Published in final edited form as:
Angew Chem Int Ed Engl. 2010 ; 49(1): 34–44. doi:10.1002/anie.200904491.

Catalytic Enantioselective Olefin Metathesis in Natural Product Synthesis. Chiral Metal-Based Complexes that Deliver High Enantioselectivity and More

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Abstract

Chiral olefin metathesis catalysts enable chemists to access enantiomerically enriched small molecules with high efficiency; synthesis schemes involving such complexes can be substantially more concise than those that would involve enantiomerically pure substrates and achiral Mo alkylidenes or Ru-based carbenes. The scope of research towards design and development of chiral catalysts is not limited to discovery of complexes that are merely the chiral versions of the related achiral variants. A chiral olefin metathesis catalyst, in addition to furnishing products of high enantiomeric purity, can offer levels of efficiency, product selectivity and/or olefin stereoselectivity that are unavailable through the achiral variants. Such positive attributes of chiral catalysts (whether utilized in racemic or enantiomerically enriched form) should be considered as general, applicable to other classes of transformations.

Keywords

catalysis; catalytic olefin metathesis; enantioselective olefin metathesis; natural product synthesis; organometallic chemistry

> "The beauty of images is situated in front of things, that of ideas behind them. So that the first sort of beauty ceases to astonish us as soon as we have reached the things themselves, but the second is something that we understand only when we have passed beyond them."
>
> Marcel Proust, *In Search of Lost Time; Time Regained*
> (Moncrief and Kilmartin translation)

1. Introduction

In this brief analysis, we provide evidence indicating that the availability of chiral catalysts for olefin metathesis[i] offers synthesis routes that afford natural products more efficiently than those involving the use of the corresponding achiral complexes and enantiomerically pure substrates. We demonstrate that research in enantioselective olefin metathesis has led to identification of catalysts that not only furnish products in high enantiomeric purity, but which deliver significantly higher efficiency as well.

As with any class of reactions, catalytic alkene metathesis has a vital symbiotic relationship with target-oriented synthesis.[ii] The utility of a new catalyst and the versatility of the related methods can be best illustrated in context of natural product synthesis.[ii] Perhaps

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more importantly, the molecular architectures provided by nature fuel the development of new catalysts that permit the introduction of increasingly efficient and selective C–C bond forming protocols. Efforts to access natural products expeditiously serves a crucial role in the advancement of catalytic olefin metathesis, a widely used set of reactions, but nonetheless one that, in spite of two decades of remarkable strides, remains in need of advances in catalyst design and development.[iii] Once more active, longer living, easily available and readily modifiable catalyst classes are discovered, an assortment of otherwise inaccessible molecules, from those that might exhibit unique biological activity to polymeric materials with special properties, can be prepared and myriad applications realized.

In designing a chiral catalyst, the structure – the steric as well as the electronic characteristics – of the molecule is altered to the extent that a new type of a promoter, one that likely has a different reactivity and/or selectivity profile, emerges. A chiral catalyst need not only be used in its enantiomerically pure form nor does it have to be utilized exclusively for the purpose of enantioselective synthesis. A chiral catalyst might also offer substantially improved product- and/or site-selectivity or allow for control of olefin stereoselectivity. The significance of research in enantioselective catalysis therefore extends beyond the development of metal-based complexes that are simply considered to be chiral versions of the initial achiral catalysts.

2. Examples of Enantioselective Natural Product Synthesis through the Use of Achiral Olefin Metathesis Catalysts

We begin with a brief discussion of a select number of total syntheses wherein an achiral olefin metathesis catalyst is employed together with an enantiomerically enriched substrate. The first example is selected to illustrate how catalytic olefin metathesis is often used in enantioselective synthesis; subsequent cases are chosen to demonstrate that use of a chiral catalyst could significantly enhance their efficiency. Such initial analysis is central to an understanding of the importance of chiral olefin metathesis catalysts. We will then present an overview of syntheses wherein a catalytic enantioselective olefin metathesis plays a pivotal role.

2.1. Enantioselective Total Synthesis of Fluvirucin B_1

In the mid-nineties, we disclosed the Mo-catalyzed macrocyclization that delivers the fourteen-membered ring lactam **3** (Scheme 1) exclusively as a *Z* alkene.[iv] This instance of catalytic ring-closing metathesis (RCM) is one of the early examples illustrating that such transformations can be utilized to access macrocyclic structures during the late stages of a multistep total synthesis, and with substrates carrying (potentially catalyst deactivating) Lewis basic functionalities. The total synthesis of fluvirucin B_1 served to underline the strategic significance of the reversible nature of catalytic olefin metathesis; unlike the macrocyclization process (generating a trisubstituted alkene), homodimerization of **1**, involving reaction of its less sterically congested terminal alkene (affording a disubstituted olefin), is reversible.[v] Another notable aspect of the total synthesis is the highly stereoselective formation of the trisubstituted olefin (>98% *Z*),[vi] an attribute which led to an effective solution to the difficult problem of controlling the stereochemical identity of the remote Me-substituted stereogenic center (see Scheme 1).

Diene **1**, used to synthesize macrocycle **3**, is accessed through coupling of the corresponding carboxylic acid obtained in high enantiomeric purity by an enantioselective Zr-catalyzed carbometallation, and the requisite amine accessed through a sequence that includes a Ti-catalyzed enantioselective epoxidation.[iv] Thus, an achiral catalyst (Mo alkylidene **2**) is used in a transformation involving an enantiomerically enriched intermediate. Such a

strategy represents the manner in which different types of catalytic olefin metathesis (including enyne RCM, ring-opening/cross-metathesis (ROCM), and cross-metathesis) are commonly used in synthesis of enantiomerically enriched target molecules.[ii],[vii]

2.2. Synthesis of Targets through Diastereoselective Olefin Metathesis Reactions

One strategy used in enantioselective total synthesis involves catalytic diastereoselective olefin metathesis processes. In certain instances, a stereogenic element, temporarily installed to control stereoselectivity, is subsequently excised. The availability of an effective chiral olefin metathesis catalyst could obviate the need for installation of a stereocontrolling device and, therefore, elevate the overall efficiency of the synthesis route. Three illustrative examples are presented below.

2.2.1. Synthesis of enantiomerically enriched aspidospermine involving a catalytic diastereoselective RCM—

One example of diastereoselective RCM of an enantiomerically pure substrate is in connection with a total synthesis of aspidospermine (Scheme 2).[viii] Catalytic cyclization of triene **4**, obtained through a multi-step route that includes a Ti-catalyzed enantioselective epoxidation, is promoted by Ru carbene **5**, furnishing diene **6** in 87:13 d.r. after silyl ether hydrolysis; a diastereomerically pure sample (>98:2 d.r.) of the chiral cyclohexenol product is obtained after silica gel chromatography. Subsequent to the catalytic RCM, the original stereogenic center, used to establish the all-carbon quaternary stereogenic center in **6**, is oxidatively removed. Enantiomerically pure γ,γ-disubstituted cyclohexenone **7**, which serves to complete the total synthesis of aspidospermine, is thus accessed. An enantioselective desymmetrization process promoted by a chiral olefin metathesis catalyst, involving the enone corresponding to triene **4**, would directly afford the derived α,β-unsaturated carbonyl, rendering the total synthesis scheme more concise.

2.2.2. Synthesis of enantiomerically enriched longithorone A through two diastereoselective enyne RCM reactions—

A total synthesis of longithorone,[ix] summarized in Scheme 3, is based on the fusion of macrocyclic polyenes **11** and **12**. The two key intermediates are prepared, albeit inefficiently (50 mol % catalyst loading and <50% yield), through diastereoselective Ru-catalyzed enyne RCM. Whereas **11** is obtained in >95:5 d.r., generation of **12** is less selective (74:26 d.r.). Terminal alkynes **9** and **10**, the requisite substrates for enyne RCM, are synthesized by enantioselective additions of the appropriate vinylzinc reagents to aldehyde **8** (Scheme 3) in the presence of stoichiometric amounts of *N*-methylephedrine.

The benzylic stereogenic centers in fragments **9** and **10** (Scheme 3) are initially installed as the means of controlling the stereochemical outcome of the enyne RCM, which establishes the stereogenic plane of the *endo*-diene macrocyclic products **11** and **12**. The benzylic silyloxy groups must be deleted prior to completion of the total synthesis. A substantially more active (lower loading) and more efficient (higher yield) chiral catalyst for the enyne RCM[x] could allow for direct control of the planar stereogenicity,[xi] giving rise to a significantly more efficient synthesis route.

2.2.3. Synthesis of racemic coleophomones B and C. Control of atropisomerism through catalytic RCM reactions—

Ru-catalyzed diastereoselective RCM has been employed towards controlling atropisomerism in total syntheses of *rac*-coleophomones B and C (Scheme 4).[xii] Treatment of tricarbonyl *rac*-**13** with CH_2N_2 leads to the formation of a 3:2 mixture of **15** and **16**, each of which was subjected to Ru carbene **14**. It is likely that the metal complex reacts first with the sterically more accessible 1,1-disubstituted olefin in **15** and **16**; RCM of the resulting carbene with one of the two

diastereotopic prenyl groups establishes the identity of the quaternary carbon stereogenic center, while promoting the stereoselective formation of eleven-membered rings **17** and **18** (control of planar stereogenicity). It is noteworthy that ring-closure of **15** exclusively delivers the *E*-olefin isomer and ring-closure of **16** affords *Z* alkene **18**; both processes are diastereoselective (>98%), with the prenyl unit *syn* to the adjacent methyl group participating in the RCM. A stereoselective desymmetrization of triene **13** promoted by an appropriate chiral RCM catalyst would directly furnish the desired target structures (**17** and **18**). This particular application raises the intriguing question of whether any alterations within the catalyst structure could allow one to access either the *E* (coleophomone B) or the *Z* (coleophomone C) trisubstituted alkene isomers.

