Atom Economy—A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way

Barry M. Trost*

Enhancing the efficiency of the synthesis of complex organic products constitutes one of the most exciting challenges to the synthetic chemist. Increasing the catalogue of reactions that are simple additions or that minimize waste production is the necessary first step. Transition metal complexes, which can be tunable both electronically and sterically by varying the metal and/or ligands, are a focal point for such invention. Except for catalytic hydrogenation, such methods have been rare in complex synthesis and virtually unknown for C–C bond formation until the advent of cross-coupling reactions. These complexes may orchestrate a variety of C–C bond-forming processes, important for creation of the basic skeleton of the organic structure. Their ability to insert into C–H bonds primes a number of different types of additions to relatively nonpolar π-electron systems. Besides imparting selectivity, they make feasible reactions that uncatalyzed were previously unknown. The ability of these complexes to preorganize π-electron systems serves as the basis both of simple additions usually accompanied by subsequent hydrogen shifts and of cycloadditions. The ability to generate "reactive" intermediates under mild conditions also provides prospects for new types of C–C bond-forming reactions. While the examples reveal a diverse array of successes, the opportunities for new invention are vast and largely untapped.

Keywords: carbon–carbon coupling · catalysis · cycloadditions · synthetic methods

1. Introduction

The goal of reducing simultaneously the depletion of raw materials and the generation of waste has taken on new urgency for the chemical community as society places increasing emphasis on environmental concerns. Thus, production of the myriad of substances that are required to serve the needs of society, stretching from the worlds of materials science to health care, must address synthetic efficiency not only in terms of selectivity (chemo-, regio-, diastereo-, and enantioselectivity) but increasingly in terms of atom economy, that is, in terms of maximizing the number of atoms of all raw materials that end up in the product.[1] The ideal chemical reaction is not only selective but is also just a simple addition (either inter- or intramolecular) in which any other reactant is required only in catalytic amounts.

The producers of commodity chemicals have recognized the importance of these issues. Though many existing processes do not meet these objectives, they are mainly rather old technologies. "Newer" processes represented by hydroformylation,[2] Ziegler–Natta polymerization,[3] and hydrocyanation[4] are spectacular illustrations of how practical and important processes that possess these characteristics are. On the other hand, such issues have not been emphasized for production of smaller volume chemicals. Clearly, a high priority goal of any chemical production is an environmentally benign design.

With the increasing sophistication of the types of substances that we must produce to meet society's needs, this task is quite daunting. In many instances, the synthesis of such compounds by any means in an economically viable way is a major accomplishment; to do so with atom economy as well is an almost untenable proposition. Part of the problem lies in the lack of some type of selectivity for processes that meet this definition. For example, apart from catalytic hydrogenation, the Diels–Alder reaction comes closest to representing the ideal chemical reaction in terms of atom economy and chemo-, regio-, and diastereoselectivity.[5] However, achievement of enantioselectivity in a catalytic sense is a major challenge and a subject of intense activity.[6] In most instances, the failure arises from the lack of atom economy. In a practical sense, while we should strive for the ideal in which all reactions are simple additions, we cannot expect to always achieve the ideal. When reactions are of the form A + B → C + D where C is the desired product, the by-product D should be as small and innocuous as possible. Catalysis by transition metal complexes has a major role to play in addressing the issue of atom economy—both from the point of view of improving existing processes and, most importantly, from discovering new ones. This review will focus on the formation of C–C bonds by homogeneous catalysis in complex organ-

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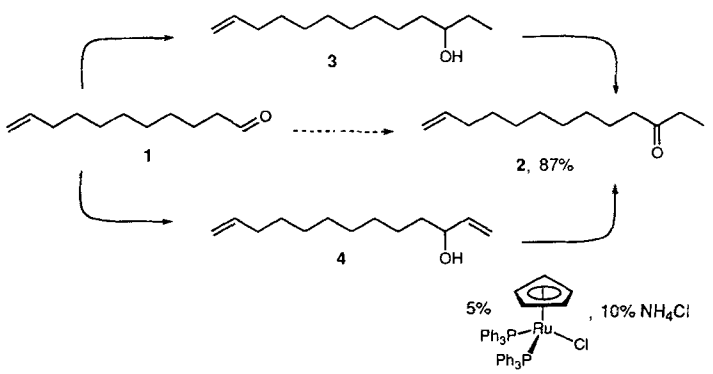
ic synthesis. Thus, polymerization methods, although extremely important, are outside its scope. Several well established transition metal catalyzed reactions represented by carbonylation are well appreciated and well reviewed; as a result, they are not covered by this overview.

