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# Molybdenum chloride catalysts for *Z*-selective olefin metathesis reactions

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## Abstract

Development of catalyst-controlled stereoselective olefin metathesis processes[1] has been a pivotal recent advance in chemistry. Incorporation of appropriate ligands within molybdenum-[2], tungsten[3] and ruthenium-based complexes[4] has made reactivity and selectivity levels that were formerly inaccessible feasible. Here, we show that molybdenum monoaryloxide chloride (MAC) complexes furnish higher energy (*Z*) isomers of trifluoromethyl-substituted alkenes through cross-metathesis (CM) reactions with commercially available, inexpensive and typically inert *Z*-1,1,1,4,4,4-hexafluoro-2-butene. Furthermore, otherwise inefficient and non-stereoselective transformations with *Z*-1,2-dichloro- and 1,2- dibromoethene can be effected with substantially improved efficiency and *Z* selectivity. Synthesis of representative biologically active molecules and trifluoromethyl analogues of medicinally relevant compounds underscore the importance of the advance. The origins of activity and selectivity levels, which contradict the previously proposed principles[5], are elucidated with the aid of DFT calculations.

Substitution of an oxygen-based ligand with a pyrrolide moiety converts a Mo or W alkylidene (e.g., **Mo-1a**, Fig. 1a) to a uniquely efficient and stereoselective[1] olefin metathesis catalyst. In *Z*-selective processes, an alkene binds *trans* to the pyrrolide[5], generating a metallacyclobutane with sterically differentiated imido (smaller) and aryloxide (larger) ligands[6]. Kinetically *E*-selective CM reactions were recently introduced as well[7]. Nevertheless, critical shortcomings persist. For instance, with Mo monoaryloxide pyrrolide (MAP) catalysts CM of *Z*-1,2-dihaloalkenes with aryl olefins or 1,3-dienes is often inefficient and non-stereoselective[8]. In addition, CM reactions generating *Z*-alkenes that

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carry a trifluoromethyl group are unknown; these moieties can impart increased bioavailability, metabolic stability, lipophilicity or binding selectivity[9],[10] to biologically active molecules[11] and are needed for future advances in agrochemicals[12] and materials research[13]. Yet, the state-of-the-art for synthesis of trifluoromethyl-substituted olefins is at a primitive stage. The available protocols are either minimally stereoselective[14,15] or afford *E* isomers predominantly[16] (e.g., CM with gaseous 3,3,3-trifluoropropene[17]), and the small number of methods for preparing *Z*-trifluoromethyl olefins are expensive and/or impractical[18,19]. Partial hydrogenation of alkynyl substrates is possible but over-reduction can be an issue[20].

As part of an initiative to synthesize halo-substituted Mo alkylidenes, intermediates in stereoselective CM reactions that afford alkenyl halides[7,8], we discovered that treatment of **Mo-1b** with 1,2-dibromoethene and pyridine gives monoaryloxide bromide complex **Mo-2** (Fig. 1a). Subjection of **Mo-2** to tris(pentafluorophenyl)borane afforded four-coordinate species **Mo-3**, which is not sufficiently stable to be isolated. Procedures for preparation of multi-gram quantities of monoaryloxide chloride (MAC) derivatives (e.g., **Mo-4**) from readily accessible and inexpensive materials were subsequently developed (details in the Supplementary Information). Coordination of pyridine *trans* to chloride in **Mo-4** suggests that an alkene substrate would likely bind similarly, reminiscent of the formerly examined MAP systems (olefin *trans* to pyrrolide)[21].

To evaluate the chemistry of MAC complexes, we first examined their effectiveness in promoting the ring-opening/cross-metathesis (ROCM) between 1,2-dichloroethene and cyclooctene (Fig. 1b). Whereas after 10 minutes there was 65% conversion to **1** with **Mo-1a** (>98% conv. after 1 h), with **Mo-5a** reaction proceeded to 94% conversion and stereocontrol was considerably higher (>98:2 vs. 76:24 *Z,Z*:*Z,E*); ROCM with the bulkier **Mo-5b** was similarly efficient and stereoselective. There was less than 5% conversion to **1** after one hour with the pyridine-bound **Mo-2**, implying that the derived four coordinate entity is catalytically active.