3. Synthesis of Natural Products with Enantiomerically Pure Chiral Olefin Metathesis Catalysts Bearing a C_2-Symmetric Diolate

3.1. Synthesis of endo-brevicomin through Mo-catalyzed enantioselective RCM

In 1999, shortly after the disclosure of the first effective chiral catalyst for enantioselective RCM,[xiii] a total synthesis of *endo*-brevicomin was disclosed (Scheme 5).[xiv] Desymmetrization of *meso* acetal **19** is promoted by Mo-based diolate **20**, affording the bicyclic acetal in 79.5:20.5 enantiomeric ratio (e.r.) and 90% yield; subsequent catalytic hydrogenation delivers the target molecule. It should be noted that the only effective chiral catalyst available at the time was complex **20**; one of the chiral Mo alkylidenes developed[iia] after the study in Scheme 5 can likely furnish the desired bicyclic acetal with improved enantiomeric purity. All the Ru-catalyzed enantioselective RCM reactions reported thus far, however, proceed with high selectivity (≥95:5 e.r.) only when the substrate bears trisubstituted alkenes.[xv]

3.2. Total synthesis of coniine through enantioselective RCM with substrates bearing a tertiary amine

In 2005, the first examples of enantioselective olefin metathesis involving substrates that bear Lewis basic amines were reported.[xvi] The catalytic activity of a number of chiral Mo-based diolates (such as **20** in Scheme 5) were probed, illustrating that the corresponding enantioselective RCM reactions can afford azacyclic structures in up to 99:1 e.r. Ru-based catalysts can, at least in certain instances, be inhibited in the presence of the same class of amine substrates.[xvii]

The preparation of enantiomerically enriched coniine, the neurotoxin found in the hemlock plant, demonstrates the utility of the abovementioned class of catalytic transformations. As depicted in Scheme 6, Mo-catalyzed RCM of benzylamine **21** with 5 mol % of chiral Mo catalyst **22** gives rise to the formation of unsaturated piperidine **23** in 93.5:6.5 e.r. and 83% yield. A two-step sequence furnishes the poisonous alkaloid.[xvi]

3.3. Enantioselective synthesis of africanol by a ring-opening/ring-closing metathesis reaction

An application of catalytic enantioselective ring-opening/ring-closing metathesis (RORCM) reaction was reported in 2004 in connection with a total synthesis of africanol.[xviii] Treatment of *meso* tertiary silyl ether **24**, obtained as a single diastereomer through stereoselective alkylation of a norbornenone, with 3 mol % of chiral alkylidene **25** gives rise to the formation of **26** in 93.5:6.5 e.r. and 97% yield (Scheme 7). Thus, a bicyclic structure that bears nearly all the desired stereochemical attributes, including the quaternary carbon stereochemistry appropriate for the preparation of enantiomerically enriched africanol, is accessed in a single catalytic process.

Conversion of **26** to **27** (Scheme 7) requires eight additional transformations; two nontrivial processes include site-selective reaction of the cyclic alkene to deliver a Me-bearing trisubstituted olefin and the transformation of the pendant vinyl to the requisite methyl unit. The somewhat lengthy sequence that connects **26** and **27** underlines a notable characteristic of catalytic desymmetrization processes promoted by enantioselective olefin metathesis reactions: such processes give rise to products bearing olefins that might not possess the desired substitution pattern and/or be readily differentiable. The issue of site-selective olefin functionalization is obviated in cases summarized in Schemes 5–6 due to catalytic hydrogenations of all alkenes in the product structure. An alternative strategy to synthesize africanol might have involved catalytic RORCM of the corresponding enantiomerically pure trisubstituted norbornyl alkene. Design of an enantioselective synthesis of such a chiral molecule, however, would not be trivial, again underlining the importance of enantioselective olefin metathesis.

Weaknesses of a total synthesis often point to intriguing problems that await effective new solutions; the route shown in Scheme 7 is a case in point. An efficient, site-selective, and preferably catalytic conversion of a disubstituted alkene to a trisubstituted olefin would strengthen the olefin metathesis-based approach developed for africanol. Such a transformation could involve alkylmetallation of the olefin followed by β-hydride elimination (Heck-type process).

3.4. Enantioselective synthesis of the lactone fragment of anti-HIV agent tipranavir

The ability of a chiral catalyst to rearrange a simple achiral molecule to a valuable chiral one in high enantiomeric purity finds an application in the context of a synthesis of tipranavir, a molecule active against the HIV-protease enzyme.[xix] An achiral substrate such as **28**, through subjection to an appropriate chiral catalyst (5 mol % **25**), is converted to a chiral product (**29**) that would otherwise be difficult to access in the non-racemic form (Scheme 8). Synthesis of **29** (95.5:4.5 e.r.) underlines the ability of catalytic enantioselective olefin metathesis to deliver molecules not easily prepared with achiral catalysts and enantiomerically enriched substrates.[xx] The latter approach would require an efficient method for enantioselective synthesis of the requisite *O*-substituted quaternary carbon stereogenic center. In spite of recent advances, efficient and facile protocols, particularly of the catalytic variety, to furnish tertiary alcohols in high enantiomeric purity remain largely unavailable.[xxi]

Another noteworthy feature of the sequence shown in Scheme 8 relates to differentiation of the two olefins of **29**. Site-selective allylic oxidation (PCC, CH_2Cl_2, 80 °C) of the cyclic allylic ether allows for a Rh-catalyzed hydrogenation [3 mol % $ClRh(PPh_3)_3$] to generate the desired lactone and the *n*-propyl side chain, respectively.

4. Design, Synthesis and Application of Stereogenic-at-Mo Olefin Metathesis Catalysts. Enantioselective Synthesis of Quebrachamine through a Challenging RCM Reaction

Application of catalytic enantioselective olefin metathesis to natural product synthesis remains relatively uncommon, compared to myriad complex molecule syntheses achieved through utilization of the corresponding achiral catalysts.[ii] One reason for such paucity is that target molecules are often identified subsequent to development of a method. As a result, a protocol may not provide an ideal solution for a particular total synthesis application. It might be more expedient to secure first the most direct synthesis route, which would undoubtedly benefit from an effective catalytic enantioselective process. The

effectiveness of the existing chiral complexes, if available, might then be evaluated and, if necessary, shortcomings can be addressed through new catalyst design.

A recent enantioselective synthesis of *Aspidosperma* alkaloid quebrachamine was accomplished through the above approach (Scheme 9).[xxii] That is, the total synthesis was principally conceived to challenge the current state-of-the-art olefin metathesis catalysts and serve as a springboard for catalyst development. As illustrated in Scheme 9, the late-stage RCM requires ring-closure onto one of two sterically hindered vinyl groups at a congested all-carbon quaternary center[xxiii] in the presence of a Lewis basic tertiary amine. Mo-based diolates, such as **20** (Scheme 5), fail to deliver the desired tetracycle **35** even under forcing conditions (up to 50 mol % catalyst, up to 80 °C, for as long as 48 h). With a chiral Ru catalyst, such as that shown in Scheme 10 (**37**, below), only *rac*-**35** is obtained with little efficiency. Even when the more active achiral Mo complex **2** (Scheme 1) is used, >98% conversion (59% yield) is only achieved with 30 mol % catalyst loading.

To address the aforementioned shortcomings and identify an effective catalyst for efficient and enantioselective RCM of **33**, a new class of stereogenic-at-Mo complexes, represented by monopyrrolide **34**, was introduced.[xxiia] The design of the more active chiral Mo-based catalysts was largely based on mechanistic considerations. One such principle is that, in any olefin metathesis process the metal center is fluxional: it undergoes repeated inversion through intermediacy of trigonal bipyramidal or square pyramidal complexes. We argued that the absence of a rigid bidentate ligand reduces the energetic barriers that accompany such transformations within the catalytic cycle, enhancing catalyst activity. Furthermore, based on recent studies by Eisenstein and co-workers,[xxiv] the stereogenic-at-Mo complexes were outfitted with one relatively stronger electron-donating (e.g., pyrrolide in **34**, Scheme 9) and a relatively weaker electron-donating ligand (e.g., aryloxide in **34**, Scheme 9). Theoretical investigations suggested that the presence of an electron donor ligand (vs two identical aryloxides in chiral Mo diolates) could facilitate and control the stereochemical course of olefin coordination as well as increase the rate of metallacyclobutane cyclo-reversion. Experimental evidence strongly supported the validity of the above hypotheses: stereogenic-at-Mo complexes such as **34**, generated *in situ* from the corresponding achiral Mo bispyrrolide and an equivalent of the chiral aryl alcohol (catalyst isolation not required), readily promote the difficult RCM (Scheme 9). The desired tetracyclic diene **35**, containing an all-carbon quaternary stereogenic center, is thus obtained efficiently (84% yield) and with exceptional enantioselectivity (98:2 e.r.).[xxv]

5. Synthesis of Baconipyrone C by Ru-Catalyzed Enantioselective ROCM

Total synthesis of baconipyrone C, disclosed in 2007,[xxvi] represents the first and, thus far only, application of a Ru-catalyzed enantioselective olefin metathesis process to natural product synthesis. Treatment of oxabicycle **36** with styrene in the presence of 2 mol % Ru carbene **37**[xxvii] delivers the fully substituted pyran **38** in 62% yield and 94:6 e.r. (Scheme 10). It should be noted that **37** is generated *in situ* by subjection of the corresponding Ag-based *N*-heterocyclic carbene (NHC) with the appropriate achiral Ru-PCy_3 complex and NaI; there is no the need for isolation or purification of the catalyst. The chiral Ru catalyst does not only deliver high enantioselectivity: the ROCM with **37** is significantly more efficient than when achiral carbenes, which contain a non-stereogenic metal center and a monodentate NHC ligand (vs a stereogenic Ru center and a bidentate NHC in **37**), are used.[xxviii]

It has already been mentioned that effective differentiation of the olefins within a product structure is a challenge typically associated with catalytic olefin metathesis reactions (particularly ring-opening processes; see Scheme 7). Alkene differentiation is achieved with

38 through a reductive cleavage (Scheme 10), which occurs with complete selectivity at the cinnamyl C–O (<2% conjugated alkene); a Birch reduction delivers only the *E* alkene as well. Acyclic diene **39** is used to access the polypropionate core (shown in red, Scheme 10).

