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Stereodefined alkenes with a fluoro-chloro terminus as a uniquely enabling compound class

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Trisubstituted alkenyl fluorides are important compounds for drug discovery, agrochemical development and materials science. Despite notable progress, however, many stereochemically defined trisubstituted fluoroalkenes either cannot be prepared efficiently or can only be accessed in one isomeric form. Here we outline a general solution to this problem by first unveiling a practical, widely applicable and catalytic strategy for stereodivergent synthesis of olefins bearing a fluoro-chloro terminus. This has been accomplished by cross-metathesis between two trisubstituted olefins, one of which is a purchasable but scarcely utilized trihaloalkene. Subsequent cross-coupling can then be used to generate an assortment of trisubstituted alkenyl fluorides. The importance of the advance is highlighted by syntheses of, among others, a fluoronematic liquid-crystal component, peptide analogues bearing an *E*- or a *Z*-amide bond mimic, and all four stereoisomers of difluororumenic ester (an anti-cancer compound).

Fluorine-containing organic molecules[1–5] are highly valuable, and trisubstituted alkenyl fluorides are a noteworthy subclass of these compounds. One stereoisomeric form of trisubstituted alkenyl fluorides mimics a secondary amide bond[6–9], the primordial link between amino acids in a peptide chain, which impacts a peptide's stability and folding tendencies, among other functions. The alternative stereoisomer is a peptide turn inducer[10,11], a metabolically stable surrogate for the higher-energy secondary amide stereoisomer, which provides a rare opportunity for probing the impact of these molecules on a polypeptide's binding ability and/or other biological attributes[12]. For example, when an amide bond of Leu-enkephalin (Fig. 1a) is replaced with a trisubstituted alkenyl fluoride, metabolic stability and physiochemical properties are improved, resulting in better oral bioavailability and distribution in the central nervous system[13]. Substitution of a C–H bond with a C–F unit can also enhance the metabolic stability, binding affinity and/or bioavailability of a drug candidate[14,15]. The fluorine atom in 5-fluoro-enone resorcynolide, a member of a kinase-targeting family of compounds (Fig. 1a), stabilizes the stereoisomeric identity of the enoate, enhancing its inhibitor activity[16].

The only way to access a fluorine-containing organic molecule is by chemical synthesis and there have been considerable contributions in this area[17–21]. Nevertheless, many trisubstituted alkenyl fluorides are inaccessible because a broadly applicable and stereoselective strategy for generating trisubstituted alkenyl fluorides remains lacking[7]. This is a major shortcoming that hampers progress not just in drug development; researchers in materials science have had to be content with investigating isomeric mixtures in the area of nematic liquid-crystal development (Fig. 1a)[22]. The available methods to access stereochemically defined trisubstituted alkenyl fluorides[6–9,23] can be limiting. For instance, aryl-substituted products are generated in most cases and/or stereoselectivity can be low. Selective syntheses nearly always yield only the *Z* isomer (that is, the lower-energy secondary amide bond analogue).

Cross-metathesis between two olefins represents an attractive approach to stereoselective synthesis of trisubstituted alkenyl fluorides. Along these lines, one report details the preparation of products that contain a geminal difluoro moiety[24], where stereoselectivity is not a concern. It was subsequently shown that ruthenium-complex-promoted reactions between methyl-2-fluoroacrylate and aliphatic monosubstituted olefins may be used to prepare *Z*-trisubstituted alkenyl fluorides (Fig. 1b)[25], and many alkenyl fluorides were obtained with useful efficiency levels (turnover number (TON), up to 175) and high stereochemical purity. Nonetheless, apart from being confined to generating α,β-unsaturated esters in only one regio- and stereoisomeric form, the method is limited to unhindered *n*-alkyl-substituted olefins; it was found that a number of useful polar groups (such as primary alkyl bromides) were not tolerated.

Results and discussion

Trisubstituted alkenes with a fluoro-chloro terminus. One way to synthesize trisubstituted alkenyl fluorides would be by selective preparation of an alkene that contains a fluorine atom and another, easily modifiable, substituent. In this respect, a few methods have been reported for preparing trisubstituted alkenyl fluorides that contain a boryl unit[26,27] or iodo atom[28,29]. The need for multistep substrate synthesis notwithstanding, these strategies are confined to a few aryl-substituted products and one isomeric form.

An enticing possibility would be to synthesize, by catalytic stereoretentive[30] cross-metathesis, alkenyl fluorides that can then be modified easily. However, among the less than a handful of kinetically controlled methods for synthesis of trisubstituted olefins in high stereoisomeric purity[31–33], only one has been used to generate chloro- or bromo-substituted olefins, and none deliver a fluoro-substituted alkene preferentially. This is unlike the reactions with 1,2-disubstituted alkenes, which can readily furnish alkenyl fluorides[34]. Instead, reaction between a trisubstituted alkene and *Z*-1-bromo-2-fluoro-ethene, via a bromo-substituted molybdenum alkylidene, gives a trisubstituted alkenyl bromide (97:3 Br:F; Fig. 1c). Generating a fluoro-substituted alkylidene would require the use of considerably less practical 1,2-difluoroethene, a compound

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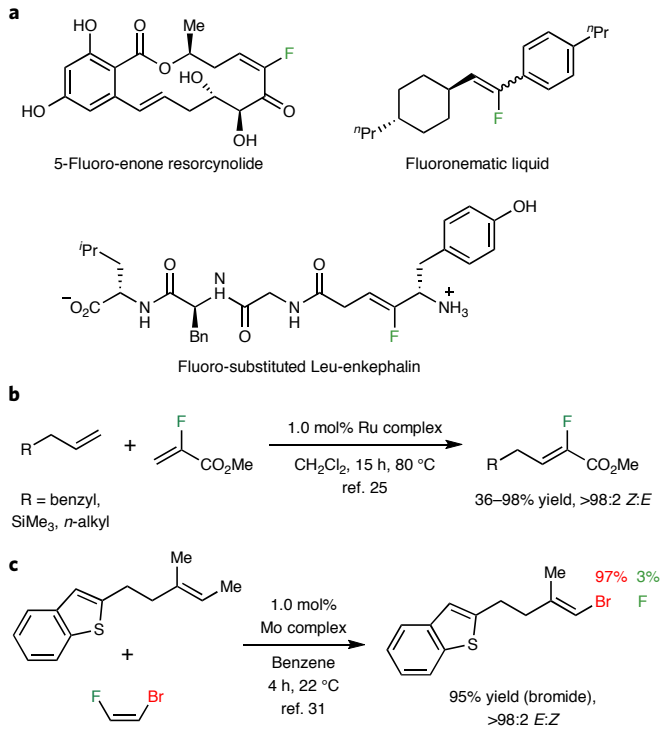


Fig. 1 | The importance of trisubstituted alkenyl fluorides and existing approaches to their stereoselective synthesis. a, Trisubstituted alkenyl fluorides are key to advances in medicine and materials research. One example is fluoro-substituted Leu-enkephalin, which has superior physiochemical properties, is more metabolically stable, more orally bioavailable and more effectively distributed in the central nervous system compared with its non-fluoro variant. Another example is 5-fluoro-enone resorcynolide, where the alkenyl fluoride undergoes cysteine conjugate addition more slowly, resulting in improved kinase inhibitor activity. The importance of trisubstituted alkenyl fluorides extends to materials research, as exemplified by fluoronematic liquid-crystal components. **b**, Existing olefin metathesis methods for preparation of trisubstituted alkenyl halides are limited in scope: only *Z*-*n*-alkyl-substituted products can be generated. **c**, Cross-metathesis processes that involve a 1,2-bromo,fluoroethene generate trisubstituted alkenyl bromides preferentially.

that is costly and explosive with the challenging boiling point of −72 °C.