2. Prototropic Rearrangements

The ability of transition metal complexes to make and break C–H bonds forms the basis of many catalytic processes beyond the obvious catalytic hydrogenation. Olefin isomerizations[7] may involve insertion into an allylic C–H bond (Scheme 1),

Scheme 1.

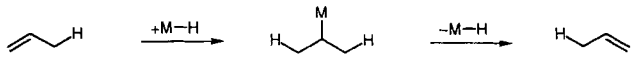
which has been proposed for a ruthenium catalyzed intramolecular redox reaction of an allylic alcohol (Scheme 2, **4** → **2**).[8] While many metal complexes effect olefin isomerizations, their lack of chemoselectivity render them useless with substrates like **4**. This example illustrates the potential such methodology offers in terms of atom economy. Whereas the "normal" conversion of aldehyde **1** to **2** would employ two steps involving stoichiometric organometallic reagents to form **3** followed by



Scheme 2.

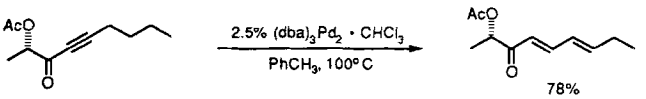
adjustment of the oxidation level with some stoichiometric oxidant, this reaction supplants the latter with a simple prototropic isomerization. While **4** may be formed from **1** by use of a stoichiometric vinyl organometallic reagent, it may also be formed by catalytic additions of acetylene[9] followed by hydrogen thereby transforming aldehyde **1** into ketone **2** with excellent atom economy.

Isomerizations by C–H insertion take advantage of the stability of π-allyl metal complexes. However, such pathways are not always feasible. An alternative mechanism invokes a metal hydride addition followed by a β-elimination (Scheme 3).



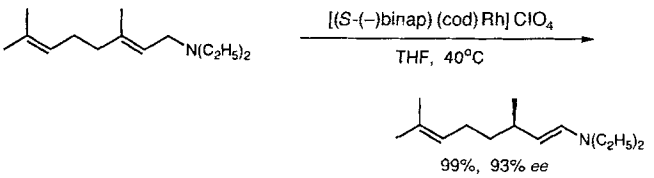
Scheme 3.

This pathway permits isomerizations of alkynes to dienes (Scheme 4), which are geometrically precluded from reacting by a π-allyl mechanism.[10, 11] In addition to palladium complexes, those of iridium,[11] ruthenium,[12] and rhodium[13] also catalyze similar reactions.



Scheme 4. dba = dibenzylidene acetone.

The analogous isomerization of *N*,*N*-diethylgeranylamine with chiral rhodium complexes (Scheme 5) to produce natural citronellal after hydrolysis of the enamine[14, 15] serves as the key step in the synthesis of the side chain of α-tocopherol[16] and a commercial synthesis of menthol.[17]

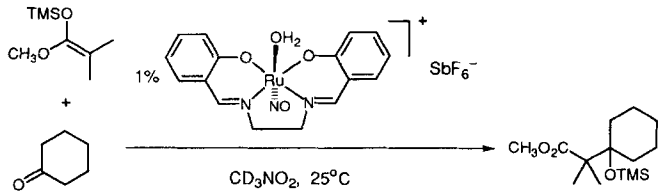


Scheme 5. cod = cyclooctadiene, binap = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

Born in Philadelphia, Pennsylvania in 1941, where he obtained his BA (1962) at the University of Pennsylvania, Barry M. Trost completed his Ph. D degree in Chemistry at the Massachusetts Institute of Technology in 1965 under Professor Herbert O. House. He moved immediately to the University of Wisconsin where he was promoted to Professor of Chemistry in 1969 and subsequently became Vilas Research Professor in 1982. He joined the faculty at Stanford as Professor of Chemistry in 1987 and became Professor of Humanities and Sciences in 1990. In addition, he has been visiting professor in Germany (Marburg, Hamburg, Munich), France (Universities of Paris VI and Paris South), Italy (University of Pisa), Denmark (Copenhagen) and Spain (University of Barcelona). In 1994 he was presented with an honorary doctorate from the Université Claude-Bernard (Lyon I), France. He has garnered numerous awards for both teaching and research, the most recent being the Roger Adams Award of the ACS (1995) and was elected a member of the U. S. National Academy of Sciences (1980) and a fellow of the American Academy of Sciences (1982).

