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Synthesis of *Z*-*gem*-Cl,CF_3-Substituted Alkenes by Stereoselective Cross-Metathesis and the Role of Disubstituted Mo Alkylidenes

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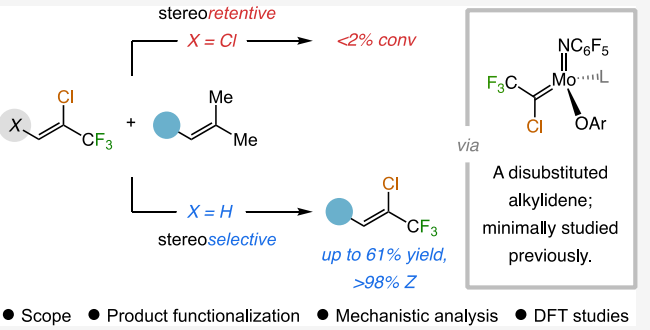
ABSTRACT: Stereochemically defined organofluorine compounds are central to drug discovery and development. Here, we present a catalytic cross-metathesis method for the synthesis of *Z*-trisubstituted olefins that contain a Cl- and a CF_3-bound carbon terminus. Notably, the process is stereo*selective*, which is in contrast to the existing stereoretentive strategies that also involve a trisubstituted olefin as starting material. Reactions are catalyzed by a Mo monoaryloxide pyrrolide alkylidene, involve a trisubstituted alkene and *gem*-Cl,CF_3-substituted alkene, and are fully *Z*-selective. Catalytic cross-coupling can be used to convert the C−Cl bond of the trisubstituted olefin to C−B, C−D, and different C−C bonds. We elucidate the role of Cl,CF_3-disubstituted Mo alkylidenes. Experimental and computational (DFT) data show that in some instances a disubstituted alkylidene is formed and then transformed to a more active complex. In other cases, the Cl,CF_3-disubstituted alkylidene is a direct participant in a catalytic cycle. The studies described shed new light on the chemistry of high oxidation-state disubstituted alkylidenes−scarcely investigated entities likely to be pivotal to approaches for stereocontrolled synthesis of tetrasubstituted alkenes through olefin metathesis.



1. INTRODUCTION

We will describe below the results of an investigation regarding the development of a cross-metathesis (CM) method for preparing *Z*-trisubstituted alkenes bearing a chloro and a trifluoromethyl terminus. Despite the involvement of a trisubstituted alkene, the optimal process turned out to be stereo*selective* and not stereoretentive, that is, unlike the approaches recently disclosed.[1,2] Equally notable is the new light shed on the chemistry of Cl,CF_3-disubstituted Mo alkylidenes[3] and their role in catalytic olefin metathesis.[4] Information is scant regarding such organometallic entities, likely to be vital to the development of methods for synthesis of *E*- and *Z*-tetrasubstituted olefins.[5]

The importance of stereodefined organofluorine compounds aside,[6,7] we were keen on exploring the limits of olefin metathesis reactions involving two trisubstituted alkenes.[1] We opted for stereodefined olefins bearing a *gem*-Cl,CF_3-substituted terminus as products. The value of these compounds is exemplified by *trans*-bifenthrin, two strategies for preparation of which were reported by Hiyama in 1986 (Scheme 1a).[8] The routes commence with reductive coupling of an aldehyde and 1,1,1-trichloro-2,2,2-trifluoro ethane with one starting with a chiral cyclopropyl aldehyde. The resulting polyhalogenated alcohol was converted to the corresponding acetate and subjected to reductive cleavage, generating the insecticide. Alternatively, 3-methyl-crotonaldehyde was converted to an α-diazo ester. Intramolecular cyclopropane formation and reductive C−O bond cleavage then delivered the bifenthrin framework at higher *Z*:*E* ratio (Scheme 1a).

gem-Cl,CF_3-Substituted olefins may be converted to other stereodefined trisubstituted trifluoromethyl alkenes by catalytic cross-coupling (CC). Stereoselective protocols have been introduced for generating similar, modifiable alkenes (Scheme 1b). In many instances,[9] such as those introduced by Konno et al.[10] and Bizet and co-workers,[11] the starting point is a CF_3-substituted alkyne. In a procedure by Zhou et al.[12] a ketone and ethyltrifluoroacetate were used. CM offers a complementary approach. Apropos, we had shown that a *gem*-F,CF_3-substituted olefin can be prepared by stereoretentive CM between a trisubstituted alkene and 1,2-dichloro-1-fluoroethene followed by CC (Scheme 1c).[13] However, a C−F bond cannot be modified as easily as a C−Cl bond.

As noted, a key aspect of our studies turned out to be vis-à-vis the reactivity of disubstituted Mo alkylidenes. Monosubstituted alkylidenes and carbenes have thus far dominated the field. Little

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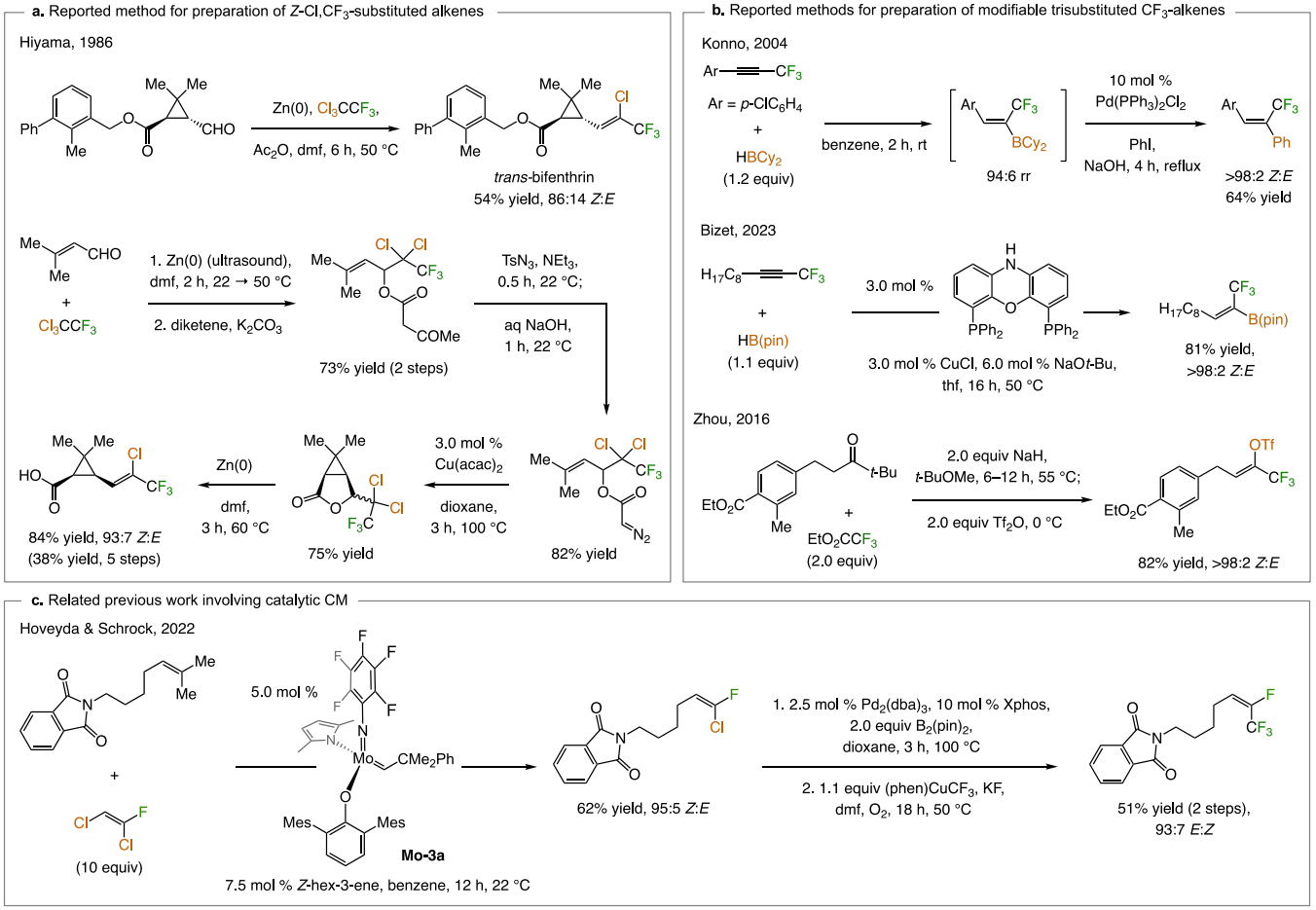
Scheme 1. State of the Art in Synthesis of Stereochemically Defined Trisubstituted Alkenes Bearing a CF_3 Moiety[a]



[a]acac, acetylacetone; dba, dibenzylideneacetone; Ts, 4-toluenesulfonyl; Tf, trifluoromethanesulfonyl; Mes, 2,4,6-$Me_3C_6H_2$; pin, pinacolato; phen, 1,10-phenanthroline; XPhos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; rr, regioisomeric ratio.

is known about the disubstituted variants, even when a transformation affords a trisubstituted alkene.[14] Disubstituted Mo alkylidenes were first reported in 1994 by Schrock as initiators of diyne polymerization (Scheme 2a),[15] an observation that was referred to as "surprising." At the time, such complexes were believed to be catalytically inactive.

