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Catalytic *Z*-selective olefin cross-metathesis for natural product synthesis

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Alkenes are found in many biologically active molecules, and there are a large number of chemical transformations in which alkenes act as the reactants or products (or both) of the reaction. Many alkenes exist as either the *E* or the higher-energy *Z* stereoisomer. Catalytic procedures for the stereoselective formation of alkenes are valuable, yet methods enabling the synthesis of 1,2-disubstituted *Z* alkenes are scarce. Here we report catalytic *Z*-selective cross-metathesis reactions of terminal enol ethers, which have not been reported previously, and of allylic amides, used until now only in *E*-selective processes. The corresponding disubstituted alkenes are formed in up to >98% *Z* selectivity and 97% yield. These transformations, promoted by catalysts that contain the highly abundant and inexpensive metal molybdenum, are amenable to gram-scale operations. Use of reduced pressure is introduced as a simple and effective strategy for achieving high stereoselectivity. The utility of this method is demonstrated by its use in syntheses of an anti-oxidant plasmalogen phospholipid, found in electrically active tissues and implicated in Alzheimer's disease, and the potent immunostimulant KRN7000.

Carbon-carbon double bonds reside within a large variety of molecules that possess desirable properties[1], and catalytic cross-metathesis[2] (CM; Fig. 1) represents one of the most attractive approaches to stereoselective preparation of these versatile functional groups. Through fusion of two terminal alkenes, available in ample quantities as by-products of petroleum purification or readily accessed by a variety of methods, 1,2-disubstituted alkenes can be obtained; the other product generated is gaseous ethylene. However, the only reported instances of *Z*-selective CM (65–90% *Z*) involve substrates with an *sp*-hybridized substituent (acrylonitrile or enynes[3,4]). In an efficient *Z*-selective CM, it is not only required that reaction between the two substrates proceed selectively (versus homocoupling), it must exhibit a preference for the thermodynamically less favoured stereoisomer (Fig. 1). The inherent reversibility of olefin metathesis (products can re-enter the catalytic cycle) and the higher reactivity of *Z* alkenes (versus *E* isomers) further exacerbate the problem. Through careful consideration of various mechanistic aspects of the process, conditions must be identified where the catalyst promotes CM but fails to react with the product *Z* alkene to effect equilibration, favouring the lower energy *E* isomer.

Challenges of catalytic *Z*-selective cross-metathesis

As the preliminary steps towards the eventual development of an efficient class of *Z*-selective CM reactions, we investigated two related—but much simpler—versions of the process. Alkylidenes and carbenes **1**–**5** (Fig. 1) represent the catalyst classes used in our studies. Stereogenic-at-Mo **1a**, **1b** and **2**[5,6] were recently designed in these laboratories to promote enantioselective ring-closing metathesis; theoretical[7] and experimental explorations[8] suggest that these complexes exhibit high activity partly as the result of stereoelectronic effects induced by the electron donor pyrrolide and acceptor monoaryloxide ligands. The fluxional nature of complexes such as **1a**, **1b** and **2**, facilitated by the absence of rigid bidentate ligands, allows the metal alkylidenes to adapt to the structural strains imposed during the catalytic cycle. As a result, the stereogenic-at-Mo complexes are generally more effective olefin metathesis catalysts than other Mo-based complexes **3**[9] and **4**[10] or Ru carbene **5**[11]. We thus established that alkylidene **2** readily catalyses *Z*-selective alkene formation through ring-opening/cross-metathesis (ROCM)[12] with strained oxabicyclic alkenes and styrenes. Homocoupling of terminal alkenes was subsequently shown to proceed with high efficiency and *Z* selectivity in the presence of members of the same catalyst class[13]. The general mechanistic features that engender *Z* selectivity in the above reactions, and would be expected to do so in a CM process, are depicted in Fig. 1. The preference for *Z* alkene formation can be attributed to the ability of the large monodentate aryloxide to rotate freely (compare **I** in Fig. 1), causing the incoming alkene to be oriented such that its substituent (R_2) is situated *syn* to that of the alkylidene (R_1).

Designing a *Z*-selective CM is substantially more difficult: in a homocoupling, only one type of alkene is involved and no more than two stereoisomeric alkenes can be formed; in contrast, there are two substrates in CM, which can generate up to six different products. In the case of a catalytic ROCM[14], a strained cyclic alkene and a terminal alkene that are reluctant to undergo homocoupling (for example, a styrene) must be selected as substrates for the catalytic process to be efficient[15]. Transformations are carefully crafted such that the alkylidene derived from the terminal alkene favours association with the cyclic alkene (versus another of the same type) in the ring-opening stage, generating a new Mo complex that strongly prefers to react with a sterically less demanding terminal alkene (CM stage). The possibility of a transformation between the alkylidene generated through ring-opening and another strained—but more hindered—cyclic alkene is thus discouraged (that is, minimal homocoupling or oligomerization). Such deliberate orchestration is not feasible with catalytic CM, where both alkenes are mono-substituted and, in contrast to ROCM, there is no relief of ring strain to be manipulated.