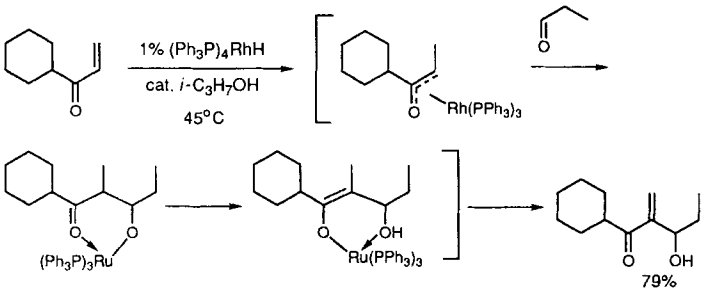
3. Intermolecular Prototropic and Related Additions

The aldol and related addition reactions to the carbonyl group of aldehydes and ketones normally entails use of Brønsted bases or acids, most commonly in stoichiometric amounts. Performing such reactions with transition metal catalysts offers two advantages beyond the avoidance of stoichiometric reagents: 1) more neutral reaction conditions that can enhance chemoselectivity and 2) prospects for asymmetric induction. The enol silyl ether version of the aldol addition may be effectively catalyzed by a ruthenium catalyst (Scheme 6) and



Scheme 6.

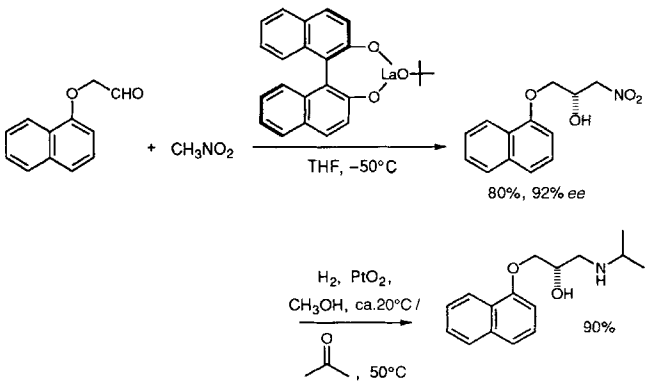
proceeds to > 90% completion in less than 3 minutes. The ruthenium center may be considered to enhance the electrophilicity of the carbonyl partner by coordination; that is, it functions as a Lewis acid.[18] However, mechanistic diversity of transition metal catalyzed reactions permits unorthodox types of aldol reactions. As illustrated in Scheme 7, formation of an enolate by



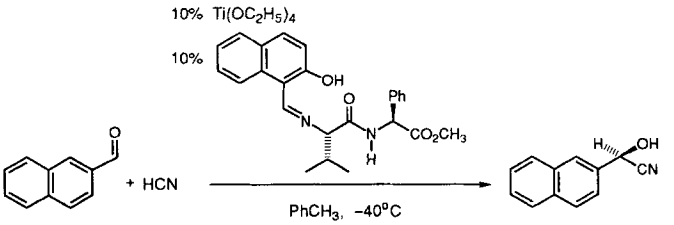
Scheme 7.

hydrometalation of an enone sets the stage for a net aldol reaction of unsaturated ketones as the aldol donor partner—a role they cannot play in simple acid or base catalyzed chemistry.[19]

The promise that such transition metal catalyzed versions may proceed with good enantioselectivity is beginning to be fulfilled. The addition of nitromethane to aldehydes (the Henry reaction) proceeds with good asymmetric induction on use of a catalytic lanthanide base.[20] A simple synthesis of (*S*)-(−)-propranolol utilizes this reaction (Scheme 8).[21] In another variation a titanium complex serves as the equivalent of a chiral Lewis acid in promoting cyanohydrin formation (Scheme 9).[22]

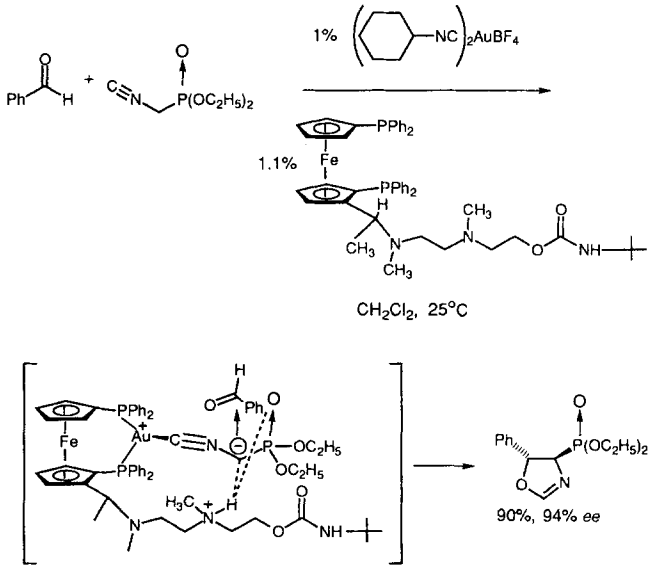


Scheme 8.



