a lower abundance of two species from the family Rikenellaceae, *Alistipes finegoldii*, and *Alistipes senegalensis*, whereas blood lipids were associated with two other species, *Alistipes shahii* and *Alistipes putredinis* (table S11). Notably, these species were also associated to certain dietary factors and drugs. For instance, a high level of *A. shahii*, which was associated to low triglyceride (TG) levels, was linked to higher fruit intake (q = 0.00027). Individuals with a higher abundance of *A. shahii* had a higher number of different species in the gut (species richness) (Spearman r = 0.2, adjusted $P = 3.96\text{x}10^{-11}$), suggesting a beneficial effect on the microbial ecosystem (table S18). Correlations with the number of different species were also found for other bacteria, including *Roseburia hominis*, *Coprococcus catus*, and *Barnesiella intestinihominis* and unclassified species from genus *Anaerotruncus* that also showed correlation both with fruit, vegetable, and nut consumption and with intrinsic phenotypes like HDL, triglycerides, and quality of life. On the basis of these data, it would be interesting to explore the potential to modulate disease-associated species through medication or diet, although we still need to address the causality and underlying mechanism.

Our study revealed significant associations between the gut microbiome and various intrinsic, environmental, dietary and medication parameters, and disease phenotypes, with a high replication rate between MGS and 16*S* rRNA gene sequencing data from the same individuals. Moreover, our study provides many new intrinsic and exogenous factors that correlate with shifts in the microbiome composition and functionality that potentially can be manipulated to improve microbiome-related health, and we hope our results will inspire further experiments to explore the biological relevance of associated factors. Although most of the factors that we assessed exerted a very modest effect, fecal levels of CgA showed a high potential as a biomarker for gut health.

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/352/6285/565/suppl/DC1
Materials and Methods
Figs. S1 to S13
Tables S1 to S19
References (*31*–*54*)

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ORGANIC CHEMISTRY

Kinetically controlled *E*-selective catalytic olefin metathesis

Thach T. Nguyen,[1] Ming Joo Koh,[1] Xiao Shen,[1] Filippo Romiti,[1] Richard R. Schrock,[2] Amir H. Hoveyda[1]*

A major shortcoming in olefin metathesis, a chemical process that is central to research in several branches of chemistry, is the lack of efficient methods that kinetically favor *E* isomers in the product distribution. Here we show that kinetically *E*-selective cross-metathesis reactions may be designed to generate thermodynamically disfavored alkenyl chlorides and fluorides in high yield and with exceptional stereoselectivity. With 1.0 to 5.0 mole % of a molybdenum-based catalyst, which may be delivered in the form of air- and moisture-stable paraffin pellets, reactions typically proceed to completion within 4 hours at ambient temperature. Many isomerically pure *E*-alkenyl chlorides, applicable to catalytic cross-coupling transformations and found in biologically active entities, thus become easily and directly accessible. Similarly, *E*-alkenyl fluorides can be synthesized from simpler compounds or more complex molecules.

Olefin metathesis is an enormously enabling chemical process for which well-defined catalysts were discovered nearly three decades ago (*1*, *2*). Kinetically controlled *Z*-selective reactions were introduced in 2009 (*3*), but there are no corresponding transformations that are broadly applicable and through which *E* isomers can be synthesized in high yield. Although *E*-selective cross-metathesis (CM) reactions involving Ru catechothiolate complexes (*4*) were reported very recently in 2016, only the thermodynamically preferred *E* isomers of simple (unfunctionalized) 1,2-disubstituted aliphatic alkenes could be obtained in 3 to 31% yield (*5*). *E* alkenes are often lower in energy and thus generated preferentially; nonetheless, olefin metathesis strategies that furnish them are needed for several reasons: The energy gap between the geometric forms is often too small to ensure high selectivity; *E* olefin isomers are not always thermodynamically preferred; and, in many cases,

[1]Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, MA 02467, USA. [2]Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139, USA.
***Corresponding author. Email: amir.hoveyda@bc.edu**

E and *Z* alkene isomers cannot be easily separated. Perhaps the most notable instance relates to acyclic alkenyl halides, where hyperconjugative donation of electron density from a filled σ_{C-H} into a low-lying vacant $\sigma^*_{C-halogen}$ orbital causes stabilization of the *Z* isomers (*6*). Herein, we disclose the design of efficient and kinetically *E*-selective CM reactions through which *E*-alkenyl chlorides and fluorides can be obtained in good yield and with exceptional stereoselectivity.

E-1,2-Disubstituted chloroalkenes can be used in catalytic cross-coupling, one of the most influential transformations in modern chemistry (*7*). These isomers are found in biologically active molecules as well (*8*); two examples are pitinoic acid B, a potent anti-inflammatory agent (*9*), and kimbeamide A, a natural product with notable antitumor activity (*10*) (Fig. 1A). *E*-Alkenyl fluorides are of interest because of the substantial value of organofluorines in medicine (*11*) and agrochemicals (*12*). A biologically active fluoroalkenyl entity that inhibits *Bacillus subtilis S*-ribosyl-homocysteinase (LuxS) (*13*) is presented in Fig. 1A; only an *E*/*Z* mixture of this compound has been evaluated, due to the difficulties associated with accessing a stereoisomerically pure alkenyl fluoride. Functionalization of a stereochemically defined fluoro-substituted olefin would facilitate preparation of other desirable F-containing molecules (*14*).

Equally important, by conversion of an alkene to an *E*-alkenyl fluoride through catalytic and stereoselective CM, a hydrogen may be substituted with a fluorine atom within a complex molecule, such as the methyl ester of the potassium channel activator isopimaric acid (Fig. 1A) (*15*). Such modification can result in the alteration and/or enhancement of the molecule's biological activity (*16*, *17*).