CM of terminal alkenes with MAC complexes was inefficient (<10% conv.), the reasons for which remain to be determined. We therefore turned to evaluating CM with (*Z*)-1,2-disubstituted alkenes, which can be purchased or accessed in one step through catalytic cross-coupling[22] between commercially available *Z*-1-bromo-1-propene and an aryl- or alkenylboronic acid or pinacol ester (see the Supplementary Information for details). In the event, whereas with **Mo-1a** there was 34% and 73% conversion to **2** and **3**, respectively (Fig. 1b), with **Mo-5b** these compounds was isolated in ≥80% yield. Moreover, although CM with **Mo-1a** was either non-selective (**2**, 52:48 *Z*:*E*) or *E*-selective (**3**, 28:72 *Z*:*E*, probably due to post-metathesis isomerization), with **Mo-5b** only the *Z* product was detected. The same applies to *Z,E*-diene **4**, where there was 53% conversion to β-chlorostyrene with **Mo-1a** (from CM with the styrenyl olefin) and stereoselectivity was not determined because of a complicated product mixture. Similarly, CM of 1,2-dibromoethene with methyl oleate was more efficient and *Z*-selective with **Mo-5b** (Fig. 1b); use of **Mo-5a**, a less hindered complex that may generate shorter living alkylidenes, led to diminished efficiency (32% conv. to **5** and **6**). The higher *Z* selectivities in MAC-catalyzed reactions were surprising since *Z*-to-*E* isomerization is often an issue with the more active complexes. Consistent with the commonly used stereochemical model[1,5,**Error! Bookmark not defined.**], we expected the size difference between the imido and aryloxide moieties to determine stereoselectivity, not the identity of the anionic ligand *trans* to the metallacyclobutane.

The main question then was whether a MAC complex can catalyse CM reactions with *Z*-1,1,1,4,4,4-hexafluoro-2-butene (**7**; >98% *Z*), a hydrofluoroolefin that can be bought in small amounts (USD 295/5 g from Synquest) or bulk quantities as a foam-blowing agent and that has ozone depleting potential (ODP) and global warming potential (GWP) values of zero and low, respectively[23]. Furthermore, **7** is a non-flammable liquid at ambient temperature and convenient to use (boiling point, +33 °C vs. –22 °C for 3,3,3-trifluoropropene). However, compound **7**, which is utilized in industrial applications is generally inert probably because of its hindered and severely electron deficient alkene. To the best of our knowledge, this organofluoride has not been used in organic chemistry; our efforts to access *Z*-trifluoromethyl-substituted alkenes (e.g., CM of methyl oleate with **7**) with known Mo complexes or Ru carbenes were completely unsuccessful (no desired products detected).

In sharp contrast and remarkably, with **Mo-5a** and **Mo-6a** CM of methyl oleate and **7** afforded appreciable amounts of **8a** and **8b** (Fig. 2a). In considering ways that *Z* selectivity might be improved, we reasoned that, other than post-metathesis isomerization, formation of the undesired *E* isomer might originate from initial isomerization of the olefin substrate[7]. Accordingly, with **Mo-6b**, a more congested and longer living MAC complex, CM was complete in four hours, furnishing **8a** and **8b** in 98:2 *Z*:*E* selectivity and 90% and 65% yield, respectively. Further study indicated that with 2.0 mol % **Mo-6b** and five equivalents of **7** the transformation was complete in only 15 minutes with nearly the same yields and *Z* selectivities (slightly lower yields with **Mo-5b**).

Many (*Z*)-1,2-disubstituted alkenes, commercially available or accessible in one step from naturally occurring *Z*-olefins (e.g., *Z*-3-hexen-1-ol) or through cross-coupling, can be used (Fig. 2b). Products containing an ether (**8c**), an α-alkoxy ester capable of chelating to the Mo center (**8d**), or a carbamate (**8e**) were easily accessed. CM with alkenes containing a tosylate (**8f**), an alkyne (**8g**), a tertiary amine (**8h**), or a sulfide (**8i**) was efficient and *Z*-selective. A 1,4-diene (**8j**), a crotyl–B(pin) (**8k**) or a crotylsilane (**8l**) were suitable substrates. Transformations with hindered α-branched 1,2-disubstituted alkenes (**8m,n**) and β-substituted styrenes (**8o-q**) proceeded smoothly. CM with aryl olefins needed (*Z*)-β-isopropylstyrenyl substrates so that homocoupling would be less competitive. Paraffin tablets containing a MAC species[7] may be used (no glove box); for instance, with a pellet containing **Mo-6b** (~3.0 mol %; toluene, 35 °C, 2 h) **8e** was obtained in 74% yield and >98:2 *Z*:*E* ratio.

Product **8r** has been transformed to glycosidase inhibitor **10**[24] (Fig. 3a). Conversion of the commercially available aldehyde **11** to *Z*-alkene **12** followed by CM with **7** afforded **8s**, an intermediate en route to hvRI receptor inhibitor **13**[25]. Previously, **8s** was prepared by Wittig reaction with aldehyde **11** and 2,2,2-trifluoroethyl diphenylphosphine oxide (not commercially available), affording a mixture of *E*/*Z* isomers (exact ratio and yield not reported[25]). Severl examples show that synthesis of trifluoromethyl analogues of medicinally relevant agents can be facilitated (Fig. 3b). *Z*-Alkene **15**, formerly accessed in five steps and 27% overall yield from commercially available enantiomerically pure **14**, was transformed to **8t** in 84% yield and >98% *Z* selectivity, allowing for synthesis of a trifluoromethyl analogue of hormaomycin[26]. CM of **16**, derived from analgesic zucapsaicin[27], delivered **8u** (86% yield, >98% *Z*). Transformation of **17**, obtained from sulbactam[28] (β-lactamase inhibitor), to **8v** and syntheses of **8w** (from epalrestat[29], aldolase reductase inhibitor) and **8x** (from artesunate[30], anti-malarial agent), underscore the compatibility of Mo MAC complexes with polar functional groups.

