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Direct synthesis of *Z*-alkenyl halides through catalytic cross-metathesis

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Abstract

Olefin metathesis has made a significant impact on modern organic chemistry, but important shortcomings remain: for example, the lack of efficient processes that can be used to generate acyclic alkenyl halides. Halo-substituted ruthenium carbene complexes decompose rapidly or deliver low activity and/or minimal stereoselectivity, and our understanding of the corresponding high-oxidation-state systems is very limited. In this manuscript, we show that previously unknown halo-substituted molybdenum alkylidene species are exceptionally reactive and are able to participate in high-yielding olefin metathesis reactions that afford acyclic 1,2-disubstituted *Z*-alkenyl halides. Transformations are promoted by small amounts of an *in situ*-generated catalyst with unpurified, commercially available and easy-to-handle liquid 1,2-dihaloethene reagents and proceed to high conversion at ambient temperature within four hours. Many alkenyl chlorides, bromides and fluorides can be obtained in up to 91 percent yield and complete *Z* selectivity. This method can be used to easily synthesize biologically active compounds and to perform the site- and stereoselective fluorination of other organic compounds.

Olefins with a halide substituent are a mainstay in chemistry. Alkenyl chlorides and bromides are found in biologically active natural products (e.g., the recently isolated *Z*-alkenyl chloride containing neuromodulator janthielamide A[1] or bromine-containing fatty acids that are adipogenesis stimulators[2]) or can be used in some of the most central transformations in chemistry (i.e., catalytic cross-coupling [3]). Alkenyl fluorides are valued

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because of the importance of organofluorine compounds in medicine [4], agrochemicals [5] and materials development[6]. A fluoro-substituted olefin can strongly impact the property of a molecule; an example is the *Z*-fluoroalkene derivative of γ-aminobutyric acid (GABA) transaminase inhibitor[7], more active than its *E* isomer[8] 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 fluorine-containing building blocks[9]. And still, the number of approaches for accessing alkenyl halides is limited; many entail multi-step sequences demanding prior synthesis of alkenylboron[10], alkenylsilane[11] or an organometallic species[12,13], followed by conversion of the C–B, C–Si or C–metal unit to a carbon–halogen bond (for a more extensive list, see the Supplementary Information). Reactions might begin with the more costly and less widely available (vs. alkenes) alkyne substrates[13], at times proceed with moderate stereoselectivity[10], or are not sufficiently general[11,12]. Methods for preparation of 1,2-disubstituted *Z*-halo-alkenes with high stereoselectivity are even fewer in number[10-13]. One option is a Wittig reaction of an aldehyde with a halogen-substituted phosphonium salt[14,15], but stereoselectivities are variable and, at times, toxic hexamethylphosphoramide and/or severely low temperatures are needed for high *Z*:*E* ratios[16]. Approaches to synthesis of 1,2-disubstituted*Z*-alkenyl fluorides are scarce[15,17,18] and none has reasonable scope.

Certain 1,2-disubstituted *Z*-alkenyl halides can be prepared via stereo-defined alkenyl–B(pin) (pin, pinacolato) compounds[19,20], accessible by catalytic cross-metathesis (CM) with vinyl–B(pin)[21,22]. Direct CM may 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. There would be several other advantages: (1) Strong oxidants (e.g., Br_2), toxic mercury salts[23] and/or the more difficult to prepare and use alkenylboronic acids[24] [vs. B(pin) derivatives] would not be needed. (2) Severely basic conditions for (pin)B-to-halogen exchange and reactive halide sources (e.g., iodine monochloride), which may be detrimental to certain functionality (e.g., sulfides [25] or indoles [26]), would not be necessary. (3) Product purification would be more practical: organic halide reagents are more easily removable (sufficiently volatile) and do not afford pinacol byproduct 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 feasible[27].

