15% ***E*,*E*-10** (20% disappearance of ***E*-12**). A brief screening study indicated that with a bromine substituent at C4 of the aryloxide ligand,[16] specifically, with **Mo-3**, CM, which occurs only at the more electron rich trisubstituted olefin, is considerably more efficient. We were therefore able to isolate ***E*,*E*-10** in 77% yield and 95:5 *E*:*Z* ratio and ***Z*,*E*-10** in 68% yield and 97:3 *E*:*Z*. For application to phomactin A, ***Z*,*E*-10** may also be employed.

2.2.2. Application to Synthesis of Ambrein. We designed a convergent route to ambrein (Scheme 10), entailing a CC of an alkenyl bromide and an alkyl-boron fragment. To access the alkenyl bromide, we converted sclareolide (purchasable) to trisubstituted alkene **13** through four transformations and in 70% overall yield (Scheme 10a; see the Supporting Information for details). In situ protection of the tertiary alcohol followed by stereoretentive CM with ***E*-1** and formation of triethylsilyl ether delivered alkenyl bromide **14** (75% yield, 95:*E*:*Z*). CM with the silyl ether derived from **13** was less efficient (66% conv, 55% CM), probably because of the added steric pressure.

To secure the alkyl-boron segment, we first converted purchasable 3-methylcyclohexenone to allylic phosphate **15** in three steps and 48% yield (Scheme 10b; see the Supporting Information for details). This was followed by sulfonate−NHC−Cu-catalyzed[17] allylic substitution with commercially available vinyl−B(pin),[18] furnishing 1,4-diene **16** (73% yield, >98:2 $S_N2':S_N2$, 96:4 enantiomeric ration (er)). Despite extensive experimentation, we were unable to find an effective way of converting the monosubstituted alkene of **16** to an alkyl-boron compound with high regioselectivity; this is probably due to the presence of the quaternary carbon adjacent to the less substituted olefin. Consequently, we regioselectively converted **16** to the corresponding exocyclic mono-epoxide.

Ensuing treatment of the unsaturated epoxide with 9-BBN afforded trialkylboron **17** (Scheme 10c), which was used directly in CC with alkenyl bromide **14** to generate **18** (85% yield, three steps from **16**). Re-conversion of the epoxide to the exocyclic alkene[19] and removal of the silyl ether afforded ambrein in 59% yield (2 steps). The total synthesis comprises 14 steps with a longest linear sequence of six steps (sclareolide → **14**), delivering ambrein in 24% overall yield. This compares favorably with the sequence previously disclosed,[5f] which consisted of a total of 25 steps, a LLS of 14 steps, and generating ambrein in 7.6% overall yield.

2.3. Why Is an Additive Indispensable to CM with a *gem*-Chloro,Fluoro-Substituted Alkene and Not an Alkenyl Bromide? An unanticipated observation early on in these studies was that, although a small alkene additive accelerates CM, its presence is not vital. This is in stark contrast to recently reported transformations involving *Z*- or *E*-1,2-dichloro-1-fluoroethene, where there is no conversion without *Z*-hex-3-ene (Scheme 3a).[12] To probe the origin of this dichotomy, DFT studies were carried out with 2-methyl-2-octene as the model substrate. It was confirmed, as noted formerly,[8] that direct reaction of a trisubstituted olefin with a sterically hindered alkylidene (**i**, Scheme 11a; to generate the catalytically active **ii** via **mcb-i**) is less favored compared to when the catalyst initiation is caused by the more diminutive *Z*-hex-3-ene (affording *ent*-**ii** via **mcb-ii** and propylidene **iii**). But why would *Z*-hex-3-ene be so much more critical to CM with a trihalo-alkene cross partner?

Two representative catalytic cycles, one involving *Z*-1,2-dichloro-1-fluoroethene and the other *Z*-2-bromo-2-butene (***Z*-1**), and the energy values for each event are shown (Scheme 11b). As expected, the presence of *Z*-hex-3-ene facilitates regeneration of the central complex **ii** (or *ent*-**ii**) by providing a lower energy pathway in each case (**iv** → *ent*-**iii** → **ii** instead of reaction through **mcb-iv** for the trihalo-alkene, and **v** → *ent*-**iii** → **ii** instead of reaction through **mcb-vi** in the case of ***Z*-1**). The results of DFT investigations indicate that two factors distinguish these two processes. (1) In the CM with 1,2-dichloro-1-fluoroethene, a highly reactive and likely relatively unstable Cl-substituted Mo alkylidene, **iv**, is generated. Unless there is *Z*-hex-3-ene to react with it readily and transform it to the more stable propylidene ***ent*-iii**, **iv** can decompose, diminishing CM efficiency. (2) With a *Z*-1,2-dichloro-1-fluoroethene, when *Z*-hex-3-ene is absent, the reaction of Cl-substituted alkylidene **iv** in the presence of 5.0 equivalents of the trihalo-alkene to afford tetrahalo-substituted **mcb-vii** is competitive with regeneration of ***ent*-ii** from **iv** (19.0 vs 17.5 kcal/mol, respectively). Computational studies indicate that Berry pseudorotation of **mcb-vii**[20] is kinetically favorable with a barrier of 4.3 kcal/mol with respect to **mcb-vii**, affording a more stable distorted square pyramidal complex, **mcb-vii-sp** (ΔG = 12.0 and − 15.9 kcal/mol for **mcb-vii** and **mcb-vii-sp**, respectively). In this latter complex, the orientation of the C−Cl bonds allows for repulsion between the halogen non-bonding electrons to be minimized. The key here is that, as has been previously demonstrated, square pyramidal metallacyclobutanes are catalytically inactive.[20] Therefore, *Z*-hex-3-ene might be needed for CM with a trihalo-alkene to proceed efficiently because the additive can circumvent the inhibitory formation of a square pyramidal species by rapidly reacting with the halo-substituted alkylidene (**iv**). Catalytic amounts of *Z*-hex-3-ene would suffice because *Z*-1-chloro-butene, formed from the reaction between chloro-alkylidene **iv** and the additive, is similarly capable of circumventing the formation of **mcb-vii-sp** (as would the 1,2-dichloroethene generated from the transformation between **v** and *Z*-1-chloro-butene, etc.). The same does not apply to CM with ***Z*-1** for two reasons: (1) The sequence **v** → (lower energy) **mcb-vi** → *ent*-**ii** is kinetically more favored than **v** → (higher energy) **mcb-viii** → **mcb-viii-sp**. (2) It is less likely that formation of **mcb-viii-sp** causes catalyst sequestration because of it being 6.5 kcal/mol less stable than the catalytically active species **v** and pseudorotation to form **mcb-viii-sp** requiring a high kinetic barrier. In other words, the overall conversion to **mcb-viii-sp** is thermodynamically disfavored.