Two central points merit further brief discussion: 1) CM reactions with terminal alkenes would be more desirable but, as mentioned earlier, the (*Z*)-1,2-disubstituted alkenes utilized here are readily accessed. Considering the high value of the *Z*-trifluoromethyl-substituted alkenes, ease of their preparation together with the paucity of alternative methods, the present approach offers a compelling solution to a longstanding problem. For instance, the *Z*-allyl–B(pin) **8k** (see Fig. 2b), a product that may be used to access an assortment of desirable trifluoromethyl-containing products through future developments in diastereo- and/or enantioselective additions to electrophiles, was obtained by reaction of commercially available *Z*-crotyl–B(pin). 2) Development of compounds that contain a *Z*-trifluoromethyl-substituted olefin and/or a related derivative with desirable biological activity has probably been hampered because of the absence of direct and practical methods to obtain such species. Still, as indicated by the examples mentioned above, the considerable potential of such entities is well-appreciated[9,10].

DFT calculations shed light on why MAC complexes are singularly effective. We first probed the influence of several anionic ligands on the reaction of *Z*-2-butene with **Mo-7** (Fig. 4a, i). While the energy for distortion of the chloro complex is relatively high (8.9 kcal/mol), the ensuing metallacyclobutane (**mcb**) formation ($\mathbf{T_{d,dist}/pc} \rightarrow \mathbf{ts1}$) is the most facile. There is strong correlation between the barrier to **ts1** and the extent of C–C double bond activation in the Mo π-complex (**pc**), a characteristic more evident in Fig. 4a, diagram ii where $\mathbf{T_{d,dist}}$ is the reference point. Whereas methyl–Mo complex emerges as the least activated (C=C, 1.350 Å) the more Lewis acidic chloro species has the longest (most tightly) chelated alkene (C=C, 1.368 Å), a trend consistent with the lowest unoccupied molecular orbital (LUMO) energies for the distorted ground state complexes ($\mathbf{T_{d,dist}}$). The overall energy requirement appears to be derived from a combination of the cost of structural distortion ($\mathbf{T_d} \rightarrow \mathbf{T_{d,dist}}$) and **mcb** formation ($\mathbf{T_{d,dist}/pc} \rightarrow \mathbf{ts1}$); the model MAC system has the smallest barrier (12.5 kcal/mol) and the largest is for the methyl and methoxy derivatives (Fig. 4a, i). These principles are distinct from those of a previous study, which involved less substituted **mcb** intermediates, where methyl-substituted complexes were assigned higher reactivity (vs. methoxy) based on the principle that a stronger σ-donating ligand helps make available a *trans* ligation site[5]. The present work shows that neither a methoxy- nor a methyl-substituted species can deliver the activity level of a Mo chloride species.

We then investigated the transformation between *Z*-2-butene with **Mo-8** (see Fig. 4b) with the methoxy ligand replaced by a much larger 2,6-dimesityl-phenoxy moiety. We find that in transition state **I** (Fig. 4a, iv), the aryloxide ligand tilts toward the Cl ligand with longer C–

H⋯C–H distances (2.21 and 2.39 Å). In the MAP complex **II** the aryloxy group and the reacting alkene are forced into closer contact (2.10 and 2.17 Å). The increased steric pressure has stronger impact on the activation barriers (**ts1** = 12.1 and 20.4 kcal/mol for the chloro and dimethylpyrrolide complexes, respectively) compared to the more diminutive methoxy complexes (**ts1** = 12.5 and 14.0 kcal/mol for the chloro and dimethylpyrrolide systems, respectively; Fig. 4a, ii).

The improved efficiency and *Z* selectivity in generating alkenyl halides with MAC complexes arise from differences in chemoselectivity. This is indicated by a larger gap in the energy required for **ts1** in reactions of **Mo-8** (MAP) with *Z*-2-butene (17.3 kcal/mole; Fig. 4b, v) and *Z*-1,2-dichloroethene (23.0 kcal/mol; Fig. 4b, vi) compared to those for the transformation with **Mo-9** (MAC; 12.3 and 14.5 kcal/mole, respectively). Alkyl-substituted MAP alkylidenes are more prone to react with an aliphatic alkene (vs. less Lewis basic 1,2-dichloroalkene) to afford homocoupling products and thus *Z*-to-*E* isomerization/CM becomes an issue. With excess dihaloalkene CM becomes more favourable and homocoupling is less competitive. With a MAC species, capable of reacting with either alkene at comparable rates, adventitious alkene homocoupling and *E* isomer generation is minimal, especially with excess dihaloalkene; control experiments indicate that *Z*-to-*E* interconversion of these reagents is slow.