The Potential and Challenge of Alkenyl Halide Cross-Metathesis

A catalytic CM protocol that converts an alkene to an alkenyl halide directly would be complementary to the existing methods (offer a distinct disconnection) and especially advantageous if a commercially available, easy-to-handle (i.e., 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 catalyzes 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 ester[28] by an ensuing catalytic cross-coupling. Ring-opening/cross-metathesis (ROCM) of cyclooctene with an alkenyl bromide would deliver *Z,Z*-dibromoalkene **2**, an intermediate utilized to access anti-tumor and immunosuppressive

agent tetrahydrosiphonodiol[29] (Fig. 1a). The feasibility of a CM that furnishes alkenyl fluorides would allow for late-stage fluorination[30] of complex molecules, such as potassium channel activator isopimaric acid[31] in a catalytic, chemo- and stereoselective fashion (**3**, Fig. 1a).

Development of efficient alkenyl halide-generating CM reactions is anything but straightforward however. Unlike Ru carbenes or Mo or W alkylidenes with alkyl, aryl, boryl or alkoxy substituents, those bearing a halogen atom are either unstable (Ru), their transformations inefficient (Ru)[32,33,34] or there is hardly anything known about them (Mo/W). Fluoro-, chloro-, or bromo-substituted Fischer-type Ru complexes show negligible activity (**Ru-1b**, Fig. 1b)[34]. With phosphine-containing systems (e.g., **Ru-1a**) inactive species such as phosphoniomethylidene **Ru-1c** and carbide **Ru-1d**[32] are produced. There is some improvement with phosphine-free complexes (e.g., **Ru-2**, Fig. 1b)[33,34], but reactions are low yielding and minimally stereoselective despite elevated temperatures (e.g., 50 °C) and long reaction times (e.g., 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 alkoxy-substituted Mo alkylidenes are more active than the related Ru carbenes[35], 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 alkylidenes would be less stable than even the methylidenes[36]. Equally discouraging were the outcome of our attempts to prepare halo-substituted alkylidenes of Mo monoaryloxide pyrrolide (MAP) species (cf. **iv**, Fig. 1c) by utilizing *Z*-dichloroethene (**4a**). Subjection of a neophylidene MAP complex (cf. **i**) with two equivalents of **4a** resulted in <2% transformation (4 h, 22 °C; 400 MHz ^{1}H NMR analysis). The more reactive methylidene (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 living to fuel the catalytic cycles (cf. **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 *Z*-dihaloalkene (vs. the more volatile vinyl halide), affording the desired product and halo-substitued alkylidene (**iv**) via all-*syn* metallacyclobutane **iii**. Complex **iv** and the olefin could then combine to afford **v**, which would in turn release alkylidene **ii** and vinyl halide. Alternatively, the halo-substitued alkylidene could react with another substrate molecule to furnish, by means of **vi**, the *Z*-alkenyl halide product and methylidenes **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 and dispense *Z*-dichloroethene **4a** (boiling point, 60 °C vs. −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-3**[37] or **Ru-4**[38] (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 alkenyl 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**). Adamantylimido **Mo-3** provided the first hopeful data: we isolated **5a** in 27% yield and >98% *Z* selectivity (entry 7). Efficiency improved with perfluoroimido complex **Mo-4a**: ***Z*-5a** was obtained in 60% yield with none of the alternative *E* isomer being observable (^{1}H NMR analysis, 4 h, 22 °C; entry 8). We then reasoned that a larger aryloxide ligand, although likely 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% conv., 40% yield; entry 9). After 12 hours, **5a** was isolated in 84% yield (95% conv.; 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 stereocontrol, we examined 2,4,6-triethyl-substituted aryloxide 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

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 sulfide (**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 styrenes (regardless of its electronic attributes) were inefficient; this is probably due to steric hindrance within the requisite trisubstituted all-*syn* metallacyclobutane intermediate (cf. **iii**, Fig. 1c) and the relatively facile homocoupling of aryl olefins. Hence, stilbenes, which do not re-enter the catalytic cycle easily (vs. the homocoupling product of an aliphatic alkene), were produced predominantly (see below for further discussion); however, in the reactions with α-branched aliphatic alkenes, which do not as undergo homocoupling rapidly for steric reasons, CM is efficient. *Z*-Selective synthesis of polycyclic compound **5n** demonstrates applicability to alkenes with a homoallylic quaternary carbon center.

