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Journal

Journal of the American Chemical Society, 145(6)

Authors

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Publication Date

2023-02-15

DOI

10.1021/jacs.2c13245

Peer reviewed

HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2024 February 15.

Published in final edited form as:

J Am Chem Soc. 2023 February 15; 145(6): 3748–3762. doi:10.1021/jacs.2c13245.

Z-Trisubstituted α,β-Unsaturated Esters and Acid Fluorides through Stereocontrolled Catalytic Cross-Metathesis

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Abstract

Catalytic cross-metathesis (CM) that can generate trisubstituted alkenes in high stereoisomeric purity are important but remain limited in scope. Here, CM reactions are introduced that generate *Z*-trisubstituted α-methyl, α,β-unsaturated, alkyl and aryl esters, thiol esters, and acid fluorides. Transformations are promoted by a Mo bis-aryloxide (bisAr), a monoaryloxide pyrrolide (MAP), or a monoaryloxide chloride (MAC) complex; air-stable and commercially available paraffin tablets containing a Mo complex may also be used. Alkyl, aryl, and silyl carboxylic esters as well as thiol esters and acid fluoride reagents are either purchasable or can be prepared in one step. Products were obtained in 55–95% yield and in 88:12 to >98:2 *Z*:*E* ratio (typically, >95:5). The applicability of the approach is highlighted by a two-step conversion of citronellol to an isomintlactone precursor (1.7 g, 73% yield, 97:3 *Z*:*E*) and a single-step transformation of lanosterol acetate to 3-*epi*-anwuweizic acid (72% yield, 94:6 *Z*:*E*). Included are the outcomes of DFT studies, regarding several initially puzzling catalyst activity trends, providing the following information: (1) It is key that a disubstituted Mo alkylidene, generated by a competing homo-metathesis (HM) pathway, can re-enter the productive CM cycle. (2) Whereas in a CM

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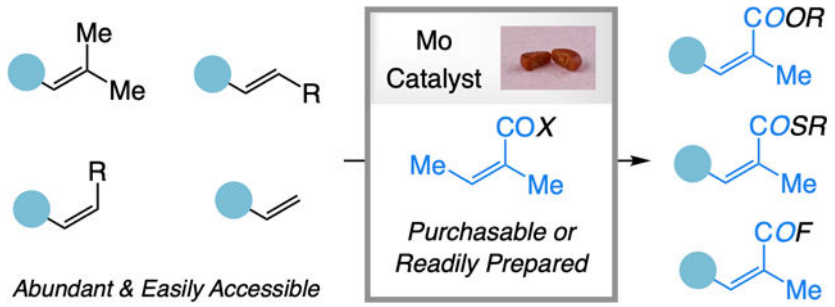
SUPPORTING INFORMATION

This Supporting Information is available free of charge via the Internet at DOI:10.1021/jacs.xxxxx Experimental details for all reactions and analytic details for all products (PDF)

The authors have no competing financial intertest.

cycle the formation of a molybdacyclobutane is likely turnover-limiting, the collapse of related metallacycles in a HM cycle is probably rate-determining. It is therefore the relative energy barrier required for these steps that determines whether CM or HM is dominant with a particular complex.

Graphical Abstract



1. INTRODUCTION

Innumerable bioactive natural products contain an α,β-unsaturated carbonyl moiety, and a key subset within this class is comprised of Z-trisubstituted α-methyl enoates; examples include anti-inflammatory agent polycerasoidol,[1] anticancer agent gambogic acid,[2] HNE inhibitor nigranoic acid esters,[3] and HDAC inhibitor manwuweizic acid[4] (Scheme 1a). Enoates are regularly used in regio-, diastereo-, and/or enantioselective transformations as well.[5] A Z-trisubstituted α-methyl enoate may be synthesized through reaction between a Z-trisubstituted alkenyl halide and a carbonyl-containing compound. For instance, in one case (Scheme 1b), an alkenyl iodide, generated in two steps from a propargyl alcohol, was converted to a trisubstituted Z-enoate by catalytic cross-coupling (CO in MeOH; 41% overall yield, >98:2 Z:E).[6] Another reported sequence begins with formation of an E-trisubstituted α,β-unsaturated carboxylic acid by a Wittig process, with the ensuing bromide addition and elimination delivering a Z-alkenyl bromide; subsequent conversion to a Z-enoate by Li/Br exchange (t-BuLi at −78 °C), was followed by trapping of the organolithium intermediate with CO_2 (50% yield (3 steps), >98:2 Z:E).[7]

Wittig-type protocols are a popular way of accessing α-methyl trisubstituted enoates (Scheme 1c). For instance, when a less functionalized enoate was needed for total synthesis of *ent*-phaeosphaeride A (Scheme 1c),[8] a polyfluorophosphonate reagent was used to convert an aldehyde to a Z-α-methyl carboxylic ester, which was then subjected to catalytic dihydroxy addition. A common way of accessing an aldehyde, which may be used for such reactions, is by oxidative cleavage of the trisubstituted alkene within a naturally occurring feedstock compound; the approaches involving geraniol and citronellol en route to transtaganolide B,[9] isomintlactone,[10] and kadcoccnic acid triester[11] are representative (Scheme 1c).

Synthesis of Z-trisubstituted α-methyl enoates – directly by catalytic stereoretentive cross-metathesis (CM)[12] – not only represents a distinct retrosynthetic disconnection, in many cases, it would be a more efficient alternative; it would entail reaction between a trisubstituted olefin, including naturally occurring prenyl-bearing compounds, and a

commercially available or easily accessible enoate (Scheme 2). Unlike an alkene-to-aldehyde conversion and a Wittig- or Horner-Emmons-type reaction, CM would not require any oxidation-state adjustment or strongly basic or oxidizing conditions and could be performed at ambient temperature. Transformations with similarly abundant monosubstituted olefins or *E*- or *Z*-disubstituted alkenes, either purchasable or easily synthesized by catalytic cross-coupling, would further enhance the appeal of such an approach. Nonetheless, whereas CM methods for preparation of *E*-trisubstituted enoates are well established, those that can deliver the corresponding *Z* isomers are unknown.[13] Here, we describe the results of investigations regarding the development of catalytic CM reactions that can be used to generate *Z*-*α*-methyl trisubstituted *α*,*β*-unsaturated alkyl, phenyl,[14] or silyl carboxylic esters,[15] and thiol esters,[16] in addition to acid fluorides. Each of these products have distinct utility in chemical synthesis, particularly the emerging acid fluorides.[17]

2. RESULTS AND DISCUSSION

2.1. Mechanistic considerations.

The efficiency of CM between a Mo-alkylidene and an *α*,*β*-unsaturated carbonyl compound, both containing a strongly polarized π-bond, depends on the extent to which, in the pivotal metallacyclobutane (mcb) formation step, electronic or steric factors dominate (Scheme 3). A catalytic cycle would likely commence with reaction with the more electron-rich alkene (vs an enoate). If electronic factors in a catalyst•enoate complex (**i**) were to dictate the outcome, the reaction would proceed via **mcb-i**, an entity stabilized on account of a Mo-bound ester-substituted C*α*. Cyclo-reversion of **mcb-i** would generate a relatively unreactive alkylidene, not only because of electronic stabilization (**ii**), but also owing to internal coordination between the Lewis basic carbonyl oxygen and the Mo center (**iii**).[18] Alternatively, if the enoate were to approach the catalyst, as in **iv**, the transformation would proceed via **mcb-ii**, collapse of which would furnish the CM product and the catalytically more competent **v** (Scheme 3). Unfavorable stereoelectronic factors must therefore be overcome for a CM product to form.

We hoped that the pathway proceeding via **iv** and **mcb-ii**, where C*β*, a less congested site, is fully substituted (vs C*α*, as in **mcb-i**) would be preferred.[19] As the carbonyl-bearing substrate becomes more polarized, it would be more difficult to oppose the electronic factors. Considering the distinct electronic attributes of an alkyl, a thiol ester or an acid fluoride, it remained to be seen if different types of substrates would present varying CM efficiency levels.

2.2. Reactions with trisubstituted alkene substrates.

2.2.1 Catalyst screening.—We made several noteworthy observations during the investigations involving methyl angelate (***Z*-1a**, Table 1) and benzyl citronellol (**2a**). Monoaryloxide pyrrolide (MAP) complex **Mo(MAP)-1** (entry 1), which contains a large aryloxide ligand,[20] and had emerged as optimal in previous CM transformations that afford trisubstituted alkenes, proved to be ineffective here (<5% conv). In contrast, there was 77% conversion to trisubstituted enoate **3a** (71% yield, 93:7 *Z*:*E*) with **Mo(MAP)-2**[21] (entry

2), which has a sterically less demanding aryloxide. When **Mo(MAP)-3** (entry 3), bearing a 2,3,5,6-tetraphenyl aryloxide,[19,22] was employed, formation of **3a** was more efficient and more stereoretentive (81% yield and 97:3 *Z*:*E*). A similar, but more striking, trend involved the monoaryloxide chloride (MAC) complexes (entries 4–6, Table 1; $B(C_6F_5)_3$ is to help dissociate the stabilizing pyridine ligand). Whereas, akin to **Mo(MAP)-1**, there was <5% conversion to **3a** when **Mo(MAC)-1** was used,[23] with **Mo(MAC)-2**, which contains the same aryloxide as **Mo(MAP)-2**, efficiency improved while stereoretentivity diminished considerably (92% conv, 25:75 *Z*:*E*). CM with tetraphenylaryloxide-bearing **Mo(MAC)-3** was efficient and highly stereoretentive (78% yield, 94:6 *Z*:*E* ratio; entry 6).

Another noteworthy observation was the lower *Z*:*E* ratio in the reaction with **Mo(MAC)-2** compared to when a Mo(MAP) complex, bearing the same aryloxide, was used (25:75 vs 93:7 *Z*:*E*; entries 5 and 2, respectively). We viewed this as a key question because the reasons of such distinctions can shed light on the origins of variations in stereoretentivity as a function of catalyst structure. Based on the formerly noted differences in mcb transition state energies,[19] it is unlikely that problem arises from low kinetic selectivity. The more probable scenario would entail pre-metathesis isomerization to form ***E*-1a** (via **mcb-iii**), the CM through which would afford ***E*-3a** (Scheme 4a), an adventitious process that would be facilitated by the especially active and comparatively uncongested Mo-chloride catalyst. Post-metathesis isomerization, namely, conversion of ***Z*-3a** to ***E*-3a** via **mcb-iv** and **mcb-v** (Scheme 4b), is possible because, as the transformation progresses, the concentration of ***Z*-1a** and the isomerized ***E*-1a** becomes more comparable to the CM product (***Z*-3a**). Time-dependent studies (Scheme 4c) revealed that within just ~15 seconds the reaction with ***Z*-1a** proceed to 44% of ***Z*-3a** in 96:4 *Z*:*E* ratio. At the same time, 36% and 85% of ***Z*-1a** had isomerized to ***E*-1a** after one and four hours, respectively. This suggests that, early in the transformation, pre-metathesis isomerization plays a more significant role (isomeric purity from 96:4 to 84:16 *Z*:*E*), whereas post-metathesis isomerization is probably the reason why there is additional diminution of *Z*:*E* ratio (from 84:16 to 25:75 *Z*:*E*). Moreover, upon re-subjection of stereoisomerically pure ***Z*-3a** to in situ generated ethylidene **v**, there was further diminution of stereoisomeric purity: **3a** was isolated as a 72:28 *Z*:*E* mixture after one hour. Addition of 50 mol % ***E*-1a** led to still more *Z*-to-*E* isomerization: 65:35 after one hour and 35:65 after four hours, an observation that is consistent with the proposed post-metathesis isomerization pathway (Scheme 4b): with excess ***E*-1a**, **mcb-v** formation becomes more favored, causing enhanced product isomerization.