Similar arguments may be extended to reactions that deliver *Z*-alkenyl bromides (Fig. 1b). Despite a more active MAC complex, capable of causing post-metathesis isomerization, and the presence of 36% *E*-1,2-dibromoethene, CM is exceptionally *Z*-selective. This may be attributed to lower reactivity of the *E* isomer, which is supported by the diminished *Z*:*E* ratio (41:59) of recovered reagent after CM of methyl oleate with 2.3 equivalents of 1,2-dibromoethene (~1.5 equiv. *Z* isomer) with 5.0 mol % of **Mo-5b** (4 h). Mo MAC complexes do not promote efficient CM reactions with *E*-1,2-dichloroethene or *E*-1,1,1,4,4,4-hexafluoro-2-butene (<10% conv.); we attribute this to rapid decomposition of the derived metallacyclobutanes. Subjection of *Z*-methyl oleate to a 3:2 mixture of *Z*- and *E*-1,2-dichloroethene and 3.0 mol % **Mo-6a** led only to 20% conversion to the CM products ($C_6H_6$, 22 °C, 4 h vs. >98% conv. and 97% yield with the pure *Z* isomer). This is unlike the case with the bulkier 1,2-dibromoethene, where the *E* isomer reacts at a sufficiently slower rate so that CM can proceed to completion.

The importance of Mo MAC complexes is evidenced by their ability to catalyse – with unprecedented efficiency and selectivity – the formation of three types of products that are of considerable importance in the preparation and identification of potential medicines and functional small molecules. The ability to promote transformations with *Z*-1,1,1,4,4,4-hexafluoro-2-butene (**7**), a compound not previously utilized in a chemical transformation, is particularly noteworthy. Computational studies teach us a key lesson as well: contrary to expectations based on former studies[5], the chloride complexes exhibit higher activity compared to MAP species due to enhanced Lewis acidity and diminution in steric repulsion within a trigonal bipyramidal intermediate.

## Methods

### General Procedure for CM with a MAC complex

In a $N_2$-filled glove box, an oven-dried 8 mL vial equipped with a magnetic stir bar was charged with alkene substrate and the corresponding organohalogen reagent (*Z*-1,1,1,4,4,4-hexafluoro-2-butene, *Z*-1,2-dichloroethene or 1,2-dibromoethene). A solution of an appropriate MAC complex in benzene was then added. The resulting mixture was allowed to stir for 15 min-12 h at 22 °C, after which the reaction was quenched by the addition of wet (undistilled) $CDCl_3$ (percent conversion was determined by $^1H$ NMR analysis of the unpurified mixture). Purification was performed through silica gel chromatography, preparative thin layer chromatography and/or Kugelrohr distillation.