The diketone fragment of baconipyrone C (shown in blue, Scheme 10) was synthesized through a tandem double-allylic alkylation, promoted by a chiral Cu complex that bears a bidentate NHC that is structurally related to that residing within Ru carbene **37**. Development of chiral NHC ligands, initially designed for use in Ru-catalyzed alkene metathesis, have thus been successfully utilized in other important classes of C–C bond forming reactions.[xxix]

In the sequence summarized in Scheme 10, the transformation involving a chiral olefin metathesis catalyst (formation of **38** catalyzed by chiral Ru carbene **37**) is performed at an early juncture. In contrast, total synthesis of quebrachamine, the final two transformations of which are depicted in Scheme 9, contains a penultimate enantioselective RCM. An application such as baconipyrone C illustrates that the catalytic enantioselective ROCM can be carried out in reasonable scale (multi-gram), so that sufficient material is made available for the completion of the total synthesis. The late-stage process involving the formation of **35** catalyzed by chiral Mo alkylidene **34** (Scheme 9) highlights a different noteworthy issue: a multi-step synthesis plan can be devised with a reasonable degree of reliability involving a set of transformations that includes a catalytic enantioselective olefin metathesis reaction.

6. A concept underlined by the development of new chiral Mo catalysts: The significance of chiral catalysts extends beyond enantioselectivity

In the course of our search for an efficient chiral complex that would promote the RCM of triene **33**, en route to quebrachamine, we arrived at a class of chiral catalysts that readily initiates the requisite process enantioselectively and with significantly higher efficiency than other existing achiral or chiral Ru- or Mo-based catalysts.[xxii] A critical observation made in the above studies, as illustrated in Scheme 11, is that in the presence of only 1 mol % *rac*-**40**, RCM of **33** proceeds to >98% conversion within one hour, affording the desired *rac*-**35** in 79% yield. As also shown in Scheme 11, reaction with achiral Mo alkylidene **2** is far less efficient. Various achiral Ru carbenes deliver 35% to >98% conversion at 5 mol % loading after 6 hours. Ru-catalyzed transformations generate a significant amount of byproducts; *rac*-**35** can only be obtained in 36%–65% yield. The desired tetracyclic diene is isolated in 83% yield only when 7.5 mol % of a more efficient Ru complex is used.[xxiib] The above findings indicate that a chiral catalyst can offer reactivity patterns that are substantially different from those offered by the achiral variants. In other words, chiral catalysts can be relevant to cases other than those where the goal is achieving high enantioselectivity.

Design of a chiral Ru complex, utilized in the racemic form, to promote sequence-selective copolymerization processes,[xxx] constitutes a notable demonstration of how chiral catalysts can deliver unusual selectivity profiles.[xxxi] As illustrated in Scheme 12, the stereogenic-at-Ru complex **41** has a relatively more stable diastereomeric form (**41** and **42**), where the carbene resides beneath the sterically less demanding phenyl substituent of the phosphine ligand. This latter isomer reacts preferably with the more reactive (e.g., strained) alkene, leading to inversion at the Ru center and generation of a higher energy stereoisomer (**43**), where the carbene is forced to reside proximal to the sterically demanding *t*-butyl unit. The newly generated complex (**43**) reacts with all types of alkenes, as there is a significant driving force for re-inversion at the Ru center (formation of the lower energy metal carbene). Thus, by using an excess amount of the less reactive cross partner (versus the

strained alkene partner), sequence-selective polymerization can be achieved when *rac*-**41** is utilized.

Two more recent instances, where chiral olefin metathesis catalysts serve to address issues other than product enantiomeric purity, are summarized in Scheme 13. Chiral complex *rac*-**46** readily promotes RCM of enyne **45** to afford diene **47** exclusively (Scheme 13);[xxxii] none of five-membered ring diene **48**, generated predominantly by reactions with Ru carbene **49**,[xxxiii] is obtained. In another example (Scheme 13), chiral Mo complex **51** promotes an exceptionally *Z*-selective (>98:<2 *Z:E*) ROCM of oxabicycle **50** and styrene.[xxxiv] Achiral alkylidene **2** (Scheme 1) delivers a 66:33 mixture of *E:Z* isomers, and chiral Mo-based diolates, such as **20** and **22** (Schemes 5 and 6) as well Ru complexes such as **14** (Scheme 4) and **37** (Scheme 10) afford only the corresponding *E* alkene (>98:2 *E:Z*).[17c,xxxv] In the most recent investigations, stereogenic-at-Mo complexes have been used to effect highly *Z*-selective polymerization reactions of norbornene-derived monomers.[xxxvi] The macromolecular systems obtained through the use of the new Mo alkylidenes were entirely inaccessible previously.

Application of chiral catalysts towards enhancing reaction efficiency or altering product selectivity trends does not pertain only to olefin metathesis. Two representative cases are provided in Scheme 14. Pd-catalyzed cross-coupling in the presence of achiral P(*o*tolyl)$_3$ is substantially less efficient in producing aniline **53** than when *rac*-**55** is used (Scheme 14; 77% vs 93% yield, respectively).[xxxvii] A related Pd-catalyzed process involving ammonia is reported to proceed most efficiently with Josiphos, a chiral bisphosphine variant of **55**.[xxxviii]

Allylic alkylation of unsaturated phosphate **56**, in the presence of various Cu salts, results either in complete recovery of the starting materials or, when stoichiometric amounts are used, a mixture of several products (**57**–**59**, Scheme 14). The NHC–Cu complex, formed *in situ* through reaction of achiral **60** and $CuCl_2{\cdot}2H_2O$, is similarly ineffective in promoting alkylation. In stark contrast, the chiral NHC–Cu complex, derived from **61** and $CuCl_2{\cdot}2H_2O$, not only delivers >98% conversion, promotes the generation of **57** exclusively (<2% **58** or **59**) and as a single enantiomer (>99:1 e.r.).[xxxix]

The allylic alkylation shown in Scheme 14 represents a class of transformations where a chiral catalyst gives rise to the introduction of a new site-selective C–C bond forming protocol, one that might not necessarily have an effective non-enantioselective variant (as is typically the case). Herein lies a crucial lesson regarding research in catalyst and method design: examination of a process promoted by an achiral catalyst need not precede the development of an enantioselective version catalyzed by a chiral complex. Through the use of a chiral catalyst, we may be able to address – effectively and simultaneously – issues of reactivity and selectivity. A chiral catalyst may well deliver previously unattainable reactivity levels, while engendering an enantioselective variant. It is possible that a chiral catalyst delivers unprecendented reactivity levels without offering high stereoselectivity; for example, enantiomerically pure adamantylimido complex **51** (Scheme 13) promotes the RCM reaction that leads to quebrachamine (**33**→**35**, Scheme 9) far more readily than achiral **2** (Scheme 1), but with low enantioselectivity (70:30 e.r.).[xl]

7. Conclusions and Future Outlook

Catalytic olefin metathesis has made an enormous impact on chemical synthesis during the past two decades, but a number of its potential applications remain unrealized as a result of deficiencies in catalyst performance.[iii] The findings briefly touched upon in this article illustrate that target-oriented synthesis can serve as an invaluable indicator of the types of

catalysts that remain to be discovered. In addition to the need for catalysts that are more efficient in promoting RCM and ROM processes that require relatively high loadings, most noteworthy, perhaps, are effective catalysts for stereoselective cross-metathesis reactions.[i] The example shown in Scheme 15, involving an inefficient cross-metathesis to obtain a trisubstituted olefin is illustrative.[viib] Examination of a variety of Ru- and Mo-based complexes revealed that optimal results are obtained with 35 mol % **49** in a transformation that affords the desired product with only 75:25 *E:Z* selectivity; *E*-**60** is obtained in only 40% yield after purification. Use of phosphine-bearing Ru carbene **14** (Scheme 4) gives rise to some loss of enantiomeric purity,[xli] and with achiral Mo complex **2** (Scheme 1), still lower *E:Z*-selectivity is obtained (66:33).[xlii] High *E:Z*- or *Z:E*-selectivity in synthesis of di-, tri- or tetrasubstituted alkenes through catalytic cross-metathesis remains out of reach. Perhaps it will be a class of chiral catalysts that will provide effective solutions to the above problems; the high *Z*-selectivity provided by chiral Mo alkylidene **51** (Scheme 13) suggests that this might indeed be the case.