With the development of methods for synthesis of *E*- and *Z*-trisubstituted olefins (mainly by Mo catalysts) gaining steam,[1] the role of disubstituted alkylidenes has come under scrutiny. In 2017, we reported a study aimed at the development of a stereoretentive CM method[16] for synthesis of stereodefined trisubstituted olefins (Scheme 2b). There, we dealt with the involvement of a disubstituted Mo alkylidene. We posited that the lower efficiency of the stereo*selective* cycle was on account of the transformation proceeding via a less reactive disubstituted Mo alkylidene (**Mo**=CR_2) and a relatively unstable methylidene (**Mo**=CH_2). Several years later, in 2020, Schrock reported the synthesis, characterization, and reactivity of several disubstituted Mo monoaryloxide chloride (MAC) and monoaryloxide pyrrolide (MAP) alkylidenes (Scheme 2c).[17] Crystallographic data suggested that agostic interactions contribute to their diminished reactivity.

2. RESULTS AND DISCUSSION

2.1. Initial Stereoretentive Approach. We began by following the tenets of stereoretentive olefin metathesis (Scheme 3a),[1,16] namely that CM of alkenes **1** and purchasable **2a** would afford *gem*-Cl,CF_3-substituted **3a**. A range of complexes were screened but none promoted CM (<2% **3a** as judged by ^{1}H NMR analysis; Scheme 3b; see the Supporting Information for additional details). This was regardless of the temperature (e.g., up to 45 °C; **2a** bp = 54 °C) or additives that could facilitate catalyst initiation (e.g., *Z*-butene).[13]

We thought that perhaps the larger size of **2a** and diminished Lewis basicity of its alkene (vs 1,2-dichloro-1-fluoroethene; see Scheme 1c) might be the issue. The more electron-rich **1** could react first, generating **Alkyd-1** (Scheme 4, *Stereoretentive Cycle*), the reaction of which with **2a** would generate the densely substituted *syn*-**mcb-2** and precursor to *Z*-**3**. However, this would likely be energetically prohibitive. Based on the previous studies,[1,18] we expected that reaction of Cl-substituted alkylidene **Alkyd-2** with **1** to start a new cycle via *syn*-**mcb-3** would not be problematic.

2.2. Revised Stereo*selective* Approach. The rocky start led us to wonder if CM with the less hindered 1,1-disubstituted alkene **2b** (commercially available)—a stereo*selective* process—might be a better option. On one hand, the smaller and more π-Lewis basic **2b** (vs **2a**) would facilitate mcb formation. On the other hand, we would need to contend with the concerns that had led to the emergence of stereoretentive protocols in the first place. One issue was that the methylidene species[19] (**Meth**; see **Alkyd-1** → *syn*-**mcb-4**→ **Meth**; *Stereoselective Cycle I*, Scheme 4)

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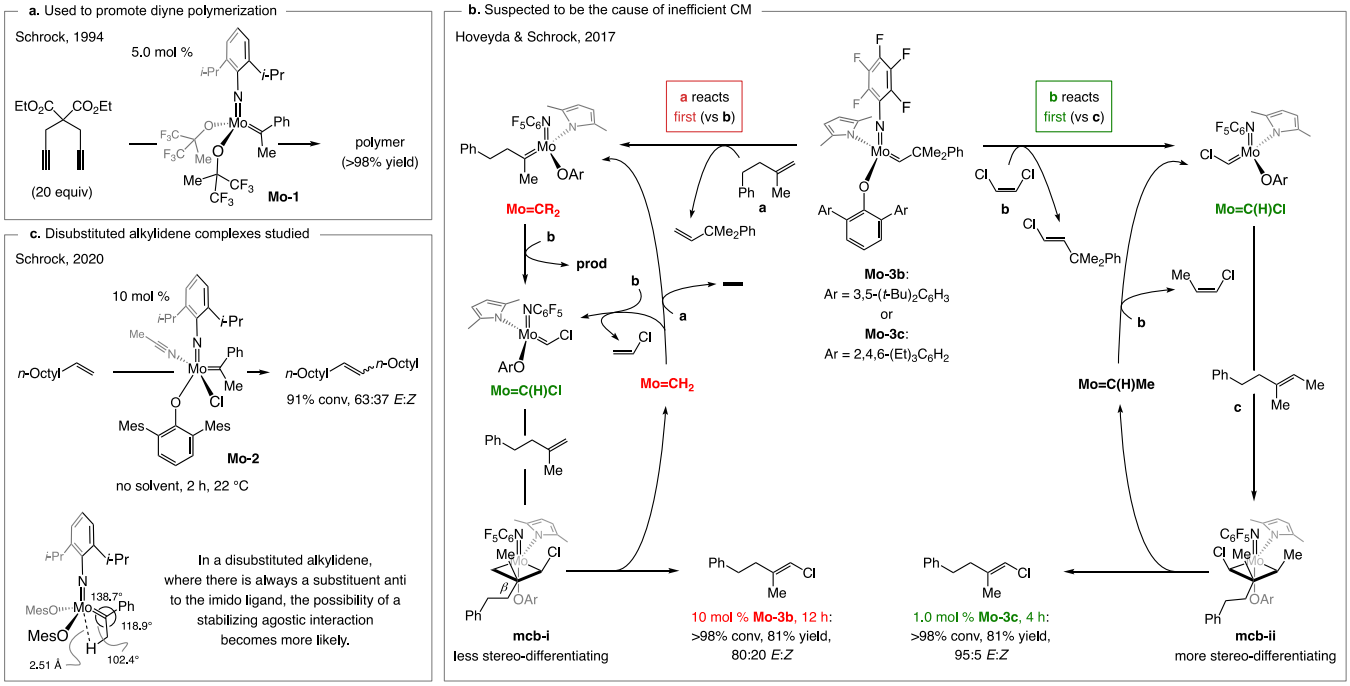
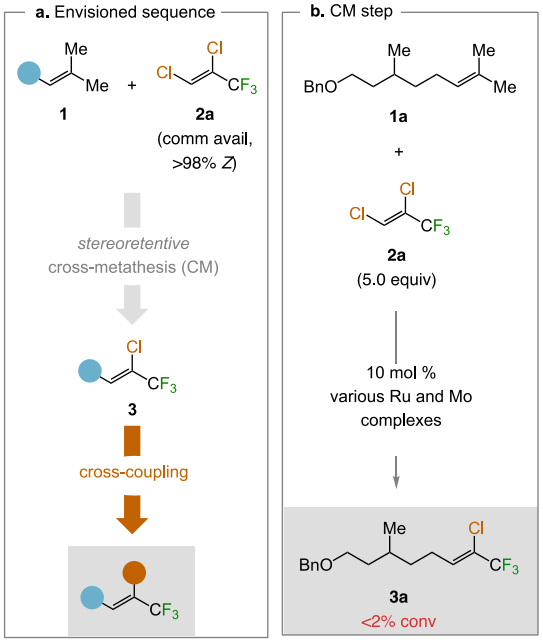
Scheme 2. Previous Findings Involving or Invoking Disubstituted Mo Alkylidene Complexes[a]



[a]CM, cross-metathesis.

Scheme 3. Initial Plan Involving Stereoretentive CM[a]



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

would not be sufficiently long-lived. It was also unclear if the energy difference between *syn*-**mcb-4** and its stereoisomer (Cl pointing toward the aryloxide ligand) would translate to much stereocontrol. In case **2b** were to react first, the resulting disubstituted Mo alkylidene (*anti*-**Alkyd-3**, *Stereoselective Cycle II*) might turn out not to be sufficiently active. We were not sure whether the reaction of *anti*-**Alkyd-3** and **1** would efficiently deliver *anti*-**mcb-7**, which bears two fully substituted Cα sites. Collapse of *anti*-**mcb-7** would yield **Alkyd-4**, which would have to react with **2b** to deliver a similarly congested *anti*-**mcb-8**.

The initial screening data were discouraging, as there was little or no CM with **Ru-1**−**3**, bisalkoxide **Mo-4**, or bisaryloxide **Mo-5** (Scheme 5). We then observed 25% CM and complete stereocontrol with MAC (monoaryloxide chloride) complex **Mo-6** (BPh_3 promotes pyridine dissociation and release of the active complex[20]). MAP complexes afforded further improvement (Scheme 5). CM with **Mo-3b** delivered *Z*-**3a** in 61% yield (>98:2 *Z*:*E*). Conversion was reduced at lower loading (5.0 mol %: 51% conv, 27% CM) or with electron-deficient aryloxides **Mo-3d**−**e**. *p*-Methoxy-substituted **Mo-3f** was as effective as **Mo-3b** (>98:2 *Z*:*E* in all cases). The greater efficiency of the stereoselective approach (vs stereoretentive) was surprising and broached several mechanistic questions, the possible involvement of disubstituted **Alkyd-3** being especially intriguing (see Scheme 4).