What was needed then was a Mo alkylidene that would deliver higher efficiency (see Scheme 3), but not to the degree that would allow (unfavorable) electronic effects to become dominant. We were thus led to probe the effectiveness of Mo-bisaryloxides (bisAr),[24] which, difficult-to-predict electronic differences notwithstanding, are more sterically demanding compared to MAP and MAC systems. In the event, with **Mo(bisAr)-1** (entry 7, Table 1), under otherwise identical conditions, **3a** was obtained in 91% yield and 95:5 *Z*:*E* ratio.

Two additional points merit note: (1) Reaction with **Mo(bisAr)-2** afforded **3a** with similar efficiency but with lower stereoretentivity (89% CM, 88:12 *Z*:*E* ratio; entry 8, Table 1). A somewhat subtle alteration,[25] a *p*-bromo-aryloxide substituent, can tip the balance in favor

of **mcb-iii** (Scheme 4a), diminishing stereocontrol. Even so, as will be discussed (see section 2.2.4), a complex bearing a *p*-bromo-aryloxide can perform at a superior level under other circumstances. (2) Reaction with **Mo(bisAr)-3** was less effective (51% conv to **3a**; entry 9). Although enoate isomerization was minimal (<5% ***E*-1a** recovered), the trisubstituted alkene product was formed in lower stereoisomeric purity (84:16 vs 95:5 *Z*:*E* for **Mo(bisAr)-1**), underlining the importance of the C3 and C5 phenyl groups. The larger moieties are likely to restrict conformational mobility of C2 and C6 phenyl groups, increasing steric pressure in the preferred mcb (compare **mcb-ii'** with **mcb-ii"**; Figure 1).

2.2.2. Z-Trisubstituted methyl esters.—Different trisubstituted olefins, including those containing a carboxylic ester (***Z*-3b**; Table 1), a phthalimide (***Z*-3c**), a benzyl ether (***Z*-3d**), an indole (***Z*-3e**), or an acetal (***Z*-3f**) were transformed to desired products (Scheme 5a). Reactions proceeded to 79–97% conversion, 76–94% of which was the CM product; yields ranged from 74–91% and *Z*:*E* ratios from 96:4–98:2. Homoallylic boronate ***Z*-3g** and allylic benzyl ether ***Z*-3h**, notably formed through CM between two electron-deficient olefins, were isolated in 72% and 75% yield and 95:5 and >98:2 *Z*:*E*, respectively.

CM is less efficient with a trisubstituted olefin that has the following features: (1) contains a larger homoallylic aryl moiety (compared to a B(pin) in the case of ***Z*-3i**); (2) bears a relatively strong Lewis basic site, such as ***Z*-3j**, or ***Z*-3k-l** where the substrate might serve as a bidentate ligand; (3) carries a relatively large allylic ether (***Z*-3m** in contrast to benzyl ether ***Z*-3h**; Scheme 5b; 34% vs 83% conv, 25% vs 78% conv to the desired product). With a sizeable substituent or a Lewis basic unit, reaction between **Mo(bisAr)-1** and a trisubstituted alkene probably becomes too slow, resulting in lower concentration of the catalytically active Mo-alkylidene.

To delve further, we allowed CM with **2k** to proceed for four hours, which led to the formation of generating ~32% **3k** (Scheme 5c). The mixture was then charged with 10 mol % *Z*-hex-3-ene, based on the expectation that this would help initiate **Mo(bisAr)-1** completely. After allowing the mixture to stir for an additional four hours, there was indeed further conversion to ***Z*-3k** (69%; 96:4 *Z*:*E*). When the slower CM processes were performed with 10 mol % *Z*-hex-3-ene (Scheme 5b), ***Z*-3i-m** were isolated 63–87% yield (65–89% CM), and 96:4 to >98:2 *Z*:*E* ratio.

More demanding cases still remained, among which were trisubstituted alkenes with a branched homoallylic site, including an allylic boronate (Scheme 6), which may be used for catalytic diastereo- and/or enantioselective additions to widely used electrophiles.[26] Regarding ***Z*-3n** and ***Z*-3o**, although the addition of 10 mol % *Z*-hex-3-ene increased efficiency (<5% conv otherwise), there was only 34% and 53% conversion to the CM products, respectively. In contemplating ways to increase efficiency, we noted that, while **Mo(bisAr)-1** was optimal for linear alkenes (**2a-m**), **Mo(MAP)-3** and **Mo(MAC)-3** were not far behind (entries 3, 6, and 7, Table 1). We reasoned that because MAP and MAC complexes contain smaller ligands compared to bis-aryloxides they should more easily associate with a more hindered alkene, and, as it turned out, with **Mo(MAP)-3** there was 70% and 80% conversion to ***Z*-3n** and ***Z*-3o** (58% and 71% yield, respectively; Scheme 6). The situation was more demanding with the trisubstituted allylboronate, precursor to

***Z*-3p**: under the aforementioned conditions, efficiency was low (35% conv), leading us to turn to the most diminutive MAC complex. With **Mo(MAC)-3** there was indeed 76% conversion to ***Z*-3p**, which was isolated in 69% yield as a single stereoisomer (92:8 *Z*:*E* before purification); with 2.5 mol % catalyst, the reaction was completed after 2 hours (vs 6 h with 5.0 mol % in previous cases). The lower *Z*:*E* ratios (95:5–89:11) might be on account of diminished competitiveness between the formation of **mcb-ii** and **mcb-ii'**, as the alkene substituent (G) becomes larger.[19] Steric pressure between G and the more sizeable methyl ester substituent (Sterimol *L* and *B1* values: 4.73 and 1.64)[27] in **mcb-ii'** can be alleviated, wherein a smaller Me group (Sterimol *L* and *B1* values: 2.87 and 1.52) is syn to G and the other is oriented towards the aryloxide.

2.2.3. Aryl, silyl, and thiol esters.—The CM method was thus used for synthesis of *i*-butyl, 2-(trimethylsilyl)ethoxymethyl (SEM), or benzyl esters (***Z*-4a-c**, Scheme 7), silyl esters (***Z*-4d**), aryl esters (***Z*-5a**), as well as thiol esters (***Z*-6a**). The requisite reagents are either purchasable or were easily prepared in one step. Reactions performed under 100 Torr (6 h) or ambient pressure (12 h) delivered nearly identical results (except for thiol esters; see the Supporting Information for details).

2.2.4. Acid fluorides.—We then evaluated the possibility of accessing *α*-methyl *Z*-trisubstituted acyl fluorides,[17] a set of CM reactions about which little is known. Making matters more tenuous, the presence of a highly electrophilic acyl unit has been found to accelerate catalyst decomposition.[28] CM leading to acid fluorides did in fact prove to be difficult (Scheme 8a). There was minimal conversion when ***Z*-1h** and **2a** were subjected to 7.5 mol % **Mo(MAP)-3** or **Mo(bisAr)-1** (12 h, 22 °C). With 10 mol % *Z*-hex-3-ene included, CM with **Mo(bisAr)-1** afforded ***Z*-7a**, albeit less efficiently, despite the higher catalyst loading (vs with ***Z*-1a**; 37% CM vs 93% conv to ***Z*-3a**, Table 1, entry 7); there was also appreciable amounts of homo-metathesis (HM) product (18% conv). CM with **Mo(MAP)-3** was less effective (29% conv, 28% HM, <2% to ***Z*-7a**). Efficiency improved when **Mo(MAC)-3** together with BPh_3, a milder Lewis acid than $B(C_6F_5)_3$, which was introduced to activate the catalyst and prevent acyl fluoride decomposition: there was 69% conversion to ***Z*-7a** (92:8 *Z*:*E* selectivity), which was isolated in 59% yield as the pure *Z* isomer (no *Z*-hex-3-ene additive). Further screening led us to find that *p*-bromo-substituted **Mo(MAC)-4** is more optimal: there was 81% conversion to ***Z*-7a**, formed in 90:10 *Z*:*E* ratio and isolated in 75% yield (pure *Z*). These data suggest that the *p*-bromo substituent can enhance catalyst activity while slightly compromising the degree of stereoretentivity. Other *Z*-*α*-methyl trisubstituted acid fluorides were prepared (Scheme 8b), represented by *β*-aryl substituted (***Z*-7b**), an acetal-containing (***Z*-7c**), and one that bears a homoallylic boronate (***Z*-7d**; 65–73% yield, 88:12 to 91:9 *Z*:*E*). Substrates with an allylic substituent still proved problematic, as complex mixtures of byproducts were generated.

Improved CM with **Mo(MAC)-4** may be rationalized as follows. After the Mo neophylidene is converted to alkylidene **vi** (Scheme 8c), it may deliver the desired acid fluoride via **mcb-vi** or be transformed to **mcb-vii** and then the HM byproduct and disubstituted alkylidene **vii**. Whereas the latter process is dominated by steric effects, due to a more congested C*α* in **mcb-vii**, CM can be facilitated if the mcb were to be stabilized as a result of diminished

trans influence.[23a,24a] Thus, CM with ***Z*-1h** is facilitated by introducing a *p*-bromo-aryloxide ligand, which

2.3. Reactions with monosubstituted alkenes.

Monosubstituted alkenes are an important substrate class, particularly for preparation of trisubstituted enoates with a tertiary allylic carbon. Attempts at promoting CM with the trisubstituted olefin corresponding to **8a** (Scheme 9a) with different Mo complexes and *Z*-hex-3-ene did not afford any desired enoate (<2% conv).

2.3.1. Complex screening.—We began by probing the ability of the Mo-MAP and Mo-bisAr complexes; Mo-MAC systems were not included, as they readily decompose in the presence of a terminal alkene.[23] Preliminary results, while encouraging, were puzzling. One unexpected finding was that with **Mo(MAP)-3** and **Mo(bisAr)-1**, formerly found to be optimal, only HM occurred (90% and 98% HM, respectively; Scheme 9a). On the other hand, there was complete consumption of **8a** with **Mo(MAP)-1** and 69% conversion to ***Z*-3q** (>98:2 *Z*:*E*). With the larger **Mo(MAP)-4**, CM efficiency improved: **8a** reacted completely with 86% conversion to the desired enoate (84% yield, >98% *Z*). The trend of a more hindered catalyst performing better did not extend to the larger **Mo(MAP)-5**, however, as there was just 16% conversion to the HM byproduct (See below, section 2.7.2, for mechanistic analysis).

2.3.2. Scope.—CM of α-branched monosubstituted alkenes generally proceeded with reasonable efficiency with 5.0 mol % **Mo(MAP)-4** (Scheme 9b). Trisubstituted enoates ***Z*-3r-t** were isolated in 74–84% yield with selectivities ranging from 91:9 *Z*:*E* for ***Z*-3r** to 96:4 *Z*:*E* for ***Z*-3t**; silica gel chromatography afforded ***Z*-3r** as a single isomer. Attempts to generate sterically demanding α-branched homoallylic silyl ether ***Z*-3u** were not successful (<5% CM). Whereas there was only 38% conversion to epoxide ***Z*-3v** when a trisubstituted alkene and **Mo(bisAr)-1** were used, with the terminal olefin and **Mo(MAP)-4** there was 83% conversion to the desired product (77% yield, 96:4 *Z*:*E*). Enoates ***Z*-3w-x** were obtained in 95 and 94% yield, respectively and 96:4 *Z*:*E* selectivity.