### General Procedure for CM with a paraffin tablet containing a MAC complex

An oven-dried 8 mL vial equipped with a magnetic stir bar was charged with a paraffin tablet (9 wt% in **Mo-6b**, 20.0 mg, 2.2 μmol) and (*S,Z*)-1-*t*-butyl 2-hex-3-enyl pyrrolidine-1,2-dicarboxylate (22.0 mg, 0.0740 mmol). The vial was sealed with a septum, then evacuated and back-filled with $N_2$ three times to remove oxygen. *Z*-1,1,1,4,4,4-Hexafluoro-2-butene (**7**; 43 μL, 0.370 mmol) and toluene (74 μL) were added by syringe and the resulting mixture was allowed to stir at 35 °C for 2 hours under $N_2$ atmosphere. The reaction was quenched by addition of MeCN (1.5 mL) and the mixture was allowed to stir at 22 °C for 10 minutes. The slurry was filtered through a short plug of silica gel and eluted with MeCN (2 mL). The filtrate was concentrated and analysis of the unpurified mixture revealed 98% consumption of (*S,Z*)-1-*tert*-butyl 2-hex-3-enyl pyrrolidine-1,2-dicarboxylate. The resulting green oil was purified by silica gel chromatography (4% $Et_2O$/pentane to 20% $Et_2O$/pentane) to afford **8e** (18.5 mg, 0.0548 mmol, 74% yield) in >98:2 *Z*:*E* ratio as colourless oil.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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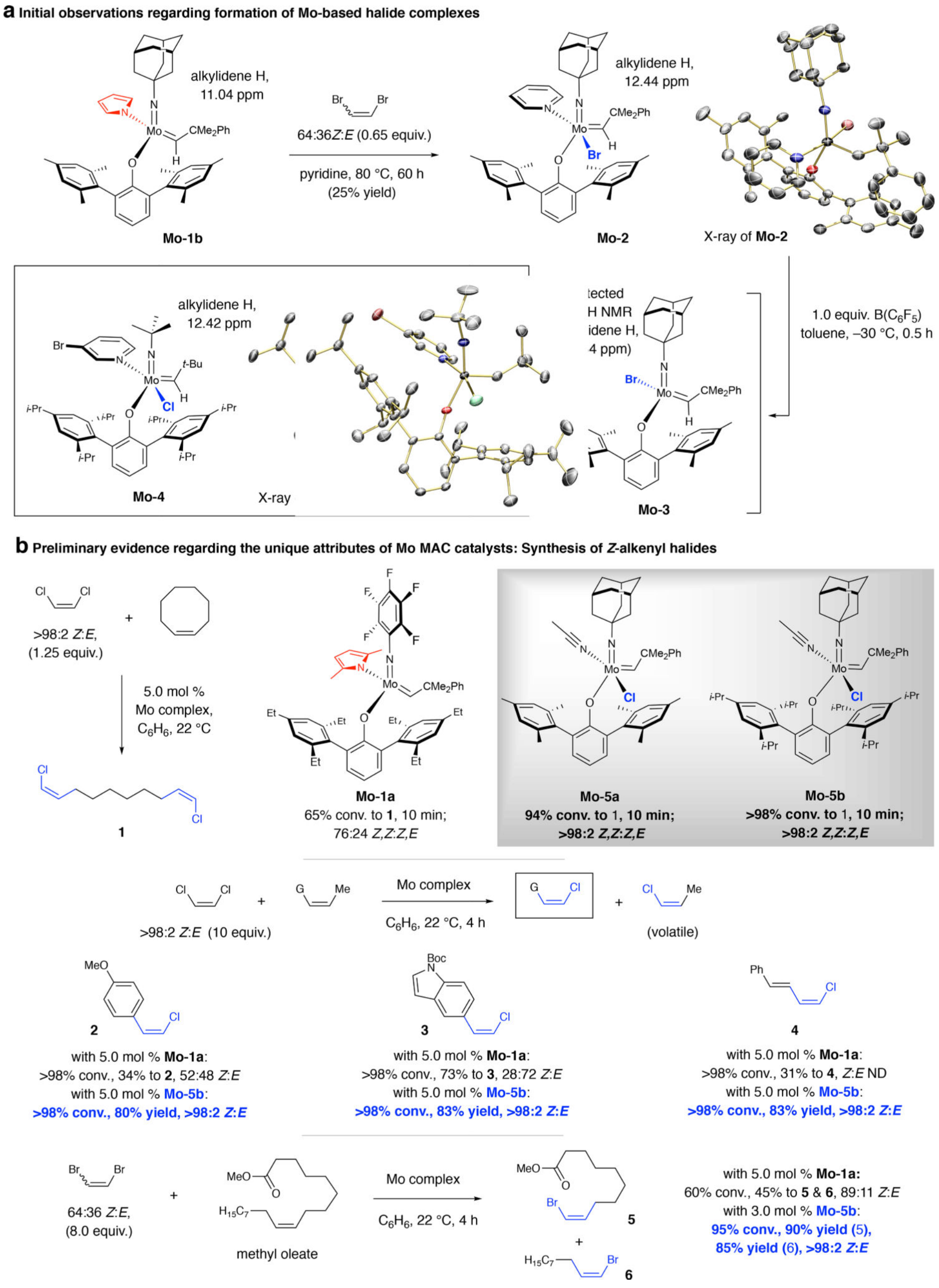


**Fig. 1. Initial findings and synthesis of *Z*-alkenyl halides**

**a**, Formation of a monoaryloxide bromide complex (**Mo-2**). Lewis acid treatment afforded the four-coordinate species **Mo-3**. **b**, Monoaryloxide chloride (MAC) complexes are most effective in promoting *Z*-selective ROCM (vs. the corresponding pyrrolide or MAP systems). CM of *Z*-1,2-dichloroethene and various types of olefins are exceptionally efficient and stereoselective with MAC complexes, which can also promote *Z*-selective CM with a 64:36 *Z*:*E* mixture of 1,2-dibromoethene. $^1$H NMR spectra were recorded in $C_6D_6$; stereoselectivities measured by $^1$H NMR analysis (±2%); yields are for isolated/purified products (±5%). See the Supplementary Information for details. Boc, *tert*-butoxycarbonyl; G, functional groups; ND, not determined.