E-1,2-Disubstituted alkenyl chlorides can be prepared in a number of ways (see the supplementary materials for comprehensive bibliography). Terminal alkynes may be transformed to nucleophilic *E*-alkenylmetal intermediates that are then treated with an electrophilic halogen source (*18*–*20*). *E*-Alkenyl boronic acids, prepared from a terminal alkyne by a two-step procedure (such as hydroboration followed by hydrolysis), can be converted by a third step to the corresponding chlorides (*21*), which may alternatively be synthesized by treatment of an aldehyde with excess chromium chloride and chloroform (*22*). A small number of procedures furnish *E*-alkenyl fluorides from aldehydes (*23*) or alkynes (*24*, *25*), but none are catalytic and several require stoichiometric amounts of strongly basic [e.g., *tert*-butyllithium (*t*-BuLi)] and/or toxic reagents (e.g., hexamethylphosphoramide). In another case, a stereochemically defined fluorine-substituted alkenyl tosylate must first be secured by the use of *n*-BuLi and $LiAlH_4$ before it is subjected to a cross-coupling reaction (*26*). Efficient and *E*-selective catalytic CM strategies that deliver alkenyl chlorides and fluorides (Fig. 1B)—involving robust, abundant, and less costly alkenes (versus aldehydes or alkynes)—would complement the aforementioned methods, offering a more direct and economical approach on most occasions.

We recently demonstrated that molybdenum-based monoaryloxide pyrrolide (MAP) complexes possess the distinctive ability to promote efficient *Z*-selective CM reactions that afford alkenyl halides (*27*). These transformations probably proceed

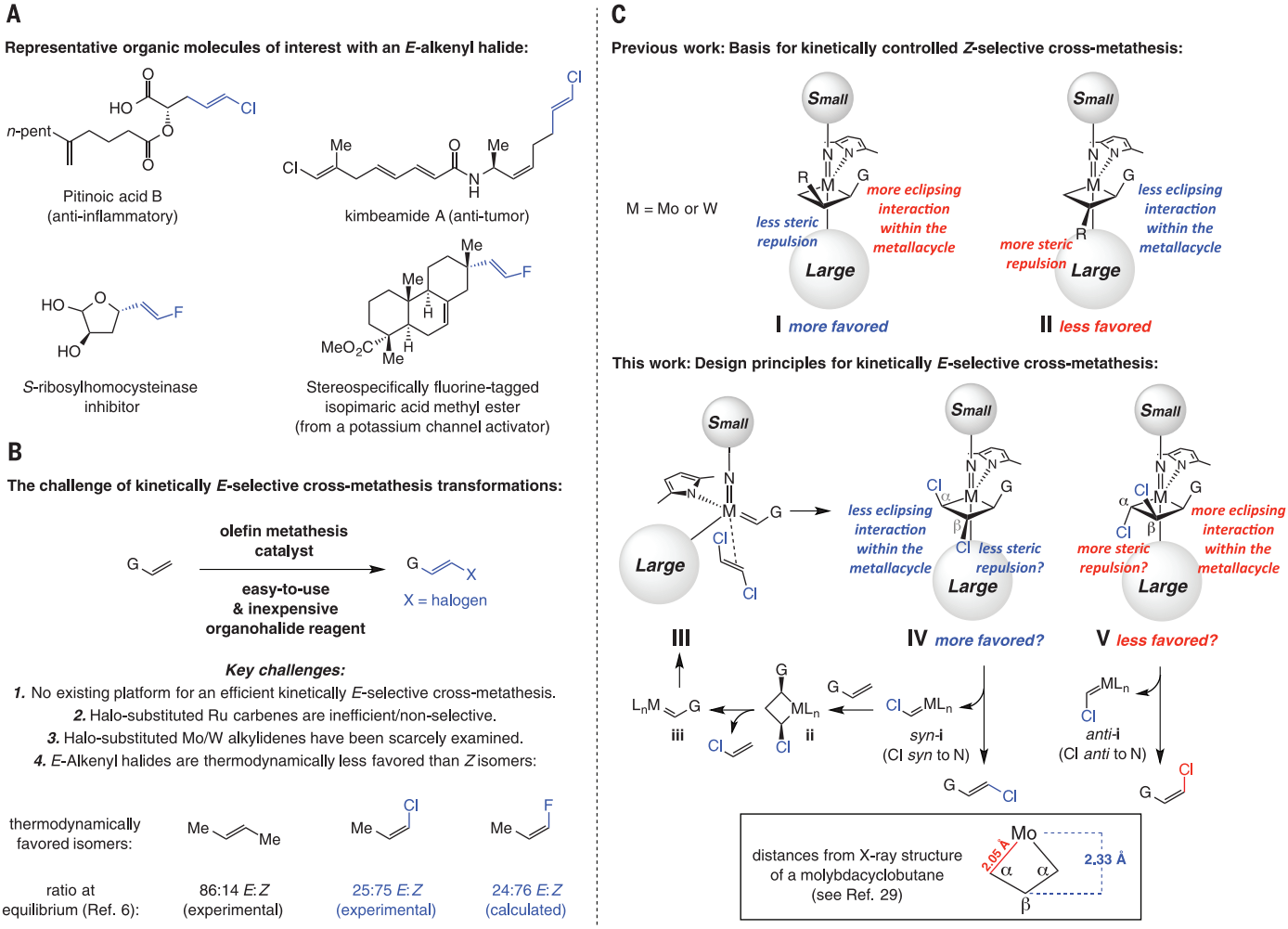

Fig. 1. Kinetically *E*-selective CM: potential effect and challenges. (**A**) Examples of biologically active organic molecules that contain an *E* alkenyl chloride or fluoride. (**B**) Challenges in designing a kinetically *E*-selective CM route to prepare alkenyl halides. (**C**) Analysis of stereochemical models that suggest a strategy for the design of kinetically *E*-selective olefin metathesis processes. pent, pentane; Me, methyl; Ln, ligand. G and R denote functional groups.

via olefin-derived alkylidenes that then react with a halo-olefin reagent. Reactions with widely used complexes (e.g., dichloro-Ru carbenes) are either inefficient and/or nonstereoselective (*27*). Designing a kinetically *E*-selective variant, however, poses several distinct challenges. Not only was there no blueprint for high-yielding and kinetically controlled *E*-selective olefin metathesis when these studies were initiated, but the desired products would also be thermodynamically less favored: The *Z*-haloalkenes are the more preferred isomers, as indicated by the relative energies shown in Fig. 1B (*6*).

