nature chemistry

ARTICLES
https://doi.org/10.1038/s41557-019-0233-x

E- and *Z*-, di- and tri-substituted alkenyl nitriles through catalytic cross-metathesis

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Nitriles are found in many bioactive compounds, and are among the most versatile functional groups in organic chemistry. Despite many notable recent advances, however, there are no approaches that may be used for the preparation of di- or tri-substituted alkenyl nitriles. Related approaches that are broad in scope and can deliver the desired products in high stereoisomeric purity are especially scarce. Here, we describe the development of several efficient catalytic cross-metathesis strategies, which provide direct access to a considerable range of *Z*- or *E*-di-substituted cyano-substituted alkenes or their corresponding tri-substituted variants. Depending on the reaction type, a molybdenum-based monoaryloxide pyrrolide or chloride (MAC) complex may be the optimal choice. The utility of the approach, enhanced by an easy to apply protocol for utilization of substrates bearing an alcohol or a carboxylic acid moiety, is highlighted in the context of applications to the synthesis of biologically active compounds.

Nitrile compounds are important to chemistry, medicine[1] and materials research[2]. Cyano-substituted alkenes are particularly attractive, as these robust and highly polarized alkenes[3] may be the source of biological activity, or provide a site for irreversible and covalent inhibition[4]. Alkenyl nitriles may be readily modified at the olefin site (for example, catalytic enantioselective hydrogenation[5–7] or conjugate additions[8]) and/or the nitrile moiety. *Z*- and *E*-di-substituted variants can be used in the stereoselective preparation of medicinally relevant compounds, such as LR5182 (Fig. 1a)[9]. A nitrile unit can be the key component of a biologically active molecule, examples being the anti-HIV reverse transcriptase inhibitors rilpivirine[10] and fosdevirine[11] (Fig. 1a). Stereochemically defined tri-substituted alkenyl nitriles are found within the anticancer agents CC-5079[12,13], phorboxazoles and their analogues[14,15], where the alkenyl oxazole moiety may also be generated by modification of a cyano-substituted olefin[16,17] and calyculin A[18] (Fig. 1b). Sequential addition of two different nucleophiles may be induced to occur to an alkenyl nitrile at the CN bond, generating N–H amines[19] without oxidation-state adjustments or protection/deprotection schemes.

There are catalytic protocols for the synthesis of di-substituted alkenyl nitriles involving palladium-[20,21], nickel-[22,23], iron-[24], gallium-[25], copper-[26,27,28] or rhodium-based[29] complexes. Major shortcomings remain to be addressed, however. Toxic[24,25] or costly reagents[28] or catalysts bearing a precious metal[20,21,29] are required in several cases. Some reactions produce hydrogen cyanide[21,27,29]. Limitation in scope is another significant issue, as methods that furnish alkyl-substituted alkenyl nitriles are uncommon[21,23,27,29]. Effective control of stereochemistry can be problematic. Wittig-[30,31] and Peterson-type reactions[32,33] have been used to obtain *Z*-alkenyl nitriles, but stereoselectivities can be moderate[30,32], and stoichiometric amounts of a strong base (that is, *n*-butyllithium or hexamethyldisilazide) and cryogenic conditions (−78 °C)[30,33] are often needed. Only two reported procedures offer access to a cyano-substituted *Z* olefin selectively[21,27], and these require a stereochemically defined *Z*-alkenyl bromide or iodide, the stereoselective synthesis of which is non-trivial.

There are catalytic approaches for the stereoselective preparation of tri-substituted alkenyl nitriles, but these are confined to aryl- or polyaryl-substituted products[21,24,34–37] or demand forcing conditions (≥120 °C)[38,39]. In some instances, high loadings of precious metal salts[39,40] or excess amounts (2.0 equiv.) of a strong Lewis acid (BCl_3)[36] are needed. To synthesize aliphatic tri-substituted alkenyl nitriles, expensive reagents must be used, slight structural variations can result in low stereoselectivity[28] or the substrates are valuable stereochemically defined tri-substituted alkenyl iodides[27].

The large majority of the above protocols, regardless of the degree of substitution in the product olefin, require an acetylenic compound as the starting material[22,23,25,29,35–40]. Methods that involve alkenes as substrates would be strategically distinct and especially desirable, as olefins are more abundant and less costly.

Catalytic cross-metathesis represents an attractive strategy for the preparation of stereochemically defined alkenyl nitriles. However, such methods are scarce. The first examples were disclosed more than two decades ago by Crowe and Goldberg, who showed that Mo bis-alkoxide complexes can be used to synthesize *Z*-1,2-di-substituted alkenyl nitriles[41]. Later studies with Ru-based complexes led to protocols that are either similarly[42,43] or less stereoselective[44]. Regardless of the catalyst type, *Z*:*E* ratios were variable, depended on the olefin type and did not exceed 90:10. What is more, only reactions of unhindered *n*-alkyl-substituted olefins were reasonably efficient. There are only three reported instances where a tri-substituted alkenyl nitrile has been prepared by cross-metathesis (again, from *n*-alkyl olefins)[45–47], and stereoselectivity was minimal in every case (for example, 66:34 *Z*:*E*).

Results

Key challenges and their origins. Because the cyano group is small, development of a highly stereoselective cross-metathesis that generates alkenyl nitriles is especially challenging. The energy difference between the isomers of cyano-propene has been calculated by Wiberg and colleagues[48] to be just $0.26 \pm 0.04\,\mathrm{kcal\,mol^{-1}}$ in favour of the *Z* isomer (61:39 *Z*:*E*). It is thus not surprising that, whereas most cross-metathesis reactions generate *E* isomers preferentially, cyano-substituted alkenes

