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Z-Selective Catalytic Olefin Cross-Metathesis

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Abstract

Alkenes are found in a great number of biologically active molecules and are employed in numerous transformations in organic chemistry. Many olefins exist as *E* or higher energy *Z* isomers. Catalytic procedures for stereoselective formation of alkenes are therefore valuable; nonetheless, methods for synthesis of 1,2-disubstituted *Z* olefins are scarce. Here we report catalytic *Z*-selective cross-metathesis reactions of terminal enol ethers, which have not been reported previously, and allylic amides, employed thus far only in *E*-selective processes; the corresponding disubstituted alkenes are formed in up to >98% *Z* selectivity and 97% yield. Transformations, promoted by catalysts that contain the highly abundant and inexpensive molybdenum, are amenable to gram scale operations. Use of reduced pressure is introduced as a simple and effective strategy for achieving high stereoselectivity. Utility is demonstrated by syntheses of anti-oxidant C18 (plasm)-16:0 (PC), 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,ⁱ and catalytic cross-metathesisⁱⁱ (CM; Fig. 1) represents one of the most attractive approaches to stereoselective preparation of these versatile functional groups. Through fusion of two terminal olefins, available in ample quantities as byproducts 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 iii,iv). In an efficient *Z*-selective CM it is not only

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required that reaction between the two substrates proceed selectively (vs homocoupling), it must exhibit a preference for the thermodynamically less favored stereoisomer (Fig. 1). The inherent reversibility of olefin metathesis (products can re-enter the catalytic cycle) and the higher reactivity of *Z* alkenes (vs *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* olefin to effect equilibration, favoring 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 utilized in our studies. Stereogenic-at-Mo **1a–b** and **2v**,vi were recently designed in these laboratories to promote enantioselective ring-closing metathesis; theoretical vii and experimental explorationsviii suggest that these complexes exhibit high activity partly as the result of stereoelectronic effects induced by the electron donor pyrrolide and acceptor monoaryloxy ligands. The fluxional nature of complexes such as **1a–b** 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 **3ix**, and **4x** as well as Ru carbene **5xi**. We thus established that alkylidene **2** readily catalyzes *Z*-selective alkene formation through ring-opening/cross-metathesis (ROCM) xii with strained oxabicyclic olefins and styrenes. Homocoupling of terminal olefins was subsequently shown to proceed with high efficiency and *Z* selectivity in the presence of members of the same catalyst classxiii. 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 aryloxy to rotate freely (cf. **I**), causing the incoming olefin 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 olefins 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 ROCMxiv, a strained cyclic alkene and a terminal olefin that are reluctant to undergo homocoupling (e.g., a styrene) must be selected as substrates for the catalytic process to be efficientxv. Transformations are carefully crafted such that the alkylidene derived from the terminal alkene favors association with the cyclic olefin (vs. 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 (i.e., 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.

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**, bearing 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** catalyzes a non-selective CM (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** while the methylidene of the relatively unhindered **2** (cf. **IV**, Fig. 1) might suffer from a shorter life span. Consistent with the above scenario, 82% **8a** is formed when CM with **1b** is allowed to continue for 16 hours, whereas conversion with **2** after 10 minutes or two hours is nearly identical (~38%).