In contemplating a strategy for achieving kinetic *E* selectivity, we evaluated the stereochemical model proposed for the corresponding *Z*-selective CM reactions (*28*), realizing an implicit principle. Reaction via metallacyclobutane **I** is preferred versus reaction via **II** (Fig. 1C) because the eclipsing interaction between the C–R and C–G bonds in **I** is less destabilizing than the steric repulsion between the C–R unit and the larger catalyst ligand in **II**. The question then became: If an alkylidene complex were to react with *E*-1,2-dichloroethene via **III**, would metallacycle **IV** or its corresponding diastereomer **V** be favored? In **IV**, the eclipsing interactions between C_α–G or C_α–Cl and C_β–H bonds in a structurally flat (*29*) molybdacyclobutane (nonpuckered due to the longer C–Mo bonds) would be less severe compared with those involving the C_α–G and C_β–Cl bonds of **V** (the C_α–C_α distance is ~2.75 Å). Whereas in **IV**, which would release an *E*-alkene, the C_β–Cl bond is oriented toward the more sizeable ligand, in **V** it would be a C_α–Cl unit that is so disposed. Moreover, collapse of **IV** would yield a presumably lower-energy *syn*-alkylidene (Cl pointing toward the imido ligand) (*30*). The resulting highly active (*27*) chloro-substituted *syn*-alkylidene (*syn*-**i**) would then react with the olefin substrate via the lower-energy α,α′-disubstituted metallacyclobutane **ii** (minimal eclipsing interaction or steric repulsion with the aryloxide ligand, with G and Cl oriented toward the smaller imido unit) to generate complex **iii**, which could be converted to **III**. It was unclear which of the latter pathways would be dominant and how high the stereoselectivity would be.

In search of more clues, we examined the crystal structure of an unsubstituted molybdacyclobutane derived from a MAP complex (*29*), noting that the molybdenum–C_β distance is longer than the metal–C_α bond length (2.33 versus 2.05 Å) (Fig. 1C). This observation suggested that there might be less steric repulsion between the halogen and the larger aryloxide ligand in **IV** (versus in **V**), which could translate to an *E*-selective process. However, the above analysis pointed to another possible complication: The vinyl chloride by-product might cause a diminution in selectivity by reaction via metallacyclobutane **I**, affording the thermodynamically favored *Z*-alkenyl halide. The use of vacuum (*28*) would not be an option: Although the volatility of *E*-1,2-dichloroethene allows it to be easily handled and readily removed (boiling point: 48°C), a substantial amount (if not all) would be lost under even mildly reduced pressure.

The above reasoning implied that an entirely distinct catalyst construct would not be needed for achieving high kinetic *E* selectivity and could be validated experimentally: CM of alkene **1** and

