The development of catalyst-controlled stereoselective olefin metathesis processes has been a pivotal recent advance in chemistry. The incorporation of appropriate ligands within complexes based on molybdenum, tungsten and ruthenium has led to reactivity and selectivity levels that were previously inaccessible. Here we show that molybdenum monoaryloxide chloride complexes furnish higher-energy (Z) isomers of trifluoromethyl-substituted alkenes through cross-metathesis reactions with the 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-dichloroethene and 1,2-dibromoethene can be effected with substantially improved efficiency and Z selectivity. The use of such molybdenum chlorides enables the synthesis of representatively biologically active molecules and trifluoromethyl analogues of medicinally relevant compounds. The origins of the activity and selectivity levels observed, which contradict previously proposed principles, are elucidated with the aid of density functional theory calculations.

Substitution of an oxygen-based ligand with a pyrrolide moiety converts a molybdenum (Mo) or tungsten (W) alkylidene (for example, Mo-1a; Fig. 1a) to a uniquely efficient and stereoselective olefin metathesis catalyst. In Z-selective processes, an alkene binds trans to the pyrrolide, generating a metallacyclobutane with sterically differentiated imido (smaller) and aryl oxide (larger) ligands. Kinetically E-selective cross-metathesis reactions were recently introduced as well. Nevertheless, critical shortcomings persist. For instance, with Mo monoaryloxide pyrrolide (MAP) catalysts, cross-metathesis of Z-1,2-dihaloalkenones with aryl olefins or 1,3-dienes is often inefficient and non-stereoselective. In addition, cross-metathesis reactions that generate Z-alkenes that carry a trifluoromethyl group are unknown; these moieties can impart increased bioavailability, metabolic stability, lipophilicity or binding selectivity to biologically active molecules and are needed for future advances in agrochemicals and materials research. Yet, the state-of-the-art for synthesis of trifluoromethyl-substituted olefins is at a primitive stage. The available protocols are either minimally stereoselective or afford E isomers predominantly (for example, cross-metathesis with gaseous 3,3,3-trifluoropropene), and the small number of methods for preparing Z-trifluoromethyl olefins are expensive and/or impractical. Partial hydrogenation of alkynyl substrates is possible, but over-reduction can be an issue.

As part of an initiative to synthesize halo-substituted Mo alkylidenes—intermediates in stereoselective cross-metathesis reactions that afford alkene halides—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 the four-coordinate species Mo-3, which is not sufficiently stable to be isolated. Procedures for the preparation of multi-gram quantities of monoaryloxide chloride (MAC) derivatives (for example, Mo-4) from readily accessible and inexpensive materials were subsequently developed (details in Supplementary Information).
of our knowledge, this organofluoride has not been used in organic chemistry; our efforts to access Z-trifluoromethyl-substituted alkenes (for example, cross-metathesis of methyl oleate with 7) with known Mo complexes or ruthenium (Ru) carbenes were unsuccessful (no desired products were detected).

In contrast, with Mo-5a and Mo-6a, cross-metathesis 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. Accordingly, with Mo-6b—a more congested and longer living MAC complex—cross-metathesis was complete in 4 h, 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 5 equiv. of 7 the transformation was complete in only 15 min 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 (for example, 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 centre (8d), or a carbamate (8e) were easily accessed. Cross-metathesis with alkenes containing a tosylate (8f), an alkynyl (8g), a tertiary amine (8h), or a sulfide (8i) was efficient and Z-selective. A 1,4-diene (8j), a crotyl–pinacolatoboron (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. Cross-metathesis with aryl olefins needed (Z)-3-isopropylstyrenyl substrates so that homocoupling would be less competitive. Paraffin tablets containing a MAC species may be used (no glove box); for instance, with a pellet containing Mo-6b (about 3.0 mol%, toluene, 35 °C, 2 h), 8e was obtained in 74% yield and >98:2 Z:E ratio.

Figure 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. The corresponding chloride complexes, such as Mo-4, can be prepared from readily available and inexpensive materials.

b, Synthesis of Z-alkenyl halides. Monoaryloxide chloride (MAC) complexes Mo-5a and Mo-5b are most effective in promoting Z-selective ring-opening/cross-metathesis (versus the corresponding pyrrolid or MAP systems). Cross-metathesis of Z-1,2-dichloroethene and various types of olefins are exceptionally efficient and stereoselective with the MAC complex Mo-5b, which can also promote Z-selective cross-metathesis with a 64:36 Z:E mixture of 1,2-dibromoethene. 1H NMR spectra were recorded in C6D6; stereoselectivities measured by 1H NMR analysis (+2%); yields are for isolated/purified products (±5%). All experiments were performed in triplicate (at least). See Supplementary Information for details. Boc, tert-butoxycarbonyl; G, functional groups; ND, not determined.

