Synthesis of $E$- and $Z$-trisubstituted alkenes by catalytic cross-metathesis

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Catalytic cross-metathesis is a central transformation in chemistry, yet corresponding methods for the stereoselective generation of acyclic trisubstituted alkenes in either the $E$ or the $Z$ isomeric forms are not known. The key problems are a lack of chemoselectivity—namely, the preponderance of side reactions involving only the less hindered starting alkene, resulting in homo-metathesis by-products and the formation of short-lived methyldiene complexes. By contrast, in catalytic cross-coupling, substrates are more distinct and homocoupling is less of a problem. Here we show that through cross-metathesis reactions involving $E$- or $Z$-trisubstituted alkenes, which are easily prepared from commercially available starting materials by cross-coupling reactions, many desirable and otherwise difficult-to-access linear $E$- or $Z$-trisubstituted alkenes can be synthesized efficiently and in exceptional stereoisomeric purity (up to 98% per cent $E$ or 95 per cent $Z$). The utility of the strategy is demonstrated by the concise stereoselective syntheses of biologically active compounds, such as the antifungal indiacen B and the anti-inflammatory colbacin D.

Linear $E$- and $Z$-trisubstituted alkenes occur widely in nature and are used regularly in preparative chemistry1,2, for example in catalytic enantioselective hydrogenations3, allylic substitutions4, or conjugate additions5. There are several approaches for the synthesis of acyclic trisubstituted alkenes, but these suffer from key shortcomings. Unless an α-alkoxy ketone is involved6, Wittig-type transformations are minimally stereoselective7,8. Protocols for converting alkenes or carbonyl-containing compounds to trisubstituted alkenes involve lengthy sequences9–11, strongly acidic or basic conditions10–13, and/or just one stereoisomer12,13 can be accessed (see Supplementary Information 1 for extended bibliography). The higher-energy $Z$ isomers can be prepared only if a suitable directing group is present15,16. There are no catalytic, high-yielding, broadly applicable, and stereoselective methods for accessing trisubstituted alkenes, particularly one that can deliver either stereoisomer. Especially desirable would be strategies that provide access to $E$- or $Z$-trisubstituted alkylidene chlorides and bromides, which are found in biologically active natural products17 and may be used to synthesize numerous other alkenes through cross-coupling.

The main challenges

There are just a small number of reports on the synthesis of trisubstituted alkenes by cross-metathesis18–21. In two cases is stereoisomerism a concern18,20 and, in each instance, reactions are either minimally selective or afford the $E$ isomer preferentially because stereoselectivity arises from substrate control.

Designing methods for kinetically controlled $E$- or $Z$-selective22,23 synthesis of trisubstituted alkenes is difficult24 for several reasons. The metallacyclobutane intermediates are relatively hindered, and there is a smaller energy difference between the $E$ and $Z$ isomers25 compared to that of 1,2-disubstituted alkenes. There is also an inherent lack of chemoselectivity: in cross-metathesis, when a trisubstituted alkene is desired, typically one starting material is a monosubstituted and the other is a 1,1-disubstituted alkene, both containing an unsubstituted terminal alkylidene methylene unit. Consequently, ethylene can be generated as the by-product of cross-metathesis or as a result of homo-metathesis of the less hindered (more reactive) substrate. Ethylene formation leads to an unstable methyldiene complex26, resulting in low turnover numbers and/or frequencies. It was therefore not surprising that our initial efforts to extend our recent approach for the synthesis of disubstituted alkylidene halides by cross-metathesis catalysed by molybdenum-based complexes27,28 to their trisubstituted variants proved to be less than straightforward. The reaction of 1,1-disubstituted alkene 1a with $Z$-1,2-dichloroethene ($Z$-2; Fig. 1a) needed relatively high loading (10 mol%) of the molybdenum complexes Mo-1 (ref. 27) or Mo-2 (ref. 28) and a long reaction time (12 h) to furnish 3a in 81% and 65% yield with no more than moderate stereoselectivity (80:20 and 70:30 $E$:Z, respectively); control experiments indicated minimal post-metathesis isomerization. The transformation involving 4-tert-butyl-o-methyl styrene was less efficient (3b, 30% yield) but more stereoselective, owing to better substrate control.