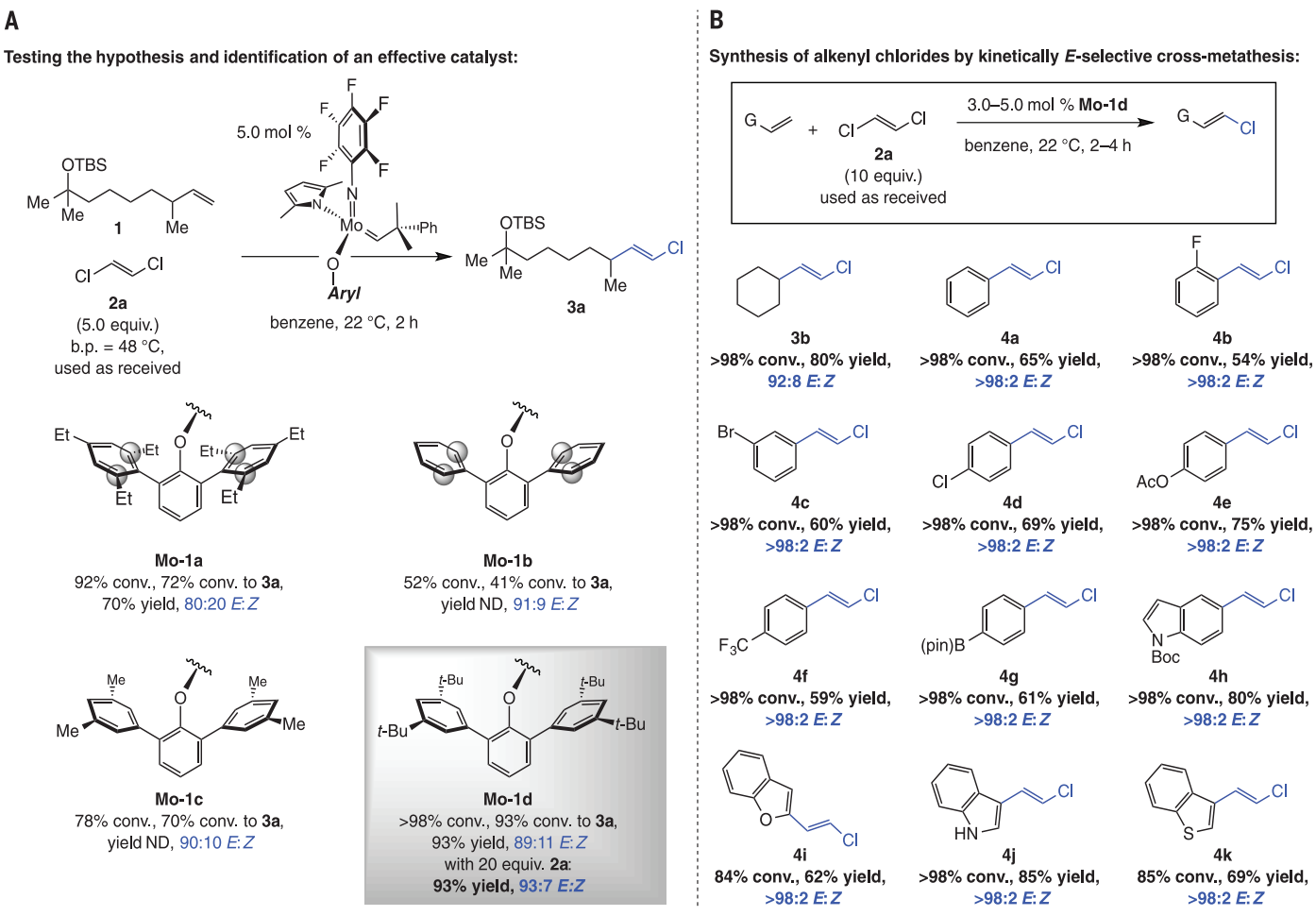

Fig. 2. Kinetically controlled *E*-selective CM reactions that generate alkenyl chlorides. (**A**) Model studies involving commercially available and easy-to-handle *E*-dichloroethene (**2a**) indicated that structural adjustment of the catalyst's aryloxide ligand is needed for maximal efficiency and stereoselectivity. b.p., boiling point; ND, not determined. (**B**) A range of alkyl-, aryl-, and heteroaryl-substituted *E*-alkenyl chlorides can be obtained in up to >98/2 *E*/*Z* selectivity. Yields are for purified products. TBS, *tert*-butyldimethylsilyl; Et, ethyl; G, functional group; Ac, acetyl; pin, pinacolato; Boc, *tert*-butoxycarbonyl. See the supplementary materials for details.

E-1,2-dichloroethene **2a** with 5.0 mol % **Mo-1a** (Fig. 2A) affords *E*-alkenyl chloride **3a** with an 80/20 *E*/*Z* ratio. Equally encouraging was that the products were obtained in 70% yield after purification, without resorting to long reaction times or elevated temperatures (2 hours, 22°C).

We envisioned that removing the ortho aryl substituents within the aryloxide ligand (highlighted in **Mo-1a** and **Mo-1b**, Fig. 2A) might alleviate steric repulsion with the C_β chlorine atom, favoring reaction via **IV**. We therefore prepared and examined the selectivity of the CM reaction with **Mo-1b**, which led to substantially improved stereoselectivity (91/9 *E*/*Z*) but lower efficiency (41% versus 72% conversion with **Mo-1a**), probably due to competitive bimolecular alkylidene decomposition (*30*). To retain high selectivity without efficiency loss, we evaluated the performance of **Mo-1c** and **Mo-1d** and established that either complex can produce **3a** with appreciable efficiency in ~90% *E* selectivity (Fig. 2A). With **Mo-1d** and 20 equivalents (equiv.) of **2a**, selectivity improved to 93% *E*, probably due to diminished competitiveness of nonselective CM involving the vinyl chloride by-product (via **I**, Fig. 1C). Excess **2a** was easily removed in vacuo.

An array of *E*-alkenyl chlorides was accessed by reaction between a terminal olefin and commercially available **2a**, which was used as received (no purification). Transformations may be performed with sterically congested alkenes: cyclohexyl-substituted **3b** was obtained in 80% yield and 92/8 *E*/*Z* selectivity. CM with various aryl (**4a** to **4g**) and heteroaryl α-olefins (**4h** to **4k**) generated the products in 54 to 85% yield after 4 hours at room temperature. The difference between the conversion and yield is largely due to the formation of homocoupling products. We did not detect the *Z* isomer in any reaction [by analysis of 400-MHz ^{1}H nuclear magnetic resonance (NMR) spectra of the unpurified product mixtures]. Product **4a** was obtained from the reaction with *E*-β-methyl styrene. Aryl halides **4c** and **4d** and arylboronate **4g** are noteworthy because their synthesis through cross-coupling could pose chemoselectivity issues (*31*, *32*).

Preparation of *E*-1,2-disubstituted alkenyl chlorides with unhindered aliphatic alkenes (versus