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Mo MAC complexes engage a typically inert trifluoromethyl-substituted alkene. a, Mo MAC complexes, of which Mo-6b is optimal, can catalyse cross-metathesis of Z-1,2-disubstituted alkenes and reagent 7 with exceptional Z selectivity. b, Various alkyl and aryl olefins, including those that contain Lewis basic esters, carbamates and amines or α-branched moieties, may be used in efficient and exceptionally Z-selective cross-metathesis reactions. The requisite Z-1,2-disubstituted alkene starting Materials may either be purchased or prepared in one step from commercially available compounds. PMB, para-methoxybenzyl; Bn, benzyl; Boc, tert-butoxycarbonyl; pin, pinacolato; Ts, tosyl group. Stereoselectivities measured by 1H NMR analysis (±2%); yields are for isolated and purified products (±5%). All experiments were performed in triplicate (at least). See Supplementary Information for details.

Product 8t has been transformed to glycosidase inhibitor 10 by conversion of the commercially available aldehyde 11 to Z-alkene 12 followed by cross-metathesis with 7 afforded 8s—an intermediate in route to hVRI receptor inhibitor 13. 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). Several examples show that synthesis of trifluoromethyl analogues of medicinally relevant agents can be facilitated (Fig. 3b). Z-alkene 15, previously 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, enabling synthesis of a trifluoromethyl analogue of hormaomycin. Cross-metathesis of 16, derived from analogic zucapsacin, delivered 8u (86% yield, >98% Z). The transformation of 17 (obtained from sulbactam, a β-lactamase inhibitor) to 8v, and syntheses of 8w (from epalrestat, an aldolase reductase inhibitor) and 8x (from artemesunate, an anti-malarial agent), emphasize the compatibility of Mo MAC complexes with some key polar functional groups.

Two central points merit further discussion. (1) Cross-metathesis reactions with terminal alkenes would be more desirable, but, as mentioned earlier, the (Z)-1,2-disubstituted alkenes used here are readily accessed. Considering the high value of the Z-trifluoromethyl-substituted alkenes, the ease of their preparation and the paucity of alternative methods, the present approach offers a compelling solution to a longstanding problem. For instance, the Z-allyl–pinacolaboron 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...
Figure 3 | Utility and functional group compatibility. a, Mo MAC-catalysed cross-metathesis provides direct access to biologically active molecules. This includes the preparation of 9r, precursor to glycosidase inhibitor 10 (ref. 24). Styrenyl compound 8s, which has been converted to hvRI receptor inhibitor 13 (ref. 25), is notable because 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 the advantages of a trifluoromethyl unit. One example is conversion of previously reported 15 (ref. 26) to 8t en route to a trifluoromethyl-substituted derivative of hormaomycin; alternatively, 8u may be applied to synthesis of the trifluoromethyl analogue of zucapsaicin. c, Despite their high Lewis acidity, Mo MAC complex tolerate Lewis basic functional groups that regularly appear in therapeutic agents (for example, 8v–8x); TBS, tert-butyldimethylsilyl; Boc, tert-butyloxycarbonyl; Tf, trifluoromethylsulfonyl; DMAP, 4-dimethylaminopyridine. Stereoselectivities measured by 1H NMR analysis (±2%); yields are for isolated/purified products (±5%). All experiments were performed in triplicate (at least). See Supplementary Information for details.

Z-crotyl–pinacolatoboron. (2) The development of compounds that contain a Z-trifluoromethyl-substituted olefin and/or a related derivative with desirable biological activity has probably been hampered by the absence of direct and practical methods to obtain such species, despite their considerable potential.

Density functional theory 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. 4Aa). Although the energy for distortion of the chloro complex is relatively high (8.9 kcal mol\(^{-1}\)), the ensuing metallacyclobutane (mcb) formation (T\(_{d,\text{dist}}\)/pc \(\rightarrow\) ts1, where T\(_{d,\text{dist}}\) is the distorted tetrahedral complex, pc is the π complex and ts1 is the transition state for metallacyclobutane formation) is the most facile, a characteristic that is more evident in Fig. 4Ab, in which T\(_{d,\text{dist}}\) is the reference point. There is strong correlation between the barrier to ts1 and the extent of C–C double bond activation in the Mo π complex (pc, Fig. 4Ac). Whereas the 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 C=C bond (1.368 Å), a trend consistent with the lowest unoccupied molecular orbital (LUMO) energies for the distorted ground-state complexes (T\(_{d,\text{dist}}\); see the Supplementary Information for detailed study of electronic effects). The overall energy requirement appears to be derived from a combination of the cost of structural distortion (T\(_{a}\) \(\rightarrow\) T\(_{d,\text{dist}}\)) and mcb formation (T\(_{d,\text{dist}}\)/pc \(\rightarrow\) ts1); the model MAC system has the smallest barrier (12.5 kcal mol\(^{-1}\)) and the largest is for the methyl and methoxy derivatives (Fig. 4Aa). These
principles are distinct from those of a previous study, which were performed on less-substituted mcb intermediates, where methyl-molybdenum complexes were assigned higher reactivity (versus methoxy-molybdenum) on the basis of the principle that a stronger σ-donating ligand helps to make a trans ligation site available. This work shows that neither a methyl- nor a methoxy-substituted species is capable of delivering the activity level of a chloro-molybdenum species.

