Olefins with a halogen substituent are a mainstay in chemistry. Alkenyl chlorides and bromides are found in biologically active and natural products (for example, the recently isolated Z-alkenyl chloride containing neuromodulator janthelamide A1 or bromine-containing fatty acids that are adipogenesis stimulants2) or can be used in some of the most central transformations in chemistry (for example, catalytic cross-coupling3). Alkenyl fluorides are valued because of the importance of organofluorine compounds in medicine4, agrochemicals5 and materials development6. A fluoro-substituted olefin can influence the properties of a molecule; an example is the Z-fluoroalkene derivative of γ-aminobutyric acid (GABA) transaminase inhibitor7, which is more active than its E isomer8 yet similarly potent and with a distinct mode of action compared to the parent non-fluorinated alkene (vigabatrin). Fluoro-olefins may be used as substrates in synthesis of fluorene-containing building blocks9. And yet the number of approaches for accessing alkenyl halides is limited; many entail multi-step sequences demanding prior synthesis of alkenylboron10, alkylsilanes11 or an organometallic species12,13, followed by conversion of the C–B, C–Si or C–metal unit to a carbon–halogen bond (for a more extensive list, see Supplementary Information). Reactions might begin with the more costly and less widely available (compared to alkenes) alkyn substrates14, at times proceed with moderate stereoselectivity15, or are not sufficiently general16. Methods for preparation of 1,2-disubstituted Z-halo-alkenes with high stereoselectivity are even fewer in number10–13. One option is a Wittig reaction of an aldehyde with a halogen-substituted phosphonium salt14,15, but stereoselectivities are variable and, at times, toxic hexamethylphosphoramide and/or severely low temperatures are needed for high Z:E ratios16. Approaches to synthesis of 1,2-disubstituted Z-alkenyl fluorides are scarce15,17,18 and none has reasonable scope.

Certain 1,2-disubstituted Z-alkenyl halides can be prepared via stereo-defined alkynyl–B(pin) (pin, pinacolato) compounds19,20, accessible by catalytic cross–metathesis (CM) with vinyl–B(pin)21,22. If direct CM were able to deliver halogen-substituted olefins in a single catalytic reaction from a terminal olefin without the need for use and/or synthesis of (at times expensive) organoboron reagents, such a reaction would have several other advantages, as follows: (1) strong oxidants (for example, Br2), toxic mercury salts23 and/or the more difficult to prepare and use alkenylboronic acids24 (compared to B(pin) derivatives) would not be needed; (2) severely basic conditions for (pin) B-to-halogen exchange and reactive halide sources (for example, iodine monochloride), which may be detrimental to certain functionality (for example, sulphides25 or indoles26), would not be necessary; (3) product purification would be more practical—organohalide reagents are more easily removable (sufficiently volatile) and do not afford pinacol by-product that can be difficult to separate from the desired product; (4) access to multifunctional molecules with an alkenyl–B(pin) as well as an alkenyl halide would be more feasible27.

**The potential and challenge of alkenyl halide CM**

A catalytic CM protocol that converts an alkene to an alkenyl halide directly would be complementary to the existing methods (it would offer a distinct synthesis strategy) and especially advantageous if a commercially available, easy-to-handle (that is, liquid at ambient conditions) and relatively inexpensive reagent could be used in a highly stereoselective process (Fig. 1a). For instance, a transition metal complex that catalyses CM of an abundant substrate such as methyl oleate and an easily accessible organo-chloride reagent would afford separable Z-alkenyl halide compounds (Fig. 1a); one (1b) could be converted to anti-inflammatory agent (S)-coriolic acid methyl ester28 by an ensuing catalytic cross–coupling. Ring-opening/cross–metathesis (ROCM) of cyclooctene with an alkyn bromide would deliver ZZ-dibromoalkene 2, an intermediate used to access anti-tumour and immunosuppressive agent tetrahydrospironodiol29 (Fig. 1a). The feasibility of a CM that furnishes alkenyl fluorides would allow for late-stage fluorination30 of complex molecules, such as potassium channel activator isopimaric acid31 in a catalytic, chemo- and stereoselective fashion (3, Fig. 1a).