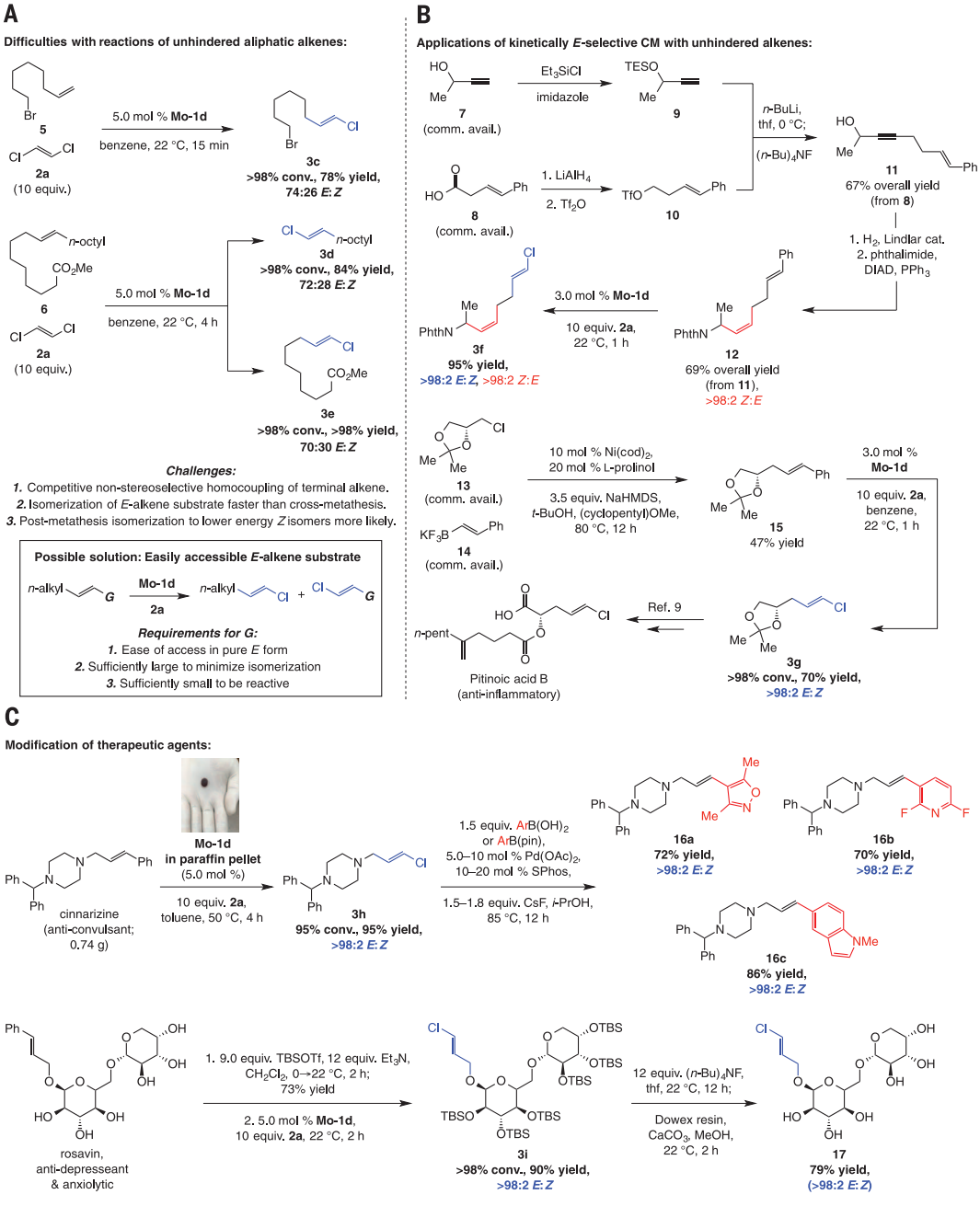

Fig. 3. Synthesis of unhindered *E*-alkenyl chlorides by catalytic and stereoselective substituent swapping. (**A**) With unhindered aliphatic α-olefins, catalytic CM with **2a** is efficient but moderately *E*-selective. This may be attributed to the rapid formation of an *E*/*Z* mixture of 1,2-disubstituted alkenes, formed by homocoupling, that reacts with **2a**. Thus, readily available *E*-1,2-disubstituted alkenes may be used instead (**G** = Ph). (**B**) Through the use of easily accessible β-alkyl styrenes, a number of biologically active compounds can be readily prepared. (**C**) The catalytic method, in combination with catalytic cross-coupling, may be used to access a variety of potentially valuable derivatives. An air- and moisture-resistant paraffin tablet containing a Mo MAP complex can easily be used. Yields are for purified products. TES, triethylsilyl; thf, tetrahydrofuran; Tf, trifluoromethanesulfonyl; DIAD, di(*iso*-propyl)azodicarboxylate; Phth, phthalyl; Ph, phenyl; cod, cyclooctadiene; HMDS, hexamethyldisilazide; *i*-Pr, *iso*-propyl; SPhos, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl. See the supplementary materials for details.

those with an allylic substituent as in **3a** and **3b**) presented another complication (Fig. 3A). CM was efficient with olefin **5**, affording chloroalkene **3c** in 78% yield, but selectivity was moderate (74% *E* isomer). Other than the possibility of a more facile post-metathesis isomerization of the relatively uncongested olefin, this discrepancy might originate from a more competitive and moderately selective generation of homocoupling products, which can then react with **2a** to afford isomeric mixtures. Further, the finding that CM with *E*-1,2-disubstituted olefin **6** produced **3d** and **3e** with similar selectivity (~70/30 *E*/*Z*) implies that 1,2-dialkyl olefins might undergo rapid nonstereoselective isomerization by self-metathesis before reaction with **2a**.

The above data show that alkylidenes derived from **Mo-1d** can catalyze CM between 1,2-disubstituted alkenes with *E*-dichloroethene **2a**: Within 4 hours at room temperature, **3d** was obtained in 84% yield despite its volatility, and **3e** was isolated in >98% yield. Such high activity indicated the need for a strategy for accessing alkenyl chlorides with better stereocontrol. We surmised that with an appropriate *E*-1,2-disubstituted olefin, chloro-olefins might become accessible with kinetic *E* selectivity by what amounts to an efficient catalytic and stereospecific group exchange. The ideal substituent would be easily and efficiently accessible and would be sufficiently large to discourage self-metathesis and adventitious *E*-to-*Z* isomerization, but not so large as to inhibit CM with **2a**. We selected *E*-β-substituted styrenes because these comparatively robust compounds can be prepared by various methods, as showcased by the findings in Fig. 3, B and C.

The first example (Fig. 3B) is a concise synthesis of the amine segment of kimbeamide A (compare with Fig. 1A). The substrate (**12**) was synthesized from commercially available (racemic or as either enantiomeric form) propargyl alcohol