A critical issue emerging through the above discussions is that a chiral catalyst should not be examined only in the context of an enantioselective process. A chiral catalyst might offer reactivity levels that are superior to those furnished by any achiral variant. If the goal of a study is the development of an enantioselective transformation, initial reactivity studies should not necessarily be focused only on achiral catalysts. One cannot help but wonder how many solutions to various problems in catalysis have been missed because only achiral catalysts have been probed?

Acknowledgments

We are grateful to the National Institutes of Health (GM-59426) and the National Science Foundation (CHE–0715138) for support of our investigations regarding development of new catalysts (Mo- and Ru-based, respectively) for olefin metathesis. We thank Professor Richard R. Schrock, Dr. Pamela J. Lombardi, Robert V. O'Brien III, Dr. Ismail Ibrahem, Miao Yu, and Dr. Yeon-Ju Lee for helpful suggestions and numerous discussions.

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vi. A recent study in connection with total syntheses fluvirucins B_2–B_5 indicates that RCM of this class of dienes with Ru-based carbenes leads to the formation of a mixture of E and Z isomers. Such observations suggest that, in contrast to the initial suppositions (ref. 4c), the high Z-selectivity obtained in the reaction illustrated in Scheme 1 is largely imposed by the Mo-based alkylidene (vs the conformational preferences of the substrate). See: Llàcer E, Urpì F, Vilarrasa J. Org Lett. 2009; 11:3198–3201. [PubMed: 19583204]

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x. Formation of macrocyclic 11 is a rare example of an endo-selective processes catalyzed by Ru-based complex; Ru-based carbenes, unlike Mo alkylidenes, typically deliver the corresponding exo-dienes. For endo- and enantioselective Mo-catalyzed enyne RCM reactions, see: Singh R, Schrock RR, Müller P, Hoveyda AH. J Am Chem Soc. 2007; 129:12654–12655. [PubMed: 17902675] Lee YJ, Schrock RR, Hoveyda AH. J, Am Chem Soc. 2009; 131:10652–10661. [PubMed: 19580318]

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xxviii. In contrast to reactions with stereogenic-at-Ru catalysts with bidentate chiral ligands, transformations of oxabicyclic alkenes in the presence of achiral Ru-carbenes bearing monodentate NHCs lead to formation of substantial amounts of oligomerization; the desired ROCM products are isolated in only 12–30% yield (unpublished results of A. R. Zhugralin, M. Yu, A. H. Hoveyda). The mechanistic details for the difference in efficiencies of these two classes of Ru-based carbenes in promoting ROCM reactions will be disclosed shortly in a separate account.

xxix. Chiral bidentate NHCs originally designed for Ru-catalyzed olefin metathesis have been used to promote other classes of transformations. See: (Cu-catalyzed enantioselective conjugate additions) Lee, K-s; Brown, MK.; Hoveyda, AH. J Am Chem Soc. 2006; 128:7182–7184. [PubMed: 16734469] Brown MK, May TL, Hoveyda AH. Angew Chem Int Ed. 2007; 46:1097–1100.May TL, Brown MK, Baxter CA, Hoveyda AH. Angew Chem Int Ed. 2008; 47:7358–7362. (Cu-catalyzed enantioselective allylic alkylations): Kacprzynski MA, May TL, Kazane SA, Hoveyda AH. Angew Chem Int Ed. 2007; 46:4554–4558.(Cu-catalyzed hydroboration reactions): Lee Y, Hoveyda AH. J Am Chem Soc. 2009; 131:3160–3161. [PubMed: 19256564]

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xli. For another notable example of complications arising from undesirable epimerization promoted by P-containing Ru-based catalysts (vs 45), see: Yee NK, Farina V, Houpis IN, Haddad N, Frutos RP, Gallou F, Wang X-j, Wei X, Simpson RD, Feng X, Fuchs V, Xu Y, Tan J, Zhang L, Xu J,

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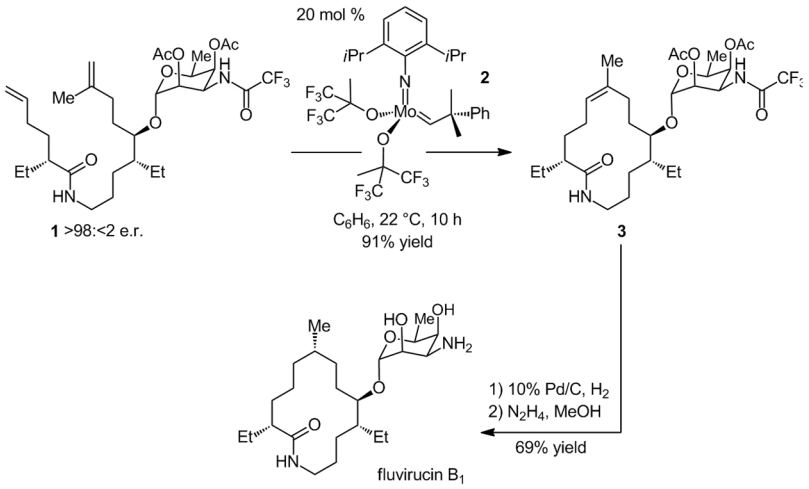
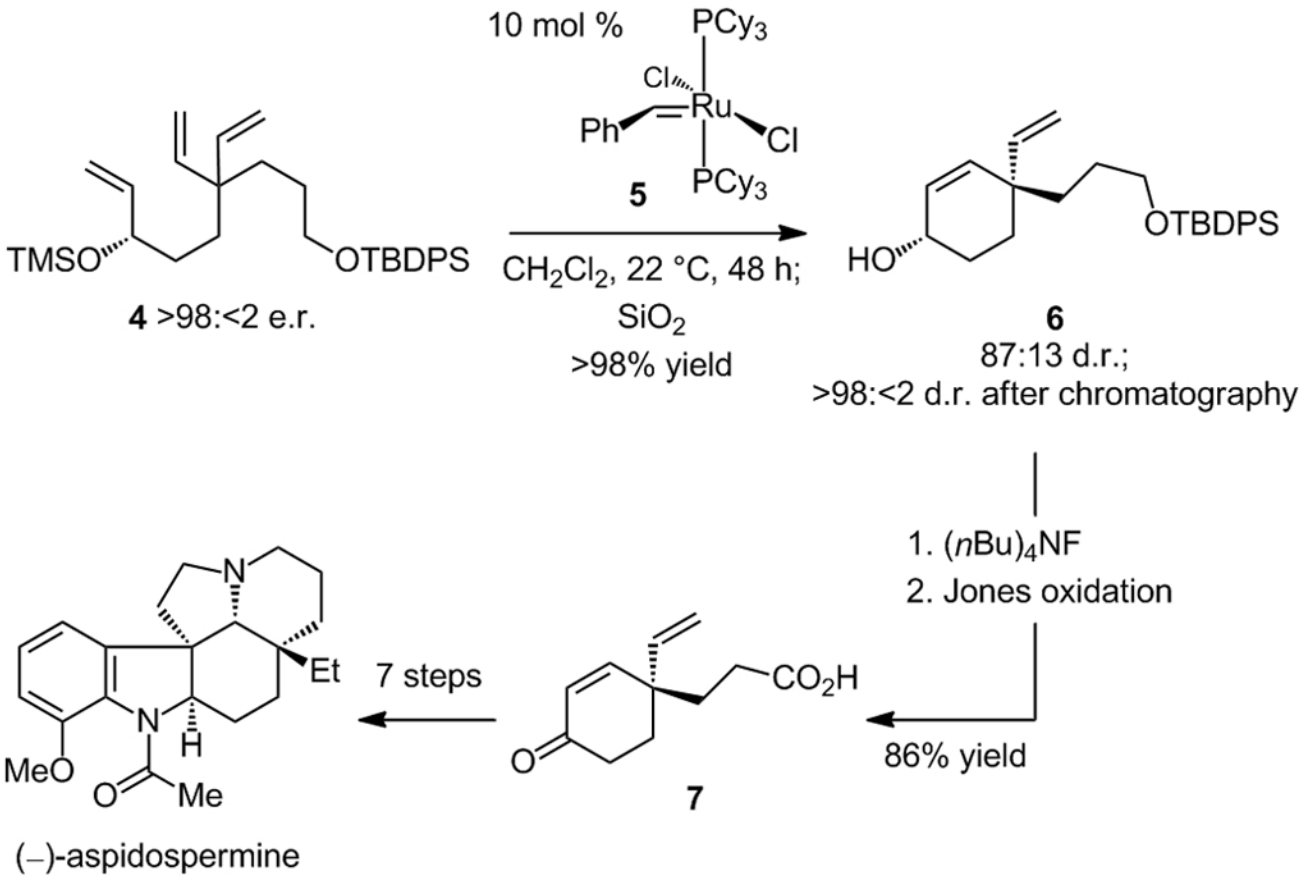
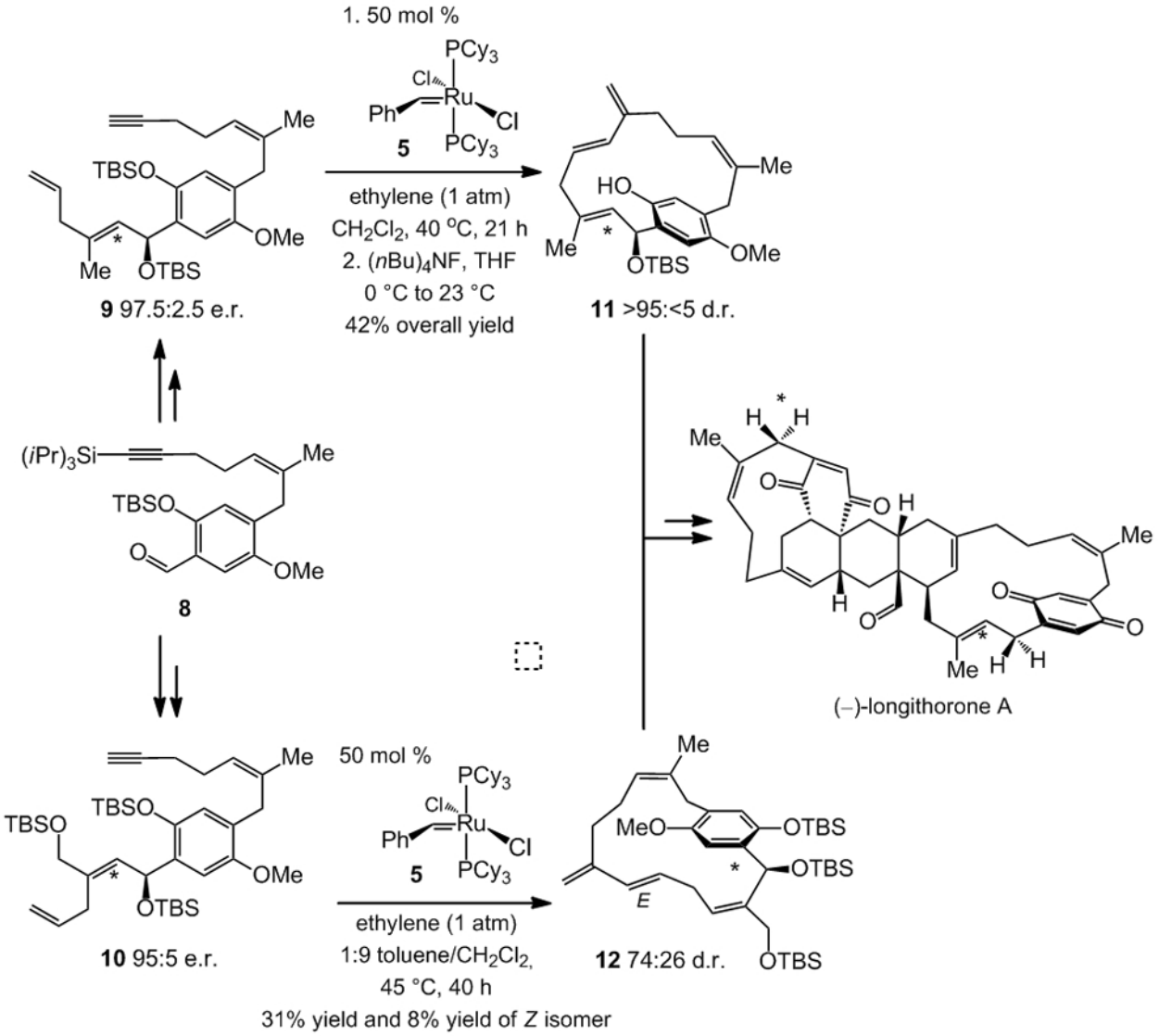