Development of efficient alkenyl halide-generating CM reactions is however not straightforward. Unlike Ru carbene or Mo or W alkylidenede with alkyl, aryl, boryl or alkoxy substituents, those bearing a halogen atom are either unstable (Ru), their transformations inefficient (Ru)32–34 or there is little known about them (Mo/W).
Fluoro-, chloro-, or bromo-substituted Fischer-type Ru complexes show negligible activity (Ru-1b, Fig. 1b)33. With phosphine-containing systems (for example, Ru-1a) inactive species such as phosphonometalates (MAP) complexes (for example, Ru-2, Fig. 1b)33,34, but reactions are low yielding and minimally stereoselective despite elevated temperatures (for example, 50 °C) and long reaction times (for example, 24 h).

**Identification of an effective catalyst**

The central issue, therefore, was whether high-oxidation-state (Mo/W) halo-substituted alkylidene complexes would be sufficiently robust yet appropriately reactive. Since alkoxysubstituted Mo alkylidene ligands are more active than the related Ru carbene35, we hoped that the same might apply to halogen-containing olefins, but we did not know of any data on the structure, stability or reactivity of a halo-substituted Mo or W alkylidene. Adding to the uncertainty is a computational study suggesting that fluoro-substituted Mo alkylidene would be less stable than even the methylidenes36. Equally discouraging were the outcome of our attempts to prepare halo-substituted alkylidenes of Mo monoaryl oxide pyridylide (MAP) species (compare iv, Fig. 1c) by using Z-dichloroethene (4a). Subjection of a neophylidene MAP complex (compare i) with two equivalents of 4a resulted in < 2% transformation (4 h, 22 °C; 400 MHz 1H NMR analysis). The more reactive methyldiene (generated from ethylene) was consumed completely, but a halo-substituted alkylidene was not found spectroscopically. Our remaining hope was that, although undetected, the putative complex might be sufficiently long-lived to fuel the catalytic cycles (compare iv, Fig. 1c). If so, reaction of a neophylidene with a terminal alkene could generate the less congested ii, which in turn might react with a...
Examination of complexes for CM

Table 1 | Examination of complexes for CM

| Entry number | Complex; loading (mol%) | Time (h); temperature (°C) | Conversion (%)*; | Z: E† |
|--------------|-------------------------|----------------------------|------------------|-------|
| 1            | Ru-2; 5.0               | 4; 50                       | 82: 59           | 58.42 |
| 2            | Ru-3; 5.0               | 4; 50                       | 10; <5           | NA    |
| 3            | Ru-4; 5.0               | 4; 50                       | <10; <5          | NA    |
| 4            | Mo-1; 5.0               | 4; 22                       | 67; <5           | NA    |
| 5            | W-1; 5.0                | 4; 22                       | 45; <10          | ND    |
| 6            | Mo-2; 5.0               | 4; 22                       | 43; <5           | NA    |
| 7            | Mo-3; 5.0               | 4; 22                       | 60; 27           | >98.2 |
| 8            | Mo-4a; 5.0              | 4; 22                       | 87; 60           | >98.2 |
| 9            | Mo-4b; 5.0              | 4; 22                       | 62: 40           | 98.2  |
| 11           | Mo-4c; 3.0              | 4; 22                       | 90; 75           | >98.2 |

Here we show the performance of various complexes (shown above the table) used for CM of a terminal alkene with Z,1,2-dichloroethene (reaction highlighted in grey). Reactions were carried out under a nitrogen atmosphere; see Supplementary Information for details. NA, not applicable; ND, not determined.

*Conversion was based on that of the limiting reagent (8-bromo-1-octene) and determined by analysis of the 1H NMR spectra of the unpurified mixtures; the variance of values is estimated to be <±2%.
†Yield of isolated and purified product (Z:E mixture); the variance of values is estimated to be <±5%. Z:E ratios were determined by 1H NMR analysis of unpurified mixtures; the variance of values is estimated to be <±2%. See Supplementary Information for details.