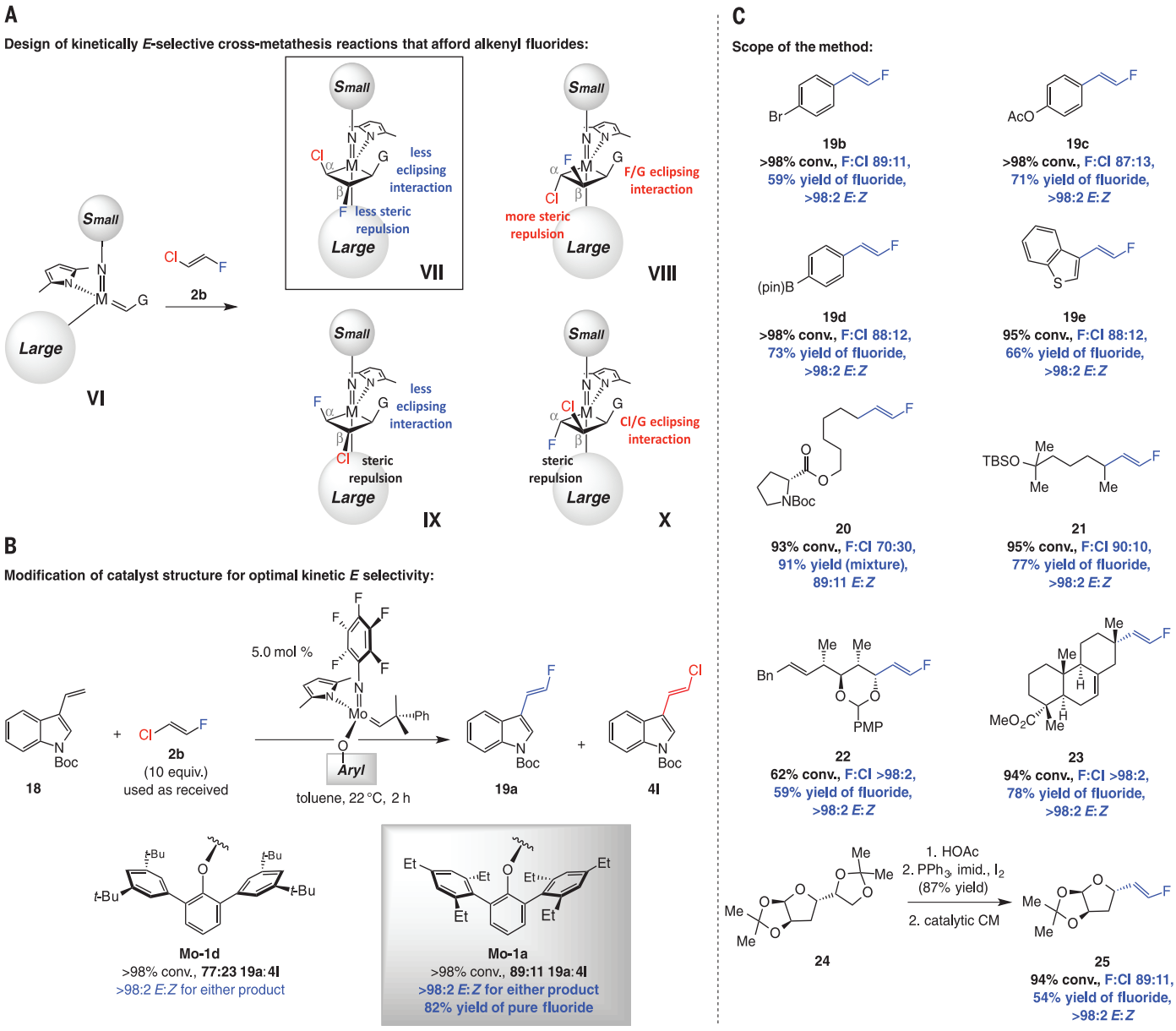

Fig. 4. Preparation of *E*-alkenyl fluorides by catalytic CM. (**A**) Mechanistic analysis that serves as the basis for the development of the catalytic processes. (**B**) Examination of a model process and identification of an effective complex. (**C**) With **Mo-1a** and commercially available *E*-1-chloro-2-fluoroethene **2b**, an assortment of *E*-1,2-alkenyl fluorides can be synthesized efficiently and with *E*/*Z* ratios that are typically >98/2. Yields are for purified products. G, functional group; Bn, benzyl; PMP, *para*-methoxyphenyl; imid., imido. See the supplementary materials for details.

(**7**) and carboxylic acid (**8**). Partial hydrogenation of enyne **11**, followed by a Mitsunobu reaction, afforded diene **12** (>98% *E*-β-alkylstyrene, >98% *Z* allylic amine; 69% overall yield). Subsequent treatment with 3.0 mol % **Mo-1d** and **2a** generated **3f** in 95% yield and >98/2 *E*/*Z* selectivity after 1 hour at room temperature. The *Z*-alkene was left untouched in the course of CM (>98% *Z* at the allylic amine site), highlighting exceptional chemoselectivity. Another case corresponds to pitinoic acid B (Fig. 3B); here, catalytic cross-coupling of commercially available and enantiomerically pure alkyl chloride **13** and trifluoroborate **14** afforded **15** (*33*) directly in 47% yield. *E*-β-Substituted styrene **15** was then converted to *E*-alkenyl chloride **3g**, which has been formerly transformed to the anti-inflammatory agent (*9*).

Other than facilitating synthesis of biologically active compounds, the approach offers a convenient route for their modification—two cases are shown in Fig. 3C. We were able to convert 0.74 g of cinnarizine, a potent anticonvulsant agent, to *E*-alkenyl chloride **3h** in 94% yield and with >98% *E* selectivity (5.0 mol % **Mo-1d**, 10 equiv. **2a**, toluene, 22°C, 4 hours). Importantly, the Mo MAP complexes can be delivered in the form of air- and moisture-resistant paraffin pellets. For example, with a pellet containing **Mo-1d** (Fig. 3C) (~5 mg in ~95 mg of paraffin wax; 5.0 mol % loading), reaction of cinnarizine with **2a** cleanly afforded **3h** in 95% yield (>98% *E* isomer). To ensure complete release of the MAP species, the transformation was performed at 50°C in toluene under nitrogen atmosphere (Fig. 3C). After 4 hours, the resulting mixture was purified by routine silica gel chromatography (see the supplementary materials for further details). The entire procedure was carried out in a fume hood.