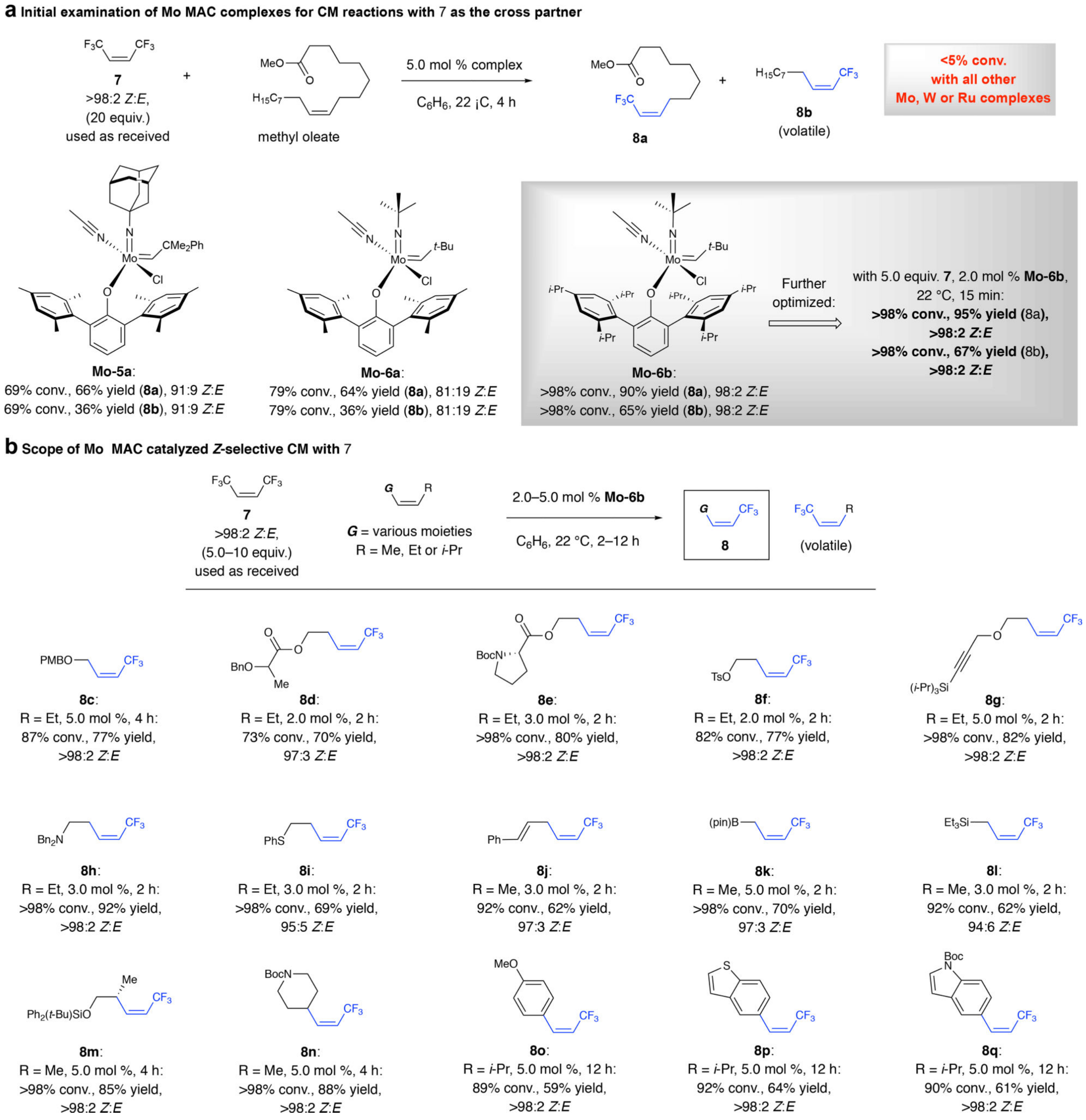


**Fig. 2. Mo MAC complexes engage a typically inert trifluoromethyl-substituted alkene**

**a**, Several Mo MAC complexes can catalyze CM of *Z*-1,2-disubstituted alkenes and reagent **7** with exceptional *Z* selectivity (**Mo-6b**). **b**, Various alkyl and aryl olefins, including those containing Lewis basic esters, carbamates and amines or α-branched moieties, may be used in efficient and exceptionally *Z*-selective CM reactions. The requisite *Z*-1,2-disubstituted alkene starting materials may either be purchased or prepared easily in one step from commercially available compounds. PMB, *para*-methoxybenzyl; Bn, benzyl; Boc, *tert*-butoxycarbonyl; pin, pinacolato; Ts, tosyl group. Stereoselectivities measured by $^1$H NMR analysis (±2%); yields are for isolated and purified products (±5%). See the Supplementary Information for details.