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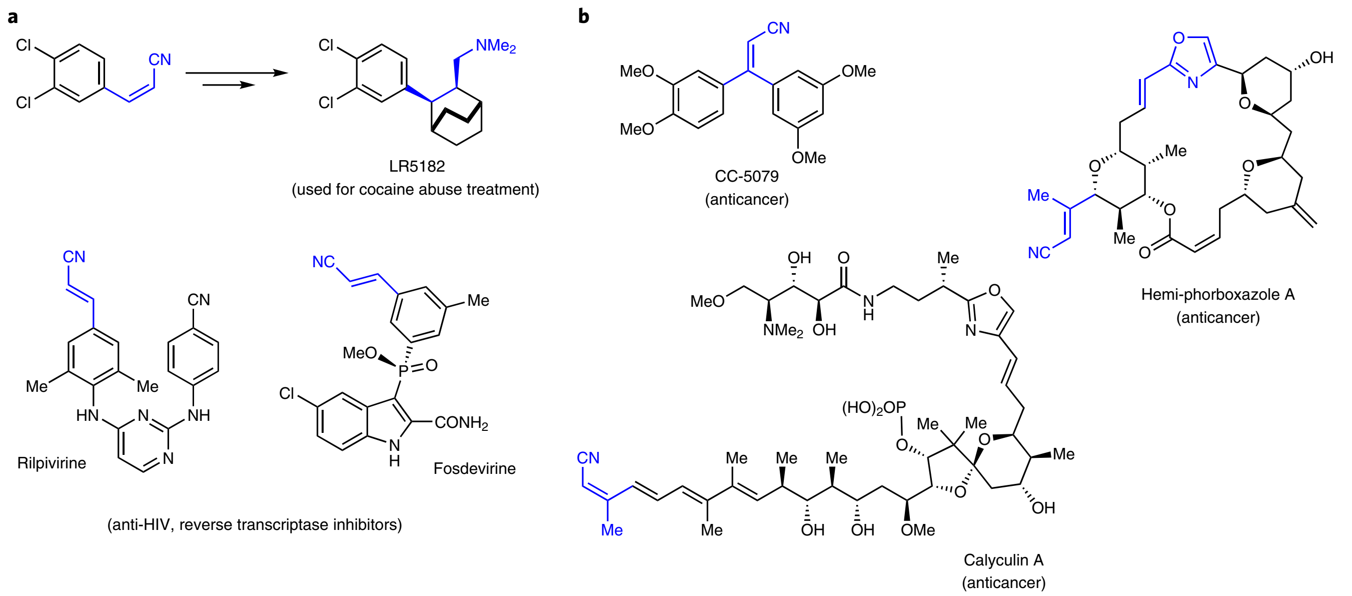

Fig. 1 | Biologically active compounds with an alkenyl nitrile or a related moiety. a, Stereoisomerically pure 1,2-di-substituted olefins bearing a nitrile substituent may be used to prepare medicinally relevant agents, such as LR5182, a polycyclic tertiary amine used to battle cocaine abuse. Furthermore, stereochemically defined alkenyl nitriles reside in a range of biologically active molecules. Examples are rilpivirine and fosdevirine, entities relevant to the fight against AIDS. **b**, Stereoisomerically pure tri-substituted alkenyl nitriles are also desirable. These moieties are found in biologically active entities, represented by anticancer agents CC-5079, various phorboxazoles and calyculin A. In the case of phorboxazoles, the oxazole ring and its adjacent olefin may also be generated from an alkenyl nitrile.

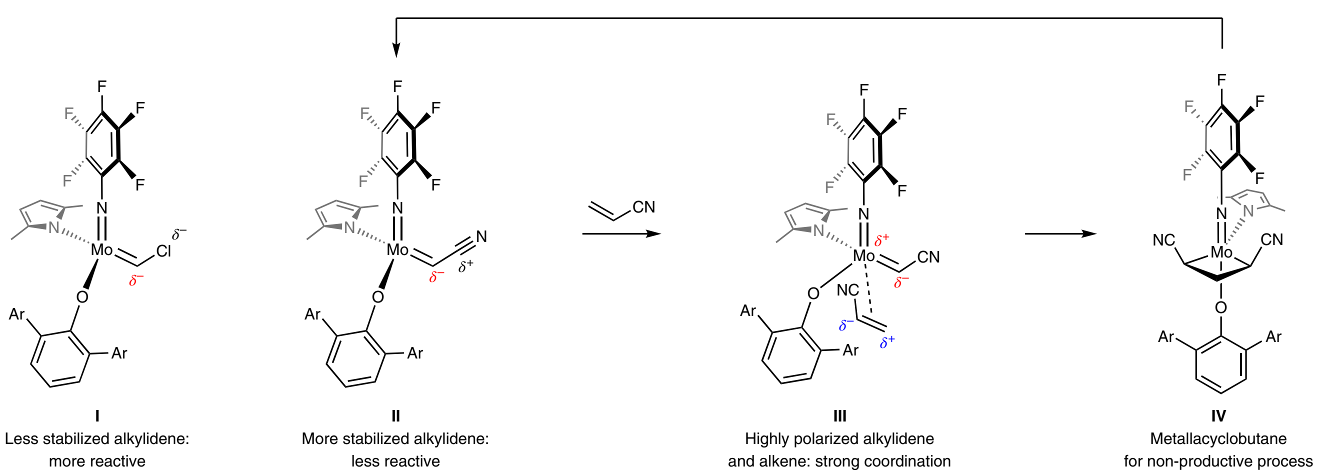

Fig. 2 | Challenges in designing reactions that deliver stereodefined alkenyl nitriles. Unlike other types of Mo alkylidene, such as those that contain a chlorine atom (**I**), a nitrile-substituted variant (**II**) is more strongly stabilized due to electronic factors, and is therefore less reactive. The higher polarizability of the Mo=C bond of a CN-substituted alkylidene and the alkene of acrylonitrile facilitates reaction via **III**, generating metallacyclobutane **IV** and causing non-productive olefin metathesis. Ar, aryl.

are formed with low to moderate *Z* selectivity, an attribute that was recently attributed to stereoelectronic factors[49].

Another complication originates from the strongly electron-withdrawing nature of a nitrile unit. With an alkenyl halide[50,51] the electron-withdrawing effect of a C–halogen bond is partially offset by electron–electron repulsion caused by the halide's non-bonding electrons and the accumulated electron density at the carbon atom of a strongly polarized Mo alkylidene (see **I**, Fig. 2). In contrast, the presence of a cyano moiety has one overarching effect: stabilization of electron density at the alkylidene carbon (**II**), which translates to diminished catalyst activity. The small size of a nitrile group and the strongly polarized C=C bond in acrylonitrile further complicate matters, as these factors favour reaction via the electronically matched **III** (Fig. 2), which is precursor to the symmetrical metallacyclobutane **IV**, an intermediate for non-productive self-metathesis.