Compounds such as **3h** are a convenient entry to analogs that cannot be accessed efficiently or with high *E* selectivity by alternative methods, including direct CM; the three examples shown in Fig. 3C (**16a** to **16c**), obtained by catalytic cross-coupling with commercially available boronic acids or pinacol esters (*34*), are illustrative. In another case, a persilylated derivative of the antidepressant rosavin was converted to *E*-alkenyl chloride **3i** in 90% yield and >98% *E* selectivity. As with cinnarizine-derived **3h**, analogs may be easily synthesized via **3i** or its deprotected form **17**. The applications to pitinoic acid B, cinnarizine, and rosavin underscore the advantages of the CM approach to synthesis of *E* alkenyl chlorides versus the existing methods involving terminal alkynes or aldehydes (see above).

Reactions with 1,2-dibromoethene, which can be purchased only as an isomeric mixture (64/36 *E*/*Z*), were inefficient and nonselective. For example, CM of alkene **1** and 1,2-dibromoethene (8.0 equiv.) with 5.0 mol % **Mo-1d** proceeded to 16% conversion after 4 hours, with 61/39 *E*/*Z* selectivity.

Kinetically *E*-selective reactions that might furnish fluoro-substituted olefins present the additional issue of cost and practicality: *E*-1,2-difluoroethene is too expensive and volatile (boiling point: −42°C). One option would be to use *E*-1-chloro-2-fluoroethene (**2b**), which is commercially available, economically far more viable, and easier to use (boiling point: −4°C). The issue was whether with **2b** the transformations would be appreciably product-selective (alkenyl fluoride versus chloride), as CM can proceed via four distinct metallacyclobutane isomers (**VII** to **X**, Fig. 4A), only one of which would produce the desired *E*-fluoroalkene (**VII**). We posited that CM might be preferentially channeled via **VII** for several reasons: (i) Overall, there should be less steric strain in **VII** and **IX** versus **VIII** and **X**, respectively. There are no severe eclipsing interactions in **VII** and **IX**, and steric repulsion between a halogen atom and the larger aryloxide ligand would be more costly at the C_α position (as compared with **VIII** and **X**, respectively). (ii) Matching polarity of the Mo=C and C=C bonds of the dihaloethene, as indicated by the distinct chemical shifts in the ^{1}H NMR spectrum of the latter [δ 6.90 and 6.15 parts per million for CH(F) and CH(Cl), respectively, in $CDCl_3$], as well as the smaller size of a fluorine atom (0.42 Å atomic radius versus 0.79 Å for Cl), should favor **VII** over **IX**. In the event (Fig. 4B), CM between aryl alkene **18** and **2b** (solution in toluene) with 5.0 mol % **Mo-1d** favored the formation of alkenyl fluoride **19a** over the chloro-substituted alkene **4l** (77/23). Both products were generated with >98% *E* selectivity.

While contemplating how we could improve the ratio of fluoroalkenes to chloroalkenes, we noted that because **19a** and **4l** are formed with >98% *E* selectivity, reaction via **IX** is probably the major competing pathway. If so, reverting to the original MAP complex **Mo-1a**, containing 2,6-disubstituted aryl moieties [versus 3,5-(*t*-Bu)$_2$ in **Mo-1d**], could prove beneficial. We hoped that this alteration would further exacerbate steric repulsion between the substituent at C_β and the aryloxide in **IX** (C_β–Cl), as compared with **VII** (C_β–F), because of the smaller size of a fluorine atom and the shorter C–F bond length (1.35 Å versus 1.80 Å for C–Cl). Indeed, with **Mo-1a**, under otherwise identical conditions, CM of **18** and **2b** proceeded to >98% conversion in 2 hours at ambient temperature (Fig. 4B), generating **19a** with improved selectivity (89% versus 77% **19a** with **Mo-1d**). Pure *E*-fluoroalkene **19a** could be isolated in 82% yield (silica gel chromatography). The use of bulkier aryloxides (e.g., *iso*-propyl versus -ethyl substituents) led to lower conversion.

A variety of *E*-alkenyl fluorides may be directly accessed (Fig. 4C); **2b** was used without purification, and reactions generated up to >98/2 fluoroalkene/chloroalkene selectivity. As with **19a**, pure alkenyl fluorides could easily be obtained in most cases (54 to 78% yield). In only one instance (**20**) did we detect any of the *Z*-alkene. Different styrenes, including those with versatile functional groups (e.g., **19b** and **19d**), were effective cross partners. Several examples involving transformations with alkyl-substituted α-olefins are presented in Fig. 4C. Similar to the cases in Fig. 3, reactions with the less congested alkyl-substituted olefins were less *E*-selective (compare **20** versus **21**). Unlike when symmetrical **2a** was used, CM between *E*-β-alkyl styrenes and **2b** led to substantial amounts of β-fluorostyrene and aliphatic chloroalkene products. Formation of **22** (>98% fluoro product, 59% yield, >98% *E*) shows that acid-sensitive moieties, such as a *para*-methoxyphenyl acetal, are tolerated. The transformation leading to fluorine-tagged isopimaric acid methyl ester (**23**) involves a particularly congested alkene. A precursor to the aforementioned LuxS inhibitor, alkenyl-fluoride **25**, was prepared in three steps from **24** in 51% overall yield with >98% *E* selectivity. The present approach affords the *E*-fluoroalkene in its stereoisomerically pure form and is substantially more efficient than the previously reported route (7% overall yield from **24**) (*13*).

Thus, we have devised strategies that allow for olefin metathesis processes to proceed with high efficiency and kinetic *E* selectivity, delivering a valuable set of organic halides where *Z* isomers are thermodynamically favored. The possibility of using easy-to-handle paraffin tablets, soon to be commercially available, further enhances the potential effect of this approach (*35*). The strategies delineated above are expected to lead to the development of other efficient, practical, and kinetically *E*-selective olefin metathesis transformations; this is especially relevant to cases where there is minimal energy difference between the two stereoisomeric forms and/or the *Z*-alkene is preferentially generated with the more commonly used catalysts (e.g., alkenyl sulfides, alkenyl nitriles, or enynes) (*36*).