Scheme 9.

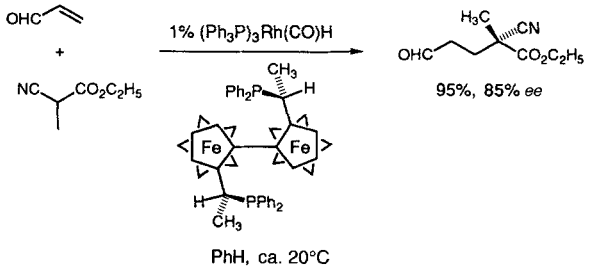
The gold and silver catalyzed aldol addition of isonitriles proceeds with high asymmetric induction in the presence of a chiral ligand. An asymmetric synthesis of α-amino acids ensues on use of α-isocyanocarboxylates.[23] Phosphorus analogues derive from use of α-isocyanophosphonates (Scheme 10).[24]



Scheme 10.

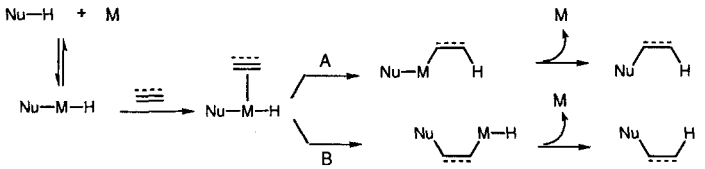
The ability of the isonitrile to coordinate to gold or silver provides the activation of the isonitrile—promoting deprotonation and addition to the carbonyl group.

This same type of activation serves as the basis of the metal catalyzed Michael addition of nitriles in which coordination of the nitrogen of the nitrile initiates the events leading to addition.[25] The asymmetric addition of ethyl α-cyanopropionate to prop-2-enal highlights the utility of this metal catalyzed version of the Michael reaction (Scheme 11).[26]



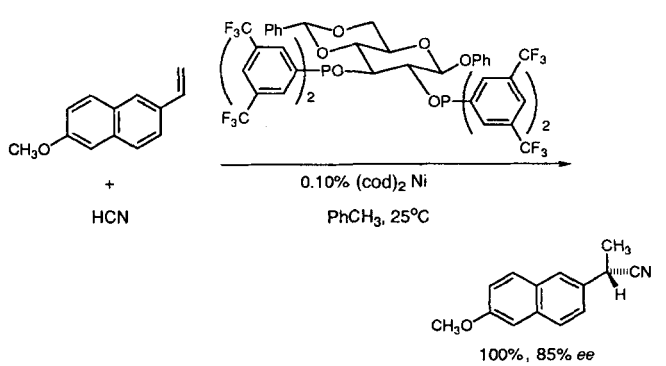
Scheme 11.

Using a transition metal to activate a pronucleophile for addition reactions creates a new level of reactivity that is not present with main group elements, namely the ability to add to nonpolarized unsaturated systems. The important facile processes of hydrometalation and carbametalation, characteristic of the transition elements, initiate additions of a C–H bond across double and triple bonds as formalized in Scheme 12.

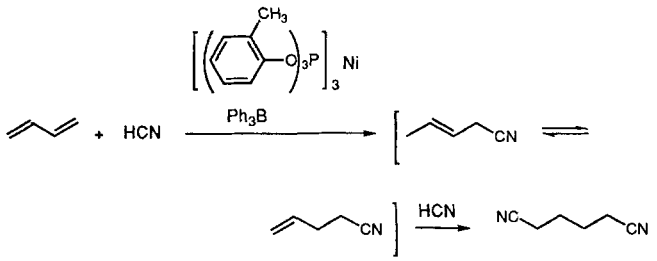


Scheme 12. Formal representation of the hydrometalation A and carbametalation B as routes to the addition of C–H bonds to nonpolar double and triple bonds.

The nickel catalyzed hydrocyanation of olefins[4, 27] is initiated by a hydrometalation (Scheme 12, path A), which may proceed with high asymmetric induction in the presence of a chiral ligand (Scheme 13).[28] The *cis* nature of the addition[29] suggested by (Scheme 12) leads to *E* isomers of substituted acrylonitriles by hydrocyanation of 1-alkynes.[30] Dienes are excellent acceptors, since the intermediate is a π-allylnickel complex.[4, 31] Combining hydrocyanation with olefin isomerization led to a commercially viable synthesis of adiponitrile (Scheme 14).[4, 32]

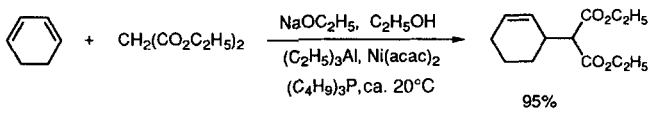


Scheme 13.