We therefore contemplated the possibility of developing a catalytic strategy for the diastereodivergent synthesis of trisubstituted olefins bearing a fluoro,chloro-substituted terminus (Fig. 2a). No methods for the stereoselective synthesis of a 1,1-chloro,fluoro-, or 1,1-bromo,fluoro-trisubstituted olefin (catalytic or otherwise) appear to have been reported. We reasoned that such entities could become accessible by reactions involving *E*- or *Z*-1,2-dichloro-1-fluoroethene (***Z*-1** or ***E*-1**), which are commercially available in high stereoisomeric purity (96:4 *Z*:*E* or *E*:*Z*) and possess suitable physical properties (for example, boiling points of 32 and 38 °C, respectively). Nevertheless, surprisingly, these latter polyhalogenated alkenes have rarely been utilized in reaction development. We further argued that the chloro,fluoro-substituted alkenes could be chemoselectively modified at the C–Cl site by dependable catalytic cross-coupling processes, allowing conversion to sundry other stereochemically defined trisubstituted alkenyl fluorides. In regard to the projected site-selective carbon–halogen bond functionalization, while reactions involving C–F bonds are known[26], there is precedent for chemoselective transformation at the C–Cl bond within the same entity[28,35]. If successful, we would have identified a reasonably general strategy for stereocontrolled preparation of these valuable entities, which include peptide chains with an *E*-alkenyl fluoride serving as a turn inducer (Fig. 2b), or stereoisomeric fluoro-substituted analogues of bioactive entities such as rumenic acid, a compound that reduces metastatic regrowth in breast cancer[36], or oleoyl coenzyme A, a regulator of Raas (renin–angiotensin system) interaction with DNA in mycobacteria[37].

Preliminary studies. We had two concerns with regard to the above plan. One was that, as noted, stereoretentive olefin metathesis reactions that generate trisubstituted alkenes are uncommon (an example is shown in Fig. 1c). This is largely because substrates that are considerably less reactive than disubstituted olefins must be used. Additionally, olefin metathesis with trisubstituted electron-deficient alkenes, such as ***E*-1** or ***Z*-1**, is unprecedented, casting an even longer shadow on whether a catalytic cycle, in which a molybdenum alkylidene must undergo consecutive reactions with trisubstituted olefins, is viable. Nonetheless, we decided to investigate a model process with a 1,2-disubstituted alkene (for example, **ia** (R = H); Fig. 3a). This way, an unstable methylidene generated from homocoupling of a monosubstituted olefin would be avoided[31,38], and the less hindered alkene (compared with the trihaloalkene) would react first with a molybdenum neophylidene complex (for example, **ii**). To maximize efficiency, the faster initiating *Z* isomer would be used. Our hope was that catalytically active **iii** would react with ***Z*-1** to give **mcb-i** (mcb, metallacyclobutane), wherein the larger chlorine atoms would probably be oriented towards the smaller arylimido ligand. This would allow the fully substituted carbon to be at the less congested Cβ[34]. Productive collapse of **mcb-i** would afford the fluoro,chloro-substituted olefin (***Z*-prod**) and chloro-substituted alkylidene **iv**, which might react with the 1,2-disubstituted alkene[39].

Another issue was that the transformation could either proceed via **mcb-ii** (desirable) or **mcb-iii**, depending on the regioselectivity with which a trisubstituted olefin adds to a chloroalkylidene. Reaction via **mcb-ii** would re-generate molybdenum alkylidene **iii** and release *Z*-1-chloro-1-propene, a volatile by-product. Alternatively, transformation via **mcb-iii** would afford a *Z*-1,2-disubstituted alkenyl chloride (**v**) and methyl-substituted alkylidene **vi** (R = H), which can react with ***Z*-1** to give **2**, a less valuable methyl-containing fluoro,chloro-substituted alkene. It was unclear how high the **mcb-ii**:**mcb-iii** (R = H) selectivity would be, especially with a bulky alkenyl moiety (blue circle), in which case it would be preferentially positioned at the central and less congested Cβ in **mcb-iii** (R = H). In short order, experimental data (Fig. 3b) indicated that our reservations were justified: reaction between ***Z*-1** (94:6 *Z*:*E*) and *Z*-1,2-disubstituted alkene **3** in the presence of 5.0 mol% **Mo-1a** afforded a mixture of **4a** (41% conversion) along with significant quantities of by-products **5** (20% conversion) and **2** (24% conversion), probably formed via **mcb-iii** (R = H). The lesson was clear: to enhance efficiency, formation of **mcb-iii** (R = H) must be avoided. One solution would be to use a trisubstituted alkene instead because then the positioning of a *gem*-dimethyl group at the more congested Cα would become less favourable (compare **mcb-ii** and **mcb-iii**, R = Me).

Cross-metathesis of two trisubstituted alkenes. The one option left—cross-metathesis between two trisubstituted olefins with one being an electronically depleted trihaloalkene—was unorthodox. The major issue was efficiency because trisubstituted alkenes do not easily re-enter a catalytic cycle[31,32,40,41]. In regard to stereocontrol, we were reasonably confident, based on previous studies[31,33], that stereoretentivity would probably be high. The small number of kinetically controlled cross-metathesis processes, which may be used to convert one trisubstituted alkene to another, either involve exceptionally reactive molybdenum alkylidenes bearing an activating and diminutive substituent (for example, a chlorine, a

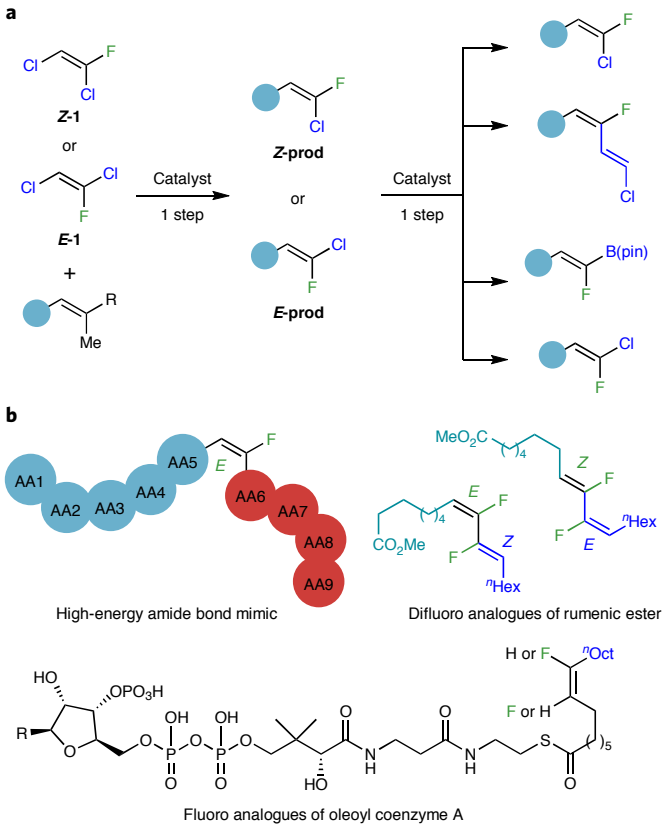


Fig. 2 | The adopted strategy and its mechanistic basis. a, A fully catalytic approach for direct formation of trisubstituted alkenyl fluorides in either stereoisomeric form would entail stereoretentive cross-metathesis between a commercially available, stereochemically defined trihaloalkene and an appropriate, readily accessible olefin. Subsequent site-selective and stereoretentive cross-coupling may then be used to convert the C–Cl bond to a variety of other substituents. **b**, If successful, a number of highly desirable but difficult-to-access compounds would become readily available. This would include peptide chains that contain an *E*-trisubstituted alkenyl fluoride, which serves as the mimic of the higher-energy isomer of an amide linkage, various stereoisomeric forms of difluoro analogues of rumenic acid (a compound that is important in the fight against breast cancer) or analogues of oleoyl coenzyme A (a Raas inhibitor, in which there is a fluoro tag at one or the other alkenyl site). AA, amino acid residue. R = purin-6-amine.

bromine[31] or a nitrile group[33]), or are confined to an allylic hydroxy or ether moiety[32]. Here the same benefit would apply to one of the two steps in the proposed pathway (**iv** → **mcb-ii**; Fig. 3a), but only if an alkyl-substituted alkylidene were to survive the demanding early stages of the process (see **iii** + ***Z*-1** → **mcb-i**). Another worry was whether the molybdenum alkylidene system would be able to react with two different trisubstituted alkenes, and at the same time be long-lived enough to promote a process efficiently, but not so reactive that it would also react with the final product, causing erosion of kinetic selectivity.