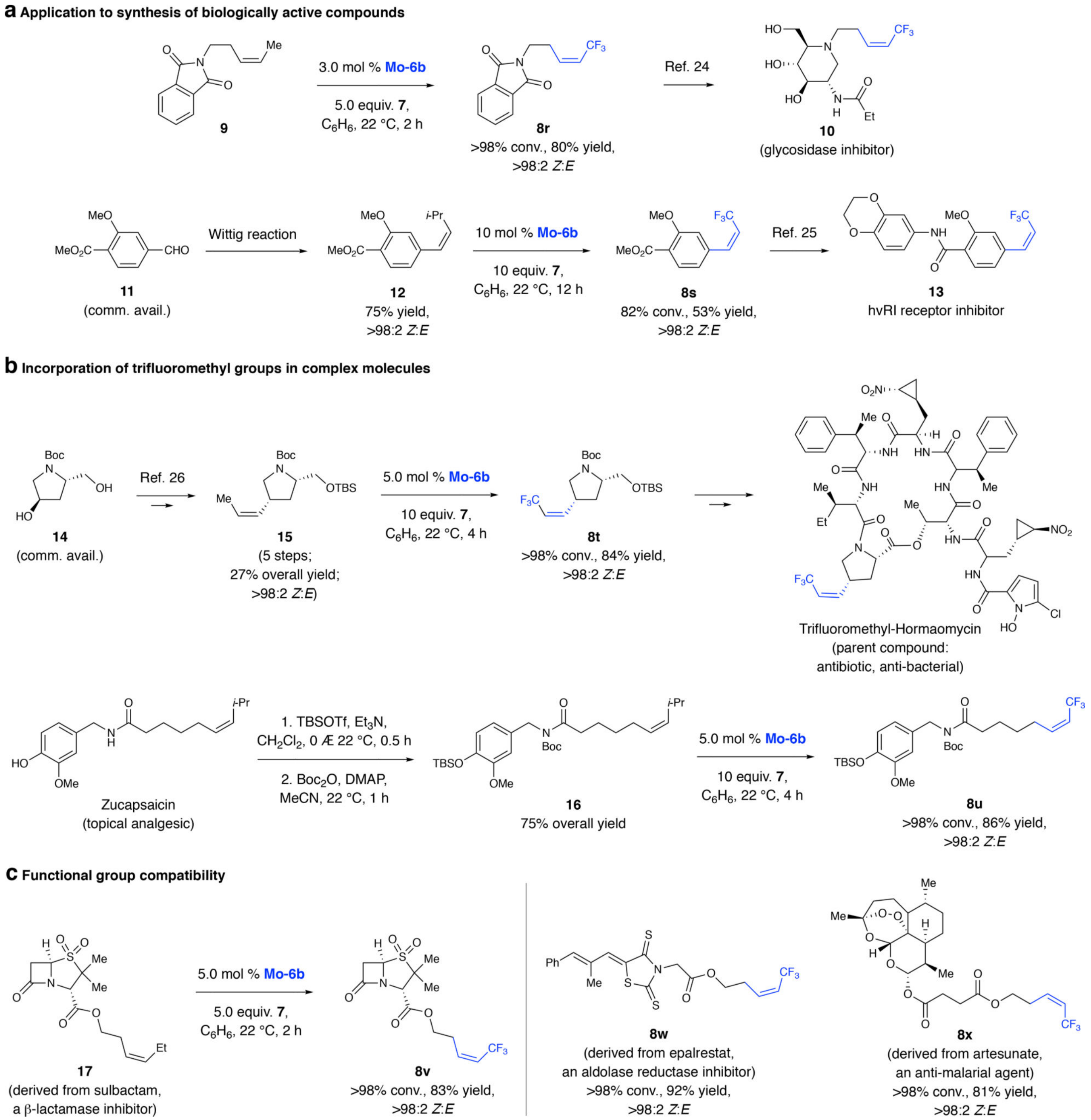
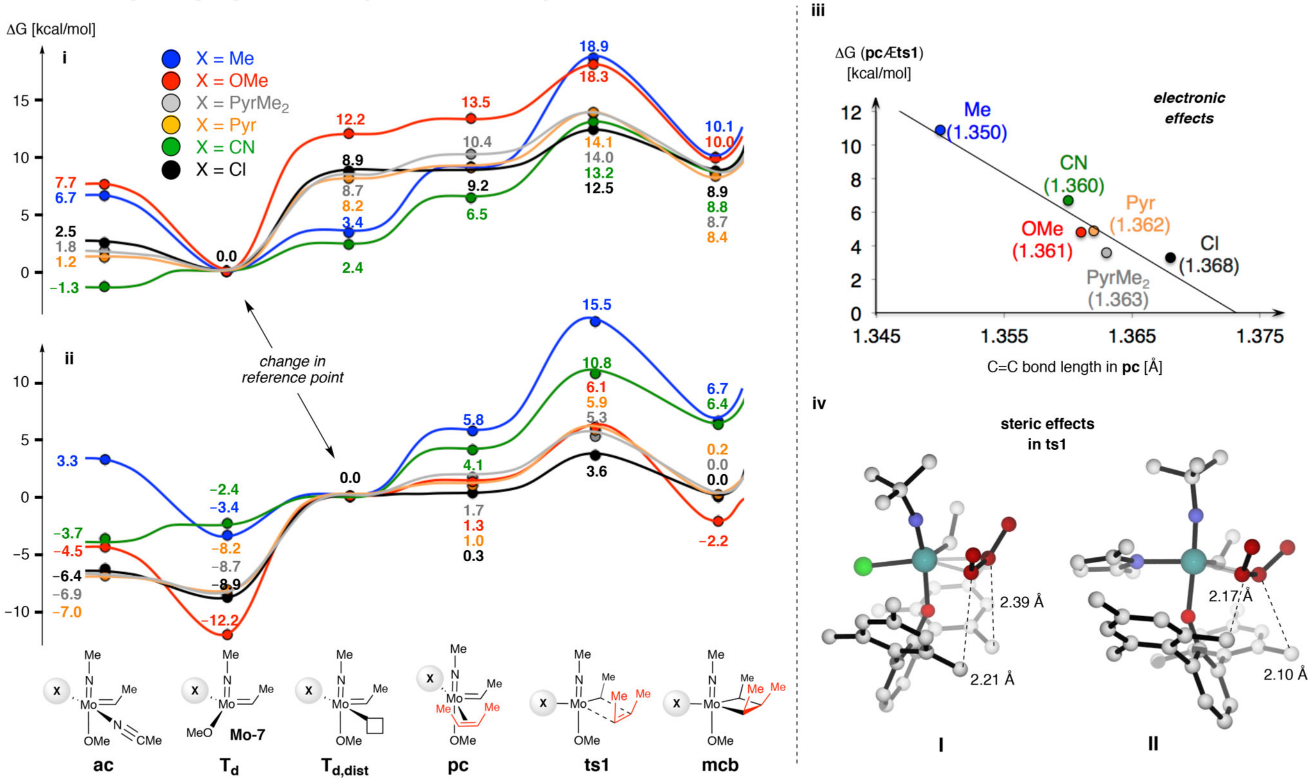