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**[39], alkenyl chloride **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 sulfide **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 alkenes are effective substrates. Treatment of commercially available *Z*-5-decene and *Z*-dichloroethene with 1.0 mol % **Mo-4c** for two hours followed by the addition of alkyne **8** (5.0 mol % $PdCl_2(PhCN)_2$, 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 clathculin B[40]. Reactions can be easily carried out on 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 alkenylboronate **10**, obtained from site- and *E*-selective catalytic protoboryl addition of the commercially available propargyl alcohol[41], completed the two-step synthesis of (*S*)-coriolic acid methyl ester[28] from a renewable resource in 65% overall yield and 97:3 *Z*:*E* selectivity (vs. 5 steps previously; see the Supplementary Information for bibliography).

Z-Alkenyl Bromides and Fluoride Synthesis

Z-Selective synthesis of alkenyl 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 isomers[42], our concern was possible interference by *E*-**4b**, leading to diminution in stereoselectivity. It was also unclear whether the more sizeable dibromoethene would cause significant lowering of efficiency. In the event, a range of *Z*-alkenyl bromides were obtained in 57–83% yield and 87:13–91:9 *Z*:*E* selectivity (**11a-f**, Fig. 3a). With the more volatile vinyl bromide (vs. **4b**), yields were significantly lower (<25%) because the increased amount of ethylene boosts the concentration of the comparatively unstable methylidene complexes (cf. **vii-viii**, Fig. 1c). The lower *Z* selectivity in the case of bromoalkene products (vs. alkenyl chlorides) may be attributed to a minor pathway involving metallacyclobutanes derived from the *E* isomer of the dibromo-alkene reagent (see the Supplementary Information for details).

The present strategies are applicable to ROCM; two instances are depicted in Fig. 3b. *Z*,*Z*-Dibromoalkene **2** was obtained in 88% yield and 89:11 *Z*,*Z*:*Z*,*E* selectivity (10 mol % **Mo-4c**, 1 h); as mentioned (cf. Fig. 1a), diene **2** has been utilized in the preparation of tetrahydrosiphonodiol[29]. The need for larger amounts of the more active pentafluoroimido **Mo-4c** is so that maximum amounts of the ring-opening polymerization (ROMP) byproduct 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 (vs. **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.

Development of *Z*-selective CM reactions that afford organofluorine products posed a new complication (Fig. 4). Vinyl fluoride has a notoriously low boiling point (−72 °C vs. –13 °C for vinyl chloride); *Z*-difluoroethene is exorbitantly 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. Firstly, ^{1}H NMR spectrum ($CDCl_3$) of **4c** contains a significantly more upfield signal for the proton at the base of the C–Br bond, indicating electron density is higher at this carbon (stronger π donation and σ withdrawing inductive effect by fluorine), favoring its association with the Lewis acidic Mo center (cf. **I** vs. **II**). Additionally, the metallacyclobutane generated via **II** would suffer from steric repulsion between the more sizeable halogen and the alkylidene subsituent (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** vs. **II**), with an α-branched terminal alkene, the product mixture is 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 distillation.

Contrary to transformations of styrenes with dichloro- or dibromoethene (**4a**,**b**), CM with **4c** and aryl olefins proceeds readily and stereoselectively: β-(*Z*)-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 (eclipsing 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 (e.g., **13e**,**f**) would likely suffer from chemoselectivity complications. The present processes would offer an attractive pathway for accessing a variety of organofluorine compounds[43]. *Z*-Alkenyl fluoride **13g** has been converted to the afore mentioned GABA transaminase inhibitor **14**[7]; 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 center in the intermediate alkylidene complex[44].

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 ether[45]. 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[31] methyl ester (cf. Fig. 1a); here, the alkene is next to a sterically demanding all-carbon quaternary center.

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 perphenazine [46]) was obtained efficiently and stereoselectively (91:9 fluoro:bromo, 78% yield, >98:2 *Z*:*E*), underscoring tolerance toward aryl or alkyl amines

and aryl sulfides. Synthesis of *Z*-fluoro-alkene **17** (from β-lactamase inhibitor sulbactam[47]) by the two-step sequence of *Z*-selective CM with vinyl–B(pin)[21] followed by conversion of the C–B unit to a C–F bond, according to the only available reported procedure[48], led to outright substrate decomposition. The first step afforded the *Z*-alkenyl–B(pin) compound as expected (22 °C, 24 h, 70% conv., >98:2 *Z*:*E*); but attempts to generate **17** by treatment with NaOH and AgOTf and then Selectfluor yielded an unidentifiable mixture of compounds, likely due to sensitivity of the substrate's bicyclic core[49]. In contrast, *Z*-alkenyl fluoride **17** was obtained through direct CM in 80% yield (>98:2 fluoro:bromo) as a single stereoisomer (>98% *Z*).