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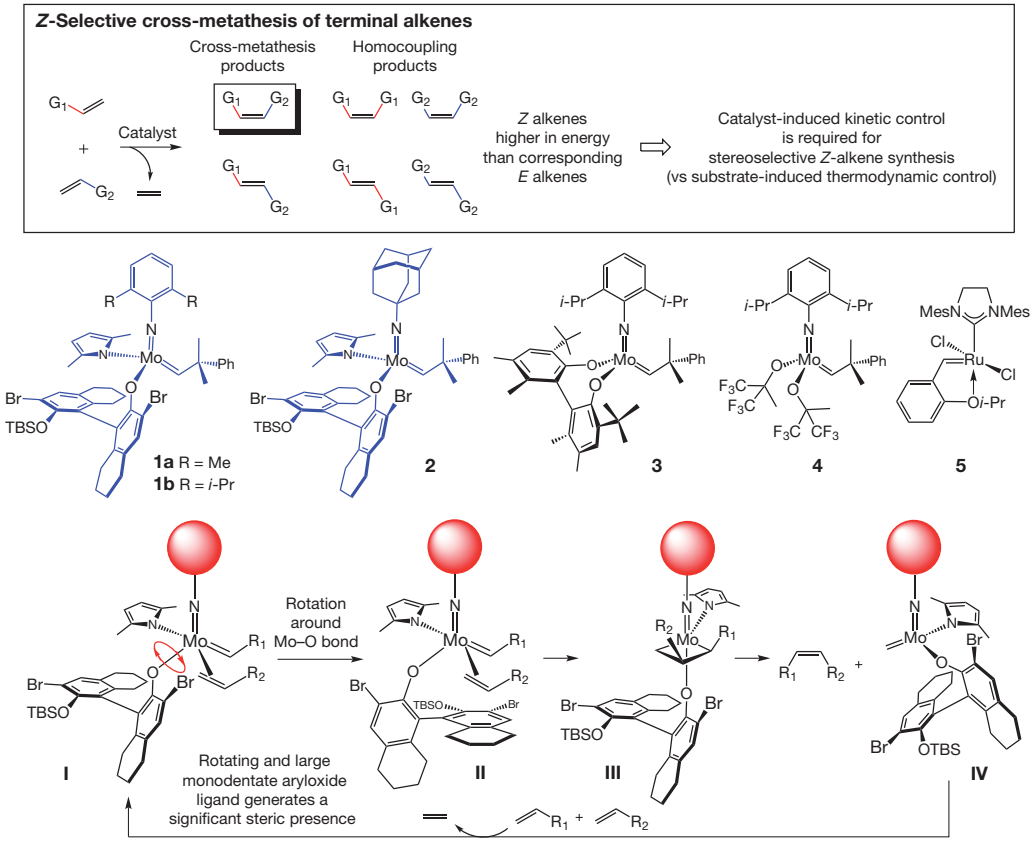
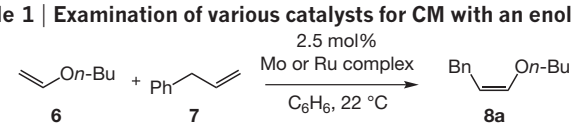


Figure 1 | A catalytic CM reaction can afford as many as six alkenes, so the challenge is designing an efficient process that favours formation of the cross products. Particularly difficult is the development of a process that affords the higher-energy *Z* alkene predominantly. To accomplish a *Z*-selective CM, a variety of catalysts were considered, such as stereogenic-at-Mo complexes (**1**, **2**) or other previously reported Mo- and Ru-based complexes (**3**–**5**). The structural flexibility of the stereogenic-at-metal complexes **1** and **2** can give rise to exceptional reactivity, and free rotation around the Mo–O bond of these alkylidenes might serve as the basis for development of highly *Z*-selective olefin metathesis reactions of terminal alkenes. The sphere represents an appropriate size imido substituent.