***Z*-di-substituted alkenyl nitriles.** We began by examining a model transformation that could generate a *Z*-alkenyl nitrile, opting to use a terminal alkene (**1a**) and commercially available acrylonitrile (Fig. 3a). To minimize homo-metathesis of **1a**, we initially used excess acrylonitrile (that is, 3.0 equiv.). Among the Mo monoaryloxide pyrrolide (MAP) complexes, **Mo-1a** emerged as the most effective. *Z*-alkenyl nitrile **2a** was formed with complete stereochemical control (<2% *E* isomer), but there was only 45% consumption

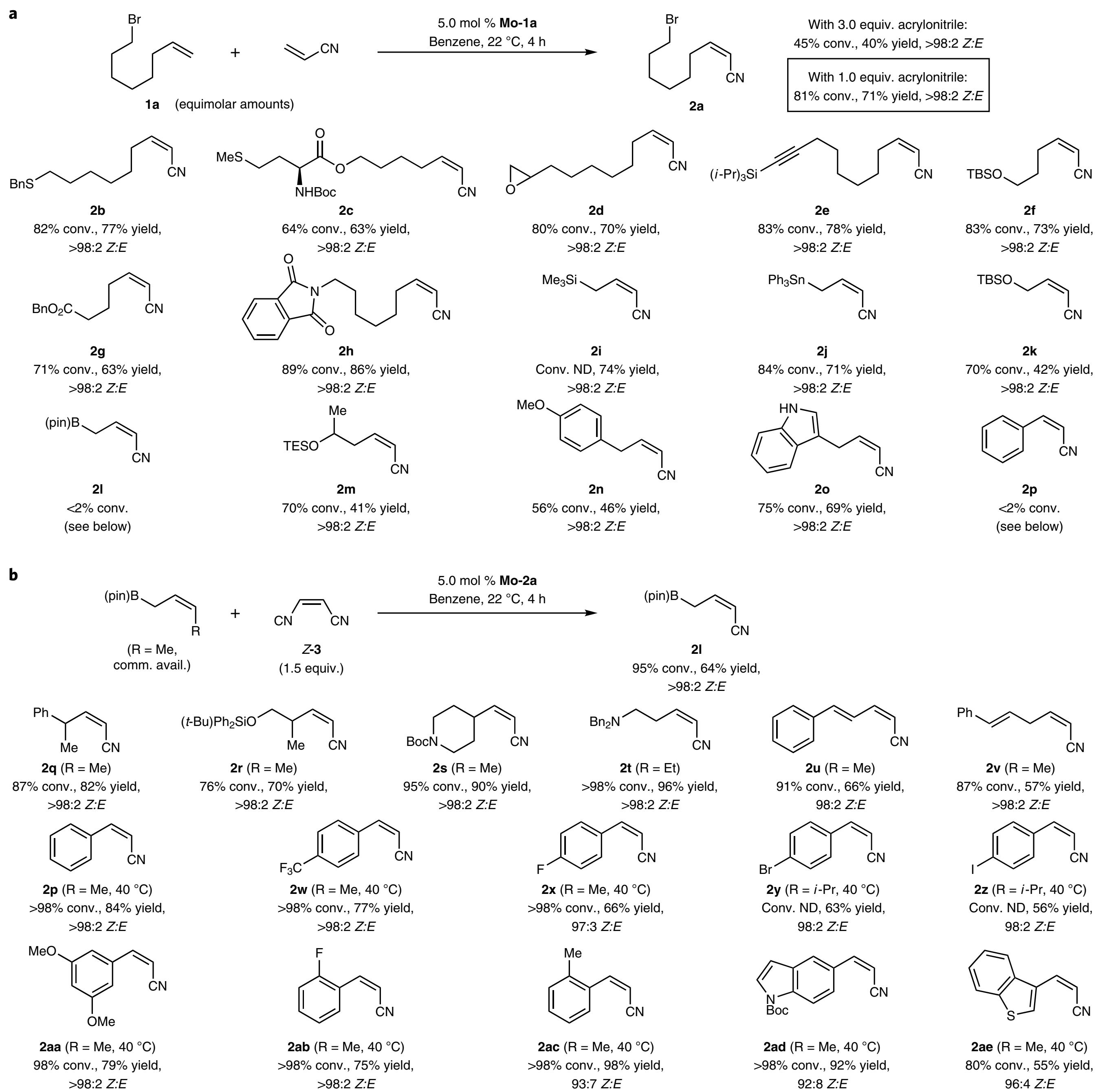

Fig. 3 | A broadly applicable approach to *Z*-di-substituted alkenyl nitriles. a, In the presence of **Mo-1a**, *Z*-selective cross-metathesis between a terminal alkene and acrylonitrile may be performed efficiently and with high stereoselectivity. Transformations are more efficient with equimolar amounts of the alkene substrates (versus excess acrylonitrile), probably because non-productive metathesis is minimized. The method is applicable to an assortment of α-olefins. However, reactions with sterically demanding olefins are severely inefficient (for example, **2l** and **2p**). **b**, The latter shortcoming may be addressed by stereoretentive processes involving easily accessible *Z*-di-substituted alkenes and maleonitrile (*Z*-**3**), and a monoaryloxide chloride (MAC) catalyst (**Mo-2a**). See Supplementary Information section 3 for experimental and analytical details. comm. avail, commercially available; Bn, benzyl; pin, pinacolato; Boc, *tert*-butoxycarbonyl; TBS, *tert*-butyldimethylsilyl; TES, triethylsilyl; ND, not determined.

of **1a** after 4 h at ambient temperature, with no further progress after extended periods. On the basis of the hypothesis vis-à-vis the adventitious influence of non-productive self-metathesis (via **IV**, Fig. 2), we probed the effect of lower acrylonitrile concentration on efficiency. With equimolar amounts of the two olefin substrates, there was 81% conversion to **2a**, which was isolated in 71% yield as the pure *Z* isomer (Fig. 3a). It is noteworthy that, typically, an excess amount of one reaction partner is needed for high conversion, especially in kinetically *Z*-seletive[52,53] or *E*-selective[51,54] cross-metathesis.

Various linear alkenes were transformed to the corresponding *Z*-alkenyl nitriles under the conditions used to access **2a** (Fig. 3a). Products bearing a sulfide (**2b–c**), an epoxide (**2d**), an alkyne (**2e**), a silyl ether (**2f**) or a Lewis basic carbonyl unit (**2g–h**) were isolated in 63–86% yield. Linear alkenes wherein a relatively long C–Si or C–Sn bond separates a large substituent and the alkene were similarly efficient (**2i**–**j**). A bulky and/or an electron-withdrawing olefin substituent, however, had an adverse effect on efficiency. *tert*-Butyl(dimethyl)silyl ether **2k** was isolated in 42% yield (compared to 74% and 71% yields for **2i** and **2j**, respectively), and there was no conversion to allylic boronate **2l**. This last finding underscores the greater difficulty associated with the formation of alkenyl nitrile products in comparison to alkenyl halides, because **Mo-1a**, despite bearing a bulkier 2,6-bis(2,4,6-triethylphenyl)phenoxy ligand, was effective in generating *Z*-γ-chloroallyl boronates (5.0 mol% loading, 22 °C, 4 h, 66% yield, >98:2 *Z*:*E*)[50]. β-Branched secondary homoallyl silyl ether **2m**, and **2n**, containing a benzylic substituent, were isolated in 41% and 46% yields, respectively. While **2o**, a *Z*-alkenyl nitrile with an unprotected indole, was obtained in 69% yield, there was <2% conversion when styrene was used as the substrate. Complete *Z* selectivity was observed in all cases (<2% *E*; more on this later).