Scheme 14.

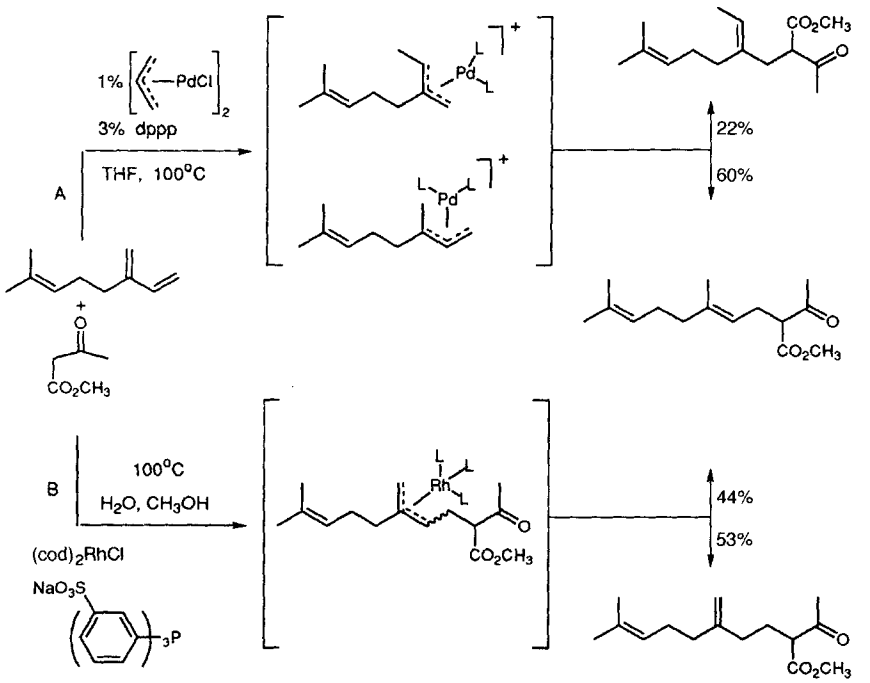
Nickel complexes also catalyze the addition of active methylene compounds like malonic esters and β-ketoesters to cyclic dienes (Scheme 15),[31] which presumably proceed by a similar mechanism (Scheme 12, path A). Extrapolation to acyclic dienes is normally plagued by diene oligomerization, itself an important and interesting process (see Scheme 31). With palladium catalysis such oligomerizations may be suppressed relative to simple additions by use of bidentate ligands (Scheme 16A).[33] With an unsymmetrical diene like myrcene, the two feasibile regioisomeric π-allylpalladium complexes yield two regioisomeric products, although one predominates. The major regioisomer isolated in 60% yield serves as a commercially important intermediate in the synthesis of vitamins A and E.



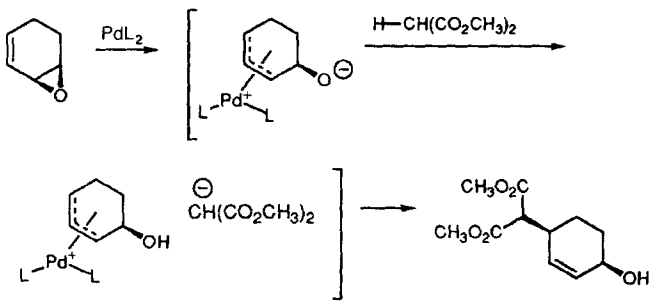
Scheme 15. acac = acetylacetonate.

Switching the catalyst may change the mechanism. Indeed, a rhodium complex catalyzes the same addition by a carbametalation (Scheme 12, path B) to produce a different mixture that results from lack of regioselectivity in the proton transfer step (Scheme 16B).[34] This latter route becomes commercially viable since both products can be taken on to pseudoionone, the key intermediate on the route to vitamins A and E.

A related but mechanistically different process is the palladium catalyzed addition of pronucleophiles to vinyl epoxides (Scheme 17). In this reaction, ionization of the epoxide by palladium creates the base to deprotonate the pronucleophile, setting the stage for the normal nucleophilic attack on a π-allyl complex.[35] The stereochemistry always involves formation of the new C–C bond on the same face of the π system from which the leaving group departed, regardless of regiochemistry. The regiochemistry normally involves attack at the allylic terminus distal to oxygen as depicted. This process differs from the simple base



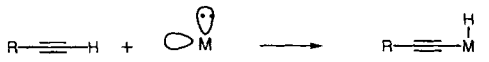
Scheme 16. dppp = 1,3-bis(diphenylphosphino)propane.