Scheme 1.

Enantioselective synthesis of antifungal agent fluvirucin B_1 through a late-stage macrocyclic Mo-catalyzed RCM.

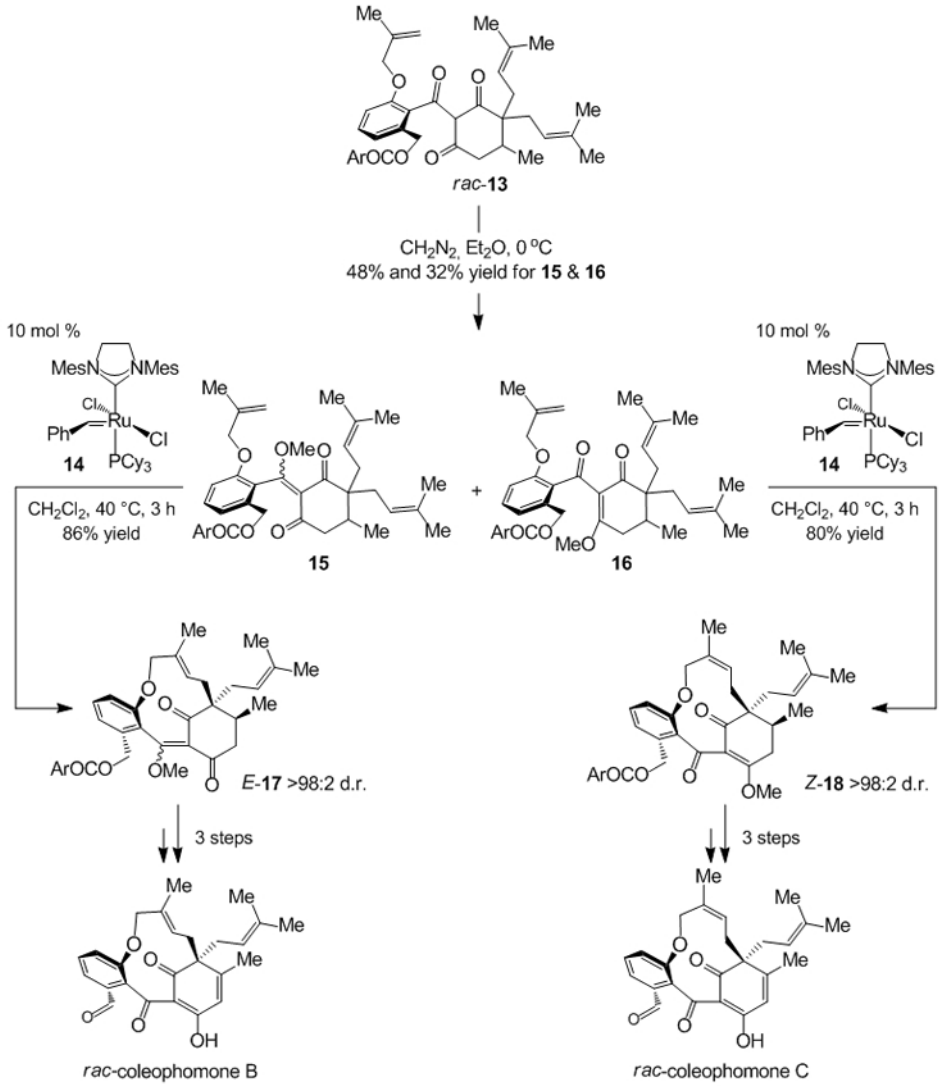


Scheme 2.
Total synthesis of aspidospermine through catalytic diastereoselective RCM.



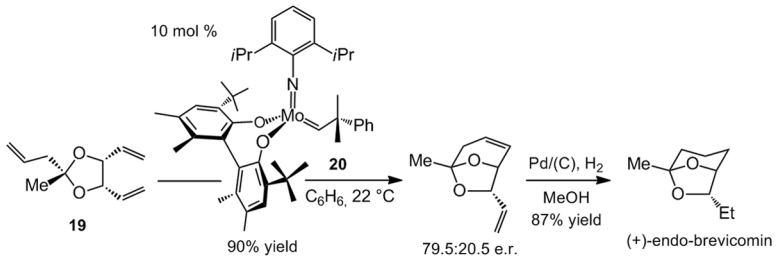
Scheme 3.

Total synthesis of (−)-longithorone A involving a diastereoselective enyne RCM. The silylether-bearing stereogenic carbon centers, installed for control of planar stereogenicity and subsequently removed, are highlighted.

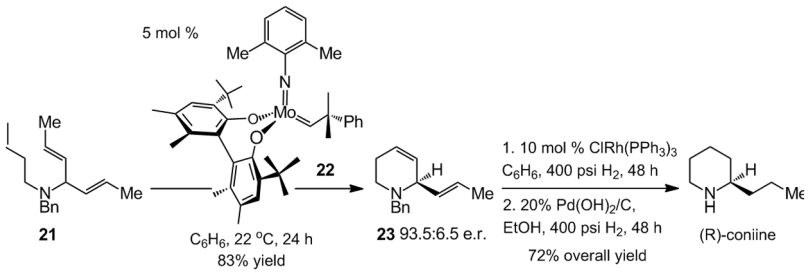


Scheme 4.