The above transformations begin with monosubstituted alkene 4 being generated exclusively (Fig. 1b), revealing that initiation involves the reaction of molybdenum complexes i with 1a (not $Z$-2) to give disubstituted alkylidene ii. Reaction of ii with $Z$-2 may subsequently lead to the putative chloro-substituted alkylidene iii (ref. 29), which can then react with 1a to give methylidene v and 3a via metallaacylobutane iv, with the quaternary carbon centre at the less hindered iii (ref. 27) (for more detailed analysis, see Extended Data Fig. 1). Hence, despite the absence of a monosubstituted alkene, sufficient methyldiene iv is still generated such that the short lifetime of methyldiene species v translates to the need for high catalyst loadings and extended reaction times. High $E$ selectivity is possible only when one $C_3$ substituent in iv is much larger.

More highly substituted alkenes as substrates

Use of a trisubstituted alkene, such as $E$-6, could improve efficiency and stereoselectivity (Fig. 1c). Complex i would react first with $Z$-1,2-dichloroethene ($Z$-2 versus $E$-6) to furnish chloroalkylidene iii; indeed, treatment of a mixture of $Z$-2 and $E$-6 with Mo-1 or Mo-2 generated chloroalkene 5 exclusively (based on $^1$H NMR analysis). Reaction via metallaacylobutane vii would be more stereoselective compared to the less substituted iv, because the competing addition mode would yield a less stable metallaacylobutane with the Co methyl group oriented.
Figure 1 | The challenge of developing stereoselective trisubstituted alkene cross-metathesis. a, The reaction between 1,1-disubstituted alkene 1a and Z-2 required 10 mol% loading for >72% conversion in 12 h, affording E-3a in <80:20 E:Z ratio. Formation of E-3b was sluggish but more stereoselective owing to substrate control. b, Inefficiency and low stereoselectivity is probably due to the poor stability of methylidene v and the minimal size difference between the substrates in 1a, c. With a trisubstituted alkene (E-6), catalysis is initiated by reaction with Z-2 to generate iii, which is more robust than a methylidene complex. Moreover, the involvement of metallacyclobutane vii (rather than iv) as an intermediate should lead to superior stereoselectivity. Ar, aryl; Conv., conversion; Ph, phenyl; t-Bu, tert-butyl. Conversion and isomeric ratios are determined by the analysis of ¹H NMR spectra of unpurified mixtures; yields are for isolated and purified products. See the Supplementary Information for details.

E- and Z-trisubstituted alkenyl chlorides
We prepared E-6 (ref. 30) (Fig. 2a) through hydroboration of styrene and cross-coupling of the resulting alkylborane with commercially available E-2-bromo-2-butene (E-7; 85% yield, >98% E). Subjecting E-6 and E-2 (used without purification) to 1.0 mol% Mo-2 afforded E-3a in 81% yield (>98% conversion) and 95:5 E:Z selectivity after just four hours (compared to 65% yield and 70:30 E:Z, 10 mol% Mo-2, 12 h); reaction with Z-2 was similarly stereoselective but the yield was lower (50%). Cross-coupling of arylboronic acid E, which is commercially available, and E-7 delivered E-9 in 81% yield (>98% E); the ensuing cross-metathesis with 3.0 mol% Mo-1 and Z-2 afforded E-3b in 90% yield and >98% stereoretention after four hours (compared to 30% yield, 10 mol% Mo-1, 12 h; Fig. 1a).

E-Trisubstituted alkylidene chlorides 3c–h (Fig. 2a) were isolated in 56–91% yield and 93:7 to >98:2 E:Z selectivity. The trialkylaluminium reagents necessary for a zirconocene-catalysed carbome-tallation approach are not compatible with an epoxide31 (see 3c; lower yield due to difficult purification), a carboxylic ester (see 3e), a B(pin) (pin, pinacolato) group (see 3f) or a Boc-protected (Boc, tert-butoxycarbonyl) indole32 (see 3h). Reactions leading to dienes 3e and 3f were chemo-selective, as cross-metathesis involving the electron-deficient but less substituted enolate or alkynyl–B(pin) groups is less favoured. Compounds 3b, 3g and 3h were secured in >85% yield and as a single stereoisomer, although more catalyst was required for 3h.
Catalytic stereoretentive cross-metathesis with aryl alkenes is often difficult[28].