Conclusions

This report introduces 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, heretofore there did not exist a catalytic CM protocol that generates 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 (e.g., vs. **Ru-2-4** or **W-1**) but not at the expense of catalyst lifetime [e.g., vs. bis(alkoxide) **Mo-1**]. The Mo center in a MAP system is likely electron-deficient enough to prevent metal-carbide formation[34], and yet, unlike Ru carbenes, π-electron donation by a halide alkylidene substituent[50] does not hamper reactivity. Another noteworthy aspect is the design of reactions where the use of a dissymmetric *Z*-bromo-fluoroethene leads to the predominant or exclusive formation of fluoro-substituted alkenes (vs. 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 (e.g., 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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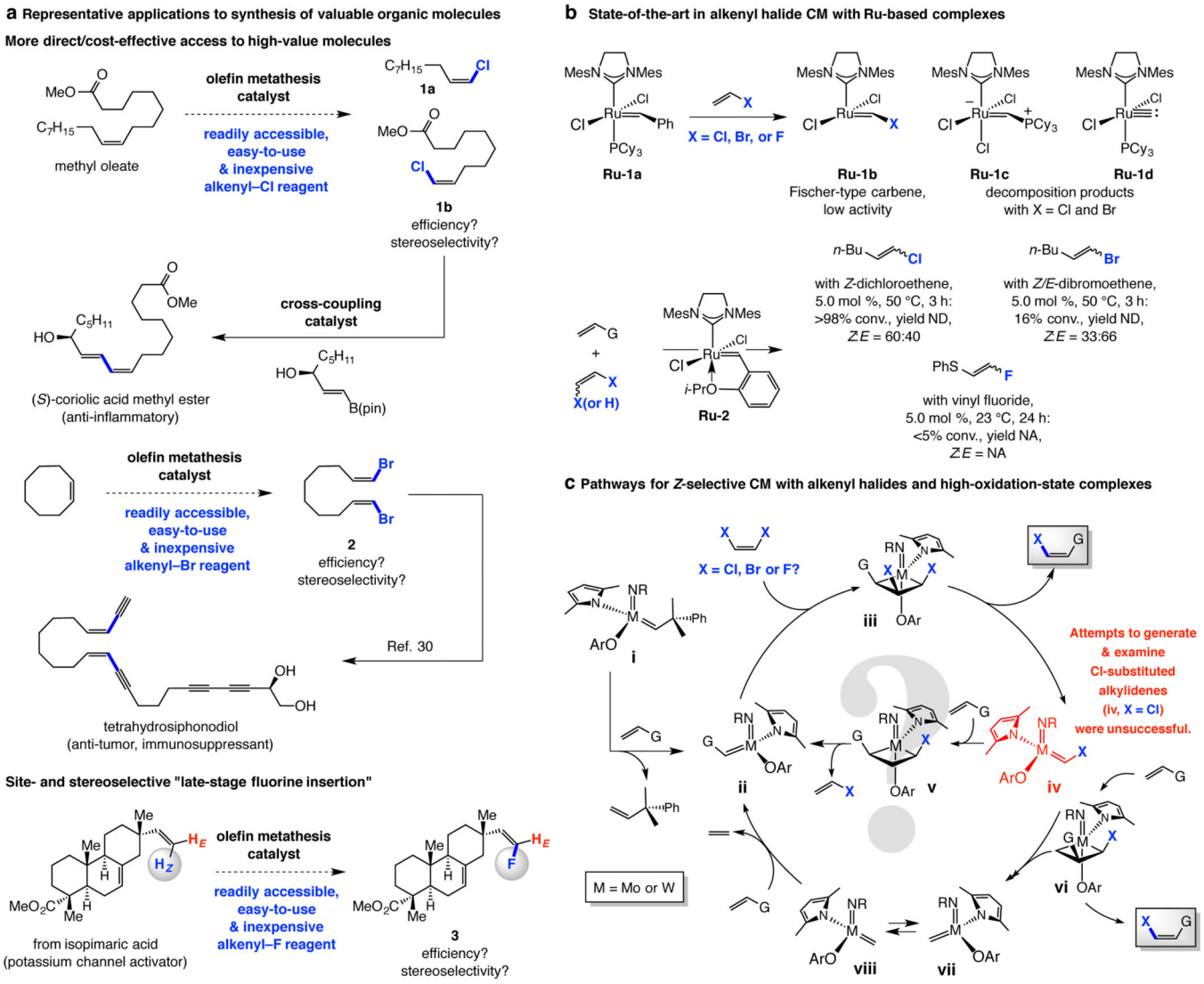