Z-Selective cross-metathesis of enol ethers

We began by evaluating the ability of stereogenic-at-Mo complexes to promote transformations of enol ethers, a class of substrates for which a CM reaction has not been previously reported (*E*- or *Z*-selective); the resulting products have proven to be of utility in chemical synthesis and can be found in biologically active molecules (see below). In the presence of 2.5 mol% **1a**, CM between **6** and **7** (entry 1, Table 1) proceeds to 85% conversion to afford disubstituted enol ether **8a** in 98% *Z* selectivity and 73% yield. With **1b**, which bears a more sizeable 2,6-di-*i*-propyl-arylimido unit, the reaction is completely *Z*-selective (>98% *Z*) but 47% conversion is achieved within the same time span. When alkylidene **2** is used, CM proceeds to 37% conversion and >98% *Z*-**8a** is generated; further transformation is not observed after six hours. Mo-based diolate **3** and Ru carbene **5** do not promote CM, and achiral Mo complex **4** catalyses a non-selective transformation (47.5% *Z*). Thus, stereogenic-at-Mo complexes prove to be effective in promoting enol ether CM, and although **1b** or the less hindered **2** also afford exceptional stereoselectivity, neither delivers the efficiency of **1a**. The 2,6-dimethylphenylimido **1a** therefore offers the best balance between activity and stereoselectivity. Such performance variations may be observed because catalyst turnover is slower with the more sizeable **1b** whereas the methylidene of the relatively unhindered **2** (compare **IV**, Fig. 1) might suffer from a shorter life span. Consistent with the above scheme, 82% **8a** is formed when CM with **1b** is allowed to continue for 16 hours; in contrast, conversion with **2** after 10 minutes or two hours is nearly identical (~38%).

Table 1 | Examination of various catalysts for CM with an enol ether



6 **7** **8a**

Entry no.	Complex	Time	Conv. (%)*	Yield (%)†	*Z*:*E**
1	**1a**	2 h	85	73	98:2
2	**1b**	2 h	47	ND	>98:2
3	**2**	2 h	37	ND	>98:2
4	**3**	2 h	<2	NA	NA
5	**4**	10 min	80	ND	47.5:52.5
6	**5**	24 h	<2	NA	NA

The reactions were carried out in purified benzene under an atmosphere of nitrogen gas; 10 equiv. of **6** was used (see Supplementary Information for details). NA, not available; ND, not determined.
* Conversion (conv.) and *Z*:*E* ratios were measured by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures; the variance of values is estimated to be <±2%.
† Yield of isolated product after purification; the variance of values is estimated to be <±5%.

There are several, mechanistically revealing, reasons for use of excess enol ether. CM generates a Mo-methylidene; this unhindered alkylidene can readily react with the *Z*-alkene product, reverse CM, cause equilibration and lower stereoselectivity. An enol ether reacts with a methylidene complex, circumventing diminution in *Z* selectivity. The more stable alkoxy-substituted alkylidene, generated from reaction of a methylidene complex and an enol ether (**I** in Fig. 1 with R_1 = O*n*-Bu), can undergo productive CM, giving rise to longer catalyst lifetime and improved turnover numbers. Furthermore, generation of the aforementioned alkoxy- or aryloxy-containing alkylidene means less of the alkyl-substituted derivative is formed and homocoupling of the aliphatic alkene is minimized. Owing to electronic factors, productive reaction between an enol ether-derived alkylidene and another O-substituted alkene is disfavored[2]. However, as use of excess enol ether is wasteful, we decided to examine the efficiency of the CM with

varying amounts of **6** (see Supplementary Information for details). The latter studies established that, although fewer equivalents of **6** lead to reduced *Z* selectivity and competitive homocoupling, with 5 equiv. of the inexpensive and commercially available enol ether, **8a** can be obtained in 93:7 *Z*:*E* selectivity and 71% yield (7% homocoupled product). Excess enol ether **6** does not complicate product isolation, as this inexpensive reagent is volatile and can be easily removed *in vacuo*.

Z-Disubstituted enol ethers are obtained in 57–77% yield through exceptionally stereoselective (94% to >98% *Z*) CM with Mo alkylidene **1a** (Fig. 2). Alkyl- (**8**) or aryl-substituted (**10**) *Z* enol ethers as well as those that bear a carboxylic ester (**8c**), a secondary amine (**8e**), a bromide (**10b**) or an alkyne (**10c**) are readily accessed. Reactions with the more electron-deficient enol ether **9** and the relatively electron-rich alkenes proceed with 2.0 equiv. of the aryl-substituted enol ether; in contrast, 10 equiv. of alkyl-substituted and easily removable **6** are required for similar efficiency. Such variations probably occur because when **9** is used there is a better electronic match[3] between the Mo-alkylidenes derived from the cross partners and either of the two alkenes, favouring CM versus homocoupling. Only 1.2 mol% **1a** and 2.0 equiv. of the *p*-methoxyphenylenol ether (for example, **10a**, **10b** and **10d**, Fig. 3c) are sufficient for an effective and exceptionally *Z*-selective CM to take place.