For want of a more secure alternative, we set out to find out whether a hindered and more electron-rich all-carbon substituted alkenyl substrate or the halogenated trisubstituted olefin can preferentially react with a molybdenum neophylidene (for example, **Mo-1a**) to afford alkylidene **iii** (Fig. 3a). Treatment of ***Z*-1** (5.0 equiv.) and trisubstituted alkene **6a** (Fig. 3c), under otherwise identical conditions, led to minimal transformation and most of the **Mo-1a** remained intact (^{1}H NMR spectroscopy).

To facilitate catalyst initiation, we added a small amount a *Z*-1,2-disubstituted alkene additive to the mixture (**vii**, Fig. 3d). Although we hoped that the resulting alkylidene (**viii**) would react with a substrate molecule (**ib**), affording **mcb-iv** and then ***ent*-iii**, it remained to be seen if this would jump-start the transformation. Another question was whether coordination of a second trisubstituted olefin, leading to the formation of a more substituted mcb, would be too demanding. When the reaction involving trisubstituted alkene **6a** was carried out with 10 mol% *Z*-hex-3-ene (Fig. 3e), there was 76% conversion to *Z*-trisubstituted alkenyl fluoride (**4a**), which was isolated in 70% yield after purification (95:5 *Z*:*E*). (For details regarding the choice of butene or hex-3-ene as an additive, see Supplementary Fig. 2.) There was minimal (2%) conversion to **5**, and **7** could not be detected (<2%), indicating that there was no longer any competitive formation of **mcb-iii** (R = Me). The presence of excess ***Z*-1** ensured maximum efficiency.

Broadly applicable and stereodivergent. Many *n*-alkyl-*Z*-trisubstituted chloro,fluoroalkenes were synthesized under the conditions described above in up to 86% yield with >98:2 *Z*:*E* ratio (Table 1). These include products bearing a bromide (**4b**), a tertiary amine (**4c**), a B(pin) group (pin, pinacolato) (**4d**), an acetal (**4e**), an unprotected indole (**4f**), a benzofuran (**4g**), a benzothiophene (**4h**), a lactone (from the natural product auraptene, **4i**), or a highly functionalized and electronically activated cyclopropane (**4j**). In situ protection/deprotection with commercially available HB(pin) (ref. [42]) allows for one-pot catalytic cross-metathesis with an alcohol (directly from the natural product bisabolol, **4k**). Synthesis of **4l**, involving reaction of a diene bearing a disubstituted enoate, was highly chemoselective, favouring reaction at the more electron-rich, but hindered, trisubstituted olefin (**4l**).

Products bearing an α-branched alkene, ubiquitous in bioactive compounds and especially challenging to access by olefin metathesis, were obtained with similar efficiency and stereochemical purity (**4m**-**n**, Table 1). Monosubstituted alkenes were used in these instances on account of slow homocoupling and the minimal likelihood of a short-lived molybdenum methylidene being formed. Synthesis of trisubstituted olefin **4o** shows that β-branched olefins can be accessed. Another substrate class, challenging because of their tendency to undergo facile homocoupling, are aryl alkenes. In such instances, *Z*-β-methyl alkenes, available in a single step from commercially available materials, are more effective starting materials, and alkylidenes derived from the more electronically activated and less sterically demanding monoaryloxide chloride complex **Mo-2** (ref. [43]) (Fig. 4a) are optimal, as indicated by the synthesis of **4p** (see Fig. 4a for additional cases).

The *E*-trisubstituted alkene isomers were accessed in similarly high stereoisomeric purity from ***E*-1** (**8a**-**i**, Table 1). These transformations are somewhat less efficient than those furnishing the corresponding *Z*-alkenes, a difference that may be attributed to increased steric pressure in the intervening metallacyclobutanes (Cβ chlorine oriented towards the larger aryloxide ligand; see **mcb-i**, Fig. 3a).

Practical, scalable and economical. Several additional points that highlight the broad scope and practicality of the approach are noteworthy. One is that the dihalo olefins can sometimes be too volatile to be isolated in high yield. In such instances, the cross-metathesis product may be converted to a more readily isolable and similarly desirable compound. One example is formation of fluoro-substituted enones **10a**–**c** (Fig. 4a) by catalytic cross-coupling with alkenylzinc halide **9** (prepared in one step and >98% yield from the commercially available alkenyl bromide). It should be mentioned that Horner–Emmons reactions afford *E*-enoates preferentially[16]. Another key attribute of the approach is that, apart from aryl-substituted olefins, hindered alkyl olefins can also be used as substrates. Cross-metathesis with sterically demanding