Scheme 17.

promoted nucleophilic ring opening of the epoxide in both regio- and diastereoselectivity.

The ability of transition metals to insert readily into acetylenic C–H bonds, as represented formally in Scheme 18,

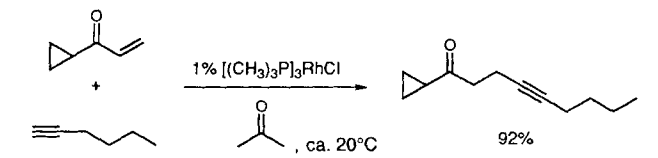


Scheme 18.

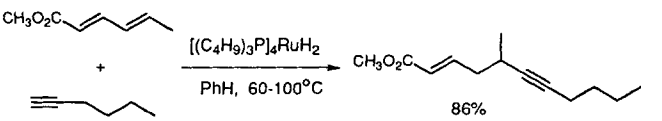
derives both from the acidity of this proton and the excellent coordinating ability of the acetylenic linkage. Thus, a 1-alkyne may function similarly to HCN and active methylene compounds as summarized in Scheme 12.

Rhodium [36] and ruthenium (Schemes 19 and 20)[37] complexes catalyze the addition of terminal alkynes to activated olefins and dienes. Appropriate deuterium labeling experiments demonstrate that with dienes the reaction proceeds by a clean *cis*-1,2-addition. The low conversions of the rhodium catalyzed reaction diminish its utility in spite of the high yields.

The addition to unactivated multiple bonds is complicated by the normally dominant self-addition. For example, with a palladium catalyst the dimerization proceeds well, even in the pres-

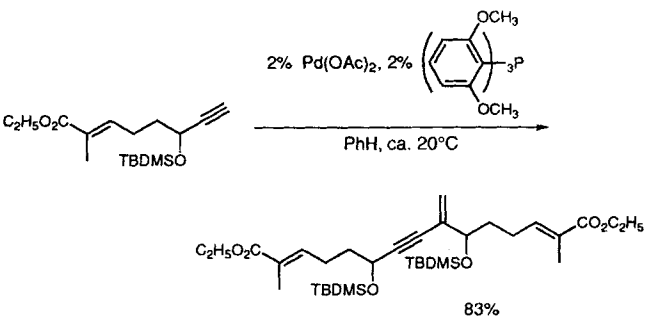


Scheme 19.



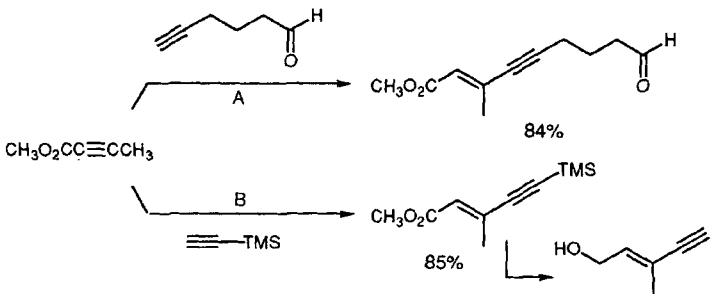
Scheme 20.

ence of an activated olefin (Scheme 21).[38] On the other hand, an activated 1-alkyne completely intercepts the organopalladium intermediate in a highly chemoselective fashion. For ex-



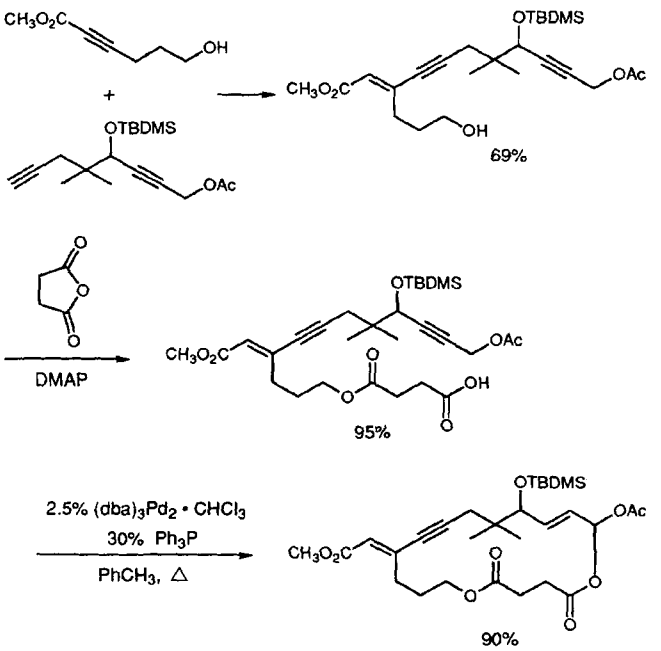
Scheme 21. TBDMS = *tert*-butyldimethylsilyl.