Synthesis of natural product C18 (plasm)-16:0 (PC)

Next, we set out to demonstrate the utility of the catalytic CM process by a diastereo- and enantioselective synthesis of an anti-oxidant plasmalogen phospholipid, C18 (plasm)-16:0 (PC) (Fig. 2)[16,17], the corresponding *E* isomer of which has been shown to be less active[17]. This initiative required addressing a challenge that is of general concern in catalytic CM: the inefficiency associated with the use of excess of one cross partner. The enol ether to be used (**11**) in the CM step is more valuable than the commercially available and inexpensive 1-octadecene (**12**), rendering utilization of excess amounts of the former unfavourable. Reducing the enol ether concentration diminishes efficiency and *Z*-selectivity, as detailed above and substantiated by the data in Table 2 (85% and 47% conversion with 5:1 and 1:1 **11**:**12**; entries 1 versus 2). Larger quantities of the less valuable **12** could improve yield and selectivity, as Mo-methylidene concentration is probably lowered through its reaction with excess alkene. However, increased amounts of an aliphatic alkene, unlike an enol ether, give rise to homocoupling and ethylene generation. Ethylene, in addition to being detrimental to the rate of CM (because it competes with the substrates for reaction with the available alkylidene), causes diminished stereoselectivity by increasing methylidene concentration, which promotes *Z* alkene isomerization (see above). We thus surmised that, if the negative effects of the generated ethylene were to be attenuated by performing the reaction