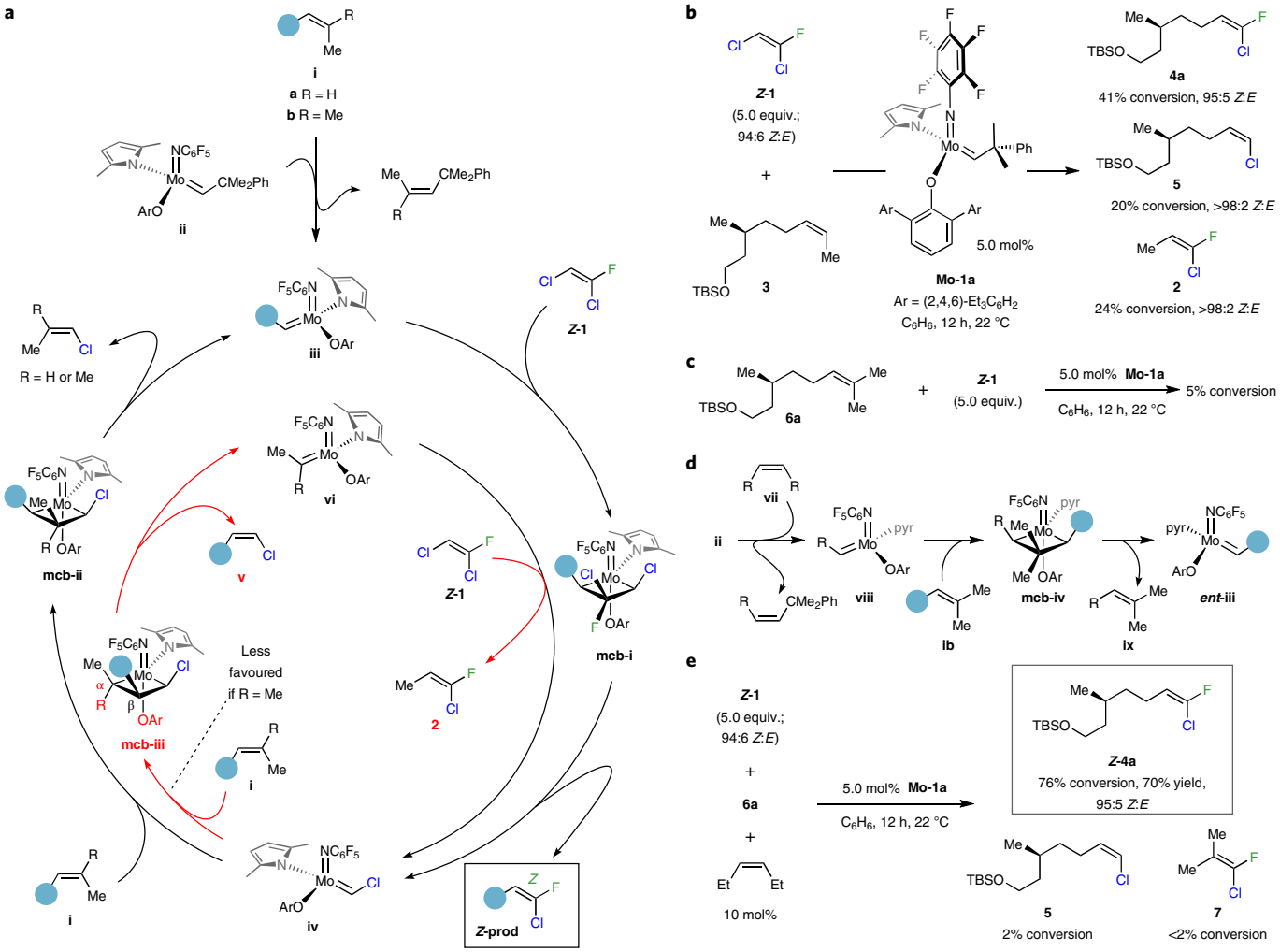


Fig. 3 | Mechanism-based development of the cross-metathesis approach. a, Based on previous studies, it was expected that a *Z*-disubstituted alkene (**ia**) might be a suitable substrate, and the reaction would proceed via **iii**, **mcb-i**, **iv** and **mcb-ii** to afford the desired trisubstituted alkenyl fluoride (outer catalytic cycle). **b**, The reaction between ***Z*-1** and **3**, while highly stereoretentive, was inefficient (41% conversion), but afforded significant amounts of by-products **5** and **2**. Mechanistic re-evaluation (**a**, inner cycle) indicated that cross-metathesis involving two trisubstituted alkenes would probably be more efficient because reaction via **mcb-iii** to generate **v** and **vi** would be less favoured (red reaction arrow). **c**, Nonetheless, cross-metathesis between ***Z*-1** and trisubstituted alkene **6a** hardly proceeds. **d**, To address this, we envisioned facile initiation of the initial complex (**ii**) by an appropriate alkene additive (**vii**), affording **viii**, which would more readily react with a trisubstituted olefin (**ib**) to give **mcb-iv**, **ix** and the desired intermediate ***ent*-iii**. **e**, In the event, with 10 mol% of a *Z*-1,2-disubstituted olefin, the reaction takes place readily and with exceptional stereochemical control. TBS, ^{t}butyldimethylsilyl; *ent*, enantiomeric.

silyl ether **11** (Fig. 4b) and subsequent catalytic cross-coupling, concomitant with silyl ether removal, afforded **12a** in 41% overall yield as a single olefin isomer (>98:2 *Z*:*E*). Allylsilane **12b**, which may be used for additions to different carbonyl compounds, was synthesized in a similar manner (40% overall yield, >98:2 *Z*:*E*).

As noted earlier, a trisubstituted alkene is needed to avoid methylidene complex formation, namely, for optimal efficiency[31]. Nevertheless, monosubstituted olefins can be used as starting materials. For instance, treatment of terminal olefins **13a** or **13b** (Fig. 4c) with inexpensive 2-methyl-2-butene (20 equiv.) and 1.0 mol % **Mo-1a**, removal of excess butene under mild vacuum, followed by addition of ***Z*-1** (10 equiv.), *Z*-hex-3-ene (10 mol %) and 5.0 mol % **Mo-1a** afforded **4o** and **4q** in 57% and 83% yield and 92:8 and 95:5 *Z*:*E*, respectively. Analogously, **8h** and **8j** were synthesized by a one-pot procedure in 44% and 52% yield and 98:2 and 97:3 *E*:*Z*, respectively. It is worth noting that there are naturally occurring bioactive 1,1-dimethyl-trisubstituted alkenes (for example, indomethacin (anti-inflammatory[44]), auraptene (anti-cancer[45]) or imperatonin (anti-convulsant[46])) that can be used as substrates, and some are renewable feedstock (such as geraniol, farnesol or linalool). The catalytic protocol is scalable: 1.27 g of **13c** was transformed to 1.1 g of **4m** (72% yield). Furthermore, 1.2 g of **14** was converted to 0.82 g of **4r** (62% yield, 95:5 *Z*:*E*; Fig. 3e) by a reaction involving commercially available **Mo-1c** (used as received). Excess ***Z*-1** was recovered in 80% yield (4.29 g, after distillation) and was reused to generate **4q** in 60% yield and 95:5 *Z*:*E*.

Readily diversifiable products. A host of compounds were prepared with minimal loss of stereoisomeric purity and in either stereoisomeric form by chemoselective transformation at the C–Cl bond of the trisubstituted alkenyl products (Table 2). The importance of deuterium-labelled organic molecules in drug discovery research[47] renders regio- and stereoselective synthesis of isotopically labelled fluoroalkenes, such as **15**, noteworthy. The corresponding alkenyl boronates (for example, **16**) and bromo- and iodo-substituted derivatives (for example, **17** and **18**) are effective

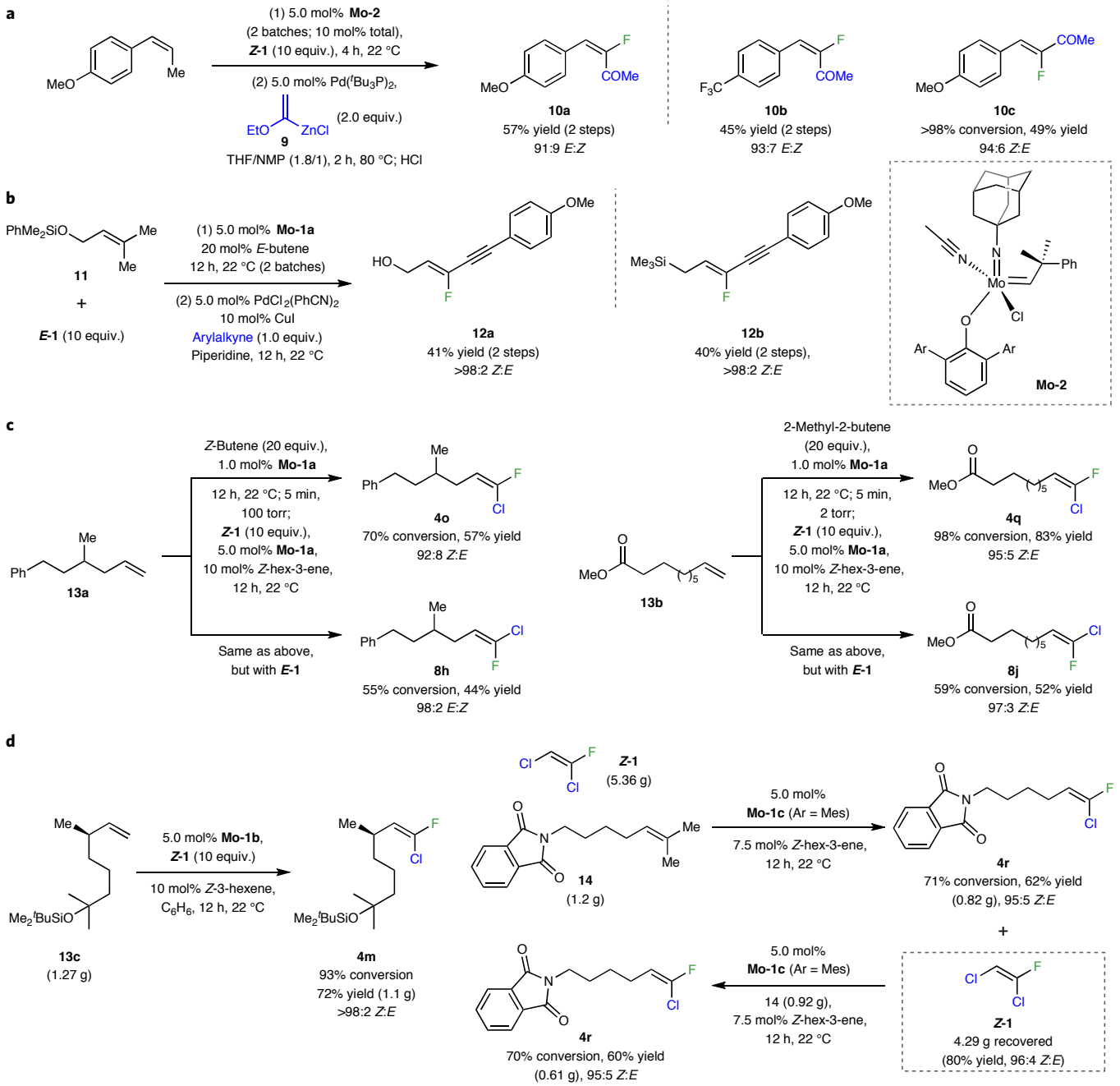


Fig. 4 | The catalytic method is broadly applicable, practical and cost-effective. a, When the product of a cross-metathesis reaction is too volatile for it to be isolated in high yield, the unpurified product may be used directly. For example, enoates **10a–c** were obtained by direct catalytic cross-metathesis of the cross-metathesis products without purification. **b**, Not only can the catalytic approach be used to generate fluoro,chloro-substituted aryl olefins, but sterically demanding aliphatic olefins, such as **11**, are suitable substrates as well. The catalytic cross-metathesis/cross-coupling sequence can be used to access a variety of valuable products, such as fluoro-substituted enynes **12a** and **12b**. **c**, Inexpensive monosubstituted olefins, such as **13a** and **13b**, can also be used as starting materials. This involves a one-pot process that generates the requisite trisubstituted alkene, followed by another cross-metathesis with ***E*-1** or ***Z*-1**. **d**, The catalytic process can be performed on a multi-gram scale, and excess trihaloalkene can be easily recycled without any diminution in efficiency or stereocontrol. See Supplementary Information part 1, section 3 for details. ***Z*-1** was used as received. **Mo-1c** was purchased and used. NMP, *N*-methyl-2-pyrrolidone; **Mo-2**, Ar = (2,4,6)-$(^{i}Pr)_3C_6H_2$.