Z-dihaloalkene (compared to the more volatile vinyl halide), affording the desired product and halo-substituted alkylidene (iv) via all-syn metallacyclobutane iii. Complex iv and the olefin could then combine to afford v, which would in turn release alkylidene vi and vinyl halide. Alternatively, the halo-substituted alkylidene could react with another substrate molecule to furnish, by means of vi, the Z-alkenyl halide product and methyldienes vii and viii, which are precursors to ii.

We probed the ability of several complexes to effect Z-selective CM between 8-bromo-1-octene and commercially available and easy to handle Z-dichloroethene 4a (boiling point 60 °C versus –13 °C for vinyl chloride). Reaction with dichloro complex Ru-2 required 50 °C to reach 82% conversion after four hours (Table 1, entry 1), affording 5a as a near equal mixture of stereoisomers; there was no transformation with Z-selective Ru-30 or Ru-48 (entries 2, 3). Use of bis-alkoxide Mo-1 led to ~70% conversion (4 h, 22 °C) but mostly to the corresponding homocoupling product without any detectable alkyl halide (entry 4).

Experiments with complexes W-1 and Mo-2 were similarly disappointing (entries 5, 6) as again there was only alkene homocoupling (<2% 5a).

Adamantylmido Mo-3 provided the first hopeful data: we isolated 5a in 27% yield and >98% Z selectivity (entry 7). Efficiency improved with perfluorooimido complex Mo-4a: Z:5a was obtained in 60% yield with none of the alternative E isomer being observable (1H NMR analysis, 4 h, 22 °C; entry 8). We then reasoned that a larger arylxoy ligand, although likely to be less active, might translate into longer catalyst lifetime and better efficiency; we therefore examined the CM with Mo-4b, but, while high stereochemical control could be retained (98.2% Z:E), conversion and yield were reduced (62% conversion, 40% yield; entry 9). After 12 h, 5a was isolated in 84% yield (95% conversion; entry 10) but with some diminution in stereoisomeric purity (93.7% Z:E), probably caused by post-metathesis isomerization. To achieve a better balance between robustness and reaction rate without forfeiting stereocore, we examined 2,4,6-triethyl-substituted arylxoy complex Mo-4c (entry 11); 5a could thus be secured in 75% yield and >98.2% Z:E selectivity after four hours at room temperature.

Synthesis of Z-alkenyl chlorides and bromides

An array of Z-alkenyl chlorides can be prepared; yields were in the 50%–91% range with uniformly high stereoselectivity (95:5 to >98.2 Z:E; Fig. 2); the dichloroethene reagent (4a) was used without purification. Commonly occurring and versatile functional groups such as a silyl ether (5b, Fig. 2a), a sulphide (5c), an alkyne (5d), an epoxide (5e), an ester (5f) or a phthalimide (5g) were tolerated. An aryl or a heteroaryl moiety at the allylic position did not hinder the CM process (5j, k), but reactions with styrnes (regardless of its electronic attributes) were inefficient; this is probably due to steric hindrance within the requisite trisubstituted all-syn metallacyclobutane intermediate (compare iii, Fig. 1c) and the relatively facile homocoupling of aryl olefins. Hence, stilbenes, which do not re-enter the catalytic cycle easily (compared to the homocoupling product of an aliphatic alkene), were produced predominantly (see below for further discussion); however, in the reactions with α-branched aliphatic alkene, which do not undergo homocoupling as rapidly for steric reasons, CM is efficient. Z-Selective synthesis of polycyclic compound 5n demonstrates applicability to alkene with a homoallylic quaternary carbon centre.

Allylboronate 5o (Fig. 2b) was isolated in 66% yield and >98.2% Z:E selectivity; this product, similar to allyltin compound 5h and allylsilane product 5i, may be used as a reagent for C–C bond formation. Two representative cases are shown; in one, allyl chloride 6a was obtained in >98% γ- and diastereoselectivity, and in the other, performed in the presence of 10 mol% aminophenol 7, alkylxoy 6b was generated with high α-selectivity without any loss in Z:E ratio (>98.2). As noted, access to several of the aforementioned CM products (such as sulphide 5c, stannane 5h, indole 5k as well as allyl boron compound 5o) by means of the two-step protocol involving vinyl–B(pin) CM/boron-to-halogen exchange would be problematic.