We then investigated the transformation between Z-2-butenes and Mo-8 and Mo-9 (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. 4Ad), the aryloxy moiety tilts towards the Cl ligand with longer C–H...H–C distances (2.21 Å and 2.39 Å). In MAP complex II, the aryloxy group and the reacting alkene are forced into closer contact (2.10 Å and 2.17 Å). The increased steric pressure has a stronger effect on the activation barriers (barrier to ts1 of 12.1 kcal mol\(^{-1}\) and 20.4 kcal mol\(^{-1}\) for the chloro and dimethylpyrrolidin complexes, respectively) compared to the more diminutive methoxy complexes (barrier to ts1 of 12.5 kcal mol\(^{-1}\) and 14.0 kcal mol\(^{-1}\) for the chloro and dimethylpyrrolidin systems, respectively; Fig. 4Aa).

The improved efficiency and Z selectivity in generating alkenyl halides with MAC complexes arise from differences in chemoselectivity. These differences are indicated by a larger gap in the energy that is required to overcome the ts1 activation barrier in reactions of Mo-8 (MAP) with Z-2-butenes (17.3 kcal mol\(^{-1}\); Fig. 4Bb) and Z-1,2-dichloroethene (23.0 kcal mol\(^{-1}\); Fig. 4Bc) compared to those for the transformation with MAC complex Mo-9 (12.3 kcal mol\(^{-1}\) for Z-2-butenes and 14.5 kcal mol\(^{-1}\) for Z-1,2-dichloroethene). Alkyl-substituted MAP alkylidenes bearing a pentfluorophenyl amido ligand are more prone to react with an aliphatic alkene (compared to the less Lewis basic 1,2-dichloroalkene) to afford homocoupling products and...
so Z-to-E isomerization/cross-metathesis becomes an issue (that is, there is repulsion between F atoms of the arylimido ligand and the Cl atoms of the dichloroalkene; see the Supplementary Information for details). With excess dichaloalkene, cross-metathesis becomes more favourable and homocoupling is less competitive. With a MAC species, which is capable of reacting with either alkene at comparable rates, adventitious homocoupling and E isomer generation is minimal, especially with excess dichaloalkene; 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, which is capable of causing post-metathesis isomerization, and the presence of 36% E-1,2-dibromoethene, Z-selectivity is exceptionally Z-selective. This might be attributed to lower reactivity of the E isomer, which is supported by the diminished Z/E ratio (41:59) of recovered reagent after cross-metathesis of methyl oleate with 2.3 equiv. of 1,2-dibromoethene (about 1.5 equiv. of Z isomer) with 5.0 mol% of Mo-5b (4h). Mo MAC complexes do not promote efficient cross-metathesis with E-1,2-dichloroethene or E-1,1,1,4,4,4-hexafluoro-2-butene (<10% conversion); 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 to only 20% conversion to the cross-metathesis products (C6H6, 22 °C, 4 h versus >98% conversion and 97% yield with the pure Z isomer). This is unlike the case with the bulkier 1,2-dibromoethene, for which the E isomer reacts at a sufficiently slower rate so that cross-metathesis can proceed to completion.

These Mo MAC complexes are able to catalyse— with unprecedented efficiency and selectivity—the formation of three types of products that are important 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 used in a chemical transformation, is particularly noteworthy. Computational studies teach us that, contrary to expectations, the chloride complexes exhibit higher activity compared to MAP species owing to enhanced Lewis acidity and diminution in steric repulsion within a trigonal bipyramidal intermediate.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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Author Contributions M.J.K. and T.T.N. were involved in the discovery, design and development of the new Z-selective cross-metathesis strategies and their applications. J.K.L., J.H. and R.R.S. were involved in the synthesis and characterization of Mo MAC complexes. S.T. performed the computational investigations, developed the models for the observed levels and patterns in reactivity and stereoselectivity. A.H.H. directed the investigation and computational investigations, developed the models for the observed levels and patterns in reactivity and stereoselectivity. A.H.H. directed the investigation and development of the new Z-selective cross-metathesis strategies and their applications. J.K.L., J.H. and R.R.S. were involved in the synthesis and characterization of Mo MAC complexes. S.T. performed the computational investigations, developed the models for the observed levels and patterns in reactivity and stereoselectivity.
METHODS

General procedure for cross-metathesis with a MAC complex. In a N2-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) CDCl3 (per cent 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 cross-metathesis 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 N2 three times to remove oxygen. Z-1,1,1,4,4,4-hexafluoro-2-butene (7 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 h under N2 atmosphere. The reaction was quenched by addition of MeCN (1.5 ml) and the mixture was allowed to stir at 22°C for 10 min. 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-t-butyl 2-hex-3-enyl pyrrolidine-1,2-dicarboxylate. The resulting green oil was purified by silica gel chromatography (4% Et2O/pentane to 20% Et2O/pentane) to afford Re (18.5 mg, 0.0548 mmol, 74% yield) in >98:2 Z:E ratio as colourless oil.

Data availability. The data generated during and/or analysed during the current study are available from the corresponding author on reasonable request.