It was curious that an unhindered monosubstituted alkene (i.e., without a branched allylic or homoallylic carbon) was efficiently converted to a trisubstituted enoate. We surmised that, although HM occurs, the resulting Mo-methylidene might be sufficiently long-lived, allowing it to convert a 1,2-disubstituted olefin to the desired trisubstituted enoate. We chose to investigate these issues further because if efficient CM of a wide range of monosubstituted olefins were possible, a wider range of α-methyl *Z*-trisubstituted enoates would become accessible.

2.4. Merging HM and CM for the more challenging substrates.

2.4.1. CM with more challenging cross partners.—We first investigated several representative reactions (Scheme 10a). CM between methyl enoate ***Z*-1a** and allyl–B(pin) (**8b**) with 5.0 mol % **Mo(bisAr)-1** led to complete allyl–B(pin) consumption but there was only 45% conversion to ***Z*-3p** and no stereocontrol (45:55 *Z*:*E*). The outcome was nearly the same with **Mo(MAP)-4** and **8c**, bearing a potentially catalyst deactivating

nitrile (>98% conv, 38% conv to prod). CM involving phenyl enoate ***Z*-1f** and thiol ester ***Z*-1g** were similarly and less inefficient, respectively. Further, the mixture contained ~10% 1,1-disubstituted enoates (**9a-c**), byproducts originating from reaction between an enoate reagents and ethylene, generated by terminal alkene HM. As demonstrated previously,[19] CM with 1,1-disubstituted olefins was inefficient and minimally stereoselective. The HM byproducts suggested that they might be suitable substrates, because then formation of ethylene, Mo-methylidenes, and 1,1-disubstituted enoates can be avoided. Further, because there would be fewer side reactions to compete with CM, lower amounts of the enoate reagent might suffice (i.e., <8.0 equiv).

2.4.2. Two-stage protocol involving a monosubstituted alkene.—Based on the above considerations, we envisaged a protocol consisting of HM (Scheme 10b), ethylene removal in vacuo, and CM. In addition to the aforementioned advantages, such a route would allow the use of a Mo(MAC) complex, entities that possess unique reactivity profiles but swiftly decompose in the presence of terminal alkenes. Screening studies indicated that, depending on the alkene and enoate, different blends of HM and CM catalysts are optimal (**HM-Mo** and **CM-Mo**, respectively). Notably, the aforementioned (see Scheme 6) allylboronate ***Z*-3p** as well as nitrile-containing ***Z*-3y** were isolated in 72% yield and 79% yield, respectively, by a combination of **Mo(bisAr)-1**/**Mo(MAP)-1** and **Mo(MAC)-3**. A different pairing, **Mo(MAP)-1** and **Mo(bisAr)-1**, was the most effective for synthesis of phenylenoate ***Z*-5b** and thiol ester ***Z*-6b** (71% and 91% yield, respectively). Nonetheless, in certain cases, the same complex may prove to be suitable for both functions: with only **Mo(MAP)-1** (total of 3.0 mol %) ***Z*-3z** was isolated in 91% yield.[29] In all cases, two equivalents of the enoate were used and CM products were isolated in pure *Z* form.

Application of the two-stage protocol to the preparation of trisubstituted acid fluorides turned out to be more challenging, because reactions with HM-derived alkenes were inefficient (<20% conv), underlining a key advantage of using trisubstituted olefins as substrates. Nonproductive processes are more prevalent with 1,2-disubstituted olefins (Figure 2), rendering CM with acid fluorides less competitive. Therefore, conversion of monosubstituted alkene to a trisubstituted olefin should lead to a more favorable outcome (Scheme 10b): treatment of a terminal alkene with 2-methyl-2-butene (methylidene capping)[30] in the presence of 1.0 mol % **Mo(MAP)-1**, removal of excess of the latter substrate in vacuo, followed by the addition of ***Z*-1h** afforded ***Z*-7b** in 57% yield (>98:2 *Z*:*E*).

2.5. Utility and practicality of the approach.

CM reactions may be carried out on gram scale efficiently and stereoretentively under ambient pressure (e.g., ***Z*-3aa** in 93% yield and 96:4 *Z*:*E* ratio; Scheme 11a), and unreacted ***Z*-1a** can be recovered and re-used. Transformations can be carried out with Mo complexes packaged in the form of air-stable and commercially available paraffin tablets;[31] synthesis of ***Z*-3v** in 61% yield and as a single stereoisomer is a case in point (Scheme 11b). Because the corresponding *Z* isomers react faster (Scheme 11c), the enoate reagent need not be stereoisomerically pure, although those used here were either purchased or could be prepared easily. CM with substrates containing an acidic proton were performed in a single

vessel by adopting the traceless protection protocol[32] (Scheme 11d). Equally notable, not only trisubstituted and monosubstituted alkenes can be used as substrates, the corresponding disubstituted variants (*Z* or *E*) may be used as well (see the Supporting Information).

2.6. Representative applications.

As noted earlier, a key application relates to CM of commonly occurring prenyl side chains. An example is the multi-gram conversion of silyl ether **10** (Scheme 12a), accessed in a single step from citronellol, to ***Z*-11**, precursor to isomintlactone,[10] in 73% yield (1.7 g) and 97:3 *Z*:*E* ratio. Even though the focus of this study has been the synthesis of *Z*-trisubstituted enoates, the corresponding *E* isomers can be generated with similar ease by the use of purchasable ***E*-1a**. An example is the preparation of 1.8 g of ***E*-11** (77% yield, 3:97 *Z*:*E*), precursor to mintlactone; 1.0 mol % catalyst loading sufficed for these gram-scale CM reactions. The catalytic approach can be used for accessing the derived enoic acids, as highlighted by the one-pot transformation of lanosterol acetate to 3-*epi*-anwuweizic acid (Scheme 12b), precursor to other bioactive triterpenoids, including manwuweizic acid (see Scheme 1a).[3b,4]

2.7. Mechanistic analysis.

We made several observations indicating notable variations in the reactivity profiles of different Mo complexes. As better appreciation of the origins of these distinctions is key to future applications as well as design of new olefin metathesis catalysts, DFT studies were performed to shed light on two key trends. (Geometry and energy optimizations were performed with ωB97X-D/def2tzvpp, SMD(benzene) involving solvation.)

2.7.1. Catalyst reactivity trends in CM with acid fluorides.—One set of puzzling data related to the unique ability of catalytically active alkylidenes derived from a Mo chloride complex, and especially **Mo(MAC)-4**, to promote CM reactions between acid fluoride ***Z*-1h** and various trisubstituted olefins (Scheme 8). In contrast, MAP and bis-aryloxide variants proved to be much less efficient at generating the desired product (***Z*-7a**), affording appreciable amounts of homo-metathesis (HM) byproducts.

To find an answer to these questions, the energy values for CM and HM cycles pertaining to the reaction between ***Z*-1h** and **2a** and three representative complexes, **Mo(MAP)-3**, **Mo(bisAr)-1**, and **Mo(MAC)-4** were obtained through DFT studies (Scheme 13). The resulting data reveal the following key points:

1. Only with **Mo(MAC)-4**, a more electronically activated complex that contains a smaller chloride ligand,[23] is the formation of ***Z*-7a** via **mcb-vi** energetically viable ($\Delta G^{\ddagger}$ = 14.6 kcal/mol; turnover-limiting). With **Mo(MAP)-3**, generation of **mcb-vi** is not feasible at ambient temperature (($\Delta G^{\ddagger}$ = 30.3 kcal/mol), and the energy barrier is still relatively high (25.2 kcal/mol) in the case of **Mo(bisAr)-1**. These findings are in line with the experimental data: with **Mo(MAC)-4** there was 81% conversion to ***Z*-7a**, while with **Mo(bisAr)-1** or **Mo(MAP)-3** CM was minimal (without *Z*-hex-3-ene).

2. Because HM byproduct was generated when **Mo(MAC)-4** or **Mo(MAC)-3** were used (see Scheme 8), we decided that the competitive HM pathway also warrants computational analysis. HM likely proceeds via disubstituted alkylidene **vii**, which is less reactive than a mono- substituted complex, such as **v**. How easily **vii** re-enters a catalytic cycle impacts the overall CM efficiency. Based on the DFT data, although HM byproduct can be formed through **mcb-vii** ($\Delta\Delta G^{\ddagger}$ = 2.3 kcal/mol, vs **vi** → **mcb-vi** → **v**), the resulting alkylidene **vii** can readily react with **2a** to re-generate **vi** via **mcb-xi** ($\Delta G^{\ddagger}$ = 17.1 kcal/mol).[33] That is, for **Mo(MAC)-4**, disubstituted alkylidene **vii** is not the resting state, as it can be turned over readily (e.g., activation barriers for **Mo(MAP)-3** and **Mo(bisAr)-1** are 37.9 and 43.4 kcal/mol, respectively). Accordingly, CM was efficient with **Mo(MAC)-4** (81% conv to ***Z*-7a**) and there was just 4% HM byproduct observed.

2.7.2. Catalyst reactivity trends in CM with α-branched monosubstituted alkenes.—

Another perplexing trend emerged regarding the CM between ***Z*-1a** and *α*-branched monosubstituted alkene **8a** (Scheme 9). The more sizeable Mo-MAP complexes were more efficient at delivering a trisubstituted olefin via **mcb-ii** (Scheme 14a). It was unclear why, contrary to what might be initially expected, when the aryloxide ligand in the central Mo alkylidene **viii** (Scheme 14b) is smaller (e.g., in the case of **Mo(MAP)-3**), the less substituted **mcb-xii** and the HM byproduct would be more favored (vs **mcb-ii**). DFT studies suggest that in the HM cycle, collapse of the less substituted **mcb-xii** is turnover-limiting, whereas in the CM cycle, formation of the more substituted **mcb-ii** is the slow step (Scheme 14c). With a more hindered complex, the energy of both transition states is raised (compare **ts-1** and **ts-4** for the more sizeable **Mo(MAP)-1** with **ts-1** and **ts-4** for **Mo(MAP)-3**). Computational investigations show that in the case of **Mo(MAP)-1** the energy gap separating **ts-1** and **ts-4** is larger than in the case of **Mo(MAP)-3** ($\Delta\Delta G^{\ddagger}$ = −0.7 and 1.3 kcal/mol, respectively), and CM is consequently more favored for **Mo(MAP)-1** than **Mo(MAP)-3**.

3. CONCLUSIONS

The advances described here represent a key addition to the limited list of kinetically-controlled catalytic CM reactions that can deliver *Z*-trisubstituted olefins in high stereoisomeric purity.[19] An assortment of *Z*-trisubstituted *α*,*β*-unsaturated aryl and thiol esters can, for the first time, be directly accessed through catalytic CM. Such reactive moieties may be used in combination with common nucleophiles, a noteworthy example being reactions with primary amines to form secondary amide bonds. The ability to synthesize various acid fluorides, an intriguing category of compounds that continues to be at the center of a number of methodological studies, is another important outcome of this work. In light of the preponderance of bioactive compounds with a *Z*-trisubstituted *α*,*β*-unsaturated acid or ester and those bearing a tri- or monosubstituted alkene, the advances described here are likely to be of utility in chemical synthesis and drug development. This was highlighted by direct catalytic transformation of a citronellol derivative to an

isomintlactone precursor and a one-step catalytic conversion of lanosterol acetate to 3-*epi*-anwuweizic acid.