2.3. Scope. We settled on **Mo-3b** as the catalyst precursor (vs **Mo-3f**) because its preparation is more straightforward. Reactions were clean (Scheme 6a) and other than the desired product there was <10% 1,2-disubstituted olefin derived from homocoupling of trisubstituted olefin. We isolated **3a** (69% conv, 61% CM) in 61% yield and >98:2 *Z*:*E* selectivity. At larger scale (1.0 mmol of **1a**), the trisubstituted alkene product was obtained in 55% yield as a single isomer. Stereoselectivity was complete in all cases. The process tolerates a tertiary amine (**3b**), a carboxylic ester (**3c**−**e** and **3g**−**k**), a phthalimide (**3f**), a carbamate (**3g**), and an α-thio-ester (**3k**). Reactions with a γ-branched trisubstituted alkene (**3a**, and **3j**−**l**), one that contains a sizable moiety at Cβ (**3m**−**n**) or a β-branched substituent (**3o**) were reasonably efficient.

Steric strain impacted efficiency, as manifested by the inefficient reactions of α-branched alkene **1p** (Scheme 6b),

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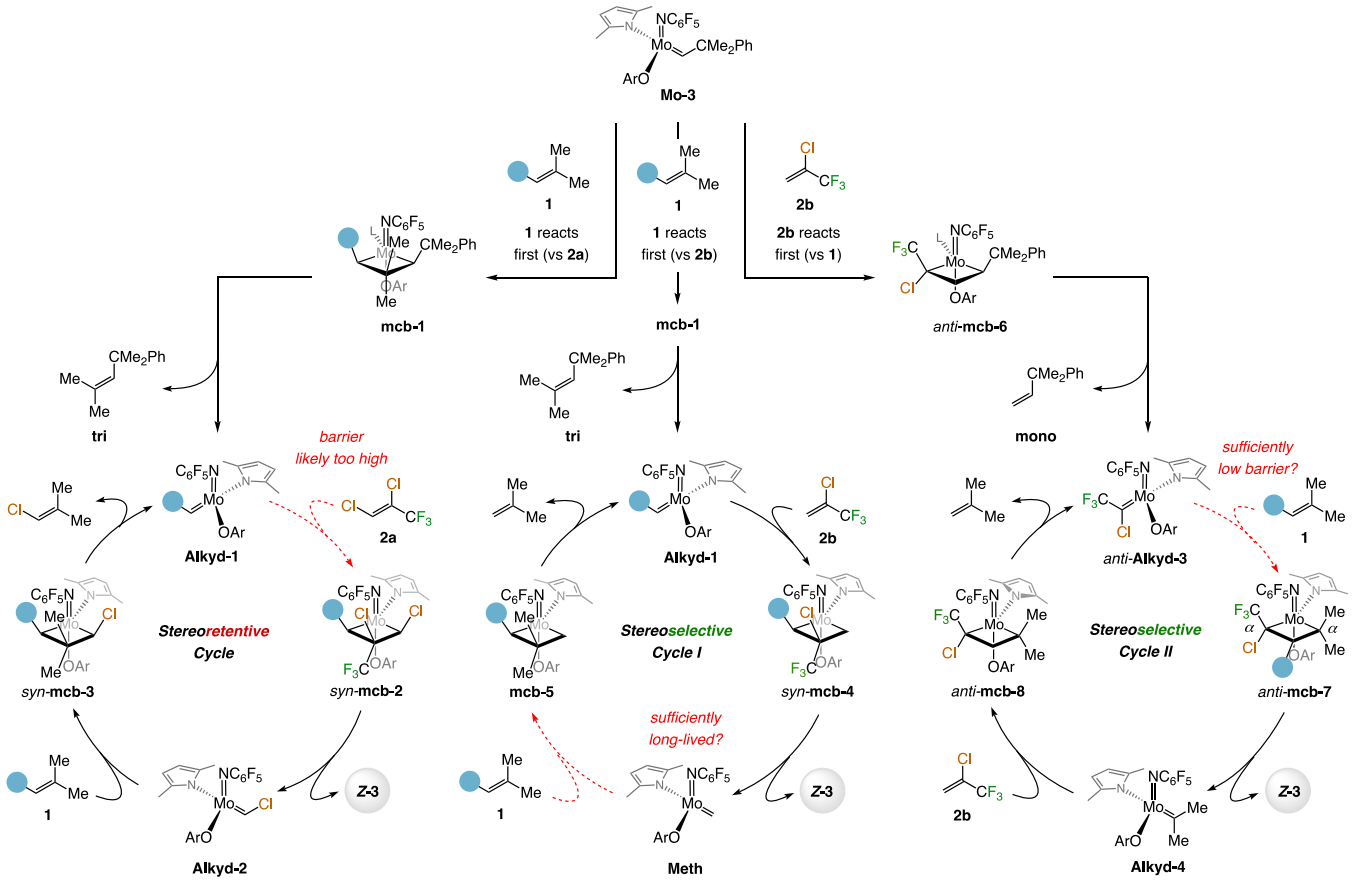
Scheme 4. Initial Mechanistic Analysis[a]



[a]mcb, Metallacyclobutane; meth, methylidene complex.

prenyl−B(pin) **1q**, and aryl-substituted **1s**−**t**. The low reactivity of allylic ether **1r** shows that a proximal electron-withdrawing group and diminished alkene Lewis basicity can be detrimental. Based on previous studies, reactions between two trisubstituted olefins, including prenyl−B(pin) (**1q**), *Z*- or *E*-2-bromo-2-butene,[21] and trisubstituted enoates[22] can be efficient. Such variation, in the face of the lower substitution in **2b**, underscores the challenging nature of the present set of CM reactions.

Underscoring the difficulty of these transformations is the impact of a Lewis basic moiety on CM rate. For example, unlike carboxylic ester **3e** (see Scheme 6a), which was obtained in 51% yield (61% conv), in the case of **1u** and its more proximal ester moiety, there was 5% conversion to **3u** (Scheme 7a). The adverse influence of a coordinating moiety may be attributed to the formation of deactivated cyclic alkylidene complex **Mo-7**.[23] The equilibrium between **Mo-7** and **Mo-7′** might not allow sufficient amounts of the latter to be present in solution long enough to give CM a chance. The presence of a less Lewis basic boronic ester is less damaging: **3n** was isolated in 61% yield (see Scheme 6a).

We capitalized on the versatility of the C−B bond and converted **3n** to primary alcohol **3v** (Scheme 7b), which was transformed to **3u** (60% yield, 2 steps). The same may be applied to preparation of other stereodefined *gem*-Cl,CF_3-substituted olefins that cannot be obtained by CM directly. Stereoselective synthesis of **3w** is illustrative.

2.4. Product Modification. The C−Cl bond offers numerous functionalization possibilities (Scheme 8a). Boryl- (**4a**), alkyl- (**4b**), allyl- (**4c**), acyl- (**4d**), aryl-(**4e**), and deuterium-substituted (**4f**) alkene derivatives were synthesized in 65−82% yield. There was no detectable loss of stereochemical purity. Catalytic CC of alkenyl−B(pin) **4a** with an alkenyl halide, including those obtained through CM, can be used for preparation of polyfluoro 1,3-dienes.[13] Allyl-substituted olefins such as **4c** have been applied to synthesis of epothilone analogs.[24] Enones represented by **4d** can serve in various selective catalytic processes (e.g., hydrogenations,[25] conjugate additions,[26] ring formations[27]). Isotopically labeled molecules (e.g., **4f**) are valuable to drug discovery and development.[28] There is also the possibility of catalytic regio- and enantioselective boryl substitution (Scheme 8b).[29] The conversion of **3e** to tetrasubstituted allylic boronate **5** is representative (63% yield, 91:9 er (enantiomeric ratio)).[30]

2.5. Spectroscopic Detection of Cl,CF_3-Disubstituted Mo Alkylidenes. The possible formation of **Mo-7** and **Mo-7′** (see Scheme 7a) implied that an alkylidene generated from the trisubstituted olefin substrate might be involved. Still, this did not rule out the involvement of a Cl,CF_3-disubstituted Mo alkylidene (see **iii**, Scheme 4). While a disubstituted alkylidene could reduce the rate of CM, if *Stereoselective Cycle I* (Scheme 4) were operative and an unstable methylidene species (**Meth**) involved, then its trapping by **2b** could prolong catalyst lifetime. We opted to explore whether disubstituted *anti*-**Alkyd-3** is formed in the course of the CM transformation (Scheme 9).