The more challenging *Z*-alkenyl nitriles. To address the limitations in scope noted above, we turned to Mo monoaryloxide chloride (MAC) complexes[55], recently demonstrated to exhibit greater reactivity than the MAP systems. Because MAC species decompose readily in the presence of a terminal alkene[55], a *Z*-alkene must be used as the starting material. We have shown that many such substrates can be prepared readily and in high yield by single-vessel operations, often involving an efficient catalytic cross-coupling of an alkenyl boronate. Furthermore, a mixture of easily separable fumaronitrile and maleonitrile (*E*- and *Z*-**3**) can be obtained by treatment of the commercially available *E* isomer with 5.0 mol% iodine (160 °C, 6 h)[55]. Therefore, subjecting commercially available *Z*-crotyl–B(pin) to 1.5 equiv. of maleonitrile and 5.0 mol% **Mo-2a** afforded cyano-substituted *Z*-allyl–B(pin) product **2l** (Fig. 3b) in 64% yield and >98:2 *Z*:*E* ratio after 4 h at ambient temperature. When the same transformation was carried out with **Mo-1a**, under otherwise identical conditions, the major product was derived from self-metathesis of *Z*-crotyl-B(pin) (72% conv.) while **2l** was the minor component (25% conv., >98:2 *Z*:*E*). This is probably because, unlike **Mo-2a**, **Mo-1a** is unable to react with the severely electron-deficient maleonitrile (*Z*-**3**). The approach is applicable to α-branched alkenes (**2q**–**s**), which are among the most challenging substrates in cross-metathesis.

Unlike when MAC complex **Mo-2a** was used, attempts to generate amine **2t**, 1,3-diene **2u** and 1,4-diene **2v** with a MAP species (**Mo-1a**) led to much less favourable results (<30% conv. to the desired product). Intramolecular N → Mo chelation may be responsible for the diminished conversion to **2t**, whereas the MAC catalyst is probably reactive enough that even a low concentration of the active four-coordinate alkylidene species can be sufficient for efficient cross-metathesis. When a MAP complex was used to prepare 1,3-diene **2u**, there was <2% conversion to the desired product. In the case of diene **2v**, significant amounts of by-products from transformation at the substrate's *E*-alkene could be observed. As noted previously[55], MAC complexes react with *Z* alkene isomers preferentially.

Equally notable are the transformations that generate different aryl- and heteroaryl-substituted *Z*-alkenyl nitriles (**2p**–**2ae**; Fig. 3b). Thus, regardless of the position or the electronic attributes of the aryl substituent, the desired products were isolated in 55–98% yield and 92:8 to >98:2 *Z*:*E* ratio. In certain cases, slight heating to 40 °C led to a higher yield, but the duration of all transformations was just 4 h. Two additional points merit note: (1) with a MAC species, reaction with unprotected indole-containing substrate (cf. **2ad**) did not lead to any significant conversion (<5%); (2) this set of products (Fig. 3b) is not in the purview of any existing cross-metathesis methods, where a more traditional Mo-[41] or Ru-based[42] complex is used. The case of *ortho*-tolyl-substituted alkenyl nitrile **2ac**, which was secured in 98% yield (93:7 *Z*:*E*), is especially noteworthy, considering the steric pressure that probably exists within the corresponding metallacyclobutane intermediate.

Nevertheless, a set of substrates that we were unable to efficiently transform to their corresponding alkenyl nitriles were allylic ethers, regardless of the nature of the Mo complex used or the nature of the protecting unit (for example, *tert*-butyldimethyl silyl, benzyl). This shortcoming is reflected in the yield with which primary allyl silyl ether **2k** was obtained (42% yield); unlike other instances mentioned above (Fig. 3b), the efficiency did not improve in the corresponding stereoretentive process involving a MAC complex. The steric hindrance imposed by the allylic substituent together with diminution of alkene Lewis basicity, caused by the adjacent C–O bond, and the relative stability of a CN-substituted Mo alkylidene (see Fig. 2) are probably responsible for the lack of reactivity.

***E*-alkenyl nitriles.** Next, we investigated reactions that would generate an *E*-di-substituted alkenyl nitrile (Fig. 4). As in the past, we chose to focus on stereoretentive[51] processes (versus stereoselective). To identify an effective catalyst, we studied the reaction of aryl olefin *E*-**4a** with commercially available fumaronitrile (*E*-**3**; Fig. 4a). The transformation with pentafluorophenyl imido MAP complexes **Mo-1a** and **Mo-1b**, while highly stereoretentive (>98:2 *E*:*Z*), were moderately efficient, despite the elevated temperature (47% and 52% conv. to *E*-**4a**, respectively, at 80 °C). To improve efficiency, we again turned to MAC alkylidenes, mindful that this class of complexes were not formerly used for reactions that generate *E* alkenes. We began with **Mo-2a**, which proved effective for the processes with hindered alkyl- and aryl-substituted olefins and leading to *Z*-alkenyl nitriles (Fig. 3b). Although there was only 20% conversion to *E*-**5a**, we were encouraged for several reasons. First, the reaction was completely stereoretentive. Second, the transformation was more efficient than when a MAP species was used, as a considerably greater portion of the product mixture consisted of the desired product (22% conv., 20% to *E*-**5a** compared to 82% conv., 52% to *E*-**5a** for **Mo-1b**). Third, whereas **Mo-1b** is already a pentafluoro-imido complex, **Mo-2a** is an adamantyl imido derivative, leaving room for the possibility of achieving better efficiency through incorporation of an activating polyfluoroaryl imido ligand.

To promote cross-metathesis between *E*-**3** and *E*-**4a**, we probed the ability of the pentafluoro-imido MAC alkylidenes derived from **Mo-2b**, most efficiently prepared and isolated as a dimethylphenylphosphine complex[56]. We used 15 mol% tris(pentafluorophenyl)borane as the additive to generate the active four-coordinate species (after loss of the phosphine) and to cap the hydroxy group of residual free 2,6-(2,4,6-triisopropyl)phenol (remainder from catalyst synthesis), a strategy that we would later use to address another important issue (see below). After 12 h at 40 °C, there was 67% consumption of *E*-**4a**, with 49% conversion to *E*-**5a**, representing a notable boost in reactivity. Unexpectedly, however, there was significant diminution in the *E*:*Z* ratio (88:12). Usually, the reason for lower product stereoisomeric purity in stereoretentive olefin metathesis is adventitious isomerization of the starting alkene. We surmised that *E*-**3**, an exceedingly electrophilic reagent, might interconvert with its similarly favoured *Z* isomer (as noted above) through an addition/elimination sequence. The likely nucleophilic promoter for this event, considering the complete retention of stereochemistry with the acetonitrile complex **Mo-2a**, would be an uncoordinated dimethylphenylphosphine. This led us to subject *E*-**3** to 5.0 mol% of tricyclohexylphosphine (easier to handle than $PhMe_2P$) and 15 mol% $(C_6F_5)_3B$ (22 °C, 4 h), which resulted in just 3% isomerization (that is, from >98:2 to 97:3 *E*-**3**:*Z*-**3**). This might seem insignificant, but, considering that *Z* alkenes generally react faster with this catalyst class[55], particularly with a larger aryloxide ligand, this could indeed be the source of the 12% loss in stereochemical purity. To confirm, we prepared **Mo-2c**, a complex that bears a less nucleophilic 3-bromopyridyl ligand, and, under otherwise identical conditions