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Figure 3 | Synthesis of Z- and E-trisubstituted alkenyl bromides. a, Attributes of a molybdenum alkylidene dictate that reaction with Z-10 preferentially generates a bromo-substituted alkylidene and an alkyl fluoride by-product (for example, 11) via A. The subsequent steps should afford E- or Z-trisubstituted alkenyl bromides (Cycles 2 and 3, respectively). b, Reaction between Z-10 and E-6 delivered E-12a in 90% yield, 95:5 bromo:fluoro ratio, and >98:2 E:Z selectivity; with 2.0 mol% Mo-2, Z-12a was obtained in 66% yield, 83:17 bromo:fluoro ratio, and 5:95 E:Z selectivity. The difference in bromo:fluoro selectivity probably originates from the increased steric pressure in metallacyclobutane ix (Cycle 3, Fig. 3a), leading to x as an intermediate and an alkyl fluoride by-product (via y, Fig. 1). When 1a was used, 12a was generated with lower efficiency and stereoselectivity. c, The method has considerable scope and may be used with substrates containing acetals. PMP, para-methoxyphenyl. Conversion and isomeric ratios are determined by the analysis of 1H NMR spectra of unpurified mixtures; yields are for isolated and purified products. See the Supplementary Information for details.

Z-Trisubstituted alkenes cannot be accessed by carboalumination without an appropriate directing group13,15. Transformations affording E-alkenyl chlorides (Fig. 2a) are generally more stereoretentive compared to those furnishing Z isomers (Fig. 2b). This can be rationalized by considering repulsive interactions within the metallacycle intermediates. For processes affording E alkenes (Fig. 2c, left), I is probably favoured as an intermediate because of the steric pressure in II, caused by the nearness of the methyl group oriented towards the sizeable aryloxide ligand (Cα substituents are nearer to the sizeable ligand compared to those at Cβ, ref. 27). Similarly notable is the proximity of the larger alkyl group (Rβ) and the adjacent chloride substituent (versus Rα, the smaller alkene substituent, and Cl in I). With processes affording Z isomers (Fig. 2c, right), the energy gap between III and IV is probably smaller, because now it is within the metallacycle leading to the Z alkene (III) that Rα and the chlorine atom are oriented in the same direction. Therefore, Z:E ratios are lower for reactions with a larger group at the fully substituted carbon of the alkene (for example, the aryl group in 3b), as there is more steric pressure in III with a phenyl group as the larger Cβ substituent (Rβ). Analogously, Z-3k was generated with greater stereoretention (95% compared to ≤91% Z) because the substrate, accessed by a phosphine–Ni-catalysed diene hydroboration13, bears a larger n-Bu unit cis to the CH3B(pin)
moiety (versus Me); IV is destabilized further by a stronger repulsion between the Cα substituent and the aryloxide ligand (n-Bu instead of Me).

**E- and Z-trisubstituted alkenyl bromides**

The pathway in Fig. 1c and the formerly established electronic and steric factors27,28 suggest that, with a dihaloalkene containing two different halogen atoms (for example, Z-1-bromo-2-fluoroethene (Z-10), Fig. 3a), the metallacyclobutane (see A, Cycle 1, Fig. 3a) generating alkylidene iii and an alkylidene fluoride should be favoured. Indeed, treatment of Mo-1 or Mo-2 with Z-10 afforded fluoro-substituted alkene 11 (based on 1H NMR analysis). The ensuing transformation via alkylidene iii and metallacyclobutane vii (Cycle 1, Fig. 3a) would then give the alkyl bromide product. This is unlike the reactions with mono- or 1,2-disubstituted alkenes, which involve bromo-substituted alkylidenedes and produce alkylidene fluorides.