cross-coupling substrates[48]. Because the latter sets of compounds are more reactive than alkenyl chlorides, they may be conveniently converted to a variety of trisubstituted fluoroalkenes. Apart from being limited to aryl olefins, only *Z*-boryl-containing trisubstituted alkenyl fluorides can be accessed through existing methods[26,27,49]. The chlorine substituent may be exchanged with other heteroatoms, exemplified by the preparation of enamine **19** (Table 2), enol ether **20** and alkenyl phosphonate **21**. Equally noteworthy are trifluoromethyl-substituted **22**, allylic alcohol **24**, 1,4-diene **25**, oxazole **26**, alkenyl nitrile **28** and carboxylic ester **29**. Although there are alternative strategies[7] for preparation of some of the same types of trisubstituted alkenyl fluorides (for example, aryloxy-substituted[50], phosphonate-substituted[51], heterocycle-substituted[52] or cyano-substituted[53]), the present

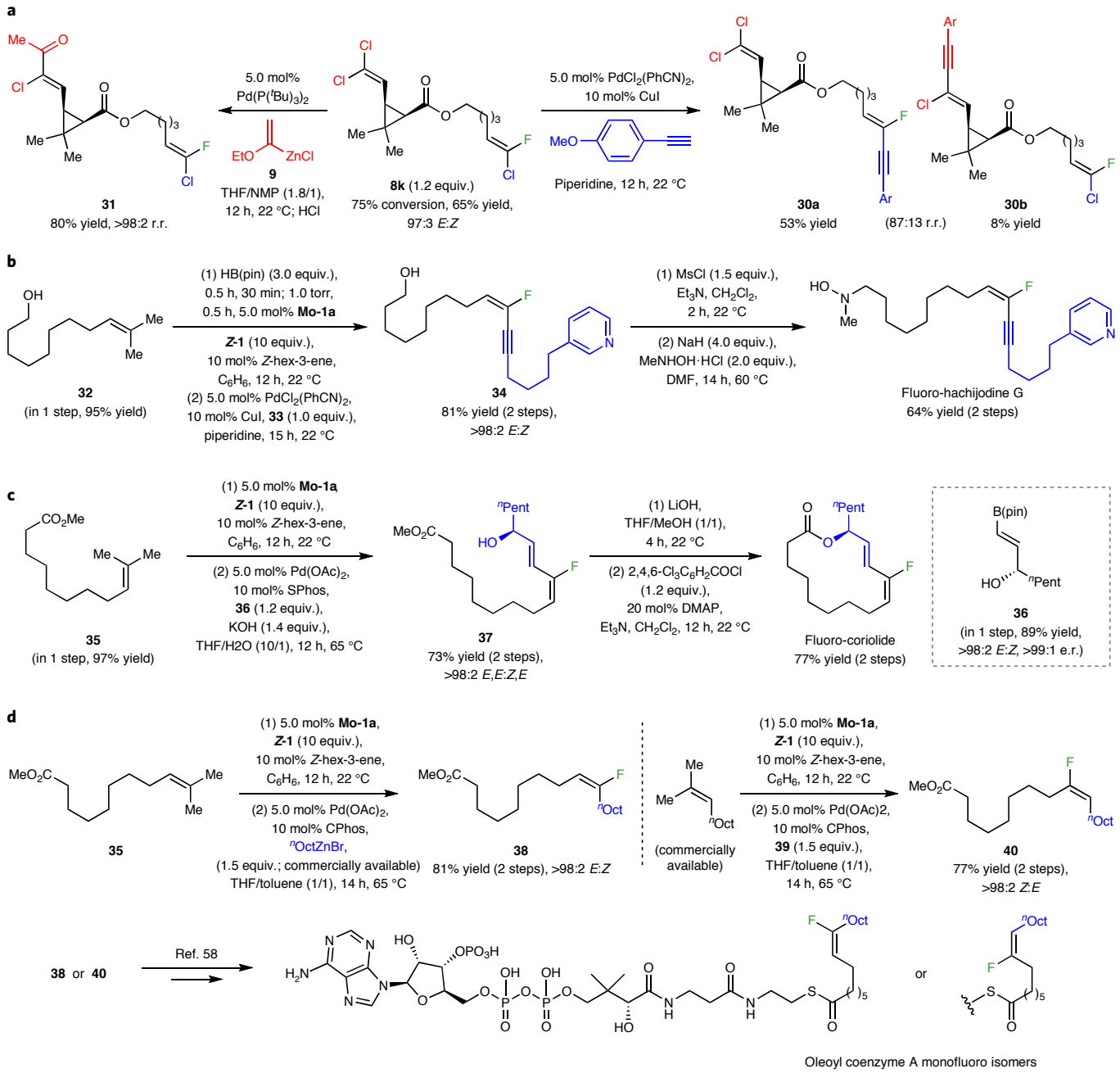


Fig. 5 | Site-selective cross-coupling, and site-selective and regiodivergent fluoro-labelling. a, Chemoselective cross-coupling reactions with a substrate containing two dihaloalkenes further expands the utility of the approach. **b**, The fluoro-substituted derivatives of hachijodine G (anti-leukaemic) can be obtained through sequential catalytic cross-metathesis and cross-coupling with a readily available terminal alkyne. Compound **33** is 3-(hex-5-yn-1-yl) pyridine, formed in one step in 79% yield. **c**, The approach is applicable to the preparation of fluoro-containing analogues of macrocyclic bioactive entities, such as coriolide (pheromone). **d**, A convenient approach to the regiodivergent preparation of monofluoro analogues of oleoyl coenzyme A (which regulates Raas interaction with DNA). Compound **39** is (8-methoxy-8-oxooctyl)zinc(II) bromide, formed in one step in 82% yield. See Supplementary Information part 1, sections 6–8 for details. NMP, *N*-methyl-2-pyrrolidone; DMAP, dimethylaminopyridine; CPhos, 2′(dicyclohexylphosphanyl)-N^2,N^2,N^6, N^6-tetramethyl[1,1′-biphenyl]-2,6-diamine.

approach is more direct, is not confined to aryl alkene substrate and products, and can be used to obtain *Z* or *E* isomers.