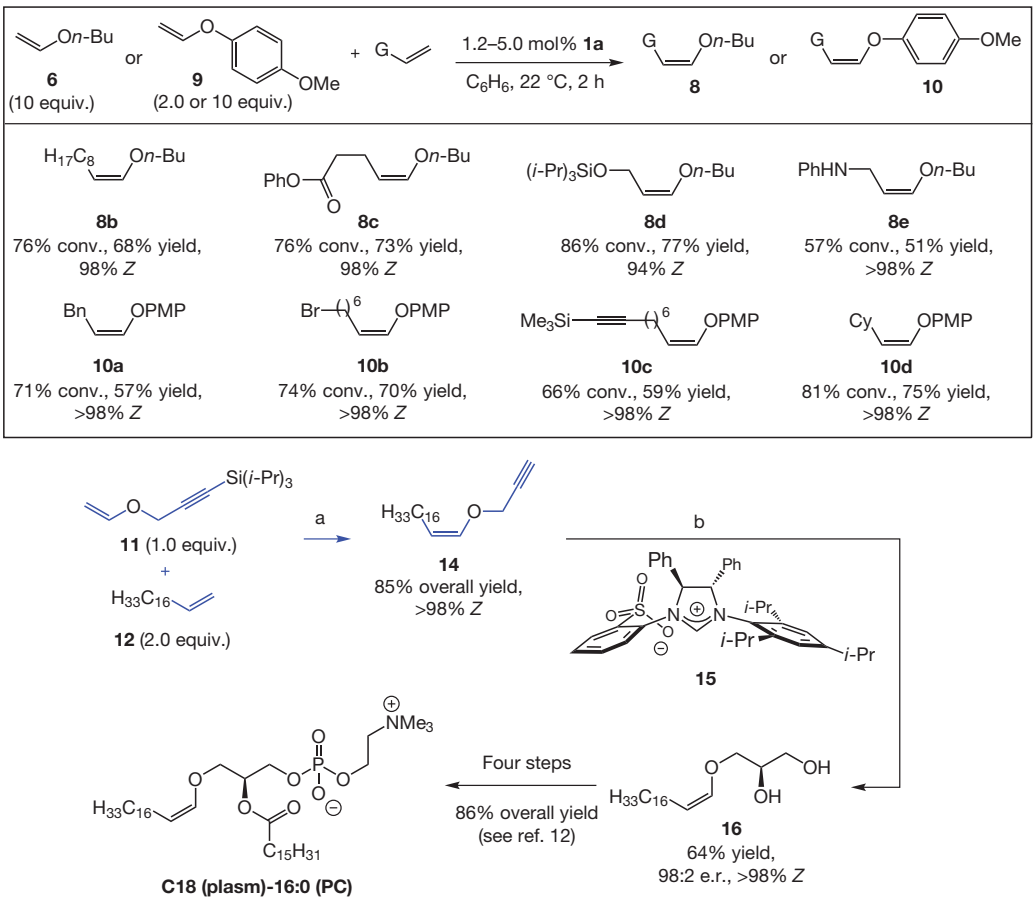


Figure 2 | *Z*-selective CM reactions of enol ethers with terminal alkenes and application to stereoselective synthesis of C18 (plasm)-16:0 (PC). Various *Z* enol ethers are synthesized with 1.2–5.0 mol% of Mo complex **1a**, and typically require 2.0 equiv. (in the case of *p*-methoxyphenylvinyl ether) or 10.0 equiv. (with butylvinyl ether) of the terminal enol ether; excess butyl vinyl ether (**6**) is easily removed *in vacuo*. The desired *Z* alkenes are obtained in 51–77% yield and in 94% to >98% *Z* selectivity. Application to synthesis of C18 (plasm)-16:0 (PC) demonstrates the utility of the *Z*-selective Mo-catalysed CM, which is used in conjunction with a site- and enantioselective Cu-catalysed dihydroboration of the terminal alkyne in **14** (see Supplementary Information for details). All reactions shown were performed under N_2 atmosphere; catalysts were prepared and used *in situ*. Conversions and *Z* selectivities were determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures; the variance of selectivity values is estimated to be $<\pm 2\%$. Yields of isolated products are shown ($\pm 5\%$). Reactions: for **8b**–**8e**, we used 2.5 mol% **1a** and 10 equiv. **6**; for **10a**, **10b**, we used 1.2 mol% **1a** and 2.0 equiv. **9**; for **10c**, **10d**, we used 5.0 mol% **1a** and 10 equiv. (**10c**) or 2.0 equiv. **9** (**10d**). See Supplementary Information for experimental details. Conditions for synthesis of **16**. Route a, step 1; 2.5 mol% **1a**, C_6H_6, 22 °C, 2.0 h, decalin, 1.0 torr: step 2; 5.0 equiv. $(n\text{-Bu})_4NF$, THF, 22 °C, 2 h. Route b; 2.5 mol% **15**, 2.5 mol% CuCl, 20 mol% NaO*t*-Bu, 2.1 equiv. *bis*(pinacolato)diboron, 3.0 equiv. MeOH, THF, 0 °C, 24 h; 30% H_2O_2, NaOH in aqueous THF, 1.0 h.

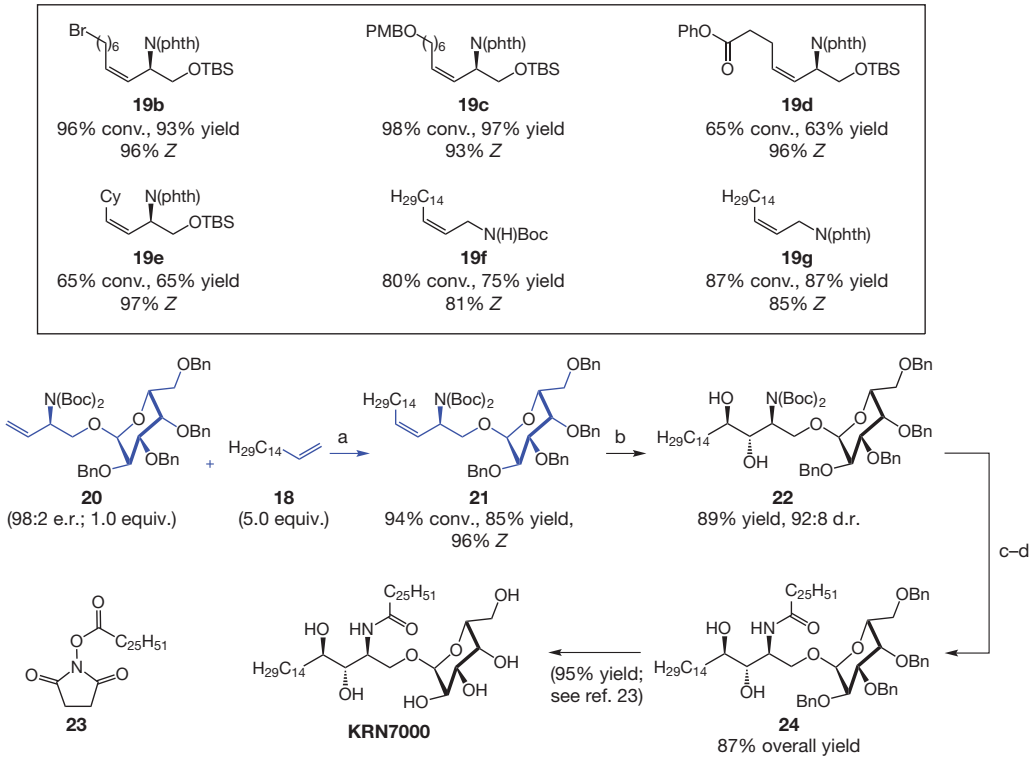
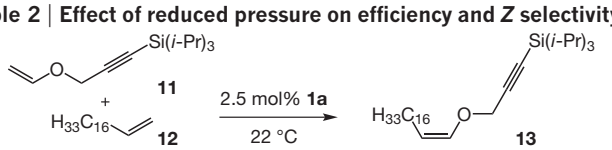