These studies continue to underline the importance of catalyst diversity to development of synthesis methods that are maximally broad in scope. Thus, whereas a Mo-bisaryloxide emerged as optimal for CM reactions afford *Z*-trisubstituted α,β-unsaturated alkyl, aryl, and silyl esters with an unhindered alkyl group (Schemes 5 and 7), Mo-MAP and Mo-MAC complexes proved to be most effective with the more sterically demanding substrates (Scheme 6). What proved to be optimal for preparing *Z*-trisubstituted acid fluorides was still a different Mo-MAC (Scheme 8). Furthermore, abundant and inexpensive monosubstituted alkenes were also found to be effective substrates (Scheme 9). A the two-step protocol, designed to facilitate CM of more demanding cases (e.g., an allyl boronate). This entailed HM of monosubstituted alkene and then using the resulting 1,2-disubstituted olefin in a CM reaction to generate the desired enoate (Scheme 10). Depending on the type of the product, different combinations of Mo-bisAr, Mo-MAP and Mo-MAC joined forces to deliver the best result.

Finally, the present work sheds new light on the inner workings of Mo-based olefin metathesis catalysts. In one instance (Scheme 13), DFT studies revealed CM efficiency can be strongly impacted by whether a catalyst can promote transformation with a less reactive disubstituted alkylidene, generated by a competing HM cycle, and whether a HM byproduct can re-enter the catalytic cycle. Otherwise, the fully substituted and less reactive species can become the resting state, reducing efficiency. On another occasion (Scheme 14), computational studies illustrated that, whereas formation of highly substituted mcbs might be turnover-limiting, with a less substituted variant it is a metallacycle's collapse that can be the most energetically demanding. Whether CM or HM is the dominant pathway, therefore, can hinge on the barrier to mcb formation in the CM cycle being higher or lower in energy than the transition state energy for mcb cyclo-reversion in the HM route.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This research was supported by a grant from the National Institutes of Health (GM-130395). K. N. H. is grateful to the NSF (grant CHE-1764328) for funding. T. K. acknowledges support as a LaMattina Family Graduate Fellow in Chemical Synthesis.

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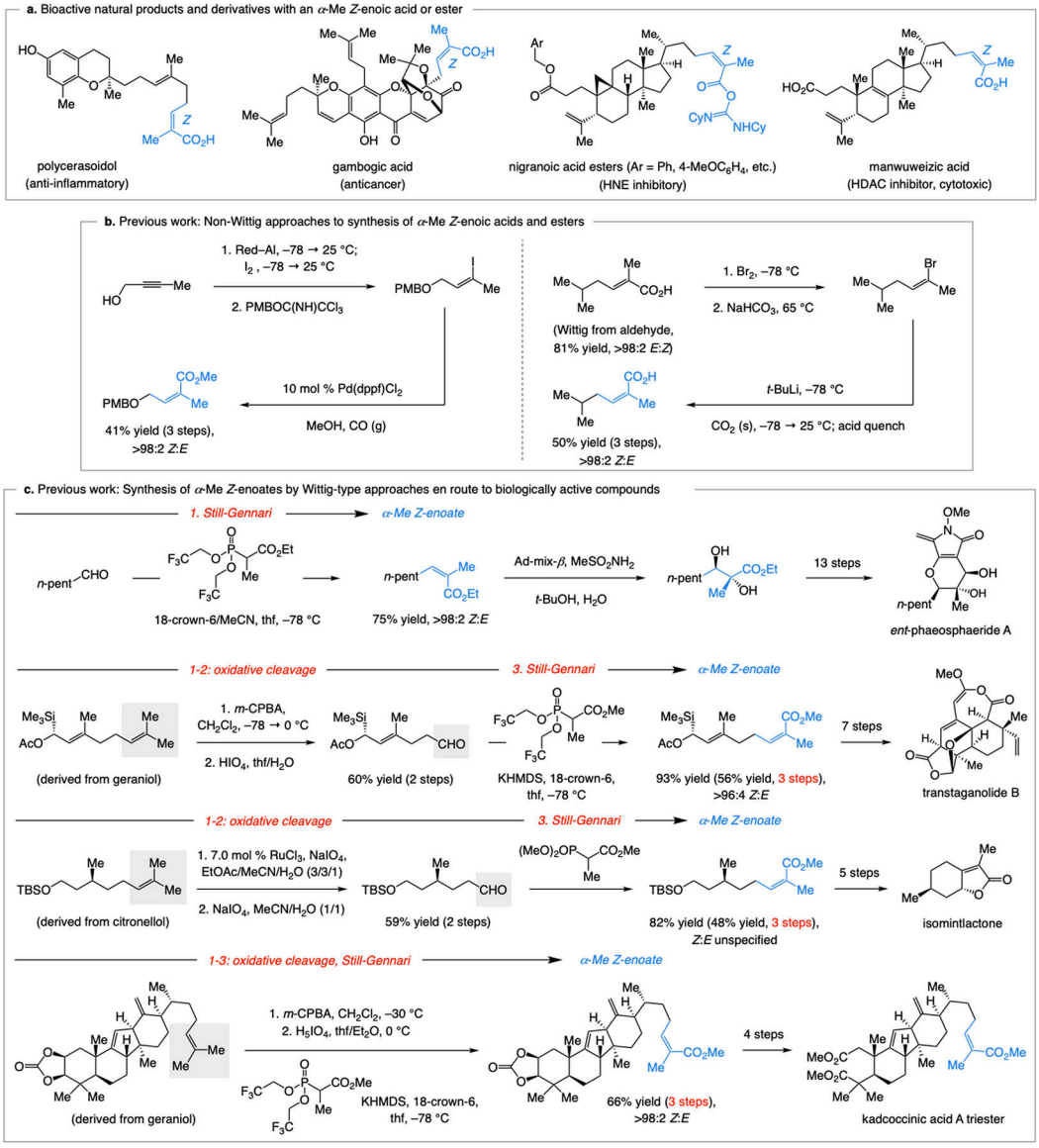
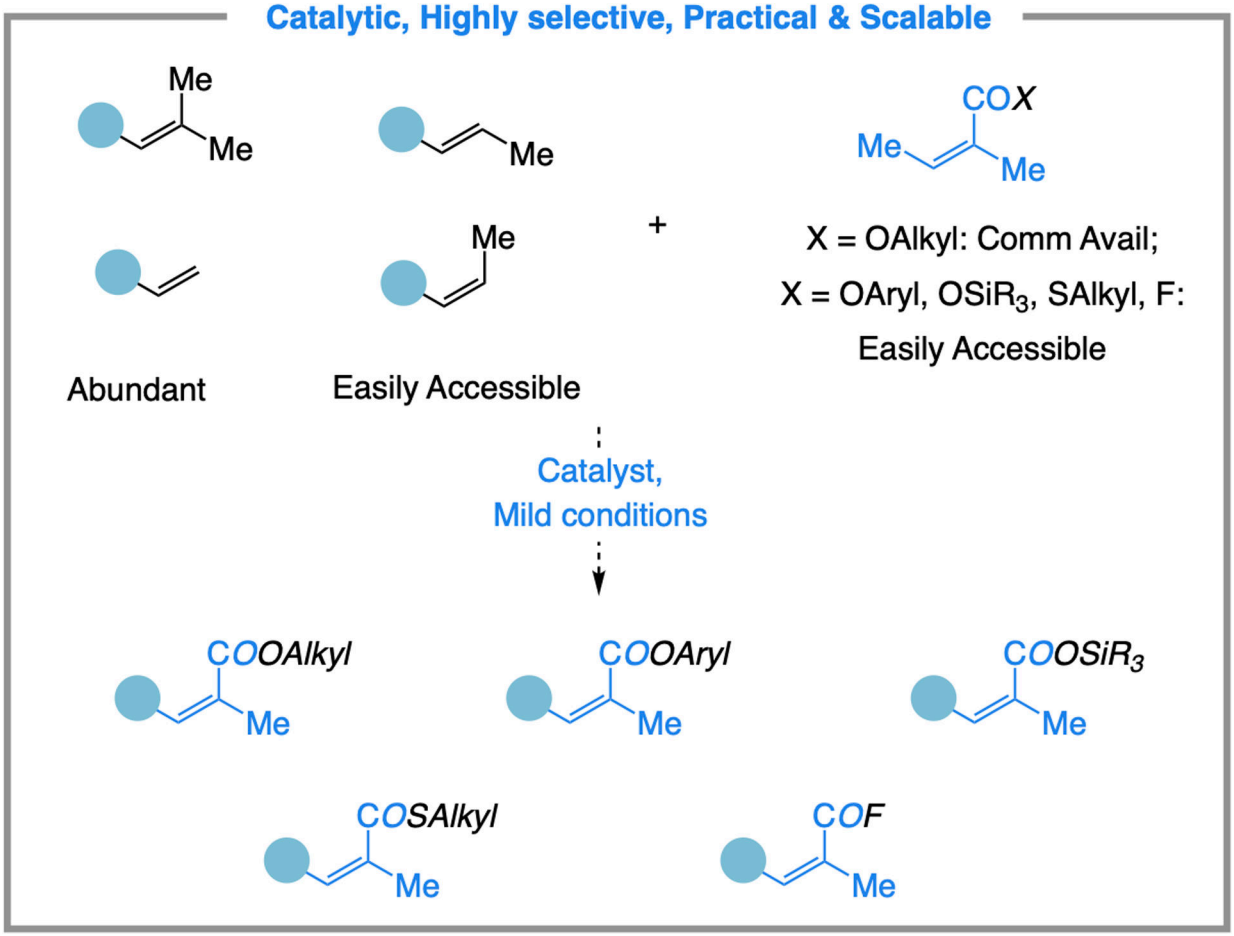
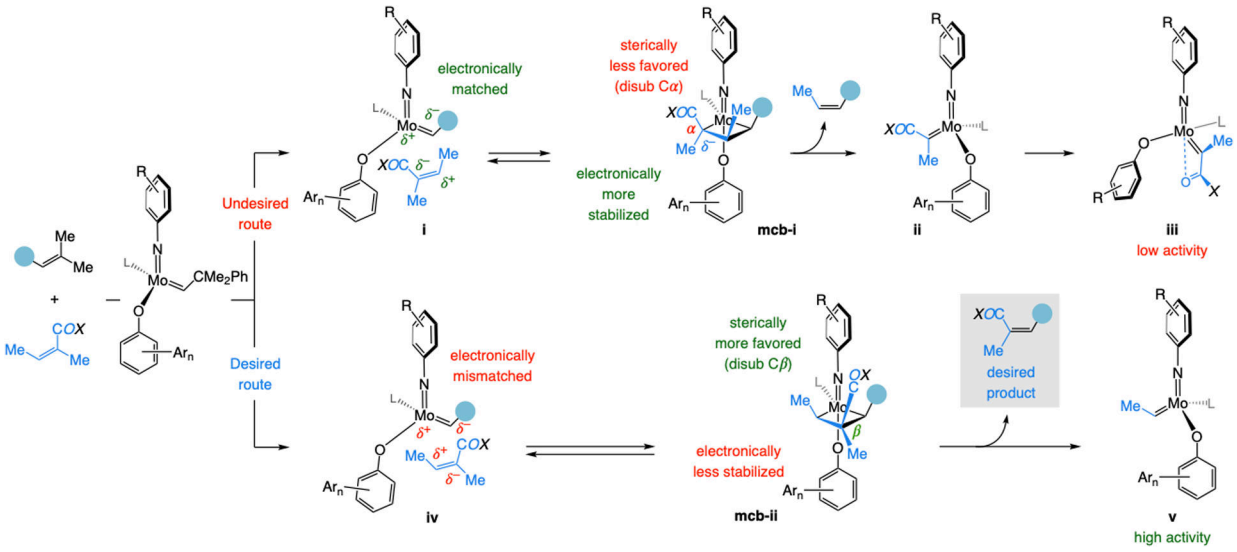


Scheme 1.