Z-Disubstituted alkene are effective substrates. Treatment of commercially available 5-decene and Z-dichloroethene 1.0 mol% Mo-4c for two hours followed by the addition of alkyne 8 (5.0 mol% PdCl2(PPh3)2, 10 mol% CuI, piperidine, 15 h), afforded 9 in 67% overall yield and 97:3 Z:E selectivity. These processes were performed without the need for isolation of volatile Z-alkenyl chloride 5p (Fig. 2b), and the enyne product has been used in the synthesis of marine metabolite clathcumin B40. Reactions can be easily carried out on a gram scale; CM of methyl oleate and 4a in the presence of 3.0 mol% Mo-4c afforded Z-alkenyl chlorides 1a and 1b in 86% and 91% yield and with 97:3 Z:E selectivity, respectively (Fig. 2b). Subsequent catalytic cross-coupling with allylboronate 10, obtained from site- and E-selective catalytic protobyrol addition of the commercially available propargyl alcohol41, completed the two-step synthesis of (S)-coriolic acid methyl ester28 from a renewable resource in 65% overall yield and 97:3 Z:E selectivity (compared to five steps previously; see Supplementary Information for bibliography).

Z-Selectivity synthesis of alkylxoy bromides brings with it the added complication that stereoisomerically pure Z-dibromoethene 4b is not readily available and difficult to prepare, but a 64:36 Z:E mixture can be purchased at relatively low cost (Fig. 3a). Although MAP complexes prefer to react with Z,1,2-disubstituted alkene isomers42, our
Figure 2 | Synthesis of Z-alkenyl chlorides and applications. a, Many Z-alkenyl chlorides (5b–5n) can be prepared with Mo-4c and unpurified Z-dichloroethene (4a; see boxed reaction at top); each product 5b–5n has synthesis conditions shown under. Useful functional units are tolerated, among them a sulphide, an allyl stannane, an indole and an allylboron. The X-ray structure of 5n confirms the predominant formation of the Z isomer. b, Chloro-substituted allylboron compounds for use in catalytic C–C bond forming transformations. Top, synthesis of 6a. b, Application to synthesis of clathculin B (middle) and (S)-coriolic acid methyl ester (bottom, on a 1 gram scale) further underscores utility. Abbreviations: G, functional groups; TBS, t-butyldimethylsilyl; Bn, benzyl; pin, pinacolato; Ac, acetyl; SPhos, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl. Reactions were performed under N₂. Conversions and Z/E ratios were measured by analysis of 1H NMR spectra of unpurified mixtures; the variance of values is estimated to be ±2%. Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). See Supplementary Information for experimental details and spectroscopic analyses.

The present strategies are applicable to ROCM; two instances are depicted in Fig. 3b. Dibromoalkene 2 was obtained in 88% yield and 89:11 Z,Z,Z,E selectivity (10 mol% Mo-4c, 1 h); as mentioned (compare Fig. 1a), diene 2 has been used in the preparation of tetrahydrospironodiol29. The need for larger amounts of the more active pentfluoroimido Mo-4c is so that maximum amounts of the ring-opening polymerization (ROMP) by-product can be converted to monomeric 2. Z,Z-Dichloroalkene 12 was isolated in 75% yield as a single stereoisomer; adamantylimido complex Mo-3 proved optimal, as this less active catalyst (compared to Mo-4c) is sufficient for the faster ROCM involving the less hindered Z-dichloroethene to compete with ROMP for attaining maximal Z selectivity. When the milder Mo-3 was
used in the more demanding transformation leading to bromo-alkene 2, there was >98:2 Z,Z,Z,E selectivity but with less conversion to the desired product (∼35%, ∼20% ROMP). Control experiments indicated that post-metathesis isomerization is minimal.