There are several, mechanistically revealing, reasons for use of excess enol ether. CM generates a Mo-methylidene; this unhindered alkylidene can readily initiate transformation 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 Scheme 1 with R₁ = *On*-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 olefin is minimized. Due to electronic factors, productive reaction between an enol ether-derived alkylidene and another O-substituted alkene is disfavored². However, since use of excess enol ether is wasteful, we decided to examine the efficiency of the CM with varying amounts of **6** (see the Supplementary Information for details). The latter studies established that, although fewer equivalents of **6** lead to reduced *Z*-selectivity and competitive homocoupling, with five equivalents 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, since 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 equivalents of the aryl-substituted enol ether; in contrast, 10 equivalents of alkyl-substituted and easily removable **6** are required for similar efficiency. Such variations are likely because when **9** is used there is a better electronic match between the Mo-alkylidenes derived from the cross partners and either of the two olefins, favoring CM versus homocoupling. Only 1.2 mol % **1a** and 2.0 equivalents of the *p*-methoxyphenylenol ether (e.g., **10a–b** 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 anti-oxidant C18 (plasm)-16:0 (PC) (cf. Fig. 2) xvi,xvii, the corresponding *E* isomer of which has been shown to be less active^{xvii}. 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 unfavorable. Reducing the enol ether concentration diminishes efficiency and *Z*-selectivity, as detailed above and substantiated by the data in Table 2 (85% and 47% conv. with 5:1 and 1:1 **11**:**12**; entries 1 vs. 2). Larger quantities of the less valuable **12** could improve yield and selectivity, since Mo methylidene concentration is likely lowered through its reaction with excess alkene. However, increased amounts of an aliphatic olefin, unlike an enol ether, gives rise to homocoupling and ethylene generation. Ethylene, in addition to being detrimental to the rate of CM, as it competes with the substrates for reaction with the available alkylidene, causes diminished stereoselectivity by increasing methylidene concentration, which promotes *Z* olefin isomerization (see above). We thus surmised that, if the negative effects of the generated ethylene were to be attenuated by performing the reaction under vacuum, an efficient CM might be induced to proceed with only a relatively slight excess of the aliphatic olefin (**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% vs. 47% conv. in entry 2) as well as stereoselectivity is substantially improved (97% vs. 91.5% *Z*). With reduced pressure, two equivalents of **12** (vs. **11**) and decalin as solvent (to prevent precipitation of the homocoupled byproduct 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-catalyzed site- and enantioselective dihydroboration^{xviii} furnishes **16** [98:2 enantiomeric ratio (e.r.)], which has been previously converted to C18 (plasm)-16:0 (PC) in four steps and 86% overall yield^{xix}. Two additional points merit mention: (1) Catalytic CM between **11** and **12** has been performed on gram-scale with 1.0 mol % of in situ-generated **1a** and two equivalents of **12**, affording *Z*-**13** with >98% stereoselectivity and in 71% yield after purification (3 h, 1.0 torr, 79% conv.; see the Supplementary Information for details). (2) The only previous synthesis of **16** involves nine transformations starting with (*S*)-isopropylidene glycerol (vs. five reactions from (*i*-

Pr₃Si-acetylene, Fig. 2) by a sequence that includes the use of highly toxic hexamethylphosphoramide and a catalytic hydrogenation with lead-containing salts^{xix}.

Z-Selective cross-metathesis of allylic amides

Another class of reactions examined involves allylic amides as substrates. Such catalytic CM reactions are of considerable value, since a large number of biologically active molecules are N-containing, and 1,2-disubstituted alkenes bearing a C–N bond at the allylic position can be functionalized in a variety of manners. 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–b** generate **19a** with similar selectivity (entries 1–2, Table 3), reactions are inefficient (26–44% vs. 88% conv.), 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 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 methyldiene 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 vs. 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 (cf. **19b**), a Lewis basic group (cf. **19c–d**) or a sterically demanding substituent (cf. **19e**), can be used (Fig. 3). Stereoselective formation of **19f–g** is noteworthy since 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 ten equivalents 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 three equivalents of the aliphatic alkene (vs. 5 mol % and 10 equiv.), **19g** is isolated in 62% yield and 90% *Z* selectivity (80% conv., 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 the Supplementary Information).

Synthesis of natural product KRN7000

Stereoselective synthesis of anti-tumor agent KRN7000^{xx,xxi} 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^{xxii}.