Z-Trisubstituted α-Methyl Enoates. Importance and Existing Methods of Preparation



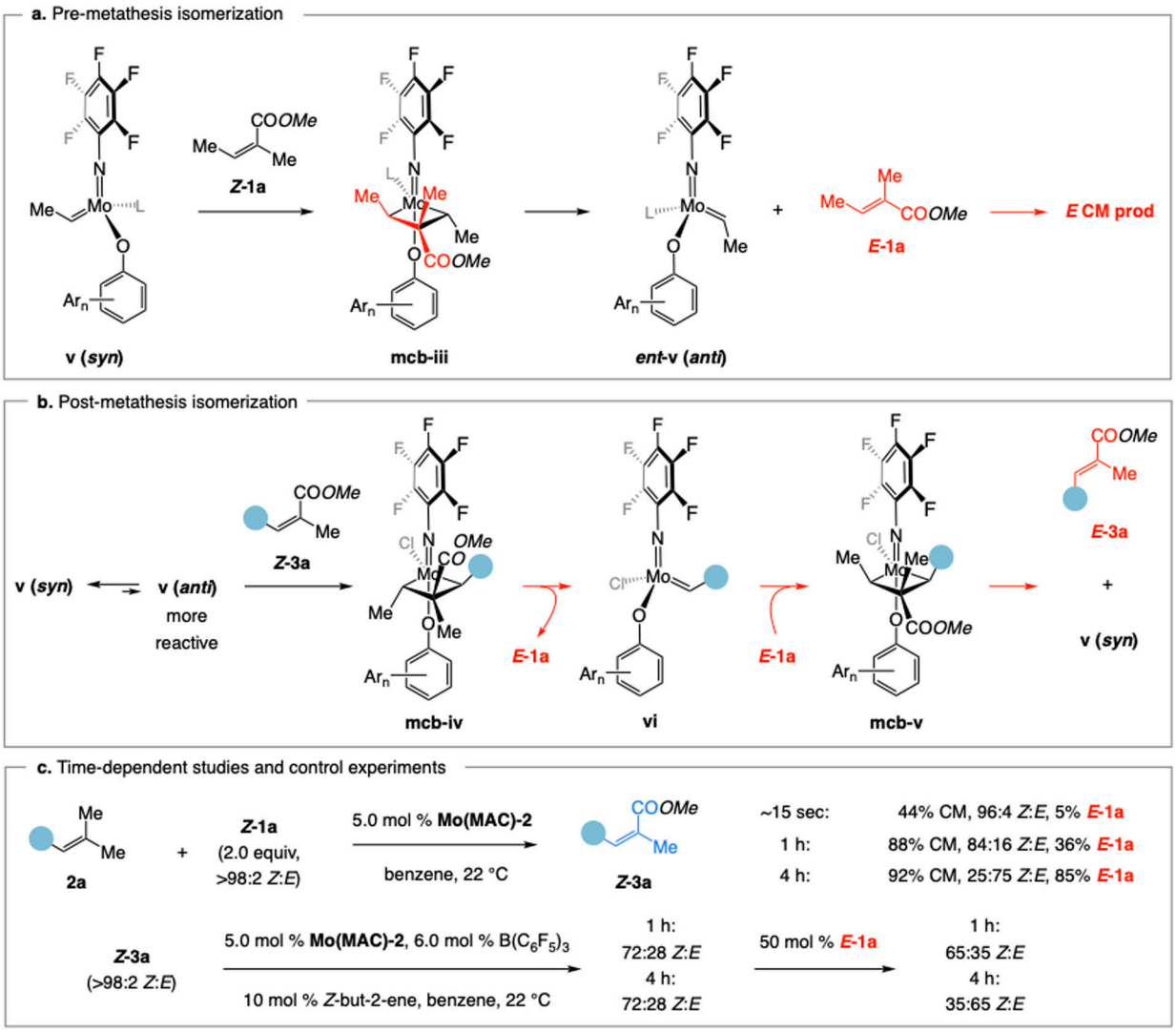
Scheme 2.
Direct Access to *Z*-Trisubstituted Enoic Acid Derivatives



Scheme 3.

Mechanistic Factors Impacting Efficiency of Cross-Metathesis Reactions that Generate a Trisubstituted Enoate[a]

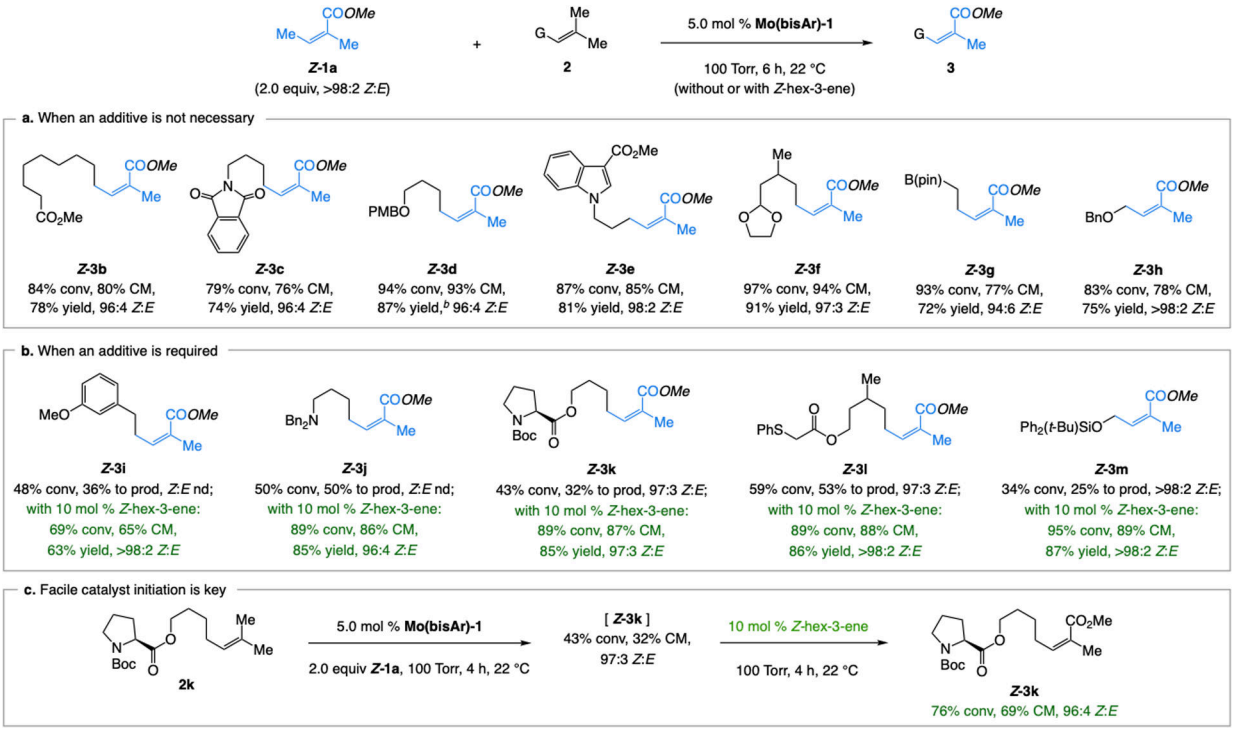
[a]See the Supporting Information for details.



Scheme 4.

Regarding Diminished Stereoretentivity Due to Pre- vs Post-Metathesis Isomerization[a]

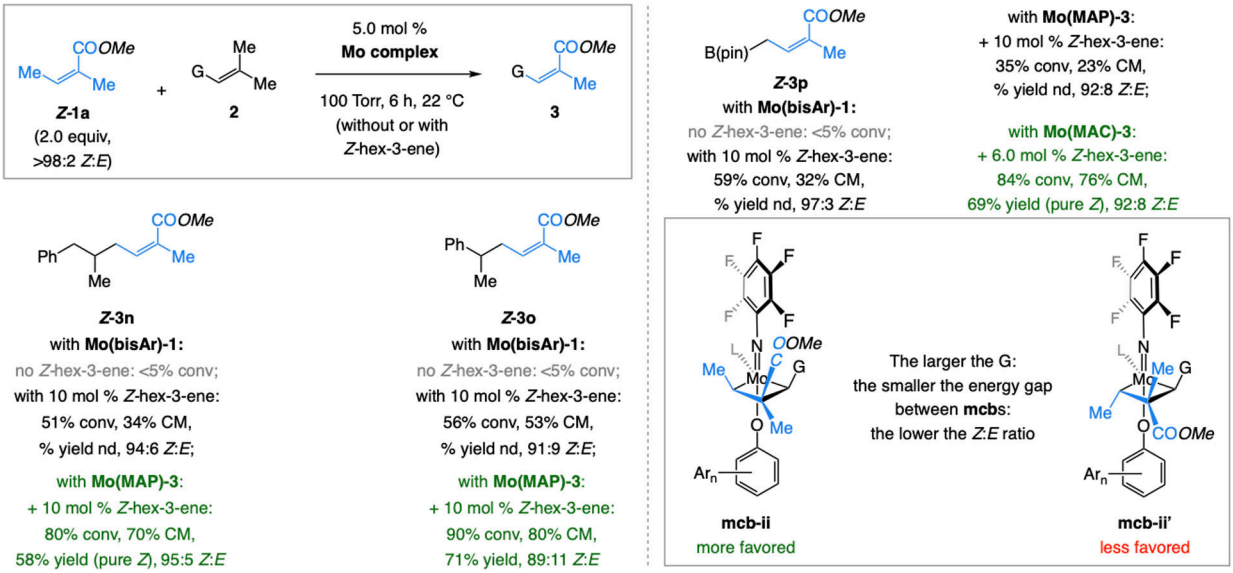
[a]Reactions performed under N_2. Conversion (disappearance of **2a**) and *Z*:*E* ratios were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). See the Supporting Information for details. nd, not determined.



Scheme 5.