**Synthesis of Z-alkenyl fluorides**

Development of Z-selective CM reactions that afford organofluorine products posed a new complication (Fig. 4). Vinyl fluoride has a very low boiling point (−72 °C versus −13 °C for vinyl chloride); Z-difluoroethene is expensive, similarly difficult to handle as well as explosive (Fig. 4a). We thus envisioned using Z-bromo-fluoroethene (4c), a commercially available, economically viable and substantially less volatile organohalide (boiling point, +36 °C), an option that raises a selectivity problem: the bromo-fluoroethene compound must interact with a Mo alkylidene according to the regiochemical mode of addition I in Fig. 4a. If the transformation were to proceed through II, a Z-alkenyl bromide would be formed. We reasoned that reaction via I might be preferred for two reasons. First, the 1H NMR spectrum (CDCl3) of 4c contains a significantly more upfield signal for the proton at the base of the C–Br bond, indicating that electron density is greater at this carbon (stronger \( \pi \) donation and \( \sigma \) withdrawing inductive effect by fluorine), favouring its association with the Lewis acidic Mo centre (compare I versus II). Additionally, the metallacyclobutane generated via II would suffer from steric repulsion between the more sizeable halogen and the alkylidene substituent (G). The catalytic CM affording Z-alkenyl fluoride 13a indeed generated bromide 11b as the minor product (72:28 fluoro:bromo; Fig. 4b). Consistent with the suggested model (I versus II), with an \( \omega \)-branched terminal alkene, the product mixture was less contaminated by the corresponding bromoalkene: pure 13b, formed from a CM reaction that proceeded with 96:4 fluoro:bromo selectivity, was isolated in 70% yield and >98:2 Z:E ratio after purification.

Contrary to transformations of styrenes with dichloro- or dibromoethene (4a, b), CM with 4c and aryl olefins proceeded readily and stereoselectively: \( \beta \)-\( \beta \)-fluorostyrenes 13c–f were obtained in 93:7–96:4 fluoro:bromo selectivity, 64%–72% yield of the pure Z-alkenyl fluoride and 93:7–97:3 Z:E selectivity. These variations in efficiency might be associated with the lower steric repulsion (elipsiding interaction of fluorine with G in the all-syn metallacyclobutane) versus the larger chlorine and bromine atoms, such that CM with 4c competes better with homocoupling of styrene. To the best of our knowledge, there are no reports regarding the synthesis of aryl-substituted Z-alkenyl fluorides by catalytic cross-coupling of 4c, and such transformations (for example, 13e, f) would probably suffer from chemoselectivity complications. The present processes would offer an attractive pathway for accessing a variety of organofluorine compounds41. Z-alkenyl fluoride 13g has been converted to the aforementioned GABA transaminase inhibitor 14f; product 13g was obtained in 55% overall yield and >98:2 fluoro:bromo and Z:E selectivity by CM with the silyl-amide substrate followed by deprotection. There was <5% conversion with the parent amide probably due to internal association of the Lewis basic amide with the Mo centre in the intermediate alkylidene complex.42

**Z-selective complex molecule fluorination**

A corollary to the present approach is the possibility of implementing net stereoselective olefinic C–H/C–F bond exchange within a complex molecule; this would allow rapid access and screening of well-defined fluorine-tagged derivatives for possible desirable properties. In this context (Fig. 4c), formation of Z-alkenyl fluoride 15 (>98:2 fluoro:bromo, 63% yield, >98:2 Z:E) demonstrates relevance to processes involving a relatively hindered allylic ether43. Tricyclic product 3 (94:6 fluoro:bromo, 70% yield in the pure form, 96:4 Z:E) is derived from the challenging CM with the isopimaric acid methyl ester (compare Fig. 1a); here, the alkene is next to a sterically demanding all-carbon quaternary centre.