Figure 1. Designing catalytic cross-metathesis (CM) reactions that afford *Z*-alkenyl halides

a, Potential applications of *Z*-selective CM reactions that afford alkenyl halides include a concise synthesis of an anti-inflammatory agent and a ring-opening/cross-metathesis process that delivers a compound with two *Z*-alkenyl bromide bonds formerly employed in the preparation of an immunosuppressant. The ability to perform late-stage stereoselective fluorination of complex molecules is another notable and high impact advantage. **b,** Ru complexes cannot promote efficient CM reactions of alkenyl halides because of the low reactivity and instability of the derived halo-substituted carbenes. **c**, The pathways that might allow a Mo or W species to promote CM transformations that generate alkenyl halides, despite the fleeting nature of the corresponding halo-substituted alkylidenes. Abbreviations: M, transition metal; X, halogen; Mes, 2,4,6-$(Me)_3C_6H_2$; G or R, various functional groups; Ar, aryl group; NA, not applicable; ND, not determined.

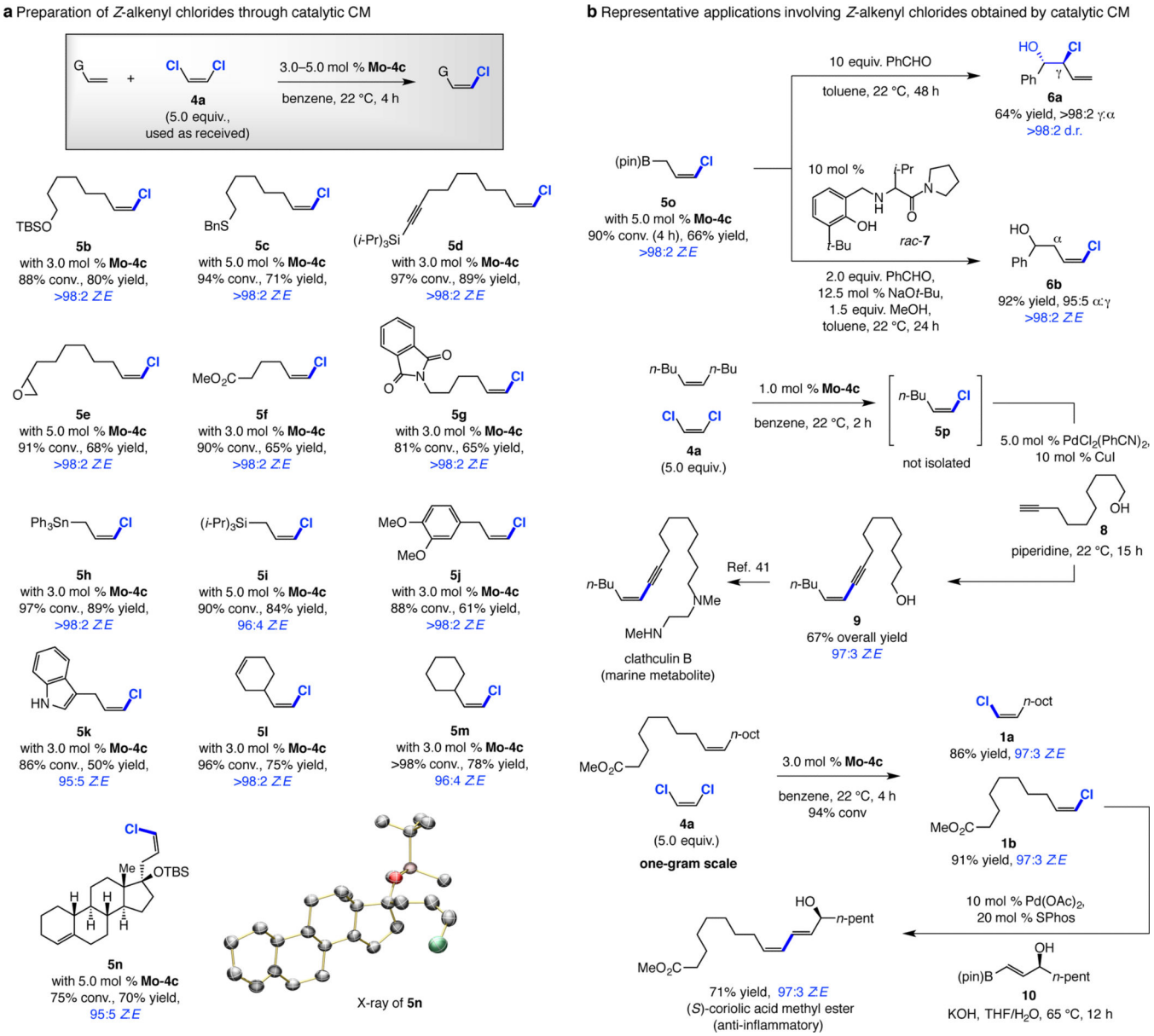


Figure 2. Synthesis of *Z*-alkenyl chlorides and applications

a, Many *Z*-alkenyl chlorides can be prepared with **Mo-4c** and unpurified *Z*-dichloroethene. Useful functional units are tolerated, among them a sulfide, an allyl stannane, an indole and an allylboron. **b**, Chloro-substituted allylboron compounds for use in catalytic C–C bond forming transformations. Application to synthesis of clathculin B and (*S*)-coriolic acid methyl ester 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 N_2. Conversions and *Z*:*E* ratios were measured by analysis of ^{1}H NMR spectra of unpurified mixtures; the variance of values estimated to be <±2%. Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). See the Supplementary Information for experimental details and spectroscopic analyses.