Catalytic CM reactions that Afford *Z*-Trisubstituted Methyl Enoates l[a]

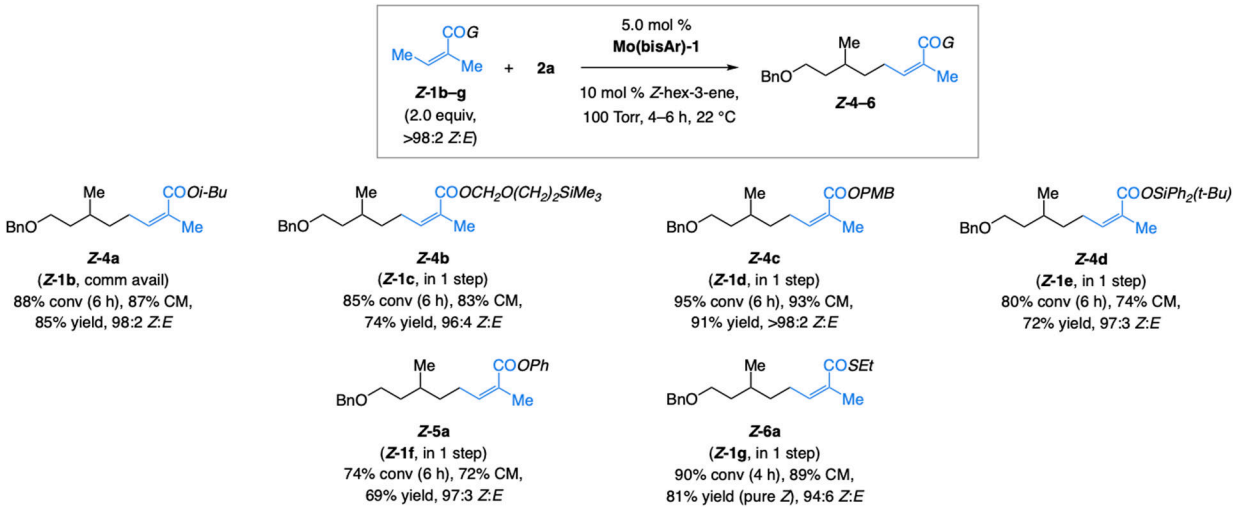
[a]Reactions performed under N_2. Conversion (disappearance of **2**) and *Z*:*E* ratios were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). See the Supporting Information for details. CM, cross-metathesis; nd, not determined.



Scheme 6.

Z-Trisubstituted Methyl Enoates II[a]

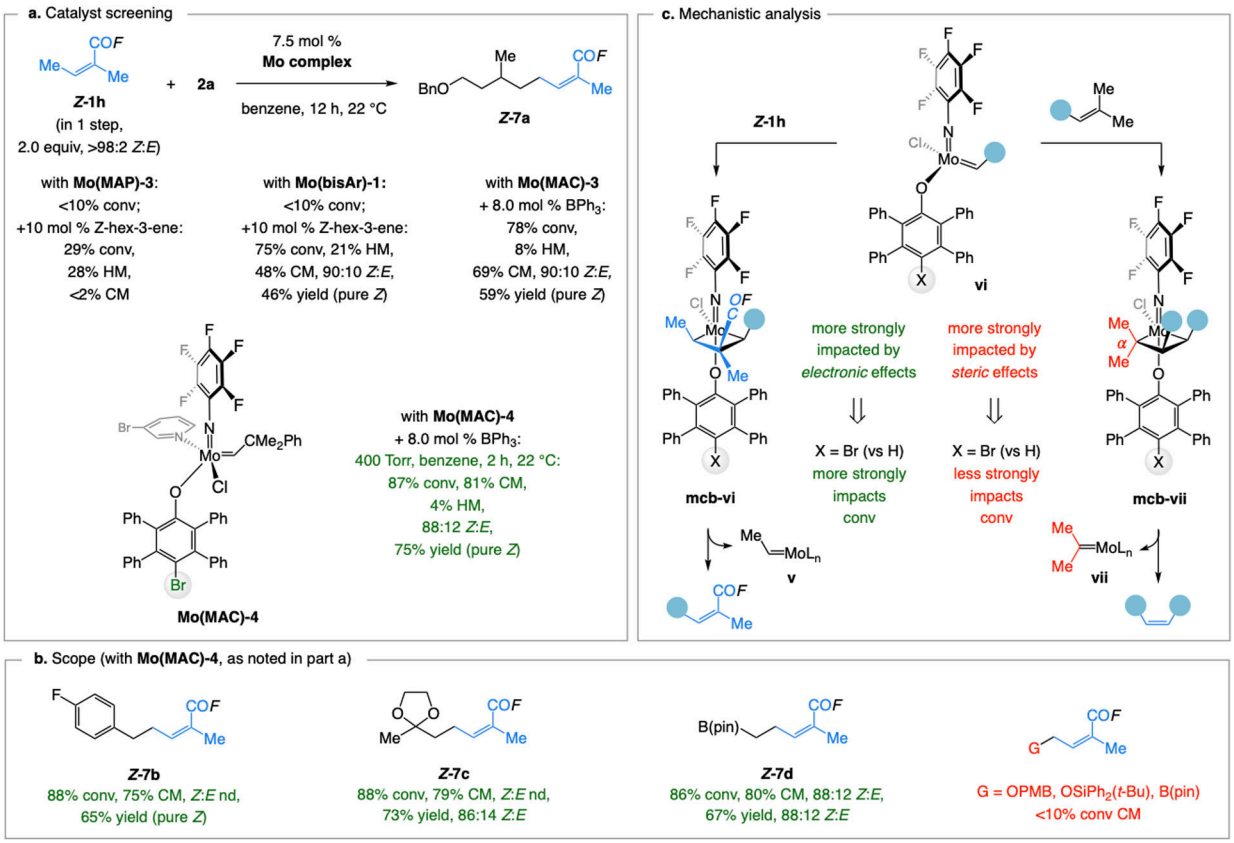
[a]Reactions performed under N_2. Conversion (disappearance of **2**) and *Z*:*E* ratios were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). See the Supporting Information for details. nd = not determined. CM, cross-metathesis.



Scheme 7.

CM with Different Types of *Z*-Trisubstituted Enoates[a]

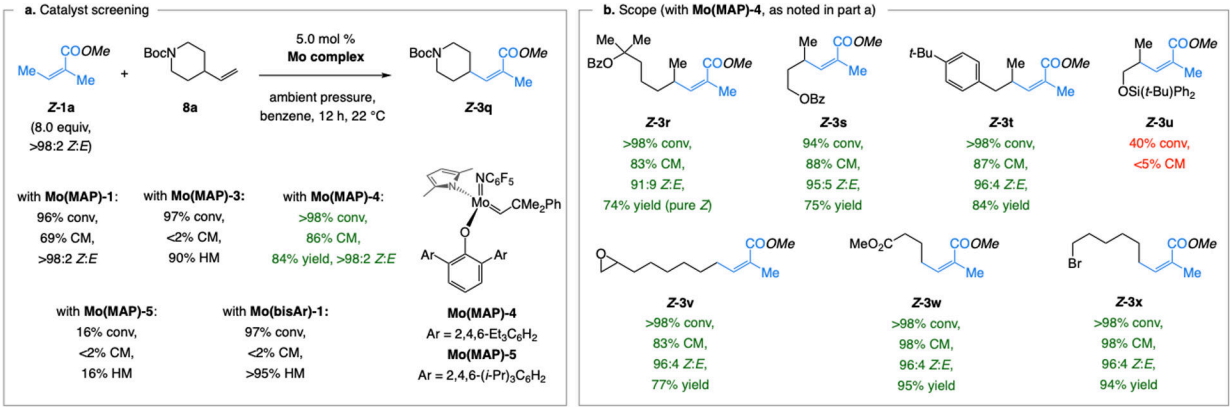
[a]Reactions performed under N_2. Conversion (disappearance of **2a**) and *Z*:*E* ratios were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). See the Supporting Information for details. CM, cross-metathesis.



Scheme 8.

Z-Trisubstituted CM Reactions Involving Acid Fluorides[a]

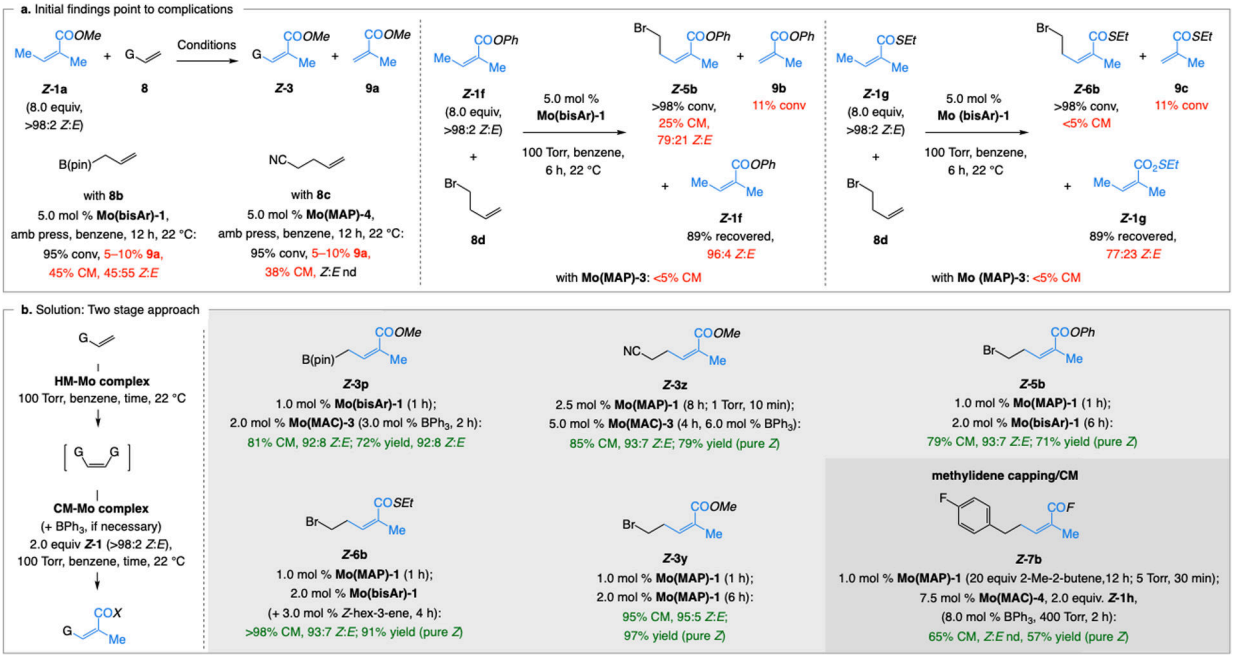
[a]Reactions were performed under N_2 atm. Conversion values (disappearance of **2**) and *Z*:*E* ratios were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). See the Supporting Information for details. CM, cross-metathesis; HM, homo-metathesis.



Scheme 9.

CM with Monosubstituted Alkenes to Generate *Z*-Trisubstituted Enoates[a]

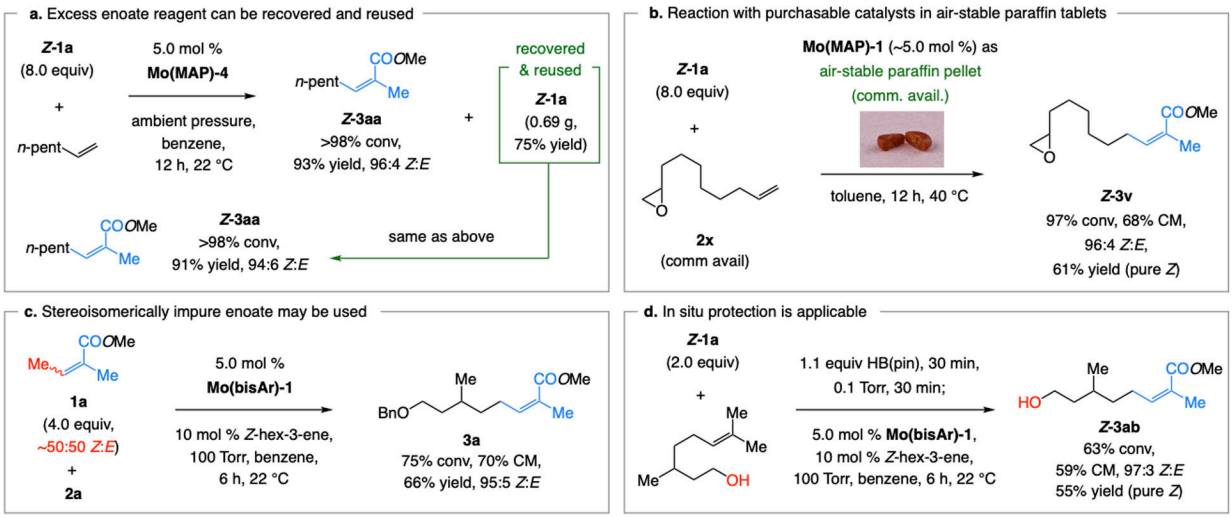
[a]Reactions were performed under N_2 atm. Conversion values (disappearance of **8a**) and *Z*:*E* ratios were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). See the Supporting Information for details. CM, cross-metathesis; HM, homo-metathesis.