We first carried out an experiment with the hope of detecting the various Mo alkylidene species generated (Scheme 9; **1a**:**2b**:**Mo-3b** = 1.0:5.0:1.0). A singlet emerged immediately in the ^{19}F NMR spectrum at −60.2 ppm (−70.2 ppm for **2b**), its

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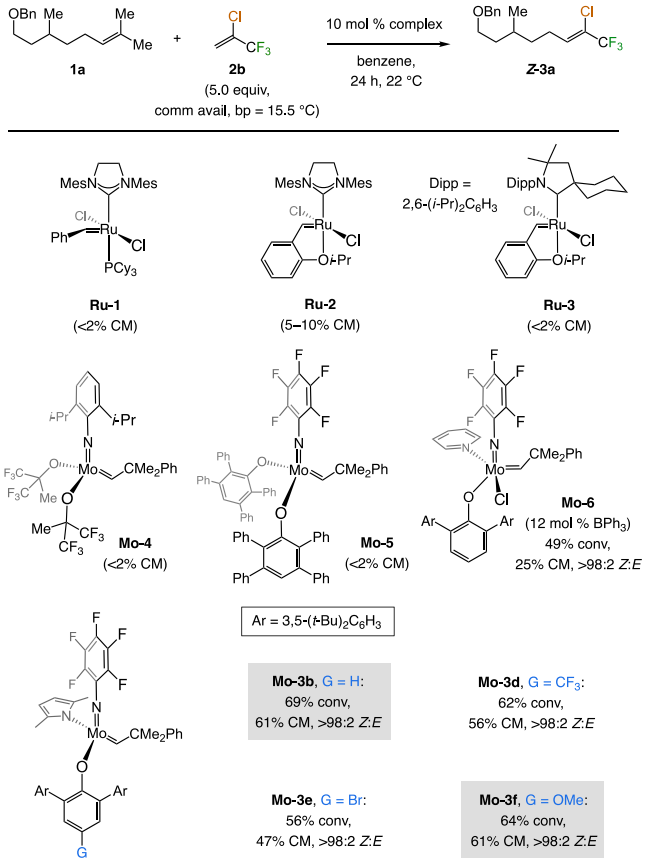
Scheme 5. Exploring the Feasibility of Stereoselective CM[a]



[a]Reactions performed under N_2. Conversion (disappearance of **1a**) and *Z*:*E* ratios were determined by analysis of ^{1}H and ^{19}F NMR spectra of unpurified product mixtures (±2%). Yield of purified products (±5%). See the Supporting Information for details. CM, cross-metathesis.

concentration increasing to 46 mol % after 6 h. A similar amount of the monosubstituted alkene (**mono**), marking catalyst initiation, was observed in the ^{1}H NMR spectrum (see Figure S1 in the Supporting Information). Accordingly, we attributed the aforementioned peak in the ^{19}F NMR spectrum to the CF_3 group of disubstituted alkylidene *anti*-**Alkyd-3** (see the Supporting Information for full characterization details). To verify, we synthesized a sample of *anti*-**Alkyd-3** by subjecting **Mo-3b** to 50 equiv of **2b** (40 °C, 16 h; see below for further analysis). Formation of *anti*-**Alkyd-3** was marked by the appearance of the aforementioned signals: a singlet at −60.2 ppm ($3F_d$), a doublet at −142.9 ppm ($2F_c$), a triplet at −151.4 ppm ($1F_a$), and a triplet of doublets at −161.8 ppm ($2F_b$).

2.6. Concentration of the Disubstituted Alkylidene Is Time-Dependent. To probe the role of *anti*-**Alkyd-3** further, we decided to investigate whether there is any variation in its concentration in the course of a catalytic process. The disubstituted alkylidene was detected early on (Scheme 10), and was present in solution in up to 7.5 mol % after 3 h, gradually diminishing and disappearing after 6 h. In the meantime, *Z*-**3a** was continuously being generated. To gain further insight, we would later perform DFT investigations (see below).

2.7. Synthesis and Characterization of Disubstituted Alkylidenes. As noted above, we were able to prepare *anti*-**Alkyd-3** by subjecting **Mo-3b** with 50 equiv of **2b** (see Scheme 9). Nevertheless, attempts to isolate *anti*-**Alkyd-3** were unsuccessful. We therefore set our sights on a more readily isolable derivative, and chose to synthesize a more robust form of the disubstituted alkylidenes. We were indeed able to synthesize its 2,2′-bipyridyl (bpy) adduct of *anti*-**Alkyd-3**, namely *anti*-**Alkyd-5**, by subjecting a solution of the former with 0.9 equiv of bipyridine. We isolated *anti*-**Alkyd-3** in 36% yield as dark-brown solid (Route A, Scheme 11a). Furthermore, we prepared **Mo-6** in 84% yield by subjecting **Mo-3b** to pyridinium chloride (Route B, Scheme 11a). An authentic sample of *anti*-**Alkyd-6** was then prepared in 35% yield through CM of **Mo-6** with **2b** ($ZnCl_2$ facilitates pyridine dissociation needed for CM; pyridine subsequently recoordinates to Mo). Analysis of the NMR spectra of *anti*-**Alkyd-6** confirmed the foregoing assignments (Scheme 11b). The key data are as follows: (1) A triplet at −67.0 ppm in the ^{19}F NMR spectrum, which we attribute to the CF_3 unit (J_{F-F} = 6.0 Hz, between CF_3 and F_c, confirmed by ^{19}F−^{19}F COSY). (2) A quartet at 282.3 ppm in the ^{13}C NMR (J_{C-F} = 40.7 Hz) indicating that the CF_3 group is an alkylidene substituent. (3) There was no detectable alkylidene proton signal in the ^{1}H NMR spectrum.

2.8. Involvement of Cl,CF_3-Disubstituted Alkylidenes in CM. The next question was how exactly might a disubstituted Mo alkylidene be involved in the catalytic CM reaction (Table 1). To probe, we performed several experiments and obtained the following data: (1) In situ formed *anti*-**Alkyd-3** promotes the conversion of **1a** and **2b** to *Z*-**3a** (entry 2, Table 1; 50% disappearance of **1a**, 28% conv to *Z*-**3a**), albeit less effectively than **Mo-3b** (entry 1; 53% disappearance of **1a**, 41% conv to *Z*-**3a**). (2) CM with isolated *anti*-**Alkyd-5** was considerably less efficient (entry 3; 10% disappearance of **1a**, 6% conv to *Z*-**3a**). (3) CM was faster with MAC *anti*-**Alkyd-6** than MAP *anti*-**Alkyd-5** (entry 4; 50% disappearance of **1a**, 37% conv to *Z*-**3a**). (4) While disubstituted MAC alkylidene *anti*-**Alkyd-6** is almost as effective as **Mo-3b** (entry 1 vs 4) both are more effective at promoting CM compared to neophylidene MAC complex **Mo-6** (entries 1 and 4 vs entry 5). Most importantly, these findings indicate that a disubstituted Mo alkylidene can enter the catalytic cycle. There are however other mechanistic implications (see below).

2.9. Computational Studies. *2.9.1. Productive Cycle and Role of Disubstituted Alkylidene* ***Alkyd-3****.* DFT studies (Scheme 12) indicated that a Mo-MAP complex reacts more readily with a trisubstituted olefin (via **mcb-1**) than **2b** (via *anti*-**mcb-6**). The resulting **Alkyd-1** was calculated to be more stable than *anti*-**Alkyd-3** by 4.2 kcal/mol. These investigations also indicated that *anti*-**Alkyd-3** is the favored isomer (i.e., Cl anti to the imido ligand; ΔG = 4.2 vs 6.7 kcal/mol for *anti*- and *syn*-**Alkyd-3**, respectively). The bulkier CF_3 moiety (vs Cl) prefers to be oriented away from the more sizable aryloxide ligand (vs pentafluorophenylimido).

Reaction of **Alkyd-1** with **2b** can generate *syn*-**mcb-4** (*Cycle A*), which could productively collapse to give **prod** and **Meth** (ΔG = 3.2 kcal/mol; see **Meth**, *Cycle A*, Scheme 4). There would be three options for **Meth** (aside from decomposition). (1) It could react with **2b** to afford *anti*-**mcb-10** (*Cycle B*; $\Delta G^{\ddagger}$ = 24.0 kcal/mol). (2) It could be converted to *anti*-**mcb-11** ($\Delta G^{\ddagger}$ = 21.5 kcal/mol). (3) It could merge with **1** to furnish **mcb-5** (*Cycle A*; $\Delta G^{\ddagger}$ = 14.2 kcal/mol). DFT studies indicate that the last scenario is favored, leading to regeneration of **Alkyd-1**, release of 2-methylpropene, and completion of the productive *Cycle A*. As was mentioned, the relatively reactive and unstable **Meth** is in all likelihood the weak link in the entire process and a reason why 10 mol % Mo complex loading is necessary.