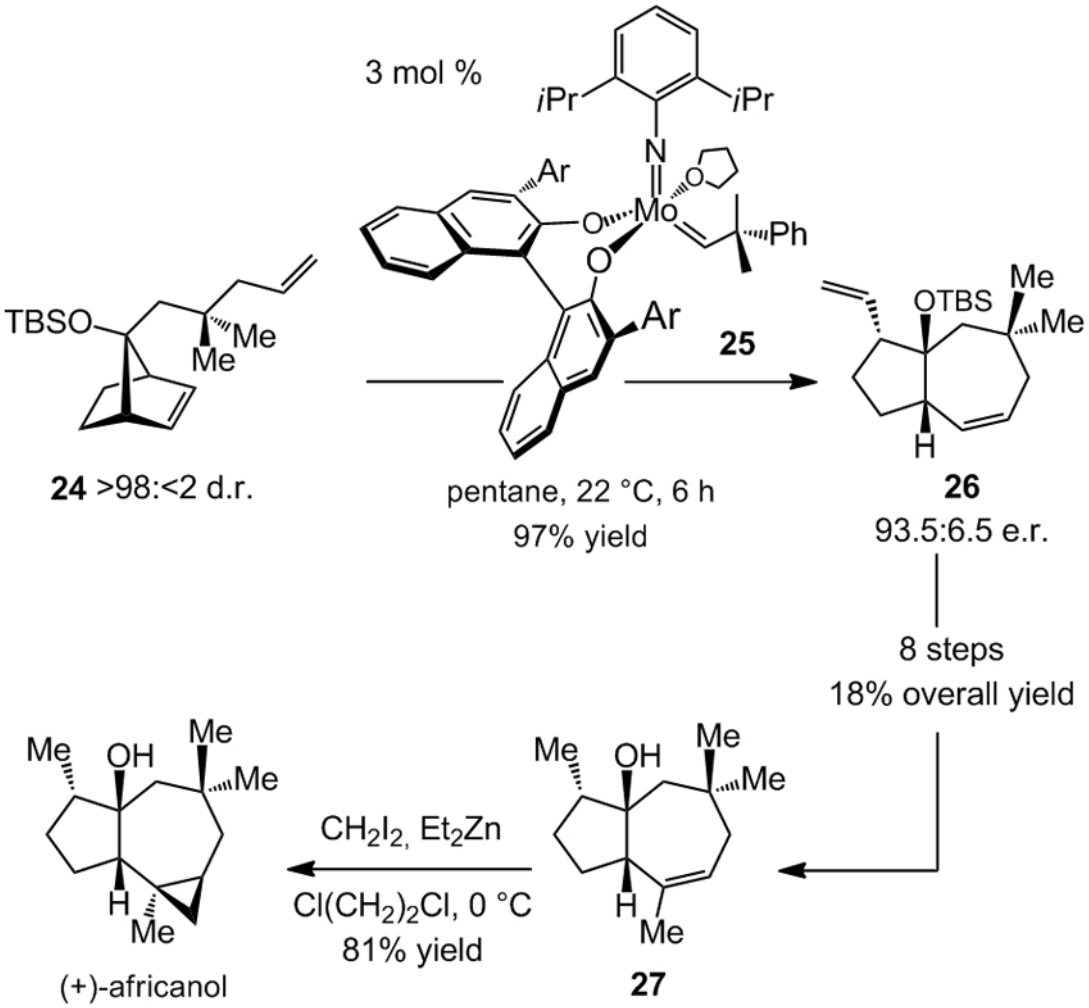
Control of atropisomerism in total syntheses of *rac*-coleophomones B and C. Ar = *p*BrC_6H_4; Mes = 2,4,6-$Me_3C_6H_2$.



Scheme 5.
Synthesis of (+)-*endo*-brevicomin through enantioselective RCM.

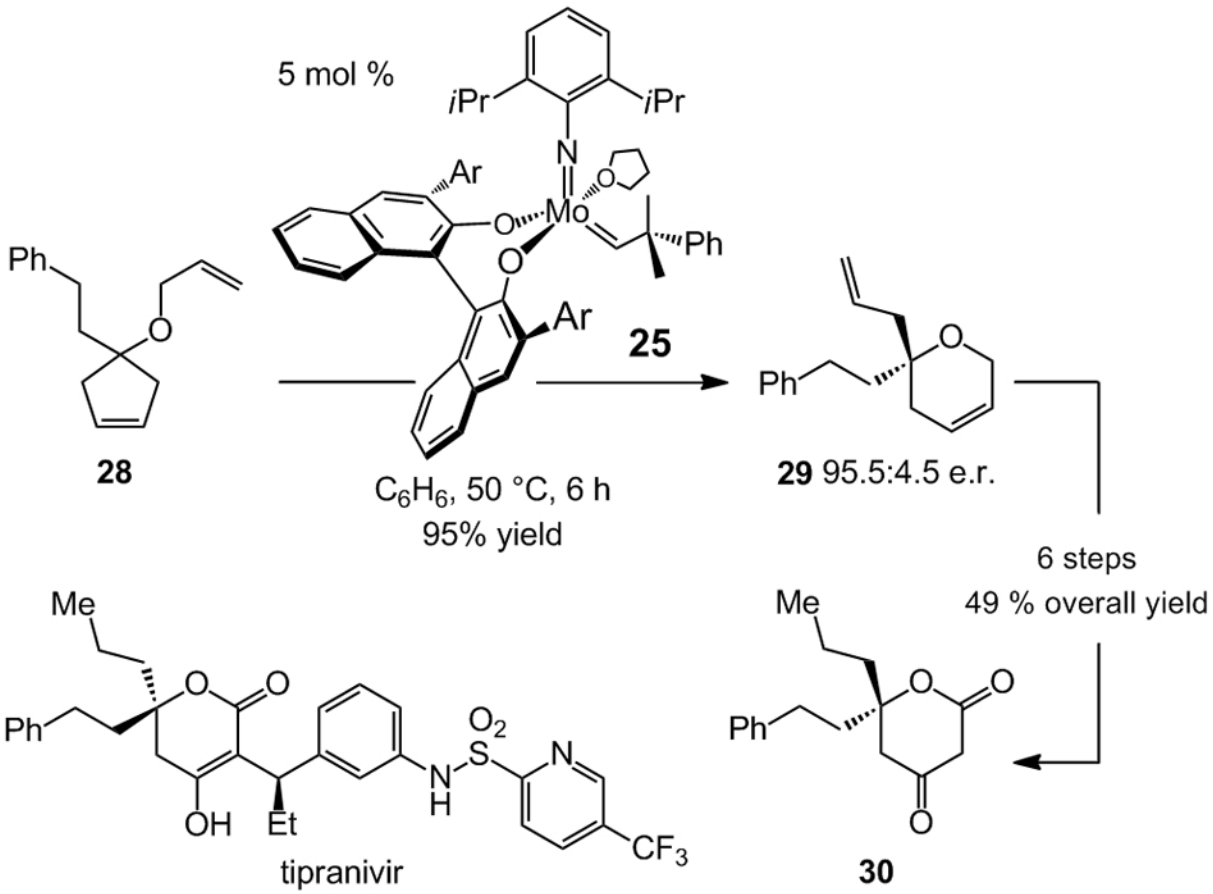


Scheme 6.
Total synthesis of coniine through enantioselective RCM.



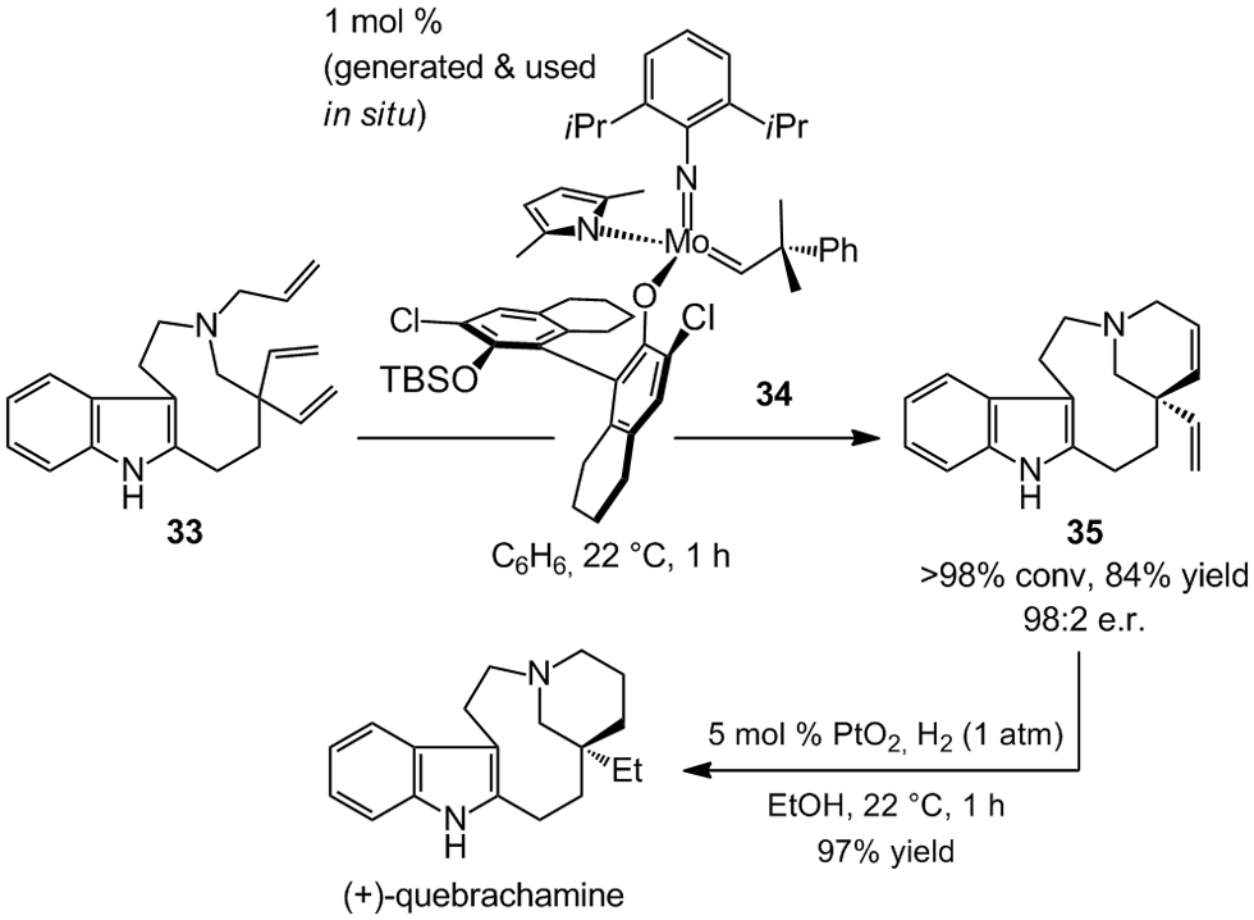
Scheme 7.