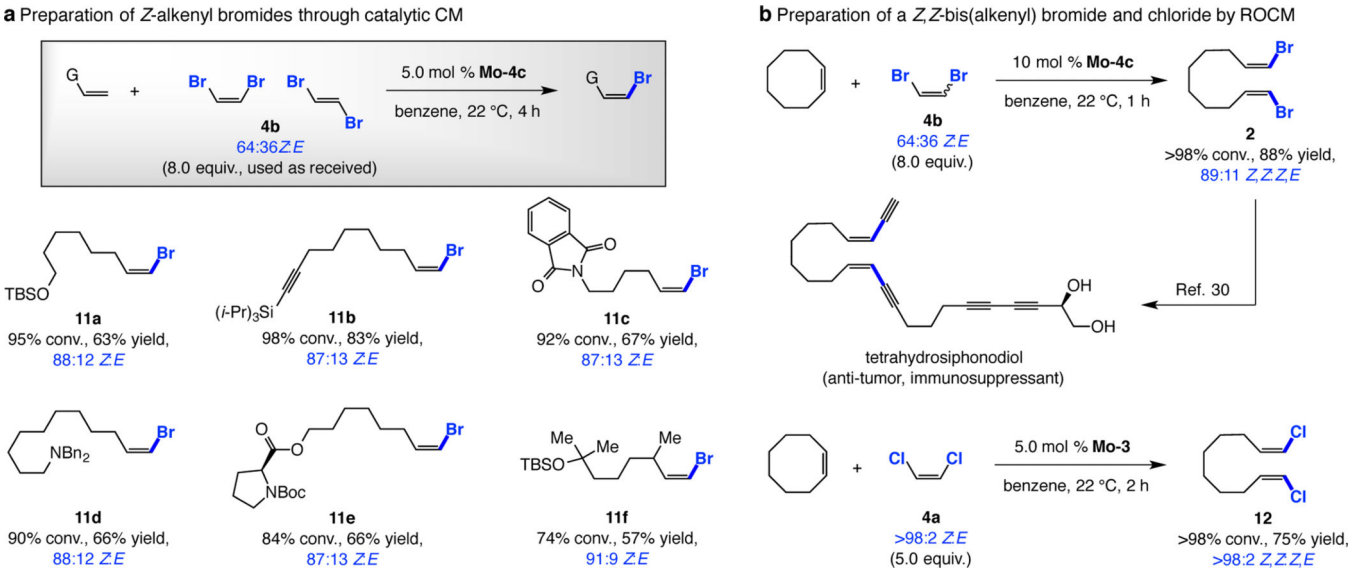


Figure 3. *Z*-Alkenyl bromides through catalytic cross-metathesis (CM) and ring-opening-cross-metathesis (ROCM)

a, Stereoisomeric mixture of 1,2-dibromoethene can be used in preparation of *Z*-alkenyl bromides. **b,** The protocol is applicable to ring-opening/cross-metathesis processes with readily accessible cyclic alkenes; *Z,Z*-bis(alkenyl)bromide has been employed in the preparation of anti-tumor agent tetrahydrosiphonodiol. The corresponding dichloride was synthesized in 75% yield and with complete *Z* selectivity. Abbreviations: G, various functional groups; Ar, aryl group; TBS, *tert*-butyldimethylsilyl; Bn, benzyl; Boc, *tert*-butyloxycarbonyl. Reactions were performed under N_2. Conversions and *Z*:*E* ratios were measured by analysis of ^{1}H NMR spectra of unpurified mixtures; the variance of values estimated to be <±2%. Yields correspond to isolated and purified products and represent an average of at least three runs (±5%). See the Supplementary Information for experimental details and spectroscopic analyses.

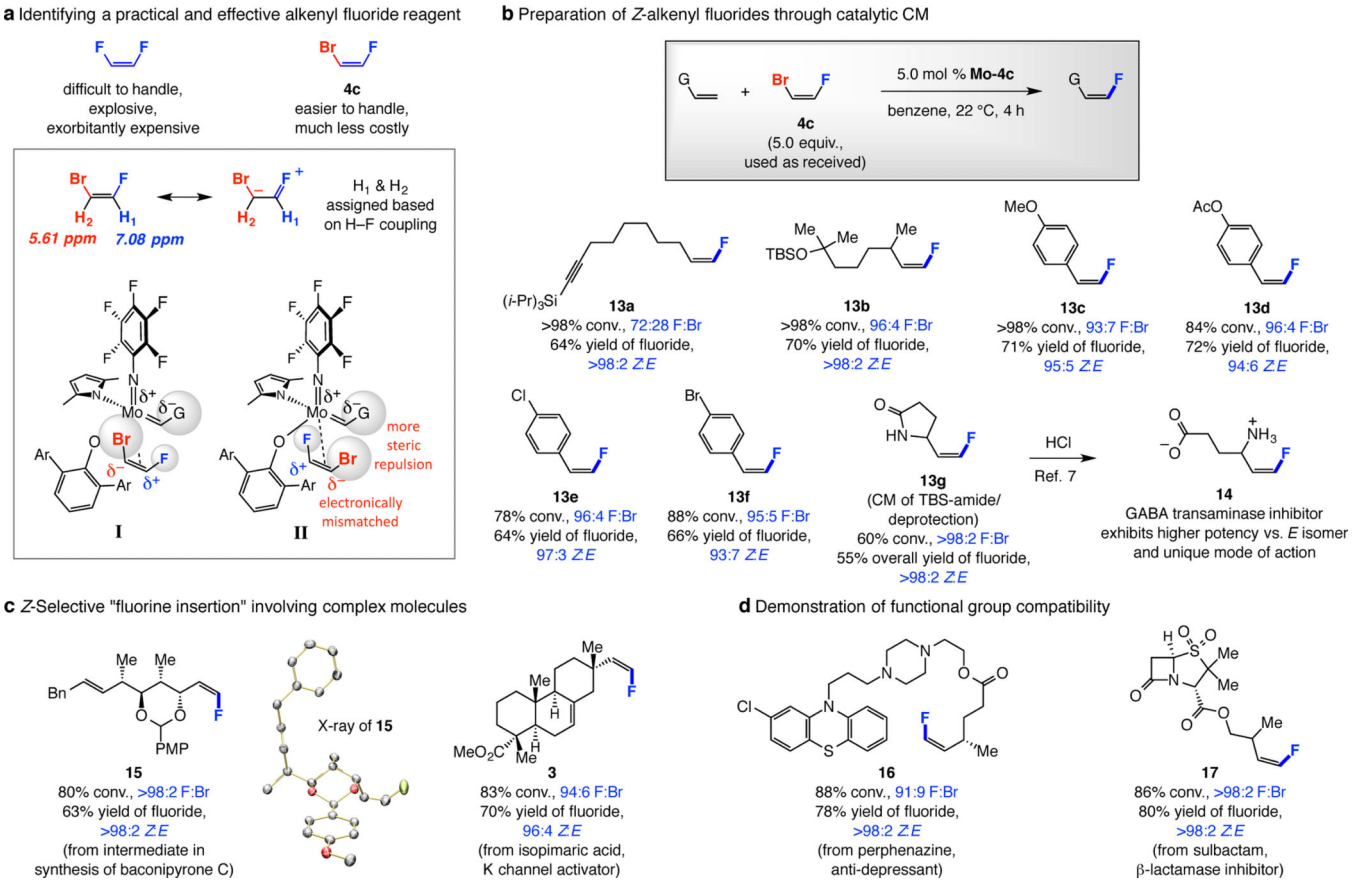
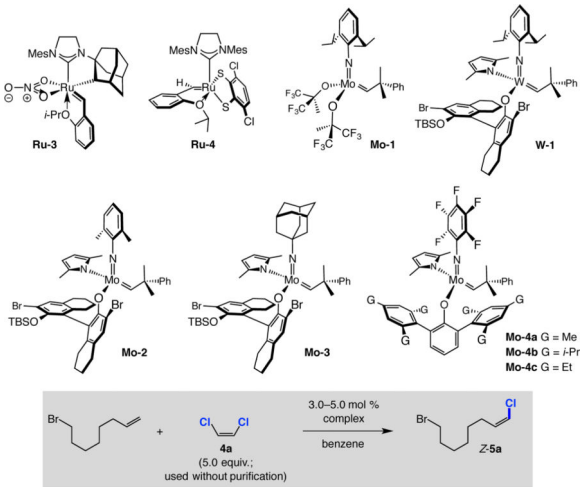