Site-selective cross-coupling. The availability of *E*-trisubstituted alkene **8k** (65% yield, 97:3 *E*:*Z*), containing a dichloro-olefin terminus, afforded us the opportunity to establish whether chemoselective cross-coupling at one of the dihalo-substituted alkenes is feasible. Under the Sonogashira conditions (Fig. 5a), the C–Cl bond proximal to the C–F underwent transformation, and fluoro-substituted enyne **30a** was isolated in 53% yield along with 8% of the chloro-substituted enyne (87:13 regioisomeric ratio (r.r.)). In contrast, and unexpectedly, the cross-coupling performed under Negishi conditions with alkenylzinc chloride **9** proceeded with the opposite selectivity, furnishing chloro-substituted enone **31** in

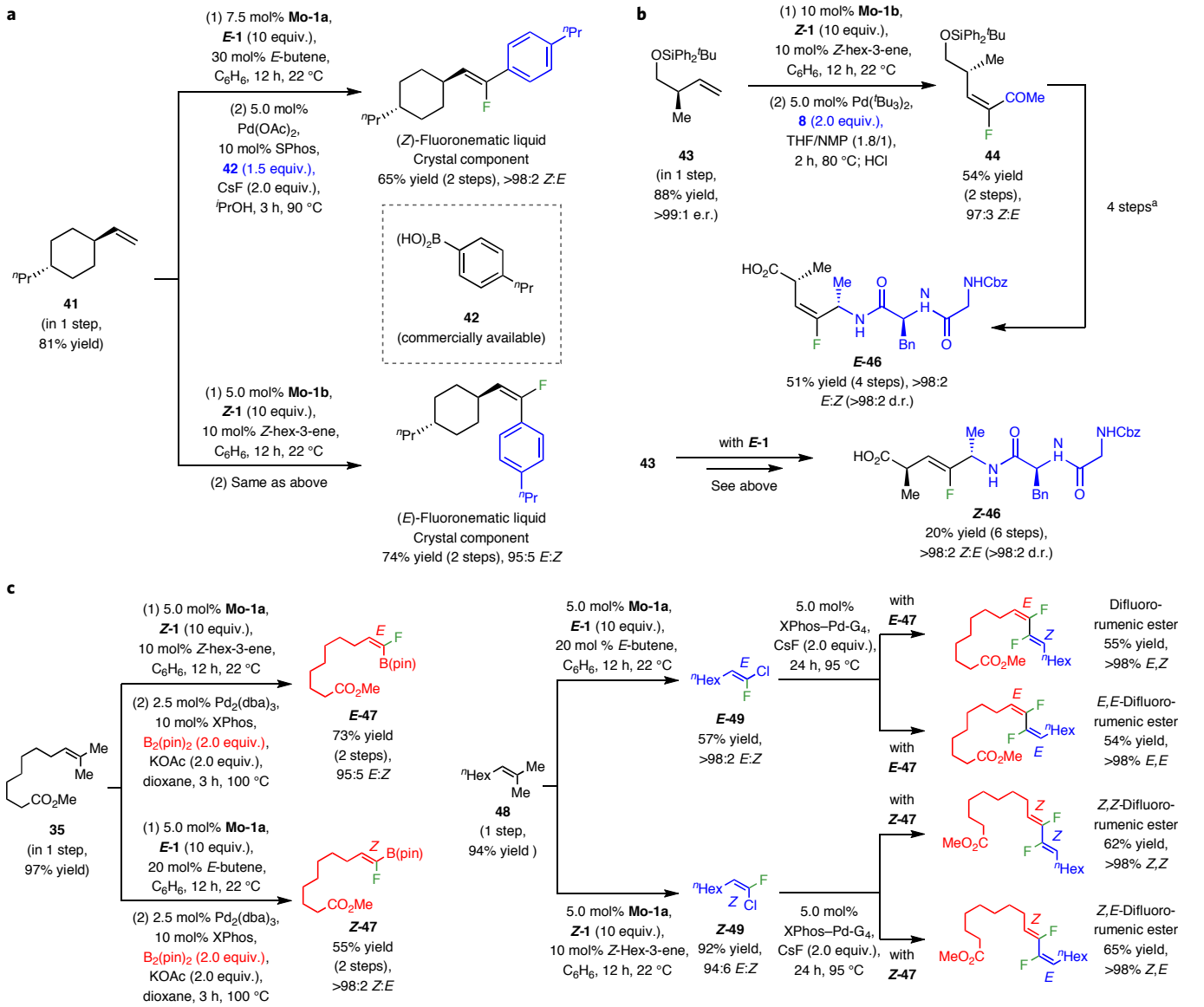


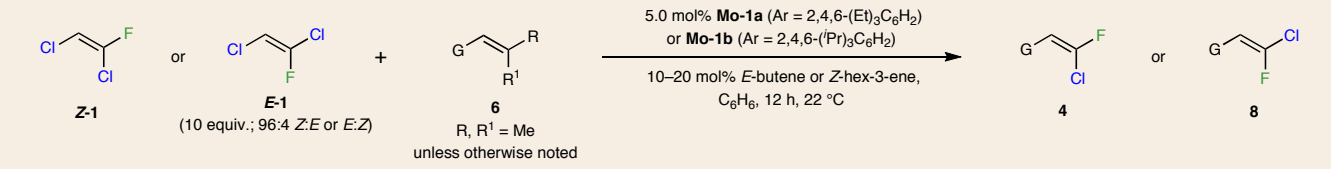
Fig. 6 | Diastereodivergent synthesis of monofluoro- and difluoro-labelled bioactive compounds. a, A fluoronematic liquid-crystal component can be prepared in either stereoisomeric form. **b**, Stereoselective synthesis of peptide-like structures with *E*- and *Z*-amide bond mimics. [a]Four steps to ***E*-46** from **44**: (1) $Ti(OEt)_4$ (2.5 equiv.), (*S*)-$^tBuSONH_2$ (2.0 equiv.), THF, 2 h, 100 °C; (2) DIBAL-H (4.0 equiv.), 1 h, −78 °C, HCl (4 N, dioxane), MeOH, 1 h, 22 °C; (3) **45** (1-((*N*,4-dimethylphenyl)sulfonamido)vinyl ((benzyloxy)carbonyl)glycyl-L-phenylalaninate, prepared in one step and used in situ) (4.0 equiv.), Et_3N, CH_2Cl_2, 24 h, 22 °C; (4) $CrO_3/H_2SO_4/H_2O$ (3.0 equiv.), acetone, 1 h, 0 °C. **c**, Site-specific and diastereodivergent synthesis of difluoro analogues of rumenic acid methyl ester (anti-cancer). See Supplementary Information part 1, sections 9–11 for details. DIBAL-H, diisobutylaluminum hydride; Cbz, carboxylbenzyl; dba, dibenzylideneacetone; G4, fourth-generation.

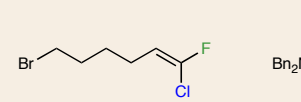
80% yield as the only regioisomer (>98:2 r.r.). Outcomes were the same when the *Z*-alkene was used (**4j**, Table 1). (The origin of the selectivity profile is under investigation.) It merits mention that attempts at using ***E*-1** or ***Z*-1** directly as the starting materials for cross-coupling led to low regioselectivity and/or low conversion in most cases. On occasion, when cross-coupling was comparatively efficient, the preferential isomer within the inseparable mixture of products was the one derived from reaction at the C–Cl bond of the dihalo-substituted carbon (that is, the alkene with a fluoro-chloro terminus was not generated).

Site-specific fluoro-labelling. A fluorine atom may be incorporated site-specifically within an unsaturated bioactive compound. For instance, in situ protection/catalytic cross-metathesis of primary alcohol **32** (Fig. 5b) with ***Z*-1**, followed by cross-coupling with alkynyl pyridine **33** (prepared in one step), afforded *E*-fluoro-substituted 1,3-enyne **34** in 81% yield and >98:2 *E*:*Z*. After two more steps, a site-specifically fluorine-tagged analogue of hachijodine G, a naturally occurring anti-leukaemic alkaloid[54], was isolated in 64% overall yield (for two steps).

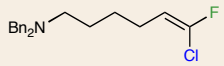
Fluoro-substituted 1,3-dienes were prepared with similar ease and efficiency. For example, the 4-fluoro analogue of coriolide (Fig. 5c), a macrocyclic pheromone[55], was synthesized via **35** and enantiomerically pure **36**, each obtained in a single step from commercially available materials, and **37**. After five steps, the final product was secured in 55% overall yield, and in high

Table 1 | Synthesis of *E*- or *Z*-trisubstituted alkenyl fluorides through catalytic stereoretentive cross-metathesis

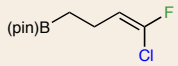




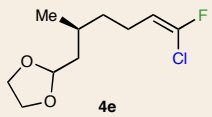
4b
96% conversion, 86% yield,
95:5 *Z*:*E*



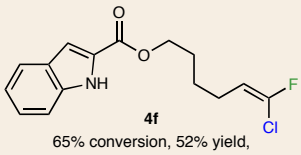
4c
90% conversion, 77% yield,
95:5 *Z*:*E*



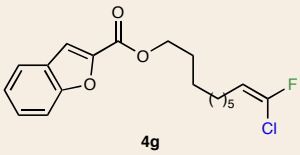
4d
85% conversion, 81% yield,
95:5 *Z*:*E*