Dihydroxylamide **24** is secured in two steps and the target is obtained after carbohydrate deprotection^{xxiii}. Z-selective CM thus provides access to a route that is significantly more concise than the 14-step sequence (vs. nine steps in Fig. 3) reported thus far as the shortest synthesis of KRN7000^{xxiv}. It is noteworthy that the convergent nature of a synthesis approach involving catalytic CM, such as the two examples provided herein, can easily translate to preparation of a variety of related analogs; 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 since the ethylene byproduct competes with the remaining cross partner molecules. High ethylene concentration might also diminish CM rate through formation of relatively stable unsubstituted metallacyclobutanes^{vii}. As mentioned before, methylenide 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 since terminal alkene concentration is diminished due to partial homocoupling.

Conclusions and discussions

In addition to catalytic olefin CM, Wittig reactions^{xxv}, catalytic alkyne hydrogenation and cross-coupling^{xxvi,xxvii} are other notable approaches for synthesis of Z-disubstituted olefins. The above four types of transformations are distinct – each delivers the desired product through a different bond disconnection. Similar to CM, in cross-coupling olefins serve as starting materials; in contrast to CM, however, it is through the synthesis of the substrate (e.g., 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 (vs. 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 byproducts that can be difficult to separate from the desired Z alkene. Catalytic CM thus offers a desirable alternative to synthesis of Z alkenes, particularly since it requires as starting materials a functional group that is stable, easily accessible and distinct from the other commonly used protocols mentioned above.

The strategies outlined in this Article, including the use of reduced pressure to enhance stereoselectivity in catalytic CM, and the Z-selective Mo-catalyzed transformations offer a unique solution to a long-standing problem in organic chemistry^{xxviii}. The findings outlined herein offer additional evidence regarding the unique ability of stereogenic-at-Mo mono-aryloxyppyrolides to effect olefin metathesis reactions extends beyond enantioselective processes^{xxxix}, with efficiency and selectivity levels that are not achievable with other catalyst classes. The catalytic processes described herein are expected to impact significantly the ventures that require stereoselective synthesis of organic molecules^{xxx,xxxi}.

METHODS SUMMARY

General procedure for gram-scale catalytic Z-selective cross-metathesis under reduced pressure

In an N₂-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 allowed to stir for 3 h. The vessel was removed from the dry box and the reaction was quenched by the addition of wet Et₂O (~1.0 mL). The unpurified product is >98% Z (as determined by 400 MHz ¹H NMR analysis). The residue was dissolved in Et₂O 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*-Bu)₄NF (1.0 M in thf, 21.0 mL, 21.0 mmol), and allowed to stir for 2 h. The mixture was diluted with Et₂O (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 (0.914 g, 2.98 mmol, 71.0% yield; >98% Z isomer).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. A catalytic cross-metathesis (CM) reaction involves two different types of alkenes and can afford as many as six products; the challenge is to design an efficient process that favors 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 was 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 **1–2** 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 olefins. The sphere represents an appropriate size imido substituent.

Figure 2. Z-selective cross-metathesis (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 (in the case of *p*-methoxyphenylvinyl ether) or 10.0 (with butylvinyl ether) equivalents of the terminal enol ether; excess butyl vinyl ether (**6**) is easily removed in vacuo. The desired Z-olefins are obtained in 51–77% yield and in 94% to >98% Z selectivity. Application to synthesis of C18 (plasm)-16:0 (PC) demonstrates utility of the Z-selective Mo-catalyzed CM, which is used in conjunction with a site- and enantioselective Cu-catalyzed dihydroboration of the terminal alkyne in **14** (see the Supplementary Information for details).

*The reactions were performed under N₂ atm; catalysts we prepared and used in situ. Conversions and Z selectivities determined by analysis of 400 MHz ¹H NMR spectra of unpurified mixtures; yields of isolated products (±5%). Conversion and Z:E ratios measured

by analysis of 400 MHz ^1H NMR spectra of unpurified mixtures; the variance of values are estimated to be $<\pm 2\%$.

§ Performed with 2.5 mol % **1a** and 10 equiv **6** (see the Supplementary Information for experimental details).