In practice (Fig. 3b, left), with 1.0 mol% Mo-2, cross-metathesis between Z-10 and E-6 afforded trisubstituted alkylbromide E-12a in 95:5 bromo:fluoro selectivity, 90% yield (pure bromide) and with complete retention of stereosechemistry (>98% E). The transformation involving Z-10 and Z-6 generated Z-12a in 66% yield (pure bromide) and 95% stereoisomeric purity. Akin to reactions of alkylidene

**Figure 4 | Synthesis of E- or Z-trisubstituted non-halogenated alkenes.** a, Trisubstituted alkenes with substituents other than a methyl group can be prepared efficiently and stereoselectively. b, The present strategies may be used to synthesize non-halogenated alkenes. An isomeric mixture of 1,2-disubstituted alkenes may be used, and sterically less hindered Mo-3 (versus Mo-2) allowed for higher efficiency to be attained. c, Z-trisubstituted alkenes may be obtained in a similar manner (for example, Z-6); as with the alkylidene halides, reactions are less stereoretentive than when E isomers are generated. For higher yield in these instances, involving especially hindered metallacyclobutanes, a molybdenum chloride complex is required. Mes, 2,4,6-trimethylphenyl; PMB, para-methoxybenzyl; TBS, tert-butyldimethylsilyl. Conversion and isomeric ratios are determined by the analysis of 1H NMR spectra of unpurified mixtures; yields are for isolated and purified products. See the Supplementary Information for details.
chlorides (Fig. 2), when 1,1-disubstituted alkene 1a was used (instead of Z- or E-6; Fig. 3b), 12a was formed with much lower stereoselectivity (70:30 E:Z). Additional cases are shown in Fig. 3c (12f–i), including 12f, which contains acetal groups; these are problematic with trialkylaluminium compounds.

The preference for the bromo-alkenyl product is higher for the E isomers (92:8–97:3 compared to 83:17–89:11 bromo:fluoro, respectively). This might be because, for Z-alkene substrates, steric repulsion between the alkyl group and bromine in the more favourable 1x renders formation of the alternative metallacycle 2 more competitive (Cycle 3, Fig. 3a). The collapse of 2 would generate disubstituted alkylidene 2i (Fig. 1b), which can react with Z-10 with the expected sense of selectivity (see A, Cycle 1, Fig. 3a) to give more of the alkynyl fluoride by-product. Reactions with 1,2-dibromoethene were considerably less efficient.

Other types of E- or Z-trisubstituted alkenes
Trisubstituted alkenes with a longer-chain alkyl unit (that is, longer than a methyl group) can be prepared (Fig. 4a). Hydroboration35 of 4-octyne followed by cross-coupling36 afforded 13 in 82% overall yield (>98% E). Subsequent cross-metathesis generated chloride 14 in 92% yield and 82:18 E:Z selectivity; bromide 15 was obtained in 92:8 bromo:fluoro selectivity, 80% yield (pure bromide) and the same stereoisomeric purity. The diminished stereoretention probably

Figure 5 | Synthesis of biologically active compounds. a, Indiacen B (antifungal) was synthesized stereoselectively in 54% overall yield in three steps. b, For synthesis of coibacin D (anti-inflammatory), diene 25, prepared by catalytic cross-coupling, was transformed to the desired target by a sequence of four catalytic processes; two chemoselective cross-metathesis reactions to give E-3n via 26, a cross-coupling reaction to afford 28 and a Ru-dithiolate catalysed cross-metathesis. Dienoate 29 may be used to prepare kimbeamide A (antitumour). c, Cross-metathesis of homoallylic silyl ether 30, synthesized in 83% yield from E-7, afforded
originates from the smaller size difference between the alkyl groups (that is, n-Pr and (CH₂)₃Ph) positioned at C3 of the corresponding metallacyclobutanes. This strategy is especially attractive when the use of higher order, less readily available trialkylaluminium reagents would be a less desirable option (compared to Me₃Al)⁴⁵.