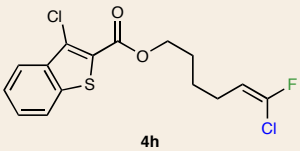
4e
76% conversion, 63% yield,
95:5 *Z*:*E*



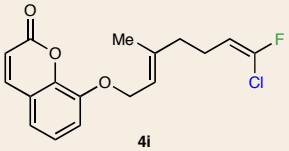
4f
65% conversion, 52% yield,
95:5 *Z*:*E*



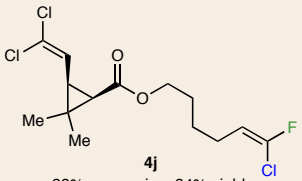
4g
88% conversion, 82% yield,
95:5 *Z*:*E*



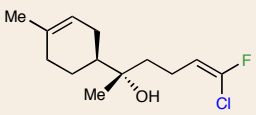
4h
62% conversion, 60% yield,
94:6 *Z*:*E*



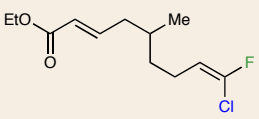
4i
61% conversion, 52% yield,
95:5 *Z*:*E*



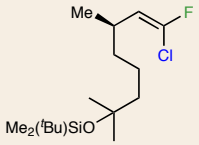
4j
88% conversion, 84% yield,
94:6 *Z*:*E*



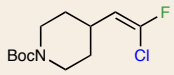
4k[a]
68% conversion, 56% yield,
97:3 *Z*:*E*



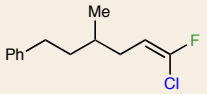
4l
61% conversion, 50% yield,
>98:2 *Z*:*E*



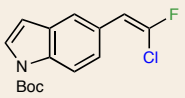
4m
91% conversion, 70% yield,
>98:2 *Z*:*E*



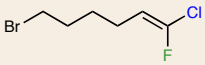
4n (R, R1 = H)
56% conversion, 52% yield,
94:6 *Z*:*E*



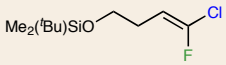
4o (R = H, R1 = Me)
61% conversion, 55% yield,
92:8 *Z*:*E*



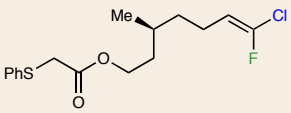
4p (R = H, R1 = Me)
81% conversion, 56% yield,
92:8 *E*:*Z*



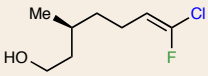
8a
72% conversion, 62% yield,
97:3 *E*:*Z*



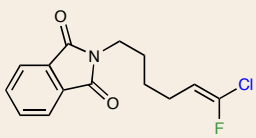
8b[b]
67% conversion, 52% yield,
93:7 *E*:*Z*



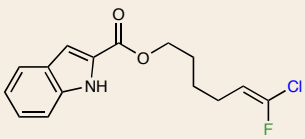
8c
57% conversion, 51% yield,
97:3 *E*:*Z*



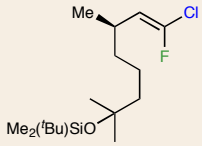
8d[a]
81% conversion, 73% yield,
96:4 *E*:*Z*



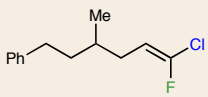
8e
69% conversion, 61% yield,
>98:2 *E*:*Z*



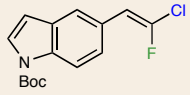
8f[b]
73% conversion, 68% yield,
97:3 *E*:*Z*



8g (R, R1 = H)
80% conversion, 61% yield,
>98:2 *E*:*Z*



8h (R = H, R1 = Me)
51% conversion, 44% yield,
98:2 *E*:*Z*



8i (R = H, R1 = Me)
>98% conversion, 48% yield,
98:2 *E*:*Z*

Reactions were carried out under N_2. Conversion to the desired product as measured by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures with DMF serving as the internal standard; the variance of values is ±2%. Yield of isolated product after purification, average over at least three runs; the variance of values is estimated to be <5%. [a](pin)BH used for traceless protection. [b]10 mol% catalyst used. See Supplementary Information part 1, section 3 for details. Bn, benzyl; Boc, *t*-butylcarbonate; DMF, dimethylformamide; Mes, 2,4,6-trimethylphenyl.

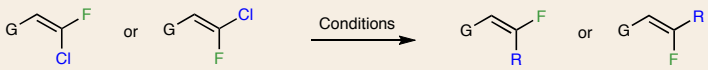
diastereomeric and enantiomeric purity (>98% *E*,*E* and >99:1 enantiomeric ratio (e.r.)).

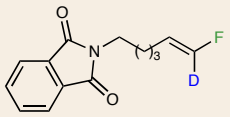
Regiodivergent fluoro-labelling. The approach can be used to generate either regioisomeric form of a trisubstituted alkenyl fluoride. For example, cross-metathesis between alkene **35** and ***Z*-1** (Fig. 5d), followed by cross-coupling with commercially available *n*-octylzinc bromide, gave *E*-trisubstituted alkenyl fluoride **38** in 81% yield and as a single stereoisomer. The same sequence but with a purchasable trisubstituted olefin and alkylzinc halide **39**, prepared in one step and 82% yield, delivered stereoisomerically pure *E*-trisubstituted alkenyl fluoride **40** in 77% yield. If synthesis of oleyl coenzyme A[56] were to involve trisubstituted alkenyl fluorides **38** or **40**, either of the fluoro-organic analogues would be obtained site-specifically (Fig. 5d).

Stereodivergent fluoro-labelling. Diastereodivergent synthesis of trisubstituted alkenyl fluorides may be implemented in several ways. Cross-metathesis of sterically hindered α-branched monosubstituted alkene **41**, prepared in one step and 81% yield, with ***E*-** and ***Z*-1** (Fig. 6a), followed by cross-coupling with commercially available boronic acid **42**, afforded the *Z* and *E* isomers of the fluoronematic liquid component in 65% and 74% overall yield (2 steps) and >98:2 *Z*:*E* and 95:5 *E*:*Z*, respectively.

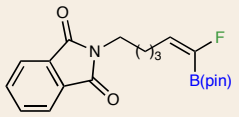
E- or *Z*-amide bond mimics ***E*-46** and ***Z*-46** were also prepared (Fig. 6b). Transformation of homoallylic silyl ether **43** (obtained enantiomerically enriched in one step), a challenging α-branched substrate that also contains a sizeable homoallylic silyl ether (see Table 1), furnished stereoisomerically pure trisubstituted alkenyl fluoride **44** in 54% overall yield (two steps). Compound **44** is an uncommon case; it is a product that has been previously prepared,

Table 2 | Diversification of trisubstituted alkenyl fluorides

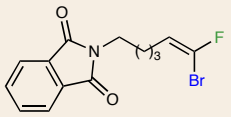




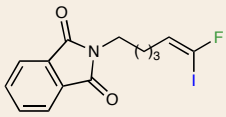
15
(5.0 mol% $Pd(OAc)_2$,
10 mol% $P(Ad)_2{}^nBu$,
CD_3OD, toluene, 2 h, 70 °C)
82% yield, 95:5 *E*:*Z*



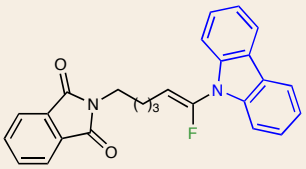
16
(2.5 mol% $Pd_2(dba)_3$,
10 mol% XPhos,
$B_2(pin)_2$, dioxane, 3 h, 100 °C)
70% yield, 98:2 *E*:*Z*



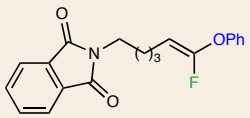
17
(Subjection of **16** to:
$CuBr_2$, $MeOH/H_2O$, 3 h, 80 °C)
84% yield, 95:5 *Z*:*E*



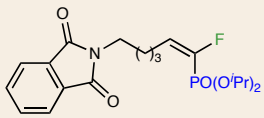
18
(Subjection of **16** to:
10 mol% CuI, 20 mol% 1,10-phenanthroline,
KI, $MeOH/H_2O$, 6 h, 65 °C)
79% yield, 94:6 *Z*:*E*