The findings summarized in Fig. 4d illustrate that the method is tolerant of a range of functional units commonly found in biologically active molecules. Z-alkenyl fluoride 16 (from anti-depressant perphenazine44) was obtained efficiently and stereoselectively (91:9 fluoro:bromo, 78% yield, >98:2 Z:E), underscoring tolerance towards aryl or alkyl amines and aryl sulphides. Synthesis of Z-fluoro-alkene 17 (from \( \beta \)-lactamase inhibitor subactam45) by the two-step sequence of Z-selective CM with vinyl–B(pin)41 followed by conversion of the C–B unit to a C–F bond, according to the only available reported procedure48, led to outright substrate decomposition. The first step afforded the Z-alkenyl–B(pin) compound as expected (22 °C, 24 h, 70%
a Identifying a practical and effective alkenyl fluoride reagent

Difficult to handle, explosive, expensive

Br
F
H2 and H2
assigned on basis
of H-F coupling
5.61 p.m. 7.08 p.m.

More electron repulsion

Electronic mismatch

b Preparation of Z-alkenyl fluorides through catalytic CM

G + Br
F
5.0 mol% Mo–4c benzene, 22 °C, 4 h

More easier to handle, much less costly

4c

Figure 4 | Z-alkenyl fluorides and late-stage fluorination. a, Z- Bromofluoroethene (4c, top) can be used for synthesis of Z-alkenyl fluorides. Based on electronic and steric factors, reactions probably proceed via I (versus II). b, An array of products (13a–14) can be accessed using the general reaction shown boxed, including those with an ary substutent. c, Stereoselective late-stage fluorination of complex molecules can be performed, giving, for example 15, 16, 17. Abbreviations: G, various functional groups; Ar, aryl group; PMP, p-methoxyphenyl; Ac, acetyl; Bn, benzyl; TBS, tert-butyldimethylsilyl. Reactions were performed under N2. Conversions and Z:E ratios were measured as in Fig. 2, with the same variance; yields were also measured as in Fig. 2. For 13a, 30 mol% Mo–4c was used, and for 13d, 10 mol% Mo–4c was used (40 °C, 12 h for 13g). See Supplementary Information for details.

c Z-Selective "fluorine insertion" involving complex molecules

conversion, >98:2 Z:E); but attempts to generate 17 by treatment with NaOH and AgOTf and then Selectfluor yielded an unidentifiable mixture of compounds, probably due to sensitivity of the substrate’s bicyclic core. In contrast, Z-alkenyl fluoride 17 was obtained through direct CM in 80% yield (>98:2 fluorobromo) as a single stereoisomer (>98% Z).

Conclusions

We have introduced halo-substituted Mo alkylidenes as highly reactive and difficult-to-detect but viable intermediates in olefin metathesis. The matter of efficiency is especially noteworthy because, regardless of stereochemical control, there did not exist previously a catalytic CM protocol that generated halo-alkenes in useful yields. The ability of MAP catalysts to provide a solution to this central problem lies in their distinct electronic attributes, striking a balance between high reactivity and sufficient longevity. The catalytically active halo-substituted alkylidenes derived from Mo–4c can thus deliver the necessary activity (for example, versus Ru–2–4 or W–1) but not at the expense of catalyst lifetime (for example, versus bisalkoxide Mo–1). The Mo centre in a MAP system is probably electron-deficient enough to prevent metal-carbide formation and, yet, unlike Ru carbenes, π-electron donation by a halide alkylidene substituent does not hamper reactivity. Another noteworthy aspect is the design of reactions where the use of a disymmetric Z-bromo-fluoroethene leads to the predominant or exclusive formation of fluoro-substituted alkenes (versus the bromo derivatives); this way, an easy-to-handle and readily accessible reagent can be used instead of the costly and impractical fluoro-olefin alternatives (for example, vinyl fluoride or Z-1,2-difluoroethene).

The advances outlined here serve as the foundation for future progress involving this intriguing set of halogen-containing Mo alkylidenes. The transformations should facilitate considerably the preparation of an assortment of desirable molecules for research in chemistry, biology and medicine, particularly since easy-to-handle (no glove box needed) paraffin-wrapped MAP complexes are becoming commercially accessible.

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