† Performed with 1.2 mol % **1a** and 2.0 equiv **9** (see the Supplementary Information for experimental details).

‡ Performed with 5.0 mol % **1a** and 10 (**10b**) or 2.0 equiv **9** (**10d**) (see the Supplementary Information for experimental details).

Conditions for synthesis of **16: (a) 1. 2.5 mol % **1a**, C_6H_6 , 22 °C, 2.0 h, decalin, 1.0 torr. 2. 5.0 equiv (*n*-Bu) $_4\text{NF}$, thf, 22 °C, 2 h. (b) 2.5 mol % **15**, 2.5 mol % CuCl, 20 mol % NaOt-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 cross-metathesis (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-catalyzed CM, leads to an expeditious route for preparation of this biologically significant natural product (see the Supplementary Information for details).

*The reactions were performed under N₂ atm with 3.0 mol % **2**, 3.0 equiv of the non-N-containing alkenes (**19b-c**) or 5.0 mol % **2** and 10.0 equivalents of cross partner, 7.0 torr, 5.0 hours, 22 °C; catalysts were prepared and used in situ. Conversions and Z selectivities determined by analysis of 400 MHz ¹H NMR spectra of unpurified mixtures; yields of isolated products after purification (±5%). Conversion and Z:E ratios measured by analysis of 400 MHz ¹H NMR spectra of unpurified mixtures; the variance of values are estimated to be <±2%.

§ Reduced pressure was not used; reaction performed at 50 °C for 12 h (see the Supplementary Information for experimental details).

† Reaction time was one hour (see the Supplementary Information for experimental details).

Conditions for synthesis of **24: (a) 8.0 mol % **2** (in situ-generated), C₆H₆, 22 °C, 5.0 h, 1.0 torr. (b) 5 mol % OsO₄, 2.5 equiv N-Me-morpholine oxide, CH₂Cl₂, 0 °C, 24 h. (c) 10% trifluoroacetic acid, CH₂Cl₂, 22 °C, 30 min. (d) 1.2 equiv **23**, Et₃N, thf, 50 °C, 12 h.

Table 1

Examination of various catalysts for CM with an enol ether

The reactions were carried out in purified benzene under an atmosphere of nitrogen gas; 10 equivalents of **6** used (see the Supplementary Information for details). ND, not determined.

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	–	–
5	4	10 min; 80	ND	47.5:52.5
6	5	24 h; <2	–	–

[§] Conversion and Z:E ratios measured by analysis of 400 MHz ¹H NMR spectra of unpurified mixtures; the variance of values are estimated to be <±2%.

[†] Yield of isolated product after purification; the variance of values are estimated to be <±5%.

Table 2

Effect of Reduced Pressure on Efficiency and Z Selectivity

The reactions were carried out in purified benzene or decalin under an atmosphere of nitrogen gas (see the Supplementary Information for details).

Entry no.	11:12	Time; Conv. (%) [§]	Solvent	Pressure	Z:E [§]
1	5:1	2 h; 85	benzene	ambient	>98:2
2	1:1	2 h; 47	benzene	ambient	91.5:8.5
3	1:1	2 h; 78	benzene	1.0 torr	97:3
4	1:2	2 h; 88	decalin	1.0 torr	97:3

[§]Conversion, Z:E ratios and the amount of the homocoupled product were measured by analysis of 400 MHz ¹H NMR spectra of unpurified mixtures; the variance of values are estimated to be <±2%.

Table 3

Examination of various catalysts for CM with an allylic amide

The reactions were carried out in purified benzene under an atmosphere of nitrogen gas (see the Supplementary Information for details). N(phth) = *N*-phthalimide.

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

[§] Conversion and Z:E ratios were measured by analysis of 400 MHz ¹H NMR spectra of unpurified mixtures; the variance of values are estimated to be <±2%.

[†] Yield of isolated product after purification; the variance of values are estimated to be <±5%.