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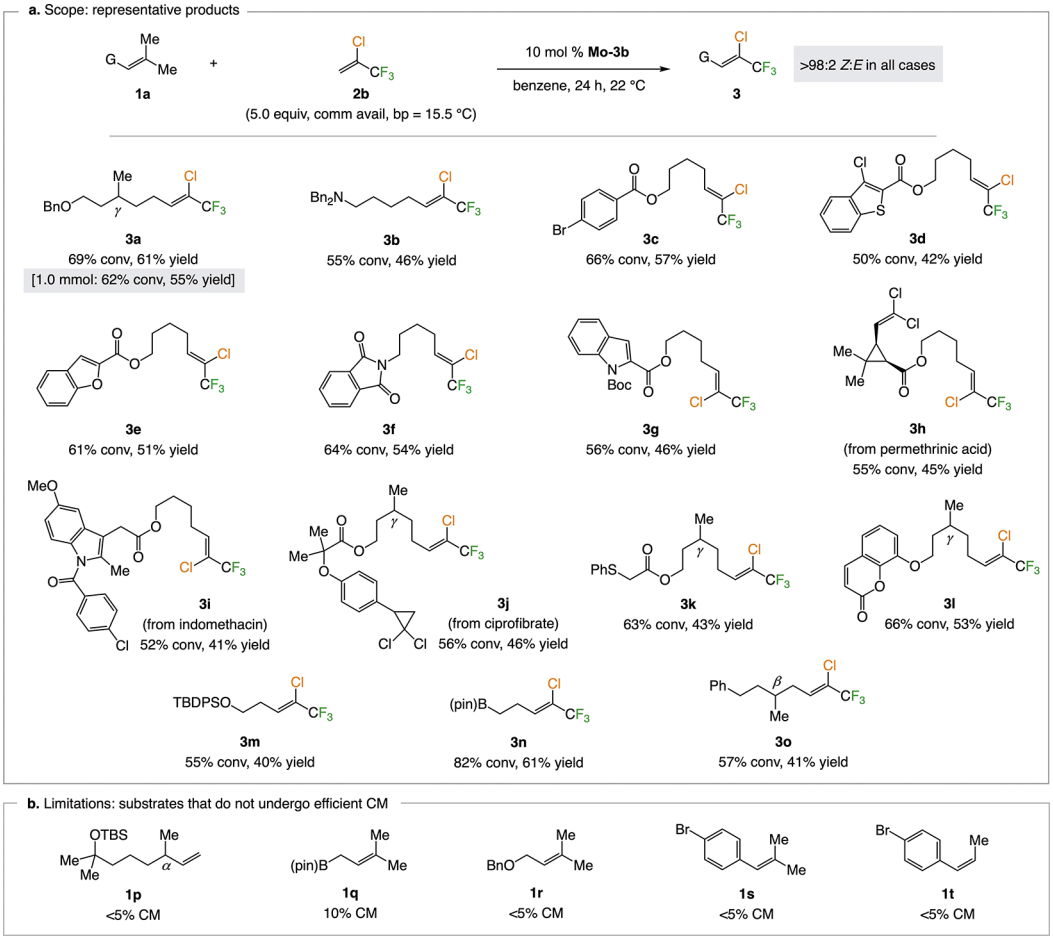
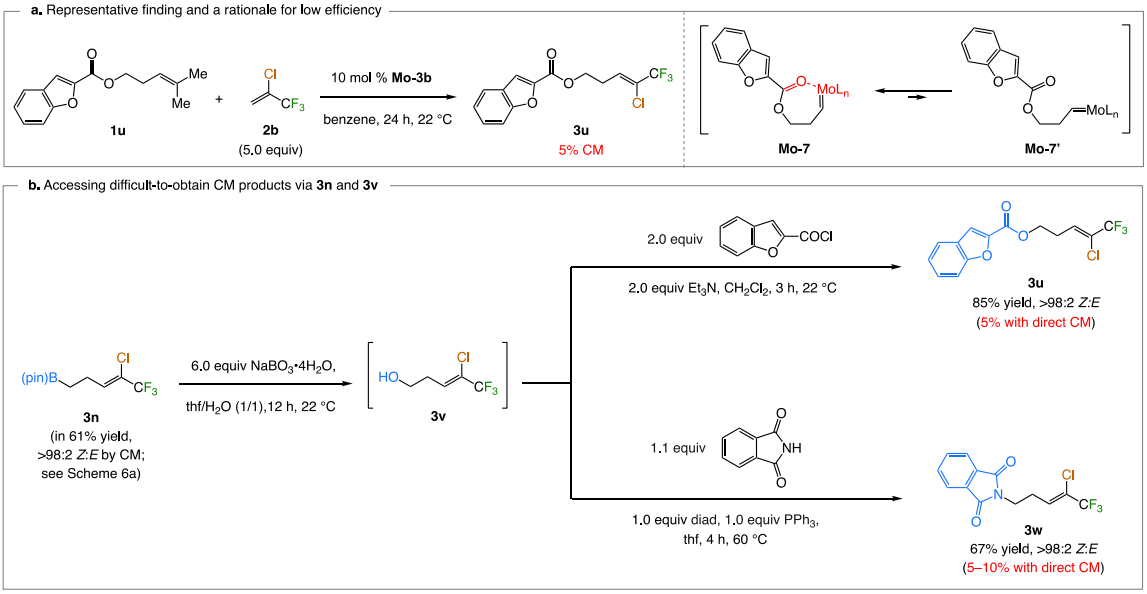
Scheme 6. Scope and Limitations of the Method[a]



[a]Reactions performed under N_2 with 10 mol % **Mo-3b**, except for **3h**, **3k** and **3m**, where 20 mol % complex was used. For **3n**, the outcome with **Mo-3e** was somewhat better. Conversion (disappearance of **1**) and *Z*:*E* ratios were determined by analysis of ^{1}H and ^{19}F NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). See the Supporting Information for details. CM, cross-metathesis.

Scheme 7. Sensitivity of CM to a Proximal Lewis Basic Moiety and a Solution[a]



[a]Reactions performed under N_2. *Z*:*E* ratios were determined by analysis of ^{1}H and ^{19}F NMR spectra of unpurified product mixtures (±2%). Yields of purified products (±5%). See the Supporting Information for details. diad, Diisopropylazadicarboxylate; CM, cross-metathesis.

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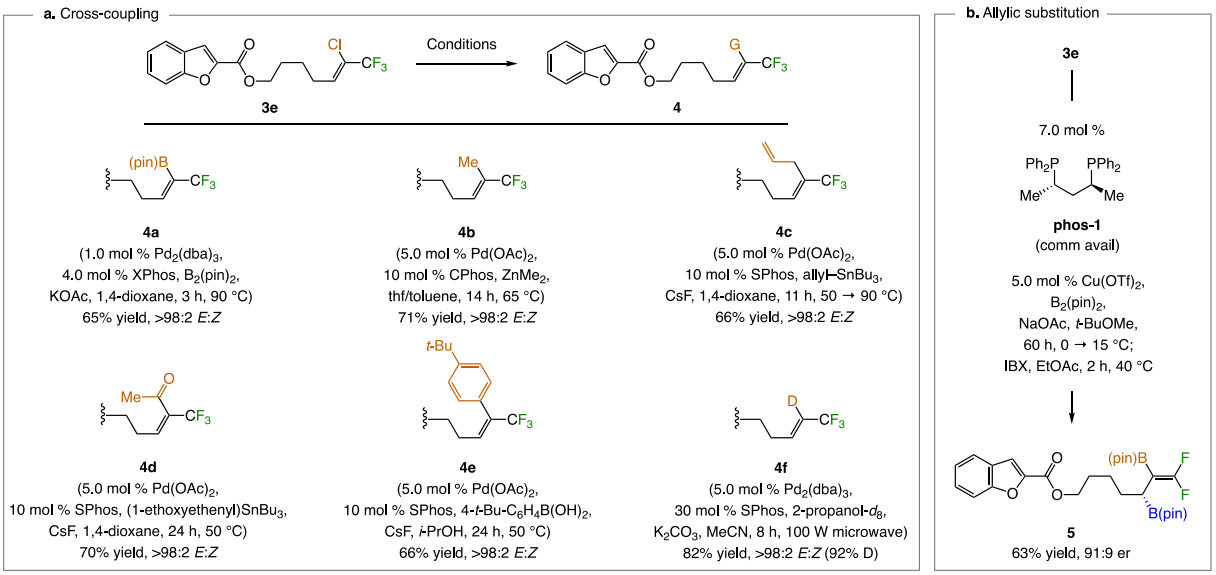
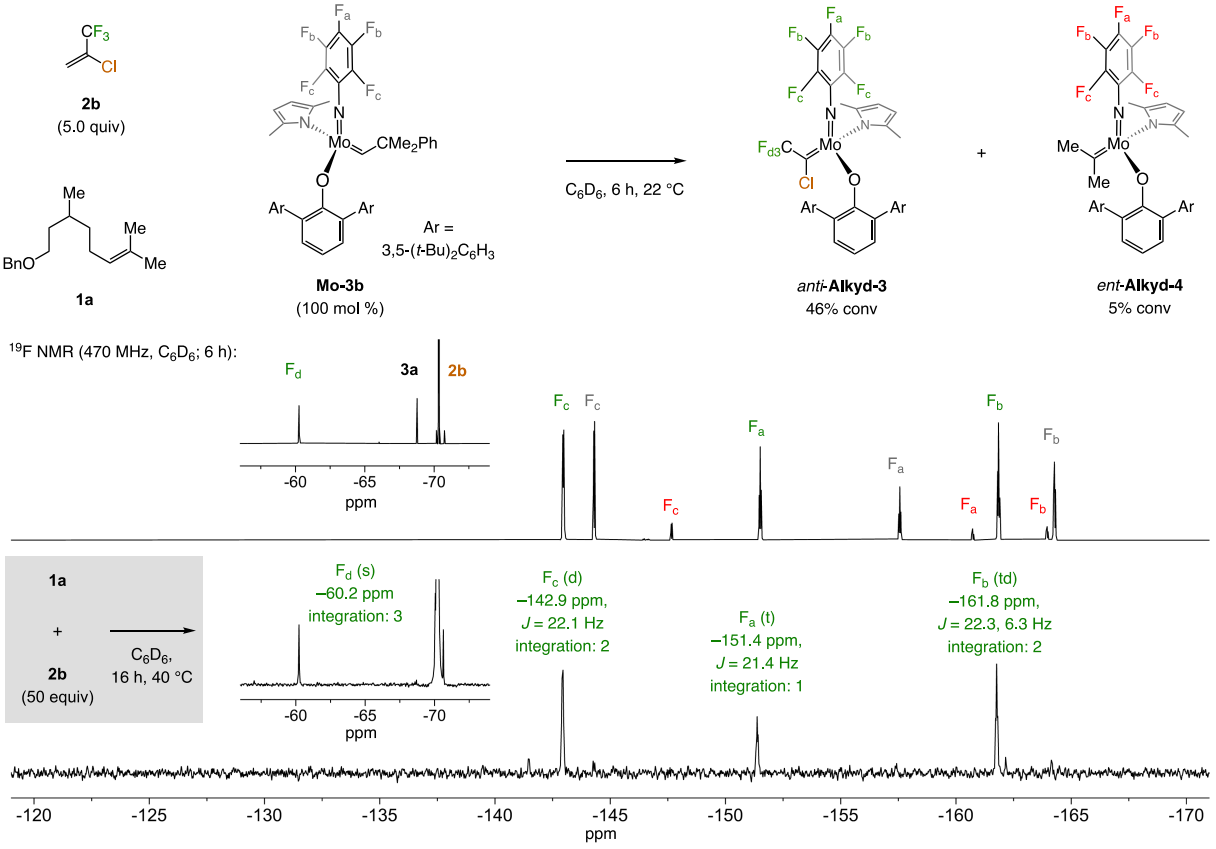
Scheme 8. Catalytic Diversification of CM Products[a]