Figure 4. *Z*-alkenyl fluorides and late-stage fluorination

a, *Z*-Bromo-fluoroethene can be used for synthesis of *Z*-alkenyl fluorides. **b,** An array of products can be accessed, including those with an aryl substituent. **c,** Stereoselective late-stage fluorination of complex molecules can be performed. **d,** A variety of widely occurring heteroatom-containing functional units are tolerated. Abbreviations: G, various functional groups; Ar, aryl group; PMP, *p*-methoxyphenyl; Ac, acetyl; Bn, benzyl; TBS, *tert*-butyldimethylsilyl. Reactions were performed under N_2. Conversions and *Z*:*E* ratios were measured by analysis of ^{1}H NMR spectra of unpurified mixtures; the variance of values estimated to be <±2%. Yields correspond to purified products and represent an average of at least three runs (±5%). For **13a**, 3.0 mol % **Mo-4c** and for **3**, **13g** and **15**, 10 mol % **Mo-4c** was used (40 °C, 12 h for **13g**). See the Supplementary Information for details.

Table 1

Examination of Complexes for CM of a Terminal Alkene with *Z*-1,2-dibromoethene



Entry number	Complex; Mol %	Time (h); Temp. (°C)	Conv. (%)[§]; Yield (%)[§§]	*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
10	**Mo-4b;** 5.0	12; 22	95; 84	93:7
11	**Mo-4c;** 3.0	4; 22	90; 75	>98:2

Reactions were carried out under N_2 atm.; see the Supplementary Information for details.

[§]Conversion (conv.) was based on the disappearance of the limiting reagent (8-bromo-1-octene) and determined by analysis of the ^{1}H 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 ^{1}H NMR analysis of unpurified mixtures; the variance of values is estimated to be ±±2%. See the Supplementary Information for details.