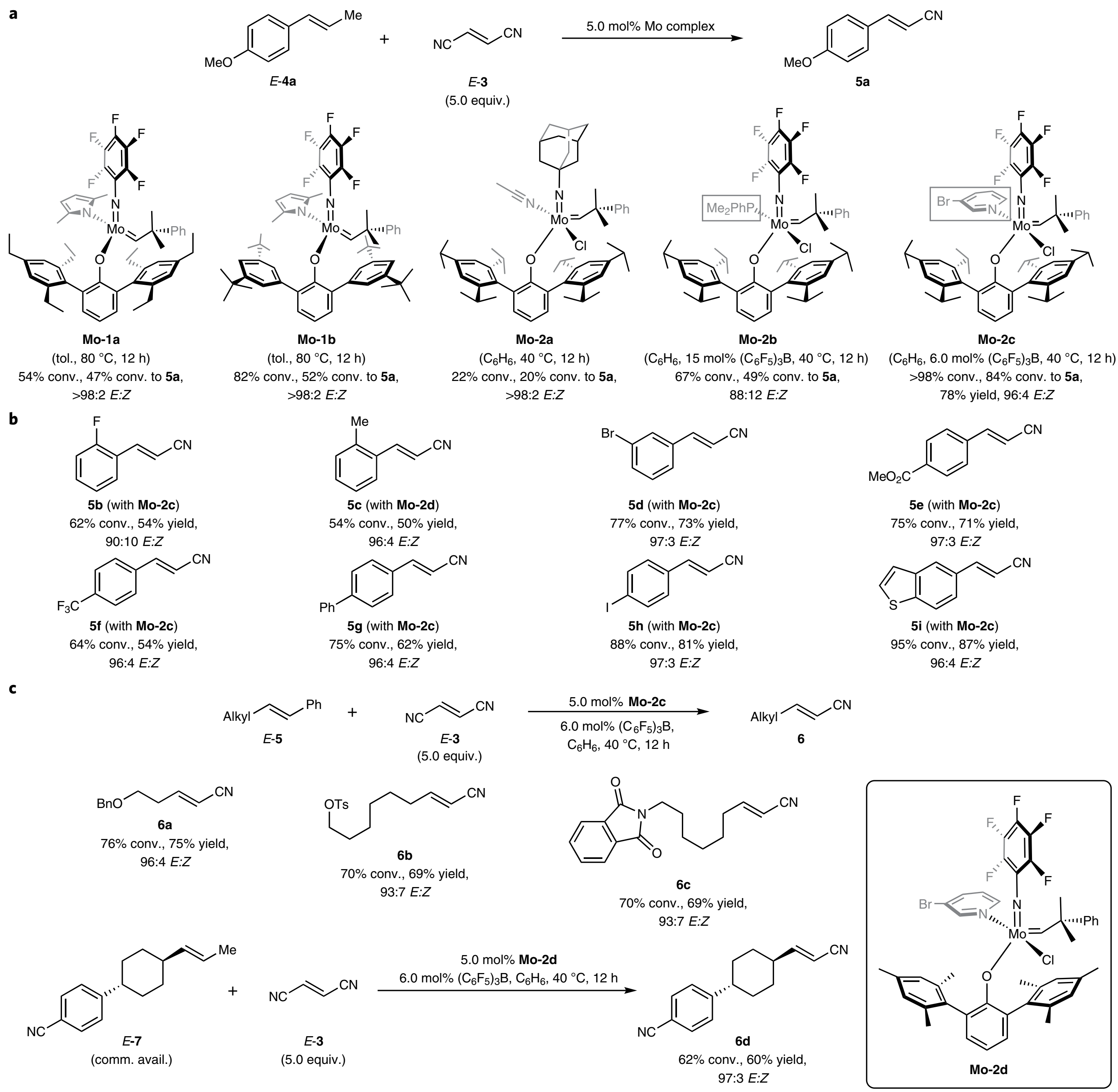

Fig. 4 | *E*-di-substituted alkenyl nitriles. **a**, Cross-metathesis between an *E*-di-substituted olefin and fumaronitrile was more efficient with **Mo-2b**, but *E*:*Z* ratios were low compared to when **Mo-1b** or **Mo-2a** were used (88:12 versus >98:2, respectively). Control experiments indicated that this is probably due to isomerization of *E*-**3** to *Z*-**3**, catalysed by the released PMe_2Ph by **Mo-2b**. Thus, with **Mo-2c** (3-bromopyridine ligand), **4a** was obtained with 96:4 *E*:*Z* selectivity. **b**, The approach can be used to access aryl-substituted *E*-alkenyl nitriles. **c**, *E*-β-alkyl-styrenyl precursors can be converted to *E*-alkyl-substituted alkenyl nitriles. With a bulky aliphatic alkene higher efficiency was observed with **Mo-2d** (smaller aryloxide ligand). See Supplementary Information section 3 for experimental and analytical details. Bn, benzyl; Ts, *para*-toluenesulfonyl; tol., toluene.

as used for **Mo-2b**, we isolated **5a** in 78% yield and 96:4 *E*:*Z* ratio after 12 h at 40 °C (6.0 mol% $(C_6F_5)_3B$ was used as there was less contaminating phenol remaining from preparation of the **Mo-2b**). Control experiments indicated that there is no post-metathesis alkene isomerization.

The method is applicable to *E*-aryl-substituted and *E*-heteroaryl-substituted alkenes of disparate steric and/or electronic properties (**5b**–**i**, Fig. 4b); products were obtained in up to 87% yield, with stereoselectivity ranging from 90:10 to 97:3 *E*:*Z* ratio. In the case of *o*-tolyl-substituted **5c**, with the substrate bearing a particularly hindered substituent, the reaction was much more efficient when the less sterically demanding **Mo-2d** was employed (50% yield, 96:4 *E*:*Z*; compared to 34% conv., 84:16 *E*:*Z* with **Mo-2c**).