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SUPPLEMENTARY MATERIALS

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NMR Spectra

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CHEMISTRY

Conformational photoswitching of a synthetic peptide foldamer bound within a phospholipid bilayer

Matteo De Poli,[1] Wojciech Zawodny,[1] Ophélie Quinonero,[1] Mark Lorch,[2] Simon J. Webb,[1,3] Jonathan Clayden[4]*

The dynamic properties of foldamers, synthetic molecules that mimic folded biomolecules, have mainly been explored in free solution. We report on the design, synthesis, and conformational behavior of photoresponsive foldamers bound in a phospholipid bilayer akin to a biological membrane phase. These molecules contain a chromophore, which can be switched between two configurations by different wavelengths of light, attached to a helical synthetic peptide that both promotes membrane insertion and communicates conformational change along its length. Light-induced structural changes in the chromophore are translated into global conformational changes, which are detected by monitoring the solid-state ^{19}F nuclear magnetic resonance signals of a remote fluorine-containing residue located 1 to 2 nanometers away. The behavior of the foldamers in the membrane phase is similar to that of analogous compounds in organic solvents.

In the field of synthetic biology, substantial progress has been made in the use of light to control biological function by customization of membrane-bound proteins with artificial chromophores (*1*). In parallel, synthetic molecular photoswitches have been used to control chemical processes such as ligand binding and catalysis in isotropic solution (*2*, *3*). Here, we report the design and synthesis of a fully synthetic photoresponsive helical molecule that can insert into a phospholipid bilayer. We show that light-induced switching between configurational isomers can be used to induce global conformational change that propagates over several nanometers in a synthetic molecule within a membrane environment. Membrane-bound artificial photoswitchable synthetic structures capable of translating photochemical information into extended conformational changes, in a manner reminiscent of the operation of natural photoswitchable proteins such as rhodopsin (*4*), could ultimately provide opportunities for controlling chemical processes within membrane-defined compartments.

A detailed understanding of how the phospholipid bilayer affects long-range conformational changes in membrane-bound molecules is impeded by the difficulty of directly observing conformational changes in the membrane phase and by a lack of examples of biomolecules that adopt well-defined structures both in the membrane phase and in solution (*5*–*7*). A simplified yet functional synthetic analog of the membrane-spanning domains of natural proteins, containing in-built spectroscopic handles that are diagnostic of conformation, would be a powerful tool. Dynamic conformational changes in a membrane-bound molecule could then be explored, free of the complexities of protein structure, and compared with analogous changes in isotropic solution.

Given the requirement for a synthetic structure with a tendency to embed into membranes and with well-understood conformational dynamics, we chose to explore the membrane insertion of foldamers [synthetic polymeric molecules with well-defined conformations (*8*)] built from oligomers of the achiral amino acid Aib (2-aminoisobutyric acid; Fig. 1A, shown in black). These Aib foldamers show a strong preference for helical conformations (*9*) and therefore have two principal conformational states, in which the helix adopts a global left- or right-handed screw sense. Furthermore, helical Aib-rich peptides have a known tendency to insert into phospholipid bilayers because they occur naturally in the form of membrane-disrupting fungal antibiotics known as peptaibols (*10*).

A chiral amino acid residue was covalently linked to the N terminus of an $(Aib)_n$ foldamer and then N-acylated by an azobenzene motif (Fig. 1A, shown in red) to enable photochemical induction of conformational change (*11*). This motif manifests well-understood photochemical interconversion between *E* and *Z* configurations and thus offers a reversible light-driven means of initiating conformational reorganization from the terminus of the oligomer. The influence of azobenzene geometry on the relative population of conformational states of the $(Aib)_n$ helix was first explored in solution using foldamers **1** (Fig. 1A) that carry a C-terminal glycinamide as a solution-state ^{1}H nuclear magnetic resonance (NMR)–compatible reporter of helical conformation (*12*). An unequal conformational population can result when the first turn of a helical Aib-containing foldamer incorporates a single chiral tertiary amino acid residue, and the magnitude of this bias depends on the detailed structure of the first (N-terminal) β-turn of the helix (*12*).

^{1}H NMR spectra of valine-containing foldamers **1a** to **1d** were acquired in deuterated methanol (CD_3OD) solution as their thermally equilibrated mixtures of *E* (major) and *Z* (minor) geometrical isomers (analogous behavior in phenylalanine-containing foldamers is reported in table S1). Methanol has a polarity similar to that of the interfacial region of the phospholipid bilayer and prevents aggregation of the foldamers in solution (*13*, *14*). Because the left- and right-handed conformational states of an $(Aib)_n$ helix interconvert on a submillisecond time scale at ambient temperature, the ^{1}H NMR spectrum that is observed results from a weighted average of both conformational states, reflecting their relative population. The diagnostic feature in the averaged spectra of foldamers **1** is the signal or signals due to the methylene protons of the C-terminal glycinamide residue. A single signal indicates equal populations of the two states; a pair of signals indicates unequally populated

[1]School of Chemistry, University of Manchester, Manchester M13 9PL, UK. [2]Department of Chemistry, University of Hull, Hull HU6 7RX, UK. [3]Manchester Institute of Biotechnology, University of Manchester, Manchester M1 7DN, UK. [4]School of Chemistry, University of Bristol, Bristol BS8 1TS, UK.
***Corresponding author. E-mail: j.clayden@bristol.ac.uk**

Kinetically controlled *E*-selective catalytic olefin metathesis
Thach T. Nguyen, Ming Joo Koh, Xiao Shen, Filippo Romiti, Richard R. Schrock and Amir H. Hoveyda (April 28, 2016)
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Editor's Summary

EZ catalyst control in olefin metathesis

A decade has passed since the partner-swapping chemical dance known as olefin metathesis garnered a Nobel Prize, and distinct routines continue to emerge. In general, olefins are most stable in an E configuration, with the two largest substituents diametrically opposed. However, chlorine and fluorine substituents often invert this trend, favoring the alternate Z geometry. Nguyen *et al.* report a molybdenum metathesis catalyst with ligands carefully optimized to produce Cl- and F-substituted E olefins more quickly than the more stable Z isomers.

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