Figure 3 | *Z*-selective CM reactions of allylic amides with terminal alkenes and application to stereoselective synthesis of KRN7000. A range of *Z*-1,2-disubstituted allylic amides can be synthesized; in most cases, use of reduced pressure leads to substantially improved yield and stereoselectivity. Application to the stereoselective synthesis of KRN7000, involving catalytic diastereoselective dihydroxylation of the *Z* alkene obtained by Mo-catalysed CM, leads to an expeditious route for preparation of this biologically significant molecule (see Supplementary Information for details). All reactions shown were performed under N_2 atmosphere with 3.0 mol% **2**, 3.0 equiv. of the non-N-containing alkenes (**19b**, **19c**) or 5.0 mol% **2** and 10.0 equiv. of cross partner, 7.0 torr, 5.0 hours, 22 °C; catalysts were prepared and used *in situ*. Conversions, *Z* selectivities, yields and *Z*:*E* ratios determined as in Fig. 1. For **19e**, reduced pressure was not used; reaction performed at 50 °C for 12 h. For **19f**, **19g**, reaction time was one hour. See Supplementary Information for experimental details. Conditions for synthesis of **24**: route a; 8.0 mol% **2** (*in situ*-generated), C_6H_6, 22 °C, 5.0 h, 1.0 torr. Route b; 5 mol% OsO_4, 2.5 equiv. N-Me-morpholine oxide, CH_2Cl_2, 0 °C, 24 h. Route c; 10% trifluoroacetic acid, CH_2Cl_2, 22 °C, 30 min. Route d; 1.2 equiv. **23**, Et_3N, THF, 50 °C, 12 h.

under vacuum, an efficient CM might be induced to proceed with only a relatively slight excess of the aliphatic alkene (**12**). Indeed, when catalytic CM is performed with an equal amount of **11** and **12** under 1.0 torr (entry 3, Table 2), efficiency (78% versus 47% conversion in entry 2) as well as stereoselectivity is substantially improved (97% versus 91.5% *Z*). With reduced pressure, 2 equiv. of **12** (versus **11**) and decalin as solvent (to prevent precipitation of the homocoupled by-product causing catalyst sequestration), 89% conversion is observed in two hours and *Z*-**13** is obtained with 97% selectivity (entry 4).

Removal of the silyl group delivers stereoisomerically pure *Z*-**14** in 85% overall yield (Fig. 2); the desired product cannot be accessed through catalytic hydrogenation of the corresponding alkyne (see also **10c**). Cu-catalysed site- and enantioselective dihydroboration[18] furnishes **16** (in 98:2 enantiomeric ratio, e.r.), which has been previously converted to C18 (plasm)-16:0 (PC) in four steps and 86% overall yield[19]. Two additional points merit mention: (1) catalytic CM between **11** and **12** has been performed on the gram-scale with 1.0 mol% of *in situ*-generated **1a** and 2 equiv. of **12**, affording *Z*-**13** with >98% stereoselectivity and in 71% yield after purification (3 h, 1.0 torr, 79% conversion; see Supplementary Information for details). (2) The only previous synthesis of **16** involves nine transformations starting with (*S*)-isopropylidene glycerol (versus five reactions from (*i*-Pr)$_3$Si-acetylene, Fig. 2) by a sequence that includes the use of highly toxic hexamethylphosphoramide and a catalytic hydrogenation with lead-containing salts[19].

Table 2 | Effect of reduced pressure on efficiency and *Z* selectivity



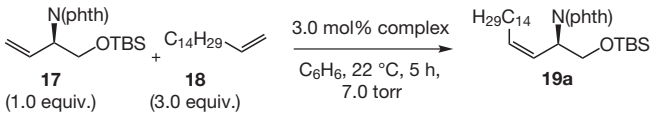
Entry no.	11:12	Time (h)	Conv. (%)*	Solvent	Pressure	*Z*:*E**
1	5:1	2	85	Benzene	Ambient	>98:2
2	1:1	2	47	Benzene	Ambient	91.5:8.5
3	1:1	2	78	Benzene	1.0 torr	97:3
4	1:2	2	88	Decalin	1.0 torr	97:3

The reactions were carried out in purified benzene or decalin under an atmosphere of nitrogen gas (see Supplementary Information for details).
* Conversion, *Z*:*E* ratios and the amount of the homocoupled product were measured by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures; the variance of values is estimated to be <±2%.