The *E*-alkenyl nitriles with an *n*-alkyl substituent were most efficiently generated by catalytic stereoretentive reactions with *E*-β-alkyl styrenes (Fig. 4c)[51]; **6a**–**c** were thus obtained in 69–75% yield and 93:7–96:4 *E*:*Z* ratio. As in the case of sterically hindered **5c**, the reaction of α-branched alkene *E*-**7** to generate **6d** was more efficient

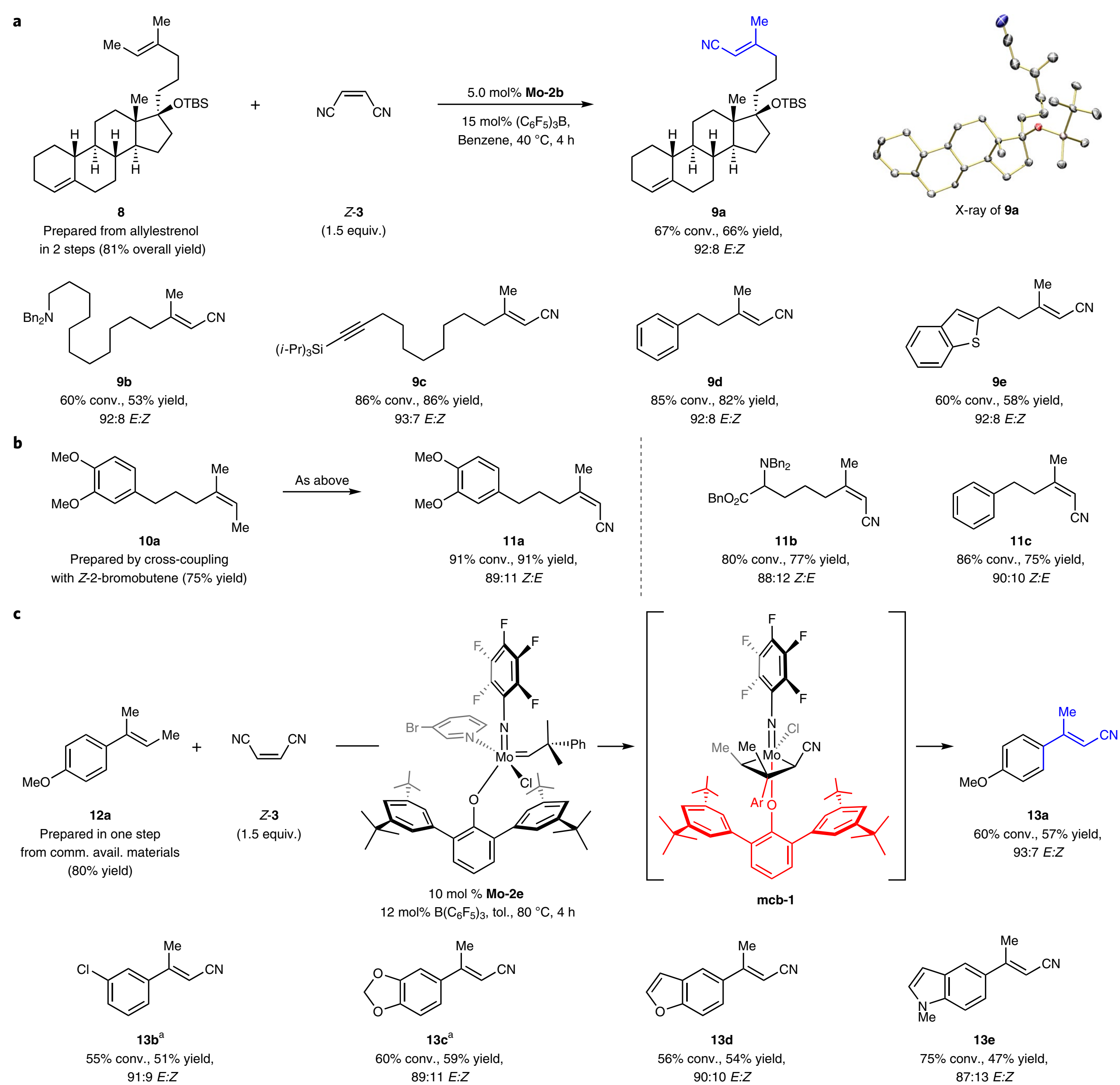

Fig. 5 | *E*- and *Z*-tri-substituted alkenyl nitriles. a, Readily accessible stereochemically defined *E*-tri-substituted alkenes, bearing a relatively diminutive methyl group terminus, can be converted in the presence of **Mo-2b** and *Z*-**3** to the corresponding *E*-alkenyl nitriles. The method is applicable to various alkyl-substituted olefins (**9a**–**e**). **b**, *Z*-tri-substituted alkenyl nitriles can be obtained similarly. **c**, An even more difficult process is one that might deliver a tri-substituted alkenyl nitrile with a sizeable aryl unit. This may be accomplished with 10 mol% **Mo-2e** at 80 °C (via **mcb-1** to give **13a**–**e**). [a]15.0 mol% **Mo-2e** and 18 mol% $B(C_6F_5)_3$ were used. See Supplementary Section 3 for experimental and analytical details.

with **Mo-2d** (60% yield, 97:3 *E*:*Z* compared to 20% conv., 54:46 *E*:*Z* with **Mo-2c**); the smaller aryloxide ligand might better accommodate the sizeable alkyl moiety, which would be projected towards it in the corresponding metallacyclobutane.

The stereoisomeric purity of the *E*-alkenyl nitrile products, although generally high, is slightly lower than the related *Z* isomers accessed through stereoretentive cross-metathesis (Fig. 3b); this difference may be attributed to increased steric pressure between an *E*-di-substituted alkene and the large aryloxide ligand of a Mo complex (for example, **Mo-2c**). Consequently, fumaronitrile-to-maleonitrile isomerization (*E*-**3** → *Z*-**3**), despite the lower nucleophilicity of the released 3-bromopyridine, can become more competitive, especially at 40 °C, and diminution in *E*:*Z* product ratios ensues. This scenario is supported by the finding that more *Z*-alkenyl nitrile is generated when the more sterically demanding *ortho*-substituted substrates are used (that is, 84:16–90:10 *E*:*Z* for **5b**–**c** when **Mo-2c** was used). In the case of less hindered alkyl-substituted alkenyl nitriles (**6a**–**c**), substrate self-metathesis and *E*-to-*Z* isomerization are probably more facile, and stereoisomeric purity suffers.