**Fig. 3. Utility and functional group compatibility**

**a**, Mo MAC-catalyzed CM provides direct access to biologically active molecules. Synthesis of **13** is notable as it involves reaction between severely hindered alkenes. **b**, MAC complexes can be used to prepare and probe the activity of *Z*-trifluoromethyl derivatives of new drug candidates, benefitting from advantages of a trifluoromethyl unit. **c**, Despite their high Lewis acidity, Mo MAC complex tolerate Lewis basic functional groups that regularly appear in therapeutic agents (e.g., **8v–8x**). TBS, *tert*-butyldimethylsilyl; Boc, *tert*-butoxycarbonyl; Tf, trifluoromethylsulfonyl; DMAP, 4-dimethylaminopyridine.

Stereoselectivities measured by $^1$H NMR analysis (±2%); yields are for isolated/purified products (±5%). See the Supplementary Information for details.

**a** Studies regarding higher reactivity of Mo MAC complexes



**b** Studies regarding higher reactivity and *Z* selectivity provided by Mo MAC complexes

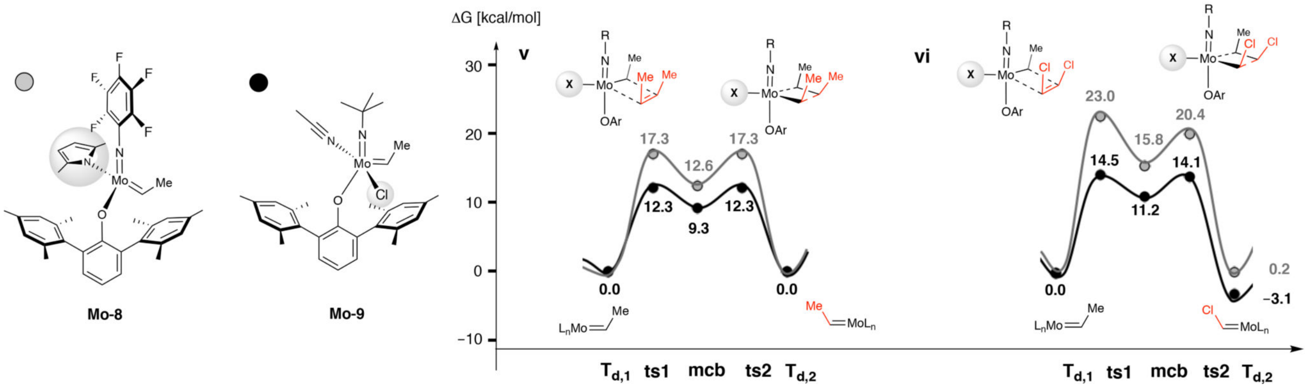


**Fig. 4. Computational/mechanistic studies**

**a**, Electronic effect of the anionic ligand on degenerate olefin metathesis of *Z*-2-butene with model complexes **Mo-7** (i–iii) and the influence of steric factors with larger aryloxide moieties (iv). **b**, Comparison of the reactivity and selectivity of **Mo-8,9** with *Z*-2-butene (v) and *Z*-1,2-dichloroethene (vi). Energy values correspond to the free energy (ΔG in kcal/mol) determined at the MN12SX/Def2TZVPP//ω−B97XD/Def2SVP level in benzene as solvent (SMD solvation model). Abbreviations: **$PyrMe_2$** = 2,5-dimethylpyrrolide; **Pyr** = pyrrolide; **ac** = acetonitrile complex; **$T_d$**, tetrahedral complex; **$T_{d,dist}$**, distorted tetrahedral complex; **pc**, π-complex; **ts1**, transition state for metallacylobutane formation; **mcb**, metallacyclobutane; **ts2**; transition state for metallacyclobutane cleavage; R, aryl or alkyl group; Ar, aryl group. See the Supplementary Information for details.