ample, the unsymmetrical cross-coupling occurs even in the presence of an unprotected aldehyde (Scheme 22, path A).[39] The adduct of methyl butynoate and trimethylsilylacetylene (Scheme 22, path B)[40] may be readily transformed into an



Scheme 22. The reaction conditions for A and B are the same as given in Scheme 20. TMS = trimethylsilyl.

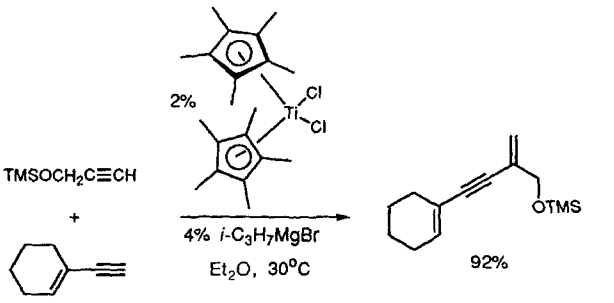
important building block for Vitamin A synthesis.[41] Scheme 23 illustrates the use of this reaction as a key step in constructing an acyclic carboxylic acid that ultimately undergoes a palladium catalyzed lactonization by cycloisomeriza-



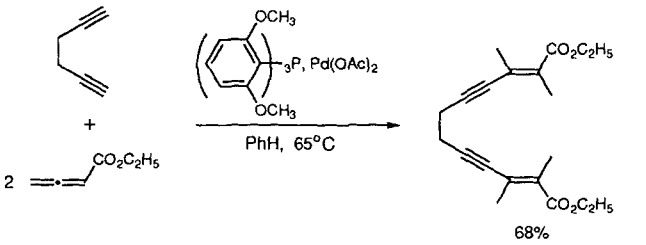
Scheme 23. Conditions for the first step as given in Scheme 20.

tion.[42] Thus, a relatively complicated eighteen-membered macrodiolide arises from two alkyne building blocks by a simple series of inter- and intramolecular additions. A most remarkable selectivity has occurred with a titanium(II) catalyst that promotes the coupling of an unsaturated terminal alkyne as the donor and a saturated terminal alkyne as the acceptor (Scheme 24).[43] Allenes serve as effective acceptors for terminal alkynes, and novel oligo(enyne)s may result (Scheme 25).[44]

Extension of these concepts to other additions depends upon the ability of the transition metal to undergo the C–H insertion.

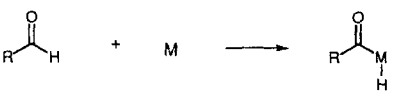


Scheme 24.



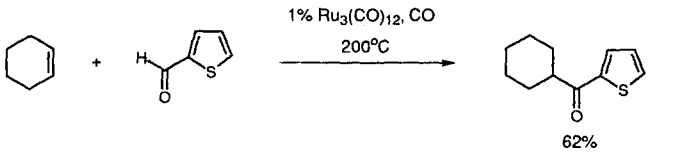
Scheme 25.

The ability of transition metals to decarbonylate aldehydes via an acyl metal hydride intermediate (Scheme 26) suggests the



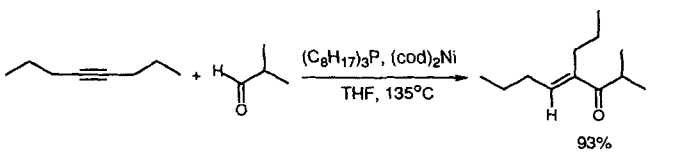
Scheme 26.

prospect of trapping that intermediate as in Scheme 12. Whereas capture with a simple olefin proceeds in only modest yields with a ruthenium complex (Scheme 27),[45] capture by a 1-alkyne occurs in good yields with a nickel catalyst



Scheme 27.

(Scheme 28).[46] Substrates containing sulfur are compatibile with homogeneously catalyzed reactions, which contrasts with their role as poisons for many heterogeneously catalyzed processes. The *E* geometry of the product in Scheme 28 is consistent with a *cis* addition.

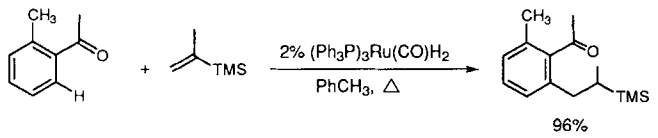


Scheme 28.