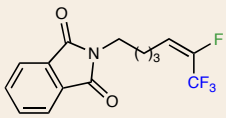
19
(5.0 mol% $Pd(P(^tBu)_3)_2$,
carbazole,
NaOH, toluene, 3 h, 100 °C)
63% yield, >98:2 *Z*:*E*



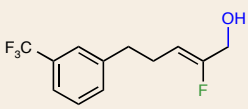
20
(2.5 mol% $Pd_2(dba)_3$,
10 mol% ^{t}BuXPhos, PhOH,
Cs_2CO_3, toluene, 3 h, 100 °C)
71% yield, >98:2 *Z*:*E*



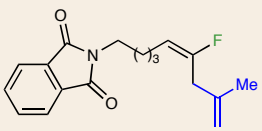
21
(5.0 mol% $Pd(OAc)_2$,
7.5 mol% dppf, $HPO(O^iPr)_2$,
$(^iPr)_2EtN$, DMF/DME, 12 h, 115 °C)
81% yield, >98:2 *Z*:*E*



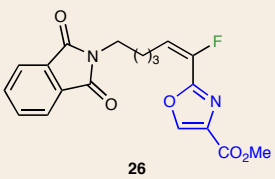
22
(Subjection of **16** to: **23**,
KF, DMF, O_2, 18 h, 50 °C)
73% yield, 93:7 *E*:*Z*



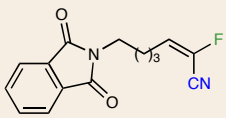
24
(^{n}BuLi, $ClCH_2I/Et_2O$,
1 h, −78→0°C, 1 h;
$NaOH/H_2O_2$, 1 h, 0→22°C,
56% yield, >98:2 *Z*:*E*



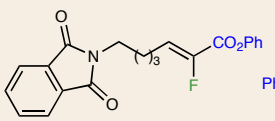
25
(5.0 mol% $Pd(P(^tBu)_3)_2$,
2-Me-allylSn(^{n}Bu)$_3$,
CsF, dioxane, 3 h, 90 °C)
84% yield, 94:6 *E*:*Z*



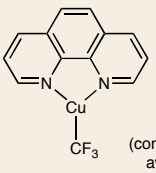
26
(5.0 mol% $Pd(OAc)_2$,
10 mol% CyJohnPhos, **27**,
Cs_2CO_3, dioxane, 18 h, 110 °C)
83% yield, >98:2 *E*:*Z*



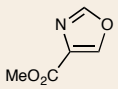
28
(3.0 mol% $Pd(PPh_3)_4$,
CuCN, NMP, 12 h, 135 °C)
80% yield, 95:5 *E*:*Z*



29
(3.0 mol% $Pd(OAc)_2$,
12 mol% $P(^tBu)_3HBF_4$;
PhOCHO, Et_3N, MeCN, 15 h, 100 °C)
89% yield, 94:6 *Z*:*E*



23
(commercially available)



27
(commercially available)

Reactions were carried out under N_2. Conversion to the desired product as measured by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures with DMF serving as the internal standard; the variance of values is ±2%. Yield of isolated product after purification, average over at least three runs; the variance of values is estimated to be <5%. See Supplementary Information part 1, section 3 for details. G, carbon-based moiety; R, carbon- or heteroatom-based moiety; XPhos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; dppf, 1,1′-bis(diphenylphosphino)ferrocene; SPhos, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; DME, dimethoxyethane; CyJohnPhos, (2-biphenyl)dicyclohexylphosphine.

and a comparison in efficiency is thus warranted. The three-step protocol described here (48% overall yield) is more efficient than the former five-step process, which afforded **44** in 24% overall yield[57]. The ensuing sequence, involving enol amide **45**[58], delivered ***E*-46**, a mimic of the higher-energy amide conformer, in 51% yield (27% overall yield, six steps) and in diastereoisomerically pure form (>98:2 *E*:*Z* and d.r.). Similarly, ***Z*-46**, was isolated in 20% overall yield (six steps; >98:2 *Z*:*E* and d.r.).

As noted earlier, one of the noteworthy features of the approach is the possibility of convergent and stereodivergent synthesis by cross-coupling between two stereochemically defined trisubstituted alkenyl fluorides. One illustrative example involves the initial conversion of alkene **35** (prepared in one step and 97% yield) to fluoro-substituted alkenyl boronates ***E*-47** and ***Z*-47** by a cross-metathesis/cross-coupling sequence (73% and 55% overall yield and 95:5 *E*:*Z* and >98:2 *Z*:*E*, respectively). Alkenyl boronates **47** cannot be prepared by the existing methods in either stereoisomeric form[31,32], which are limited to aryl olefin compounds and can only provide a *Z* isomer. Next, chloro-substituted alkenyl fluorides ***E*-49** and ***Z*-49** (57% and 92% yield, >98:2 *E*:*Z* and 94:6 *Z*:*E*, respectively) were synthesized by cross-metathesis involving **48** (obtained in one step and 94% yield). All four possible stereoisomers of difluoro analogues of rumenic acid methyl ester[36] were then synthesized by catalytic cross-coupling of the appropriate fluoro-containing trisubstituted alkenyl boronate and alkenyl chloride. The latter 2,3-difluoro-substituted 1,3-dienes were isolated in 54–65% yield and >98:2 stereoisomeric purity. In a similar manner, monofluoro rumenic methyl esters might be prepared by the union of a disubstituted (non-fluoro) alkenyl boronate and ***E*-49** or ***Z*-49** or through cross-coupling between a disubstituted alkenyl chloride and ***E*-47** or ***Z*-47**.

Conclusions

We have developed a broadly applicable and practical approach to laboratory synthesis of trisubstituted alkenyl fluorides that provides a direct route to formerly inaccessible compounds while offering

several advantages. The strategy may be used to generate a variety of fluorine-tagged organic molecules in a scalable, efficient, site-specific, diastereodivergent and/or regiodivergent fashion. Substrates and reagents are readily available; excess trihaloethylene compound may be recycled and reused. In most cases, a commercially available molybdenum complex may be used. Performing a cross-metathesis with a molybdenum complex embedded within air-stable paraffin pellets is another option[34]. Molybdenum is a relatively abundant metal, and applications involving its use are more likely to be cost-effective and have long-term impact (compared with ruthenium). There is room for improvement, however. More efficient catalytic processes that proceed with higher TON values would be desirable (up to ~17 for the transformations described above).

Considering the central position of organofluorine compounds, the prevalence of alkenes in medicine, agrochemistry and materials science, and the dearth of methods for stereocontrolled synthesis of trisubstituted alkenyl fluorides, the present approach will have a notable impact on several fronts and, in particular, on preparation of fluorine-tagged bioactive molecules and drug discovery. Access to either trisubstituted alkenyl fluoride isomers introduces a distinct way of incorporating a peptide turn. Equally important, and in contrast to much of the state-of-the-art, the approach is not confined to aryl- or heteroaryl-substituted products. The importance of this attribute is manifested by the fact that nearly all the fluoro-containing bioactive compounds discussed above contain an alkyl-substituted alkenyl fluoride. Stereoselective functionalization of the fluoro,chloro-substituted alkenes could lead to a range of fluoro-substituted stereogenic carbon[59,60], or, perhaps more uniquely, a fluoro,chloro-substituted centre, which may be viewed as a new organofluorine bio-isostere.

The findings described here debunk the generally held view that cross-metathesis between two trisubstituted alkenes is unlikely to be efficient. This presumption is understandable because it has been shown on several occasions that, irrespective of catalyst activity, trisubstituted olefins usually resist entering a catalytic olefin metathesis cycle (little or no post-metathesis isomerization). We demonstrate that if a catalyst possesses the proper reactivity/longevity balance, and the appropriate conditions are used, reactions involving two trisubstituted olefins can be promoted efficiently and stereoretentively. The results described here foreshadow olefin metathesis processes that generate other highly substituted and otherwise difficult-to-access alkenes in high stereoisomeric purity.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41557-022-00893-5.

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Data availability

All data in support of the findings of this study are available within the article and its Supplementary Information.

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Author contributions

Q.L., Y.M. and T.K. developed the methodology and designed and carried out the applications. R.R.S. and A.H.H. developed the catalyst systems used. A.H.H. directed the studies and wrote the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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