Scheme 10.

Two-Stage Conversion of Monosubstituted Alkenes to *Z*-Trisubstituted Enoates[a]

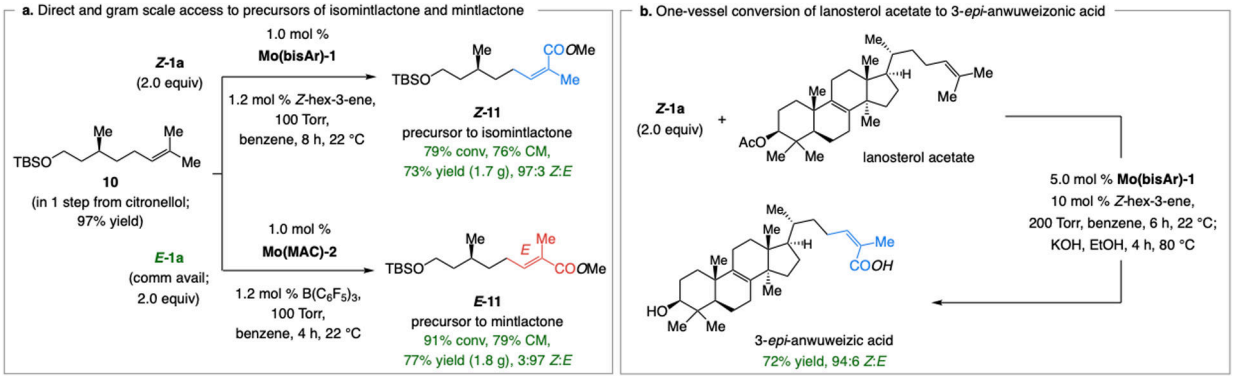
[a]Reactions were performed under N_2 atm. Conversion values (disappearance of monosubstituted alkene) and *Z*:*E* ratios were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). See the Supporting Information for details. nd = not determined. CM, cross-metathesis; HM, homo-metathesis.



Scheme 11.

Regarding Practicality of the Approach[a]

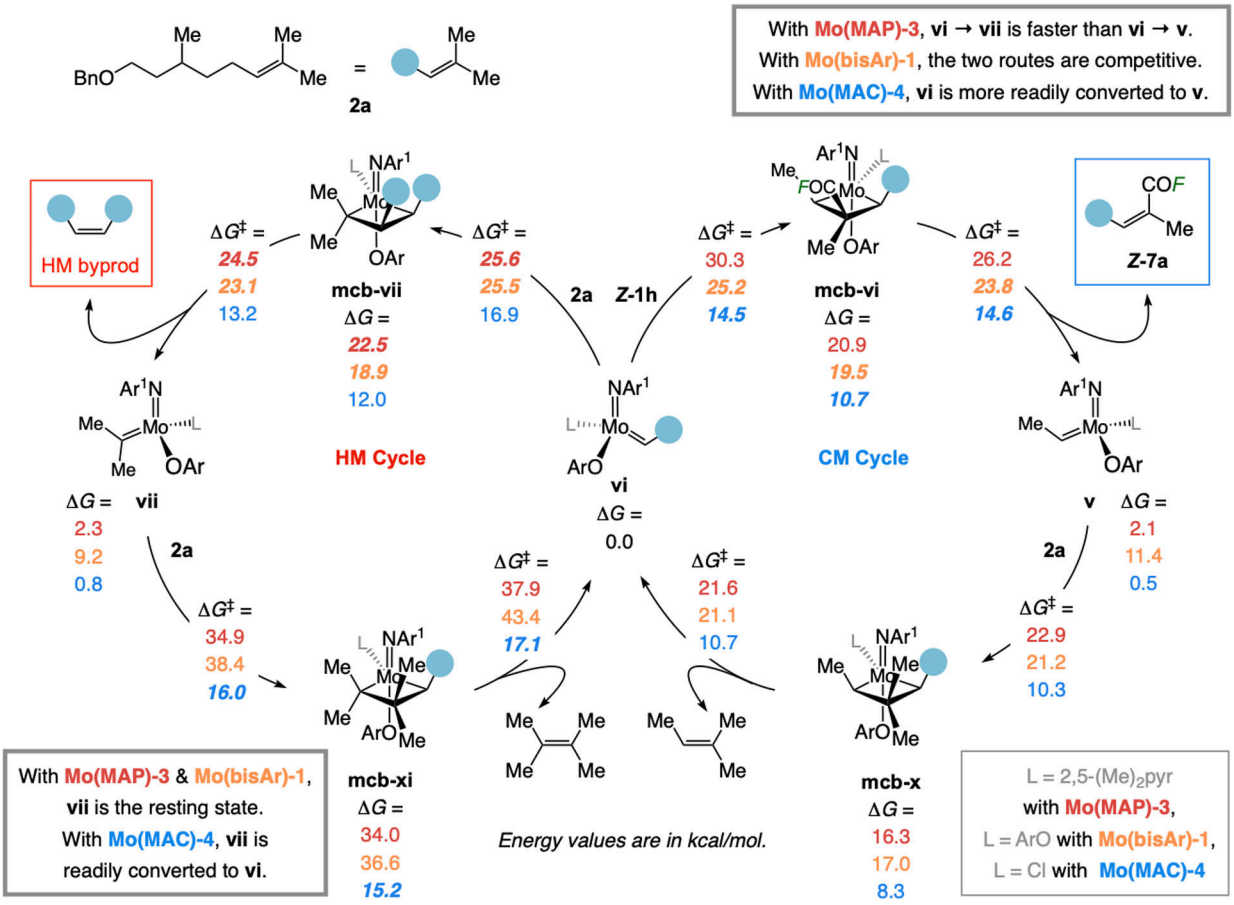
[a]Reactions were performed under N_2 atm. Conversion values (disappearance of monosubstituted alkene) and *Z*:*E* ratios were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). See the Supporting Information for details. CM, cross-metathesis.



Scheme 12.

Representative Applications[a]

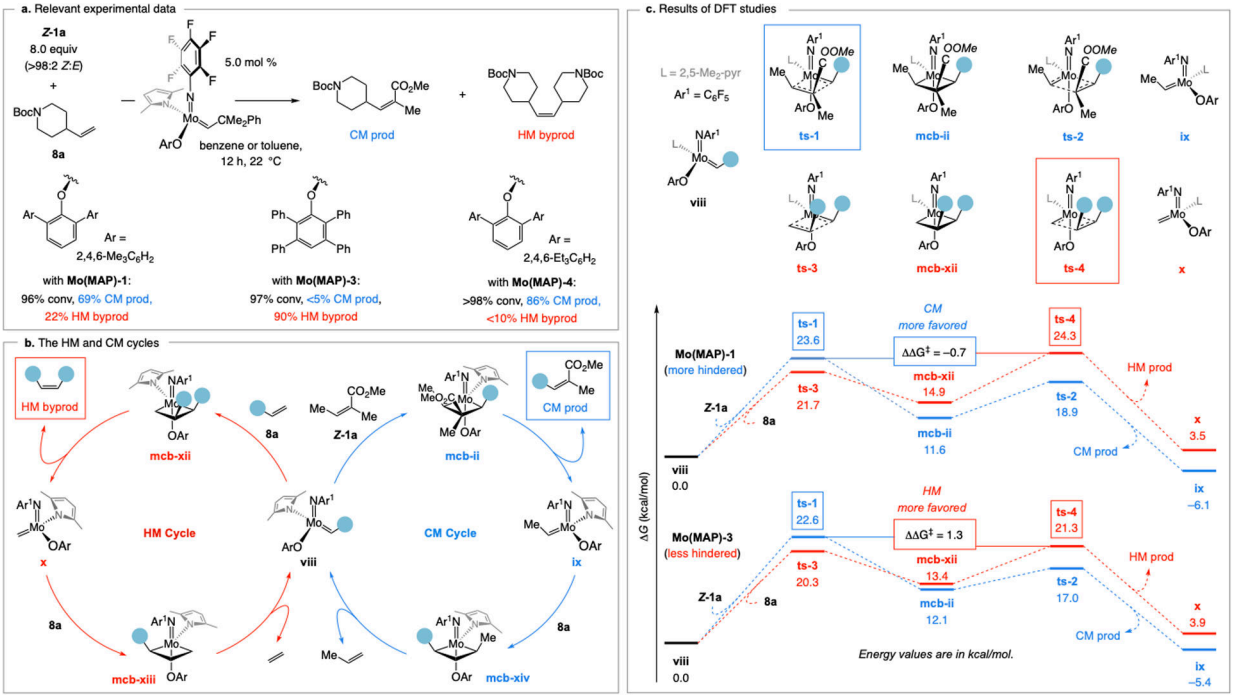
[a]Reactions were performed under N_2 atm. Conversion values (disappearance of monosubstituted alkene) and *Z*:*E* ratios were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). See the Supporting Information for details. CM, cross-metathesis.



Scheme 13.

Regarding Why Mo(MAC) Catalysts are Superior in CM Reactions of Acid Fluorides[a]

[a]Computational studies were performed with ωB97X-D/def2tzvpp,SMD(benzene)//B3LYP-D3/def2svp. See the Supporting Information for details. CM, cross-metathesis; HM, homo-metathesis.



Scheme 14.

Regarding the Mechanism of CM Reactions Involving α-Branched Monosubstituted Alkenes[a]

[a]Reactions were performed under N_2 atm. Conversion values (disappearance of **8a**) determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). Computational studies were performed with ωB97X-D/def2tzvpp,SMD(benzene)//B3LYP-D3/def2svp. See the Supporting Information for details. CM, cross-metathesis; HM, homo-metathesis.