Z-Selective cross-metathesis of allylic amides

Another class of reactions that we examined involves allylic amides as substrates. Such catalytic CM reactions are of considerable value, as a large number of biologically active molecules are nitrogen-containing, and 1,2-disubstituted alkenes bearing a C–N bond at the allylic position can be functionalized in a variety of ways. Furthermore, in contrast to transformations with enol ethers, CM with allylic amides poses the added complication that both substrates can undergo homocoupling. Preliminary investigations with enantiomerically pure allylic amide **17** (from commercially available alcohol) and 1-hexadecene **18** indicated that the optimal catalyst for this class of processes is derived from adamantylimido complex **2**, affording the desired *Z* alkene in 88% yield and with 97% stereoselectivity (entry 3, Table 3). Although arylimido derivatives **1a** and **1b** generate **19a** with similar selectivity (entries 1 and 2, Table 3), reactions are inefficient (26–44% versus 88% conversion), perhaps because an alkylidene derived from **2** is less congested and can more readily promote CM of the relatively hindered **17**. The higher efficiency of CM with **2**, in

Table 3 | Examination of various catalysts for CM with an allylic amide



Entry no.	Complex	Conv. (%)*	Yield (%)†	*Z*:*E**
1	**1a**	44	35	96:4
2	**1b**	26	21	97:3
3	**2**	93	88	97:3
4	**3**	9	6	21:79
5	**4**	71	68	12:88
6	**5**	73	64	11:89

The reactions were carried out in purified benzene under an atmosphere of nitrogen gas (see Supplementary Information for details). N(phth) = *N*-phthalamide.
* Conversion and *Z*:*E* ratios were measured by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures; the variance of values is estimated to be $<\pm 2\%$.
† Yield of isolated product after purification; the variance of values is estimated to be $<\pm 5\%$.

contrast to those involving enol ethers (Fig. 2), might be the result of CM with **17** being performed under vacuum, allowing minimal amounts of the relatively unstable methylidene to be formed. Chiral complex **3** is ineffective, and achiral Mo alkylidene **4** and Ru carbene **5** furnish the *E* isomer predominantly (79–89%). A weaker vacuum (7.0 torr versus 1.0 torr CM with enol ethers) is sufficient, indicating that such conditions can be applied to cases that involve relatively volatile substrates.

An assortment of allylic amides and terminal alkenes, including those that contain a halide (**19b**), a Lewis basic group (**19c**, **19d**) or a sterically demanding substituent (**19e**), can be used (Fig. 3). Stereoselective formation of **19f** and **19g** is noteworthy as the relatively less hindered unsaturated amides are more prone to homocoupling and the *Z* alkene products undergo equilibration to the *E* isomer readily, as manifested by the lower *Z*:*E* ratios. Although in certain cases 10 equiv. of a cross partner is used for maximum efficiency, lower amounts of alkene substrates lead to reasonably efficient processes. For example, with 3.0 mol% **2** and 3 equiv. of the aliphatic alkene (versus 5 mol% and 10 equiv.), **19g** is isolated in 62% yield and 90% *Z* selectivity (80% conversion, 5 min, 22 °C). It should be noted that in all the above transformations, use of catalysts bearing a racemic binol ligand furnishes similar levels of reactivity and stereoselectivity (see Supplementary Information).

Synthesis of immunostimulant KRN7000

Stereoselective synthesis of anti-tumour agent KRN7000[20,21] underlines the utility of the method (Fig. 3). Catalytic CM of carbohydrate-containing allylic amide **20**, prepared in four steps from commercially available agents, affords **21** in 85% yield and with 96% *Z*-selectivity. Diastereoselective dihydroxylation (89% yield, 92:8 diastereomeric ratio (d.r.)) of the *Z* alkene delivers **22**; it should be noted that similar functionalization of the corresponding *E* alkene isomer would afford an undesired diol diastereomer[22]. Dihydroxylamide **24** is secured in two steps and the target is obtained after carbohydrate deprotection[23]. *Z*-Selective CM thus provides access to a route that is significantly more concise than the 14-step sequence (compared to nine steps in Fig. 3) reported thus far as the shortest synthesis of KRN7000[24]. It is noteworthy that the convergent nature of a synthesis approach involving catalytic CM, such as the two examples provided here, can easily translate to preparation of a variety of related analogues; for example, in connection with preparation of **21** (Fig. 3), a wide range of other terminal alkenes may be used.