Tri-substituted *E*- and *Z*-alkenyl nitriles. We then turned to determining whether a catalytic method for stereoretentive synthesis of

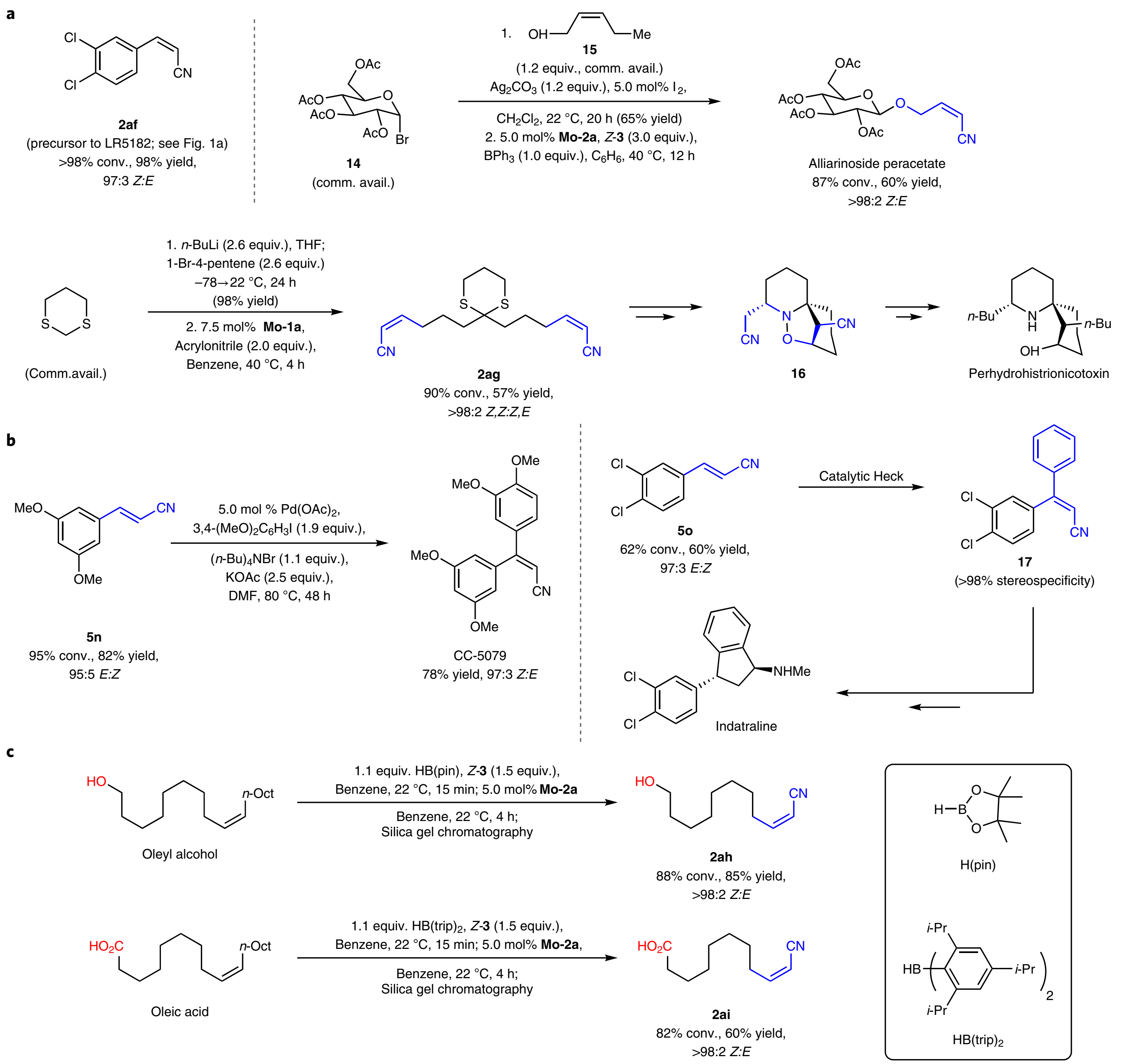

Fig. 6 | Utility of the method in chemical synthesis. a, The possibility of synthesizing aryl- or alkyl-substituted *Z*-alkenyl nitriles by catalytic cross-metathesis is likely to have a notable impact on the efficiency with which many bioactive compounds can be prepared. Representative cases are the agent for cocaine abuse treatment LR5182, agrochemical agent alliarinoside and perhydrohistrionicotoxin (step **2ag** to **16**[61]), which has been used for probing the mechanisms of neuromuscular impulses. **b**, The *E*-alkenyl nitriles are crucial for stereoselective generation of a variety of bio-active molecules. Anticancer agent CC-5079 and antidepressant indatraline are two examples. **5O** to **17**, catalytic Heck reaction[6]. **c**, In situ protection/deprotection of a neighbouring hydroxy and carboxylic acid group may be carried out, significantly enhancing the scope of the method. See Supplementary Information sections 4–9 for experimental and analytical details. pin, pinacolato; trip, 2,4,6-triisopropylphenyl; Ac, acetyl.

tri-substituted alkenyl nitriles is feasible. What distinguishes this set of transformations, other than the involvement of a more congested metallacyclobutane, is that they probably involve a cyano-substituted alkylidene exclusively, as opposed to a 1,1-di-substituted variant arising from initial reaction with a tri-substituted olefin. This means that reaction with either *Z*- or *E*-**3** should lead to the same degree of stereochemical purity, although, as already noted, reaction involving the former isomer would probably be more efficient.

Tri-substituted alkene **8** was prepared in a single-vessel operation from a silyl ether of allylestrenol (see Supplementary Information for details). Subjection of **8** to **Mo-2b** (5.0 mol%), 15 mol% $(C_6F_5)_3B$ and *Z*-**3** (1.5 equiv.) afforded **9a** in 66% yield and 92:8 *E*:*Z* selectivity (Fig. 5a). The *E*:*Z* ratio was the same with 3-bromopyridine-containing MAC complex **Mo-2c**, in line with the predominant intermediacy of the cyano-substituted *syn*-alkylidene, regardless of whether *E*- or *Z*-**3** is involved. Assorted aliphatic *E*-tri-substituted alkenyl nitriles were accessed similarly (**9b**–**e**, in 53–86% yield and 92:8–93:7 *E*:*Z*). The approach is applicable to the preparation of *Z*-tri-substituted alkenyl nitriles (see **11a**–**c**). A rationale for the lower stereochemical control in the formation of the *Z* isomers was provided recently in connection with the synthesis of tri-substituted alkenyl chlorides and bromides[57].

Perhaps the most challenging aspect of this study was designing efficient reactions between relatively stabilized cyano-substituted alkylidenes and hindered tri-substituted alkenes; particularly difficult would be processes involving an aryl olefin. Yet again, in the case of alkenyl chlorides, the corresponding products were obtained when MAP complex **Mo-1b**[57] was used. However, the same strategy was ineffective when applied to reactions proceeding via a more stabilized/less reactive cyano-substituted alkylidene species (compare **I** to **II**, Fig. 2). There was <2% conversion to **13a** with MAC complex **Mo-2c** or **Mo-2d**. To address this issue, we synthesized **Mo-2e** (Fig. 5c), which bears an aryloxide with 3,5-di-*t*-butylphenyl groups at its C2 and C6 sites. We expected reduced steric pressure in the corresponding metallacyclobutane (**mcb-1**). Through the use of 10 mol% **Mo-2e** and 12 mol% $(C_6F_5)_3B$, and at 80 °C for 4 h, we were able to isolate **13a** in 57% yield and 93:7 *E*:*Z* selectivity. As indicated by the synthesis of **13b–e**, the approach is applicable to different aryl alkenes. Reactions were slower with the more electron-withdrawing aryl alkenes, as synthesis of **13b**–**c** required 15 mol% **Mo-2e** and 18 mol% $(C_6F_5)_3B$ to reach 55–60% conversion (with 10 mol% **Mo-2e**: 36% and 41% conv., 32% and 35% yield, 91:9 and 89:11 *E*:*Z*, respectively).