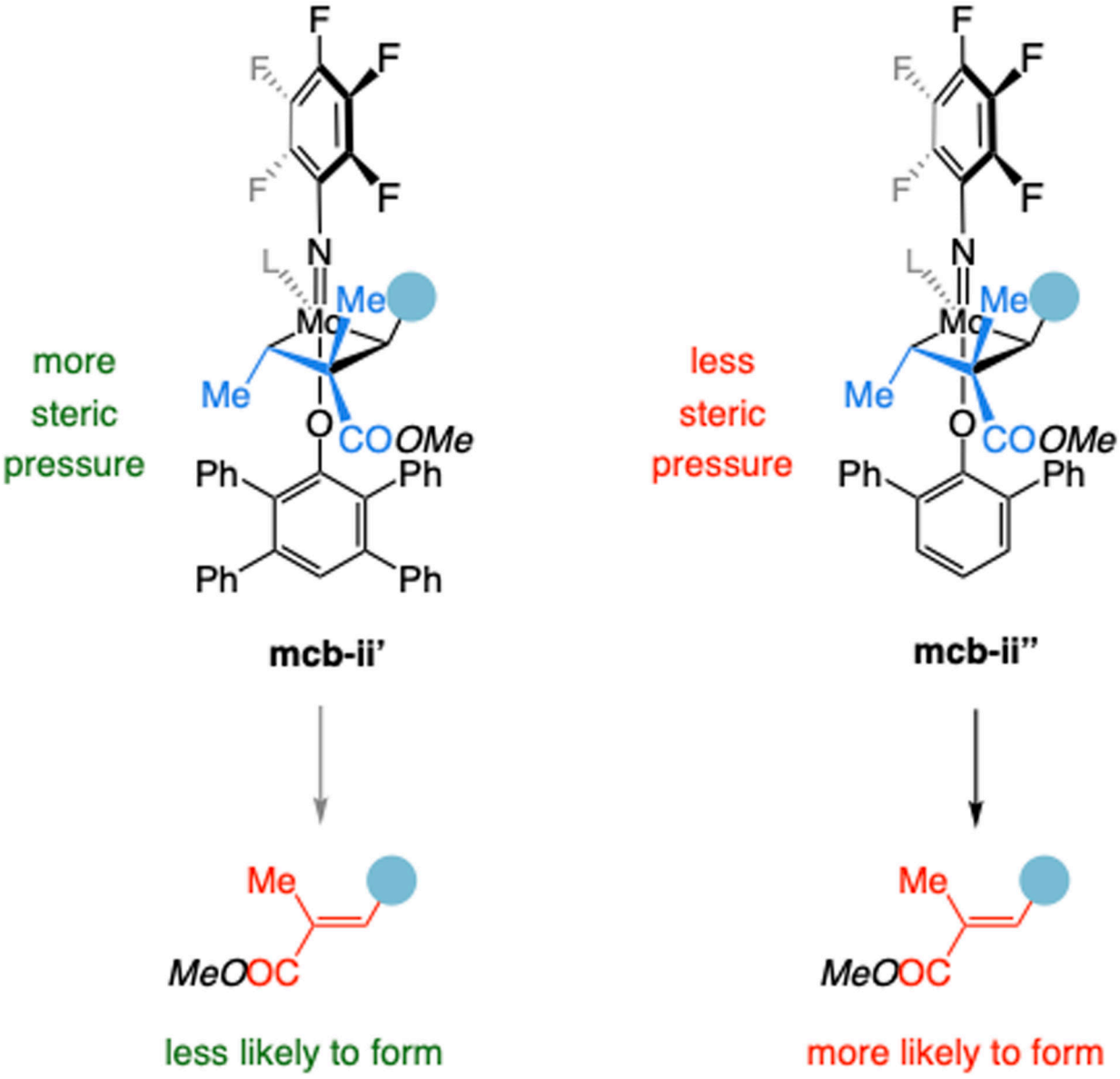


Figure 1.
The importance of the tetraphenyl aryloxide to kinetic selectivity (stereoretentivity).

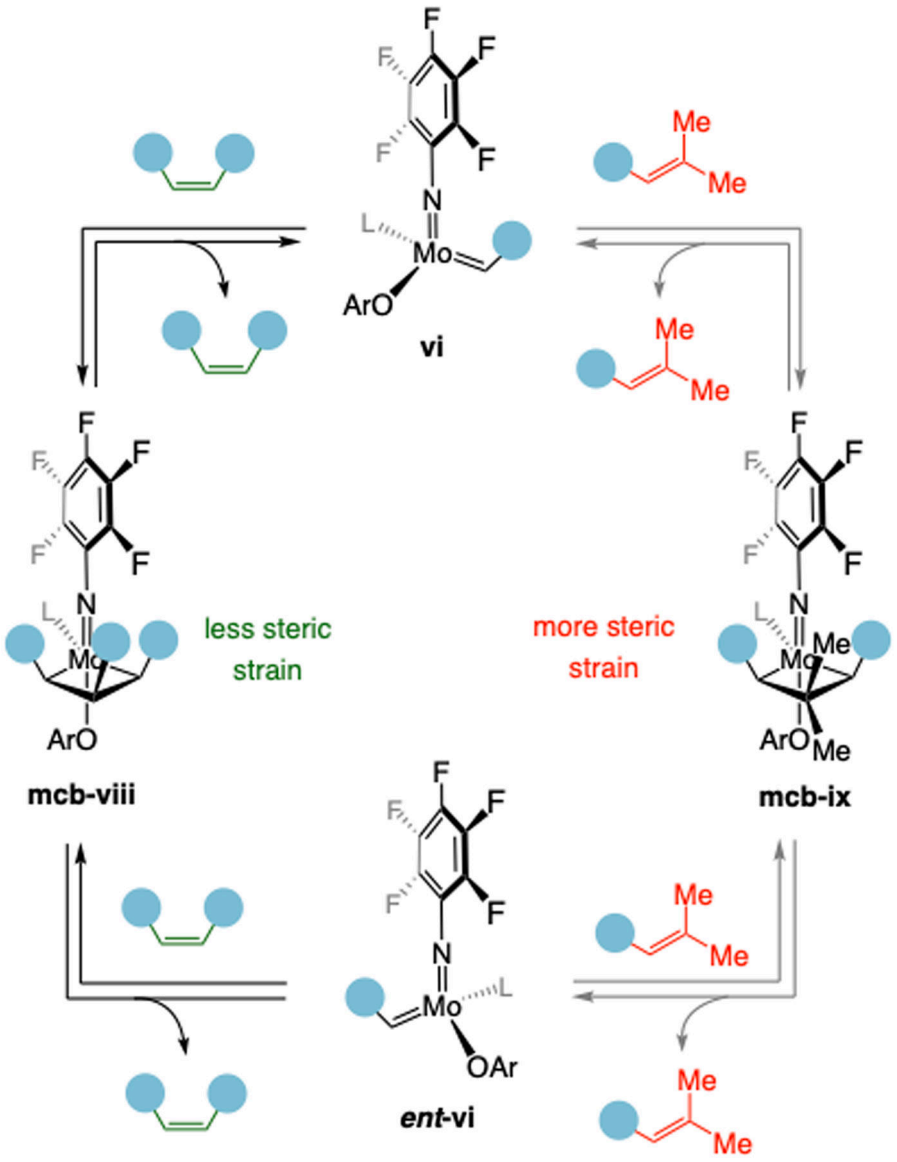
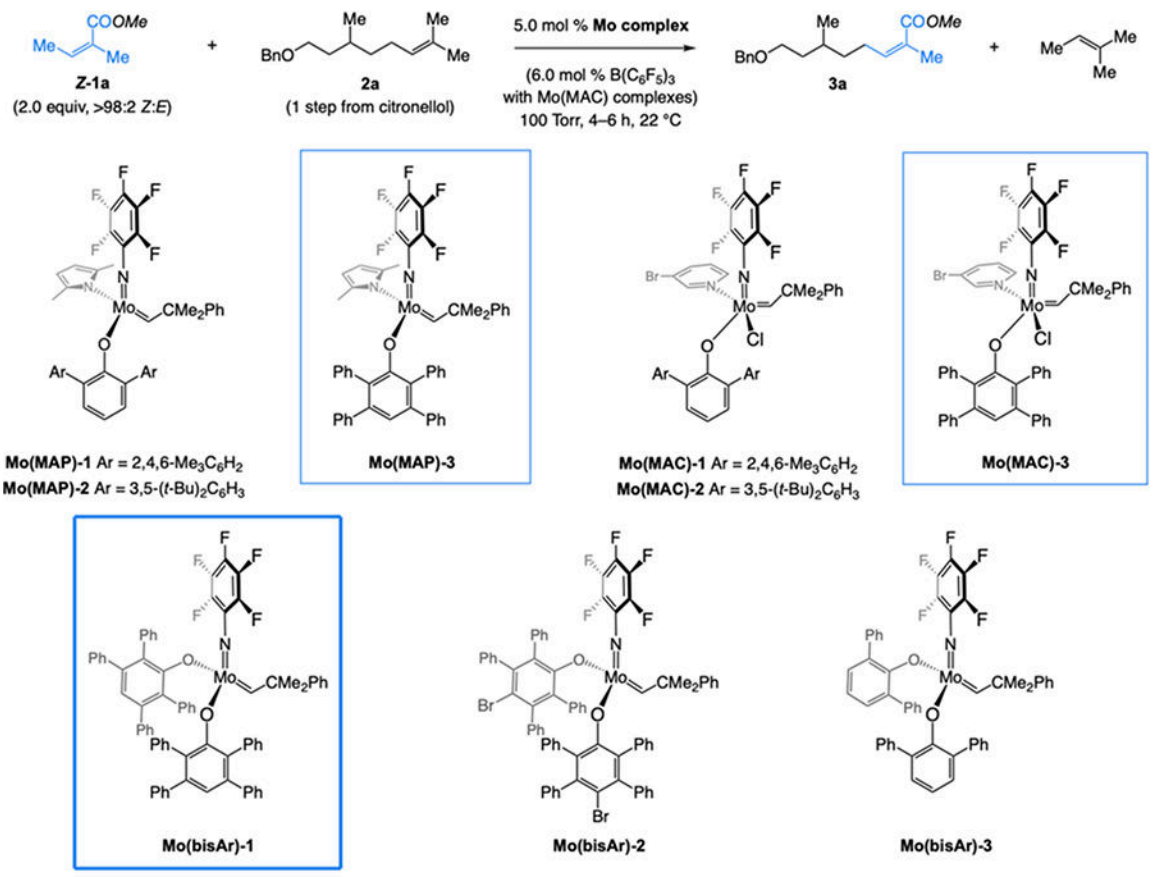


Figure 2.
More unproductive olefin metathesis with disubstituted alkenes.

Table 1.

Identification of Effective Catalysts for Reactions Involving Z-Trisubstituted Methyl Esters[a]



entry	Mo complex	time (h)	conv (%); conv to 3a *(%)*[b]	yield (3a, %)[c]	*Z:E* [b]
1	**Mo(MAP)-1**	6	<5; na	na	na
2	**Mo(MAP)-2**	6	81; 77	71	93:7
3	**Mo(MAP)-3**	6	*89; 85*	*81*	*97:3*
4	**Mo(MAC)-1** [d]	4	<5; na	na	na
5	**Mo(MAC)-2** [d]	4	94:92	nd	25:75
6	**Mo(MAC)-3** [d]	4	*91; 82*	*78*	*94:6*
7	**Mo(bisAr)-1**	6	*95; 93*	*91*	*95:5*
8	**Mo(bisAr)-2**	6	97; 89	nd	88:12
9	**Mo(bisAr)-3**	6	56; 51	nd	84:16

[a]Reactions performed under N_2. Use of mild vacuum led to slightly better results (e.g., for entry 3 at ambient pressure, 12 h: 85% conv, 83% CM, 79% yield, 96:4 *Z*:*E*).

[b]Conversion values (disappearance of **2a**) and *Z*:*E* ratios were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%).

[c] Yields of purified products (±5%).

[d] Performed in the presence of 6.0 mol % $B(C_6F_5)_3$. See the Supporting Information for details. na, not applicable; nd, not determined.