Synthesis of africanol through an enantioselective ring-opening/ring-closing metathesis (RORCM) reaction. Ar = 2,4,6-(*i*Pr)$_3$C$_6$H$_2$, TBS = *t*-butyldimethylsilyl

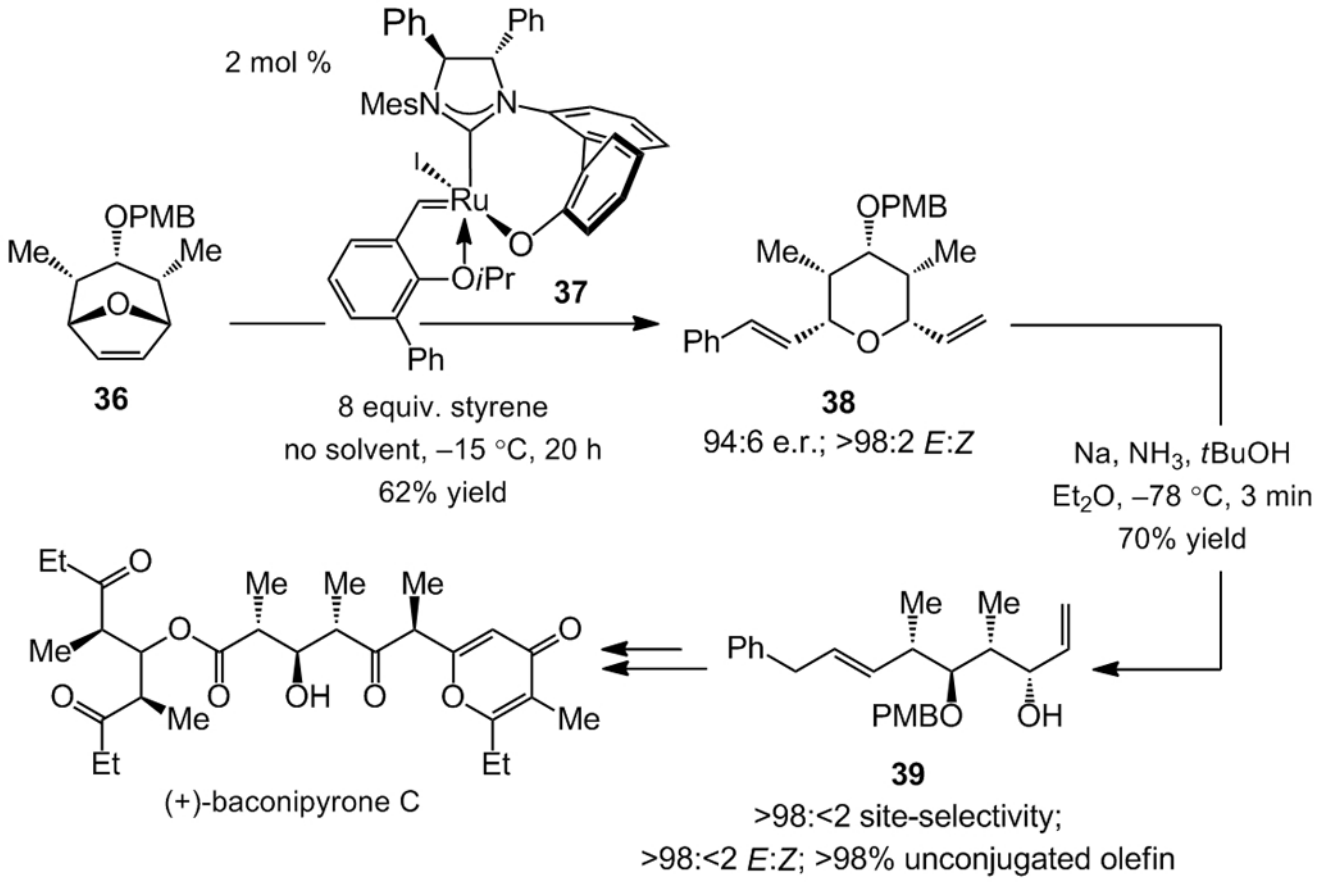


Scheme 8.

Enantioselective synthesis of the lactone fragment of HIV-protease inhibitor tipranivir through a Mo-catalyzed ring-opening/ring-closing metathesis (RORCM) reaction. Ar = 2,4,6-(iPr)$_3$C$_6$H$_2$

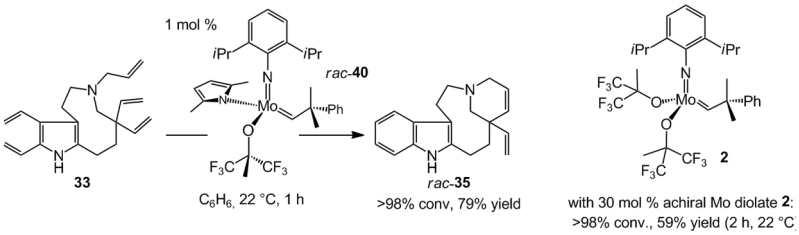


Scheme 9.
Catalyst development spurred by total synthesis: A stereogenic-at-Mo complex as a highly effective chiral catalyst developed for enantioselective RCM in total synthesis of quebrachamine.

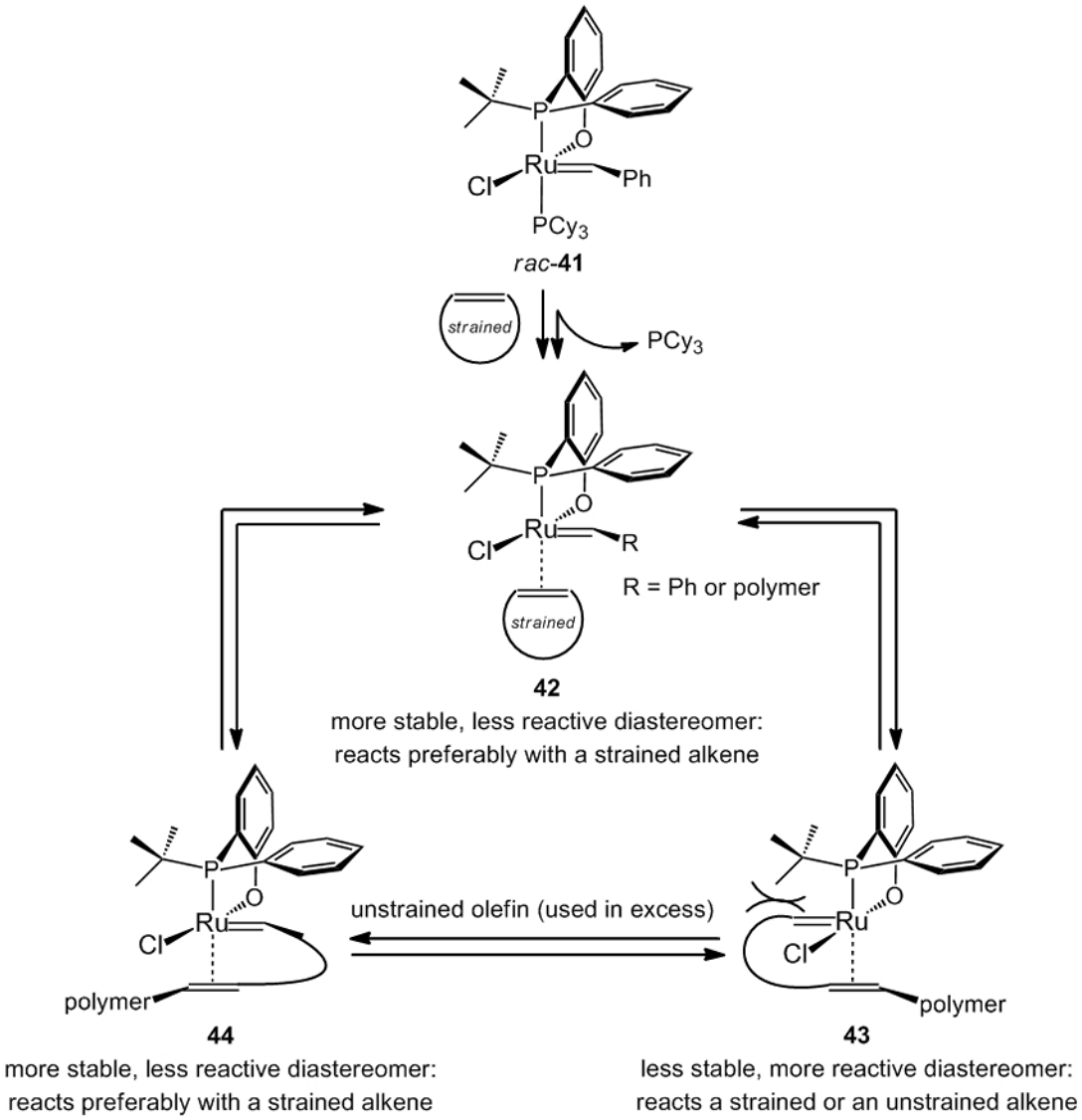


Scheme 10.