Non-halogenated trisubstituted alkenes may be prepared efficiently and stereoselectively (Fig. 4b, c). Treatment of E-6 with a 61.39 E/Z mixture of 1,2-disubstituted homoallylic ether 16 and 5.0 mol% Mo-3 (ref. 37) led to the formation of E-17 in 52% yield and 93:7 E/Z ratio (Fig. 4b). Similarly, E-18 was obtained in 69% yield as a single stereoisomer (>98% E). Because of the more sizeable reaction partners (versus a 1,2-dihaloethene), the use of a less sterically congested complex with a mesityl-substituted (mesityl, 2,4,6-trimethylphenyl) aryl oxide ligand led to higher efficiency (that is, Mo-3 instead of Mo-2). An advantage here is that, because the catalyst can react with either 1,2-disubstituted alkene isomer to generate the same alkylidene, this starting material need not be stereoisomerically pure; cross-metathesis between a 1,1-disubstituted and an either 1,2-disubstituted alkene isomer to generate the same alkylidene, Mo-2 instead of Mo-3 led to improved efficiency; for example, 3.0 equivalents) with 5.0 mol% Mo-5 afforded E-12g in 88:12: fluoro selectivity and as a single alkylidene isomer. A catalyst with a smaller aryl oxide ligand was used to achieve high efficiency because a metallacyclobutane with a larger C3 substituent must be accommodated (for example, 63% conversion to E-12g with Mo-2 under otherwise identical conditions). Cross-metathesis was again followed by cross-coupling, this time between E-12g and 3,3-diethoxy-1-propyne (commercially available). Cross-coupling with the related alkyl chloride was inefficient (less than 2% conversion). Unmasking of the diethyl acetal group afforded 31 (41% overall yield for three steps). The fragment was therefore synthesized by a shorter route (five compared to eight steps) and in similar yield (34%, compared to the 33% overall yield reported previously⁴⁹).

Conclusions
We demonstrate that there are two crucial factors for the successful development of kinetically controlled stereoretentive cross-metathesis reactions that afford trisubstituted alkenes. Various trisubstituted alkene substrates must be readily accessible in high stereoisomeric purity, and a set of catalysts that can catalyse reactions between tri- and 1,2-disubstituted alkenes efficiently and stereoselectively must be available. Accordingly, we show that a sequence beginning with cross-coupling between E- or Z-trisubstituted 2-bromo-2-butene and an organoboron compound and then a stereoretentive cross-metathesis with an appropriate molybdenum-based complex furnishes E- or Z-trisubstituted alkenes efficiently and in high stereoisomeric purity. The approach, which merges cross-coupling with cross-metathesis, underlines a key difference between two major classes of catalytic processes. Substrates in cross-coupling are more distinct and chemoselectivity is less problematic, offering facile access to the necessary trisubstituted alkene substrates. Cross-metathesis can then be used to access a wider range of alkenes and in high stereoisomeric purity. The relationship between cross-coupling and cross-metathesis has another dimension: the E- or Z-trisubstituted alkyl halides may be converted to other trisubstituted alkenes with little or no loss of stereochemical purity through one more cross-coupling.

By adopting the appropriate combination of two important catalytic C–C bond-forming processes, we have been able to address a critical unresolved problem in chemical synthesis. The present study provides additional evidence regarding the unique attributes of stereogenic molybdenum complexes as effective alkene metathesis catalysts, which further benefit from the possibility of their use as commercially available paraffin tablets⁵¹.

Data Availability The authors declare that findings of this study are available within the paper and its Supplementary Information.

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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Supplementary Information is available in the online version of the paper.

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Extended Data Figure 1 | Non-productive olefin metathesis pathways.
Cross-metathesis between v and 1a via symmetrical metallacyclobutane iv′ (right, in black) is more likely than one involving complex iv″ as an intermediate (left, in red). This is as a result of greater steric pressure between the Cα substituent and the sizeable aryloxide ligand. Cycloreversion of iv′ would then regenerate v and afford 1a (a non-productive process).
Extended Data Figure 2 | Distinctive pathways for cross-metathesis of 22 and vinyl–B(pin) with Mo-1 and Mo-2. a, Cross-metathesis between 25 and vinyl–B(pin) in the presence of Mo-1 and Mo-2 results in different product distribution and stereoselectivity profiles. The reactions proceed via mcbI Me because of severe steric repulsion between the larger Cβ aryl group in mcbIIME and the Me units of the aryloxide ligand in Mo-3. By-product 33 may react with vinyl–B(pin) to furnish Z-32.

b, There is less steric pressure at Cβ in mcbI t-Bu and mcbII t-Bu; consequently, steric repulsion between the Cα metallacyclobutane substituent and an ortho fluorine substituent of the arylimido becomes more of a factor. Therefore, cross-metathesis probably proceeds via mcbII t-Bu to afford the corresponding alkenyl–B(pin) compound (E-32). The resulting reaction of xiv with vinyl–B(pin) probably affords 34, which may then react with vinyl–B(pin) to furnish E-3n.