[a]Reactions performed under N_2. [b]*Z*:*E* ratios were determined by analysis of ^{1}H and ^{19}F NMR spectra of unpurified product mixtures (±2%). [c]Yields of purified products (±5%). See the Supporting Information for details. CM, cross-metathesis; SPhos, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; XPhos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; CPhos, 2-dicyclohexylphosphino-2′,6′-bis(*N*,*N*-dimethylamino)biphenyl; dba, dibenzylideneacetone; IBX, 2-iodoxybenzoic acid; er, enantiomeric ratio.

Scheme 9. Probing the Possible Involvement of Disubstituted Alkylidene *anti*-Alkyd-3[a]



[a]Reactions performed under Ar in a J-Young NMR tube. Conversion was determined by analysis of ^{1}H and ^{19}F NMR spectra of the reaction mixtures and normalized based on **1a** (±2%). See the Supporting Information for details.

Nonetheless, it appears that the facile reaction of **Meth** with the trisubstituted olefin to generate **mcb-5** is key to CM efficiency.

Early on in the process, there is some preference for **Alkyd-1** reacting with **2b** to afford *anti*-**mcb-9** (*Cycle C*; $\Delta G^{\ddagger}$ = 19.4 kcal/mol vs 19.8 kcal/mol for **Alkyd-1** → *syn*-**mcb-4**), collapse of

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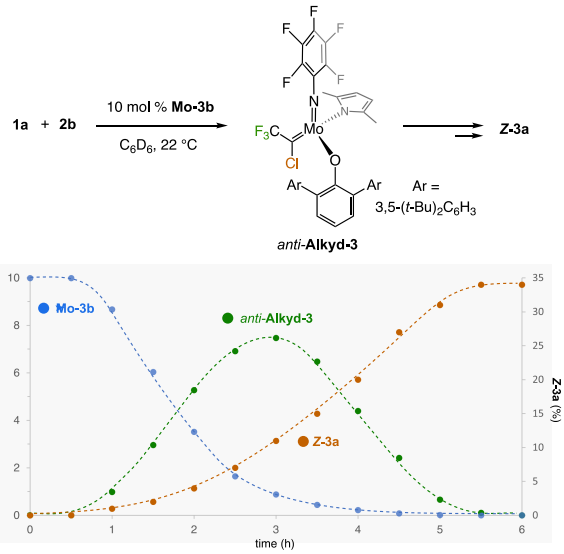
Scheme 10. Formation and Consumption of *anti*-Alkyd-3[a]

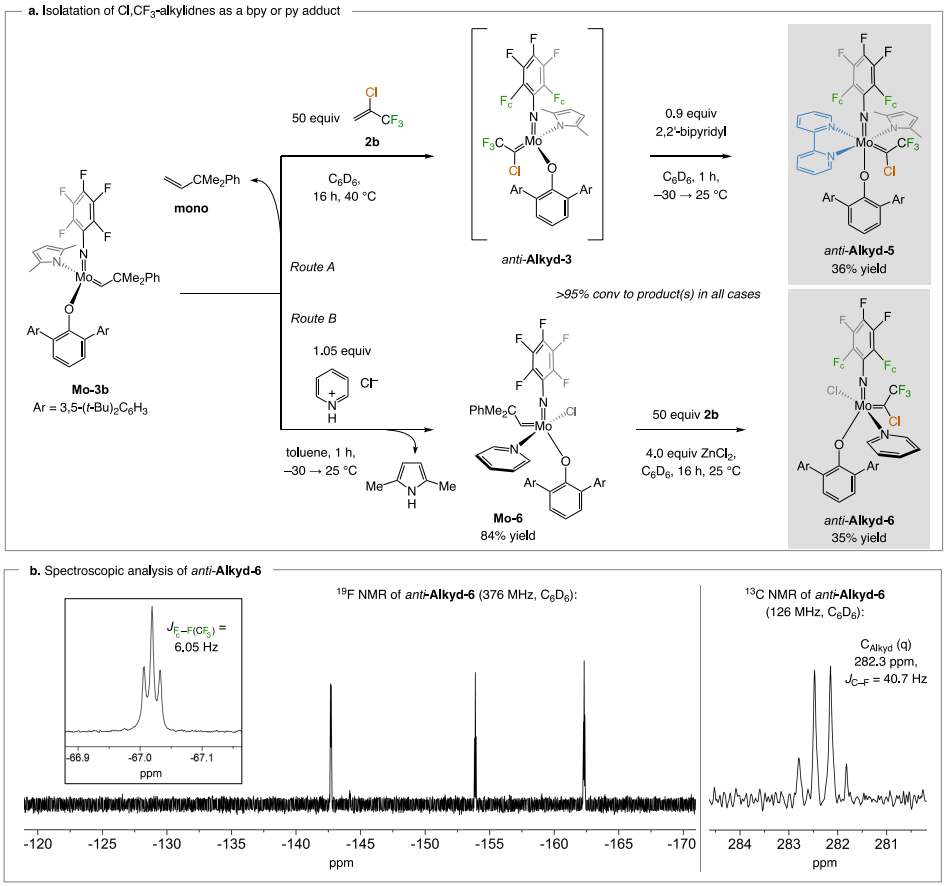


[a]Reactions performed under Ar in a J-Young NMR tube. Conversion was determined by analysis of ^{1}H and ^{19}F NMR spectra of the unpurified mixtures and normalized based on **1a** (±2%). See the Supporting Information for details. CM, cross-metathesis.

which would furnish monosubstituted alkene (**vinyl**) and *ent-anti*-**Alkyd-3** (ΔG = 4.2 kcal/mol). *ent-anti*-**Alkyd-3** would have two options: react with **vinyl** to regenerate **Alkyd-1** via *anti*-**mcb-9** or react with the more abundant **1** to afford the highly substituted *ent-anti*-**mcb-7** ($\Delta G^{\ddagger}$ = 33.0 kcal/mol). The second possibility would be energetically more taxing. This explains why *anti*-**Alkyd-3** was generated (likely via *anti*-**mcb-9**, *Cycle A*) and detected in the early phases of the process and then gradually consumed and reconverted to **Alkyd-1** via *anti*-**mcb-9** (likely through *Cycle C*). This also explains why in situ generated *anti*-**Alkyd-3** promote CM more efficiently compared to *anti*-**Alkyd-5** (see entries 2 and 3, Table 1). The alkene that is the byproduct of neophylidene initiation (**mono**) is available in the case of *anti*-**Alkyd-3** and reaction between the two reforms **Mo-3b** via *anti*-**mcb-6** ($\Delta G^{\ddagger}$ = 19.9 kcal/mol, with regard to *anti*-**Alkyd-3**). In contrast, there is no **mono** when *anti*-**Alkyd-5** is utilized and therefore it cannot enter the productive *Cycle A*.