Total synthesis of baconipyrone C through an enantioselective Ru-catalyzed ring-opening/cross-metathesis (ROCM) reaction. PMB = *p*methoxybenzyl; Mes = 2,4,6-$Me_3C_6H_2$

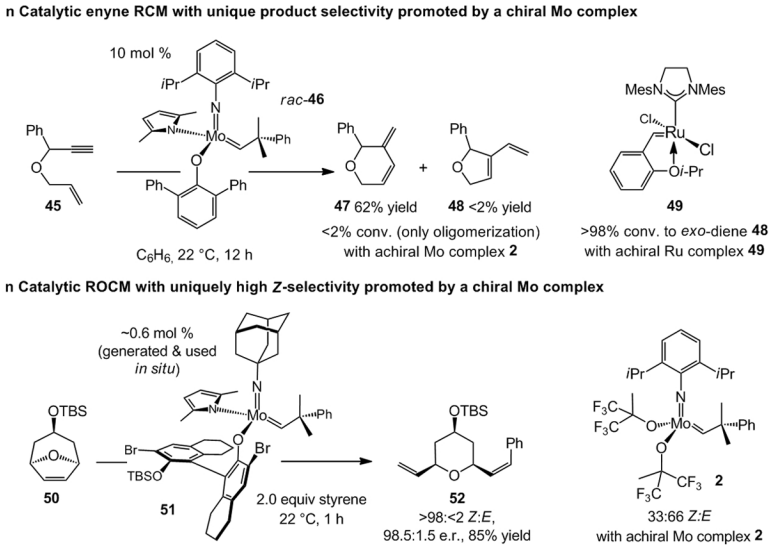


Scheme 11.
A stereogenic-at-Mo complex serving as a uniquely efficient RCM catalyst.



Scheme 12.

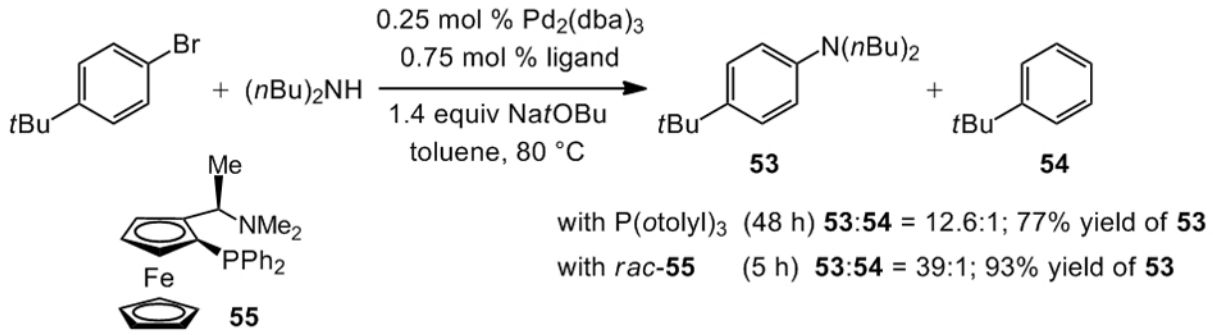
A racemic stereogenic-at-Ru catalyst used to promote sequence-selective polymerization; success of this strategy is due to energy differences between the two carbene diastereomers of the chiral complex.



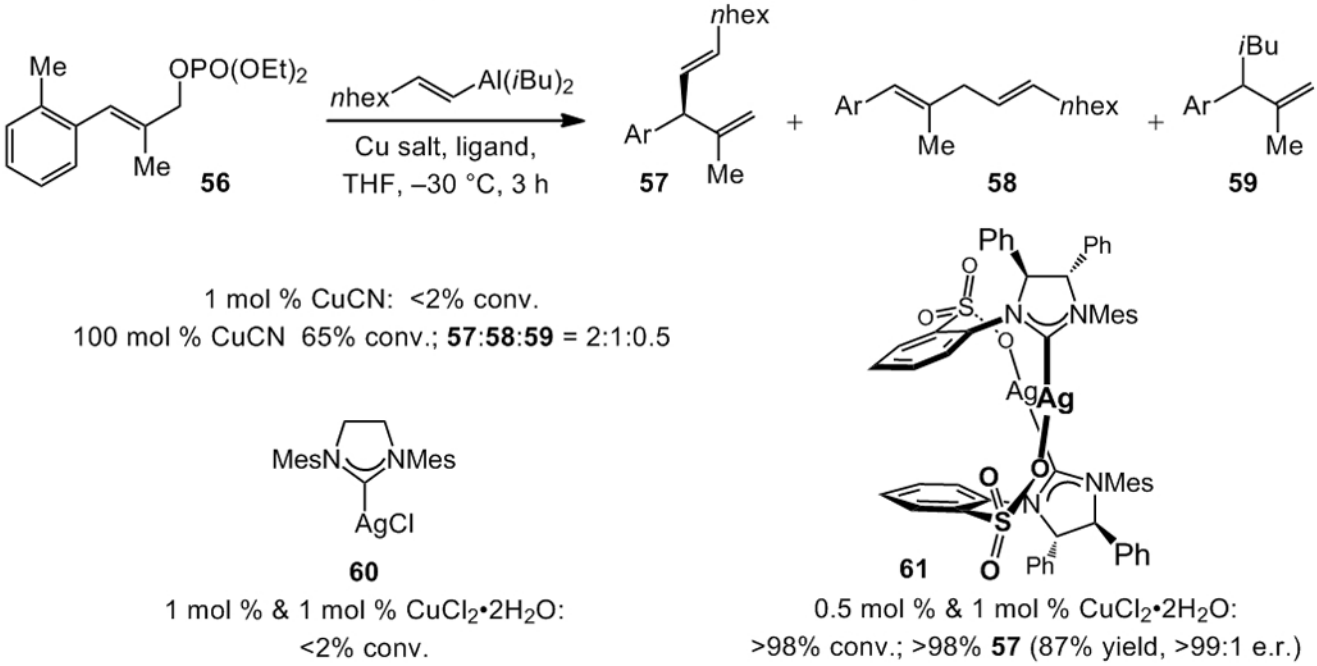
Scheme 13.

Chiral olefin metathesis catalysts are not only valuable for obtaining enantiomerically enriched products; they can also offer other types of selectivity. Mes = 2,4,6-Me_3-C_6H_2.

n More efficient Pd-catalyzed cross-coupling with a chiral phosphine

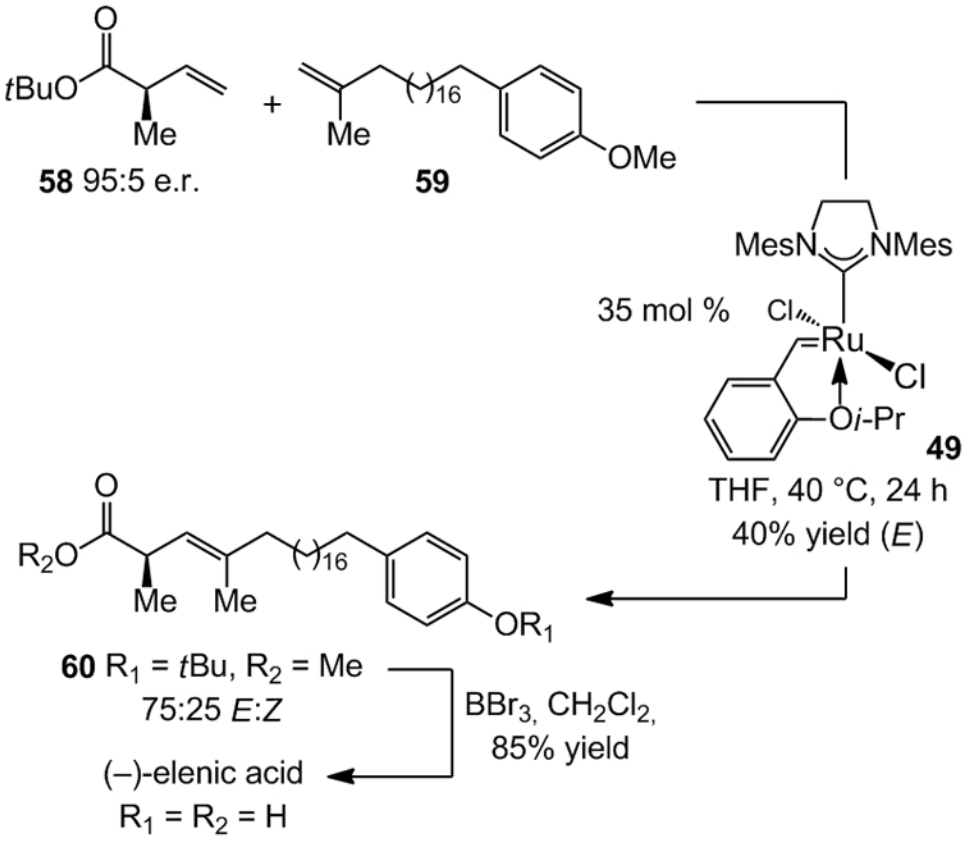


n More efficient Cu-catalyzed allylic alkylation with a chiral N-heterocyclic carbene (NHC)



Scheme 14.

Chiral Pd- and Cu-based complexes generate product-selectivity, site-selectivity and efficiency levels that are superior to those afforded by the corresponding achiral catalysts.



Scheme 15.

Natural product synthesis often underlines significant deficiencies in catalyst development, as indicated by an inefficient cross-metathesis reaction in an enantioselective synthesis of elenic acid.