Under the same conditions and with a *Z*-tri-substituted aryl olefin, there was only about 20% conversion to the desired alkenyl nitrile, formed with minimal stereoisomeric purity (~60:40 *Z*:*E*). Development of a more effective solution to these important but difficult cross-metathesis reactions is a goal of future investigations.

Utility. The present advance provides a convenient entry to many otherwise difficult to prepare stereochemically defined alkenyl nitriles, facilitating the synthesis of a large variety of biologically active compounds. 3,4-Dichloroaryl-substituted *Z*-alkenyl nitrile **2af** (Fig. 6a), obtained in 98% yield and 97:3 *Z*:*E* ratio, is an intermediate en route to LR5182 (Fig. 1). The cross-metathesis approach is more efficient than the previously utilized Knoevenagel condensation (aryl aldehyde and cyano acetic acid)/decarboxylation at elevated temperature, which generated an 80:20 *Z*:*E* mixture[9].

The union of glycosyl bromide **14** and allylic alcohol **15**, both commercially available, followed by catalytic stereoretentive cross-metathesis delivered **alliarinoside peracetate** in 39% overall yield as a single olefin isomer (>98:2 *Z*:*E*) (Fig. 6a). Previously reported protocols either generate a near-equal mixture of alkene isomers (Horner–Wadsworth–Emmons-type processes)[58,59] or demand initial generation of a *Z*-alkenyl iodide (catalytic cross-coupling), requiring at least two additional operations[27]. Also noteworthy is bis-alkenyl nitrile **2ag**, accessed by a double-cross-metathesis in 57% yield and >98:2 *Z*,*Z*':*Z*,*E*' (Fig. 6a), and utilized in the total synthesis of perhydrohistrionicotoxin (via **16**)[60]. This compound was formerly accessed by a route that included synthesis of an alkene via the corresponding bis-aldehyde, the preparation of which necessitated an additional deprotection step (acetal removal), while the highly toxic hexamethylphosphoramide was required to facilitate alkylation.

The *E*-alkenyl nitriles **5n** and **5o** were isolated in 82% and 60% yield, and 95:5 and 97:3 *E*:*Z* ratio, respectively (Fig. 6b). These compounds have been converted to anticancer agent CC-5079[13] by the catalytic Heck reaction and to the antidepressant indatraline[61] via **17**, by a similar process, followed by catalytic enantioselective hydrogenation[6]. The *Z* isomer of CC-5079[62] is more potent and must therefore be synthesized selectively. Furthermore, the cross-coupling processes are considerably more efficient with an *E* alkene[6]; in line with such findings, we were unable to detect any of the desired tri-substituted alkene when *Z*-**5n** was subjected to the conditions used for the reaction of the corresponding *E* isomer (Fig. 6b). In previous studies, the requisite 1,2-di-substituted alkenes could only be generated as 80:20 *E*:*Z* mixtures by Wittig-type reactions[6,13], and removal of stoichiometric amounts of the phosphine-oxide side product often required difficult chromatographic procedures.

We then set out to address another major shortcoming, namely the instability of such species to an alcohol or a carboxylic acid moiety. In the case of a substrate that bears a hydroxy group, we find that by simply treating the alkenes with 1.1 equiv. of commercially available HB(pin) (pin, pinacolato) at ambient temperature for 15 min and then the requisite amount of the Mo complex for 4 h, followed by silica gel chromatography, the desired alkenyl nitrile product can be obtained in high yield and stereochemical purity. The conversion of oleyl alcohol to **2ah** is a case in point (85% yield, >98:2 *Z*:*E*; Fig. 6c). For a starting material containing a carboxylic acid moiety, the most effective approach is to use $HB(trip)_2$ (trip, 2,4,6-triisopropylphenyl)[63], a reagent that can be prepared easily on a gram scale from commercially available materials in two steps (70–75% overall yield). Transformation of oleic acid to alkenyl nitrile **2ai** is representative (60% yield, >98:2 *Z*:*E* versus 47% yield, >98:2 *Z*:*E* with HB(pin)). This development promises to expand the practical utility of Mo-based catalysts considerably.

Conclusions

We have developed a broadly applicable set of catalytic methods for the preparation of *Z*- and *E*-di-substituted and tri-substituted alkenyl nitriles in high stereoisomeric purity. We have shown that, by considering the various attributes of the Mo-based complex (MAP or MAC) and the electronic and steric attributes of the intermediate alkylidenes and metallacyclobutanes, catalysts providing access to stereoisomerically enriched alkenyl nitriles, from those that bear a linear aliphatic substituent to those that contain a hindered α-branched or aryl moiety, can be identified. Similarly notable is that an equimolar amount of the two cross partners is not only sufficient, but is optimal, for achieving high efficiency in a cross-metathesis reaction. We introduce the use of easily accessible boron hydride compounds for in situ temporary protection of the hydroxy and carboxylic acid groups, which can otherwise quickly deactivate a Mo-based catalyst. The ability to access an alkenyl nitrile isomer with high stereochemical purity allows for significant enhancement in the efficiency with which many biologically active entities are prepared.

Data availability

X-ray crystallographic data for compound **9a**, are freely available from the Cambridge Crystallographic Data Centre (CCDC 1861573). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/. All other data in support of the findings of this study are available within the Article and its Supplementary Information or from the corresponding author upon reasonable request.

Received: 13 September 2018; Accepted: 12 February 2019;
Published online: 01 April 2019

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Acknowledgements

This research was supported by a grant from the National Institutes of Health (GM-59426). T.T.N. was supported as a John LaMattina Graduate Fellow in Chemical Synthesis. The authors thank S. Torker for helpful discussions.

Author contributions

Y.M., T.T.N. and M.J.K. identified the optimal catalyst and conditions, developed the method and performed the experiments to demonstrate utility. The Mo complexes used in this study were designed and developed as part of a long-standing collaboration between the research groups of R.R.S. and A.H.H. A.H.H. directed the investigations and composed the manuscript with revisions provided by the other authors.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information is available for this paper at https://doi.org/10.1038/s41557-019-0233-x.

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