Another finding of note is that *anti*-**Alkyd-6** (see entry 4, Table 1) can be transformed to product *Z*-**3a** without a monosubstituted olefin also being present (i.e., *anti*-**mcb-9** (L = Cl) in Scheme 12, *Cycle C*, can no longer be formed).[31] This in all likelihood occurs through the catalytic cycle shown in Scheme 13. That is, the disubstituted alkylidene must be directly involved in productive CM and that a disubstituted MAC complex probably reacts with a trisubstituted olefin to furnish the congested *anti*-**mcb-7′** (Scheme 13). This was corroborated by the results of the DFT studies, showing that reaction of *anti*-

Scheme 11. Synthesis and Spectroscopic Characterization of Cl,CF$_3$-Disubstituted Mo-Alkylidenes[a]



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

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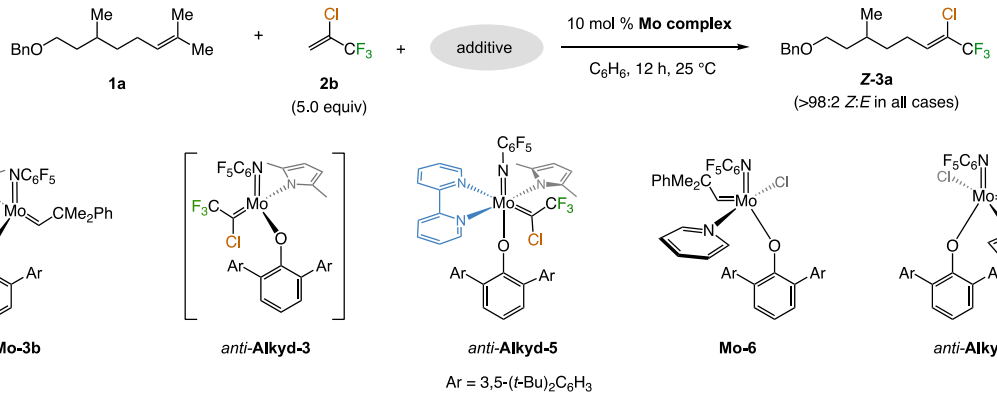
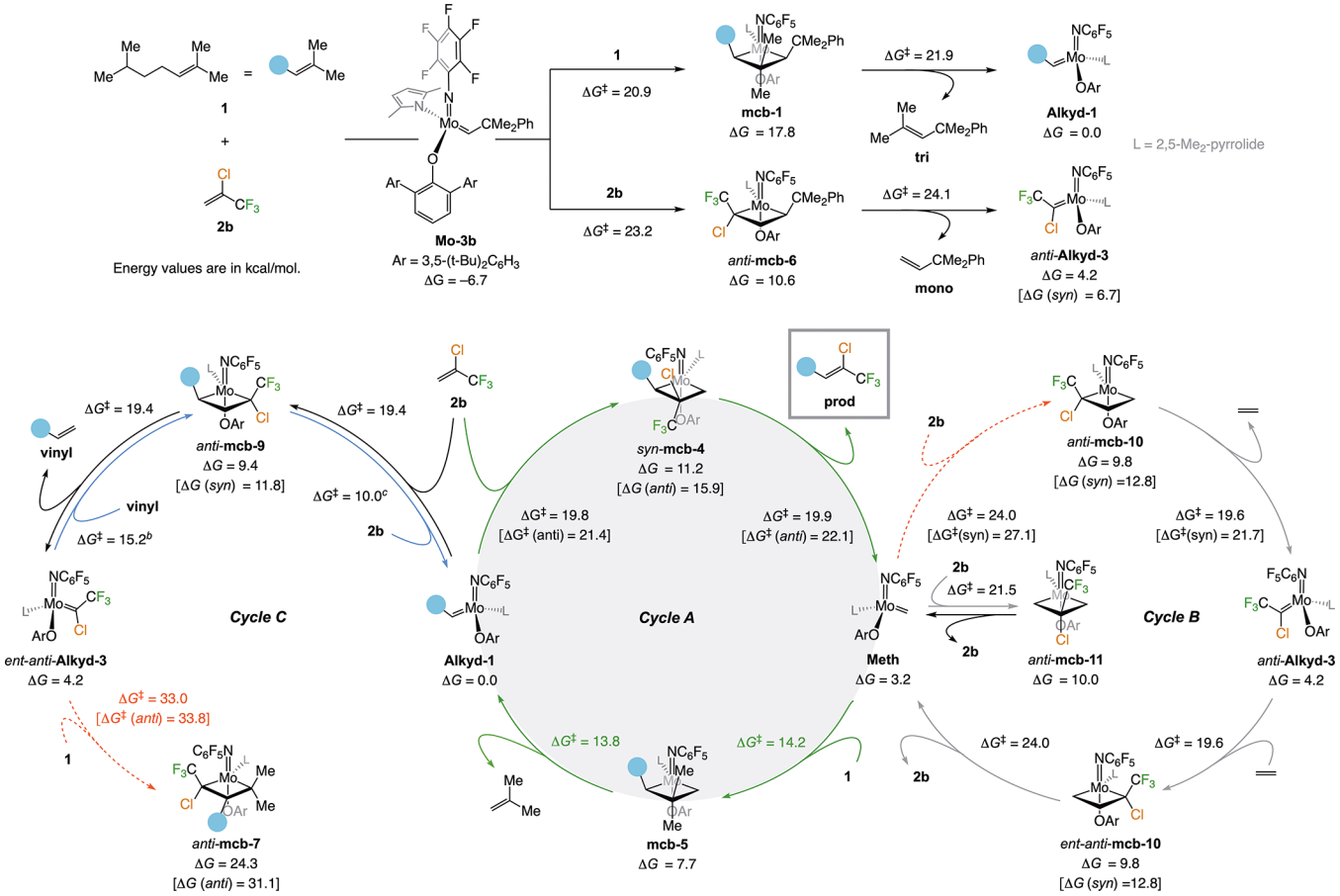
Table 1. Activity of Cl,CF_3-Disubstituted Mo-Alkylidenes[a]



entry	Mo complex	additive (mol %)	conv (%)[b]	conv to Z-**3a** (%)[b]
1	**Mo-3b**	none	53	41
2	anti-**Alkyd-3**[c]	none	50	28
3	anti-**Alkyd-5**	$ZnCl_2$; 40	10	6
4	anti-**Alkyd-6**	BPh_3; 12	50	37
5	**Mo-6**	BPh_3; 12	50	25

[a]Reactions performed under Ar. [b]Conversion (disappearance of **1a**) and *Z*:*E* ratios were determined by analysis of ^{1}H NMR spectra of unpurified product mixtures (±2%). [c]In situ generated *anti*-**Alkyd-3** was prepared according to Scheme 11a (mixture with **2b** and **mono**). See the Supporting Information for details.

Scheme 12. Computational Studies: Different Cycle and the Role of a Cl,CF_3-Disubstituted Mo-Alkylidenes (Alkyd-3)[a]



[a]Computational studies were performed at the M06/SDD(Mo)-6-311+G(d,p)/SMD(C_6H_6)//B3LYP-D3/SDD(Mo)-6-31G(d) level of theory. Unless otherwise noted, all Gibbs free energies are with respect to **Alkyd-1**. [b]With respect to *anti*-**Alkyd-3**. [c]With respect to *anti*-**mcb-9**. See the Supporting Information for details. mcb, metallacyclobutane.

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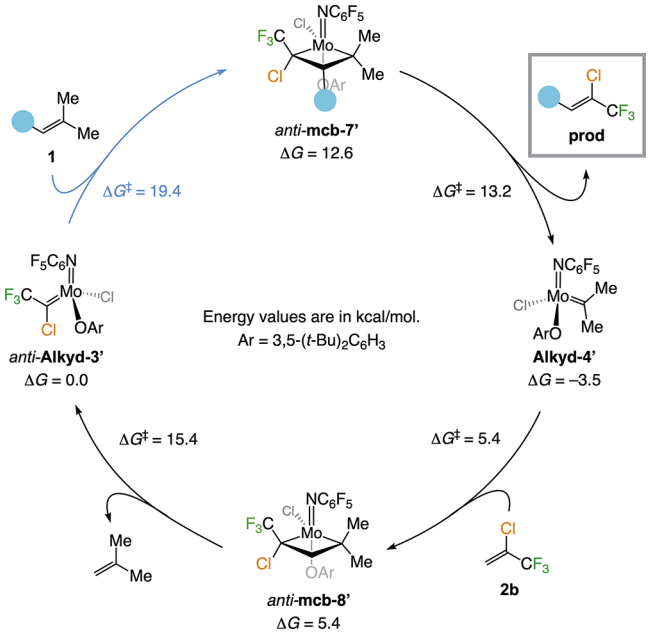
Scheme 13. Direct Involvement of a Disubstituted Mo Complex[a]



[a]Computational studies were performed at the M06/SDD(Mo)-6-311+G(d,p)/SMD(C_6H_6)//B3LYP-D3/SDD(Mo)-6-31G(d) level of theory. All Gibbs free energies are with respect to *anti*-**Alkyd-3′**. See the Supporting Information for details. mcb, metallacyclobutane.