Experimental data confirmed the low stability of a Cl-substituted Mo alkylidene, but attempts to observe a square-pyramidal mcb complex spectroscopically was unsuccessful (see the Supporting Information for details). While this endorses the first proposed role for the advantageous influence of *Z*-hex-3-ene, it does not exclude the possibility of a **mcb-sp** intermediate being involved.

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3. CONCLUSIONS

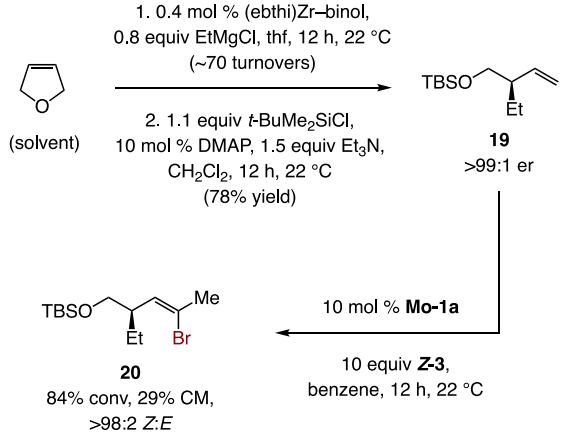
Alkenyl bromides are among the most effective substrates for cross-coupling reactions and, accordingly, the advances detailed here constitute a concise, convenient, and all-catalytic set of methods for synthesis of a large assortment of otherwise difficult-to-access and stereochemically defined trisubstituted olefins. The catalytic reactions can be performed with commercially available *Z*- or *E*-2-bromo-2-butene and Mo complexes that can either be prepared through well-established protocols (**Mo-1a**) or simply be purchased (**Mo-1b**). Applications to concise and stereocontrolled synthesis of a fragment of phomactin A and a total synthesis of diastereo- and enantiomerically enriched pure ambrein highlight the considerable utility of the approach.

Another attractive feature is that a tri-, an *E*- or a *Z*-1,2-disubstituted, or a monosubstituted olefin may be used as the substrate. Many feedstock compounds that contain a trisubstituted olefin with a dimethyl terminus can be converted to the corresponding *Z*- or *E*-trisubstituted alkenyl bromides, ready for further modification by means of catalytic cross-coupling. With a sterically hindered olefin, such as when there is a substituent at the allylic or homoallylic position, less hindered disubstituted or monosubstituted olefins react more readily and therefore represent more attractive options as starting materials.

These investigations reveal another strategic advantage to using a small alkene additive in olefin metathesis, one that extends beyond catalyst initiation. Specifically, when a Mo alkylidene contains a relatively small substituent (e.g., a chlorine atom) and a substrate is comparatively diminutive (e.g., a trihalo-alkene), the reaction between these entities can generate a catalytically inactive square pyramidal metallacyclobutane. Under such circumstances, catalytic amounts of a small alkene additive (e.g., *Z*-hex-3-ene) can circumvent this debilitating event.

The abovementioned advances notwithstanding, other key challenges remain to be addressed. For example, we find that, especially when highly substituted olefins are targeted, even seemingly subtle changes in substrate structure can cause notable fluctuations in reactivity. A case in point is the transformation of **19** (Scheme 12), readily accessible in high enantiomeric purity from dihydrofuran,[21] to alkenyl bromide **20**, a fragment that could probably render an existing total synthesis of peloruside A[6e] considerably more concise. A catalyst that can accomplish this challenging transformation more effectively than the available cadre of complexes, such as **Mo-1a**, would further enhance the applicability of this important set of reactions.

Scheme 12. Remaining Challenge[a]



[a]See the Supporting Information for details.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c13289.

Experimental details for all reactions and analytic details for all products as well as computational details and Cartesian coordinates (PDF)

Accession Codes

CCDC 2224276−2224278 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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