The balance between conversion and *Z* selectivity

The relationship between efficiency and stereoselectivity is critical and merits a brief discussion. The conversion values, at times less than complete, represent a balance struck between achieving the highest yield and maximal *Z* selectivity with minimal substrate equivalents and adventitious homocoupling. Transformations performed under ambient conditions (no vacuum) may not proceed beyond 80% conversion, probably because the ethylene by-product competes with the remaining cross partner molecules. High ethylene concentration might also diminish CM rate through formation of relatively stable unsubstituted metallacyclobutanes[7]. As mentioned before, methylidene complexes can engender reduction of *Z* selectivity; time-dependent studies indicate that stereoselectivities suffer with prolonged reaction times. With non-volatile substrates, if reactions are carried out under vacuum, complete consumption of the limiting alkene is observed only when excess amounts (~10 equiv.) of one cross partner are present. Under such regimes, however, difficulties associated with removal of the excess substrate and the homocoupled product might arise, rendering the use of lesser alkene amounts preferable. With lower substrate ratios, >98% consumption of the limiting substrate is difficult to achieve, as terminal alkene concentration is diminished as a result of partial homocoupling.

Conclusions and discussions

In addition to catalytic olefin CM, Wittig reactions[25], catalytic alkyne hydrogenation and cross-coupling[1,26] are notable approaches for synthesis of *Z*-disubstituted alkenes. The above four types of transformations are distinct—each delivers the desired product through a different bond disconnection. Similarly to CM, in cross-coupling alkenes serve as starting materials; in contrast to CM, however, it is through the synthesis of the substrate (for example, a *Z* vinyl halide)—and not in the cross-coupling step—that the stereochemical identity of the product is determined. Wittig-type processes are typically not catalytic and involve reaction of aldehydes (versus the more stable alkenes) and triphenylphosphonium ylides. Catalytic alkyne hydrogenation requires substrates derived from functionalization of a terminal alkyne; currently, relative to alkenes, methods for preparation of alkynes are less common and related synthesis routes are often lengthier. Moreover, partial hydrogenation of alkynes involves metal catalysts that contain poisonous lead salts and must be controlled to avoid over-reduction and generation of alkane by-products that can be difficult to separate from the desired *Z* alkene. Catalytic CM thus offers a desirable alternative to synthesis of *Z* alkenes, particularly as it requires as starting material a functional group that is stable, easily accessible and distinct from the other commonly used protocols mentioned above.

The strategies outlined here—including the use of reduced pressure to enhance stereoselectivity in catalytic CM, and the *Z*-selective Mo-catalysed transformations—offer a unique solution to a long-standing problem in organic chemistry[27]. Our findings offer additional evidence regarding the unique ability of stereogenic-at-Mo monoaryloxypyrrolides to effect olefin metathesis reactions that extend beyond enantioselective processes[28], with efficiency and selectivity levels that are not achievable with other catalyst classes. The catalytic processes described here are expected to affect significantly activities that require the stereoselective synthesis of organic molecules[29,30].

METHODS SUMMARY

General procedure for catalytic *Z*-selective cross-metathesis. In an N_2-filled dry box, an oven-dried (135 °C) 20-ml vial equipped with a magnetic stir bar was charged with vinyl ether **11** (1.00 g, 4.19 mmol) and 1.0 mol% of *in situ*-generated complex **1a** (419 µl, 0.100 M, 41.9 µmol; final substrate concentration = 1.70 M). A separate 2.0-ml vial was charged with 1-octadecene (**12**, 2.12 g, 8.39 mmol) and decalin (2.10 ml). The resulting solution was transferred to the mixture of **11** and **1a** by syringe; a septum, fitted with an outlet needle, was attached to the vial and an adapter was attached to the top of the septum and vacuum (~1.0 torr) applied. The resulting solution was stirred for 3 h. The vessel was removed from the dry box and the reaction was quenched by the addition of wet Et_2O (~1.0 ml). The unpurified product is >98% *Z* (as determined by 400 MHz ^{1}H NMR analysis). The residue was dissolved in Et_2O and passed through a 2.5-cm plug of neutral alumina to remove inorganic salts, and the solution was concentrated. In a 25-ml round-bottom flask equipped with a stir bar, the resulting residue was treated

with $(n\text{-Bu})_4NF$ (1.0 M in THF, 21.0 ml, 21.0 mmol), and stirred for 2 h. The mixture was diluted with Et_2O (200 ml), passed through a 5-cm plug of neutral alumina, and concentrated. The resulting white solid was purified by chromatography on neutral alumina (100% hexanes) to afford **15** as a white solid (m.p. 30–31 °C, 0.914 g, 2.98 mmol, 71.0% yield; >98% *Z* isomer).

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