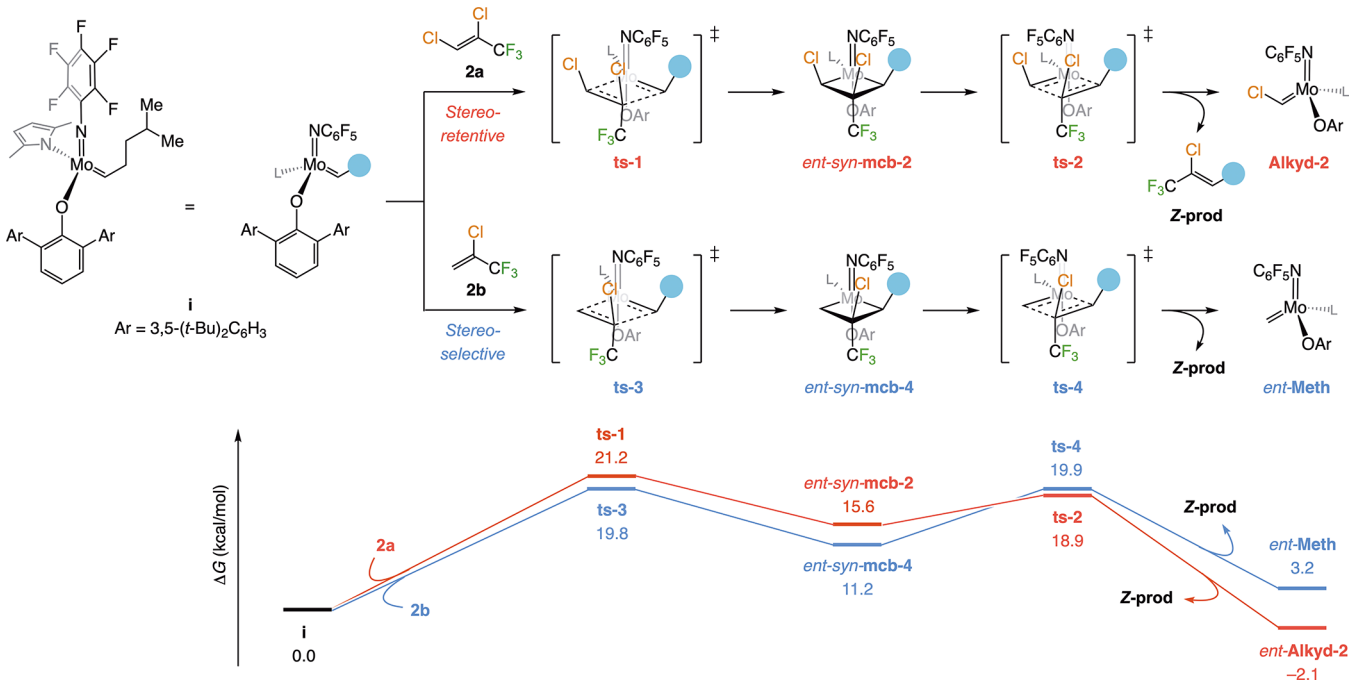
Alkyd-3′ with **1** (Scheme 13) is more favored than that of *anti*-**Alkyd-3** (L = pyrrolide vs Cl; $\Delta G^{\ddagger}$ = 19.4 vs 28.8 kcal/mol, respectively; see *Cycle C*, Scheme 12). This supports the notion that *anti*-**Alkyd-6** is more efficient at promoting CM than **Mo-6**, probably because there is none of the less stable methylidene intermediate generated in the case of the former complex.[31]

2.9.2. Energetic Attributes of CM Involving One versus Two Trisubstituted Alkenes. The lower efficiency of stereoretentive reactions with **2a**, as opposed to a stereoselective processes involving **2b**, is due to the higher barrier for formation of the mcb intermediates.[32] But there is another angle to consider. A mcb with fewer substituents is more stable and probably cleaves less readily (Scheme 14). The highest barrier in the transformation with the **2b** is then the collapse of the more easily formed and less substituted *ent-syn*-**mcb-4**, with **ts-4** representing the highest energy barrier. In contrast, in the reaction involving **2a** the turnover-limiting step involves **ts-1** and is the formation of the more substituted *ent-syn*-**mcb-2**. Lowering the barrier to mcb formation with a less substituted reaction partner does not lead to more efficient CM per se. The collapse of the resulting less substituted and lower energy mcb must be sufficiently facile as well.

3. CONCLUSIONS

We have developed a CM method for synthesis of *Z*-trisubstituted olefins that contain Cl- and CF_3-substituted carbon. The products can be used to access a variety of stereodefined CF_3-substituted alkenes. The efficiency and stereoselectivity levels were unexpected as they contradicted the principles of stereoretentive olefin metathesis reactions.[1] Specifically, the present studies thus reveal that (1) A Mo methylidene can react with a trisubstituted alkene fast enough for bimolecular decomposition to be circumvented. (2) The energy difference between two diastereomeric trisubstituted mcb intermediates containing a Cl,CF_3-disubstituted Cβ ($\Delta\Delta G^{\ddagger}$ = 2.2 kcal/mol; see *syn*-**mcb-4**, Scheme 12) suffices for complete stereoselectivity.

Scheme 14. Key Distinction between Stereoretentive and Stereoselective Pathways[a]



[a]Computational studies were performed at the M06/SDD(Mo)-6-311+G(d,p)/SMD(C_6H_6)//B3LYP-D3/SDD(Mo)-6-31G(d) level of theory. See the Supporting Information for details. ts, transition state; mcb, metallacyclobutane.

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The insights regarding disubstituted alkylidenes are noteworthy. We provide data illustrating that with the right blend of steric and electronic factors, here a Mo-MAC complex, a disubstituted alkylidene can react with a trisubstituted olefin or an electron-deficient alkene to generate a trisubstituted olefin via a densely functionalized mcb (see *anti*-**mcb-7′**, Scheme 13). It remains to be seen whether catalysts can be identified that are capable of intermolecularly generating mcbs with a fully substituted Cα and Cβ—collapse of which would afford a tetrasubstituted alkene.

The findings described here foreshadow the emergence of methods for kinetically controlled olefin metathesis reactions that are stereoselective. Prior to these studies, the great majority of the available transformations furnishing a *Z*- or an *E*-trisubstituted alkene were either between a tri- and disubstituted or two trisubstituted olefins. This necessitated a catalyst to be sufficiently active in order to bring about the union of two sterically demanding substrates. It is perhaps not surprising that a situation has arisen where available catalysts are not able to promote a stereoretentive process. For the transformations described above, a stereoselective approach emerged was an adequate solution. At some point, however, new catalysts will likely be needed if stereodefined tetrasubstituted alkenes are to be obtained through olefin metathesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c06071.

Experimental details for all reactions and analytic details for all products (PDF)

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Notes

The authors declare no competing financial interest.

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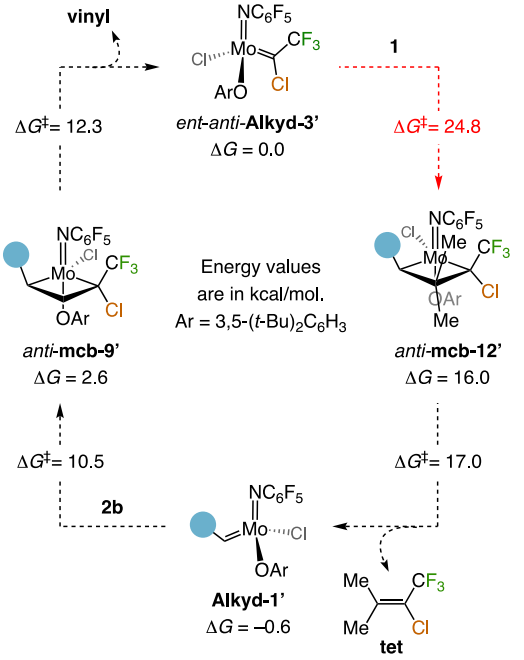
(31) For **vinyl** to be formed *ent-anti*-**Alkyd-3′** must react with a trisubstituted alkene (**1**) via *anti*-**mcb-12′** and proceed via an energetically demanding formation of a tetrasubstituted alkene byproduct (**tet**), which was not detected.



(32) The energy differences for the highest energy barrier for the two pathways do not precisely correspond to the considerable rate difference observed. This is likely owing to the uncertainty in the DFT calculations, which rule out possibilities. For example, DFT investigations indicate that preferential collapse of **mcb-2** to the corresponding inactive square pyramidal complex (see ref 21) is not competitive with the formation of the desired CM product via **ts-4** ($\Delta G^{\ddagger}$ = 22.9 kcal/mol). See the Supporting Information for details.

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