Precoordination provides an important kinetic path for many transition metal catalyzed reactions, one of which is *ortho*-metalation (Scheme 29). On use of a ruthenium catalyst which becomes coordinatively unsaturated by loss of hydrogen to pro-

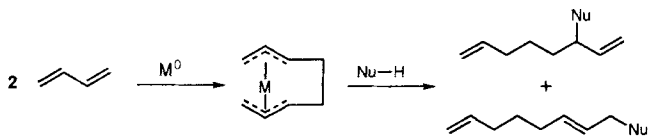
Scheme 29. CG = coordinating group.

mote *ortho*-metalation, aryl ketones add to unhindered olefins, especially vinylsilanes.[47] The example of Scheme 30 reveals the kinetic preference for insertion into a sp^2 C–H bond over a sp^3 C–H bond, in spite of the greater stabilization by conjugation of the benzylic organometallic intermediate that would have formed in the latter case and its lower bond energy.



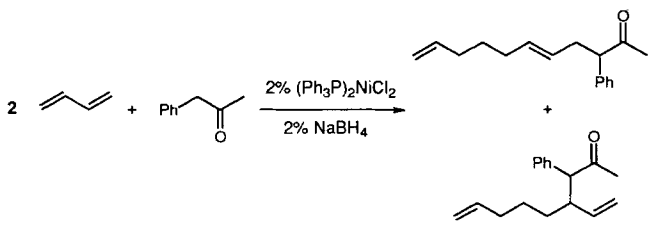
Scheme 30.

The reactions of simple dienes in additions are frequently complicated by self-oligomerization or telomerization. Such reactions are believed to involve bis(allyl)metal complexes as intermediates, which react with pronucleophiles to give regioisomeric addition products (Scheme 31). Although many metals



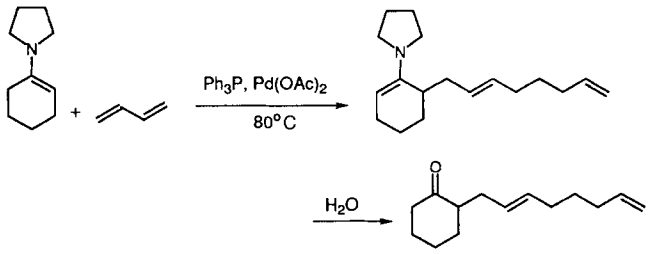
Scheme 31.

including Co, Ir, Rh, and Ru promote such reactions, most work centers on Ni[48] and Pd.[49] For example, a Ni^0 catalyst generated in situ from triphenylphosphane and nickel chloride in the presence of sodium borohydride gave an 85:15 mixture of the 2:1 adducts of butadiene and phenylacetone depicted in Scheme 32 (telomers) to the 1:1 adducts.[50] Of the 2:1 adducts,

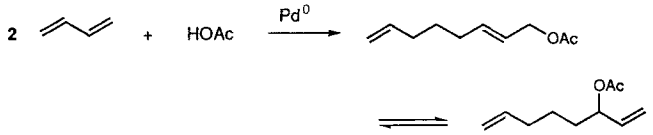


Scheme 32.

the linear to branched telomer ratio is 8.4:1. Better selectivity for the telomeric products is obtained from the palladium catalyzed reaction (Scheme 33).[51] The adduct of acetic acid (Scheme 34) has proved to be particularly useful for the synthesis of natural products. For example, the linear adduct which

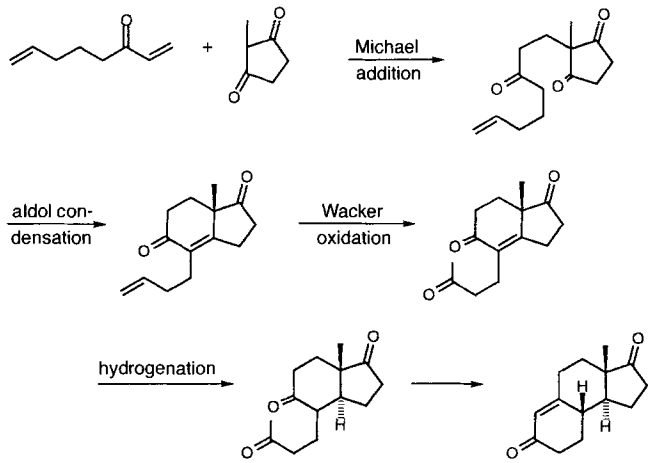


Scheme 33.



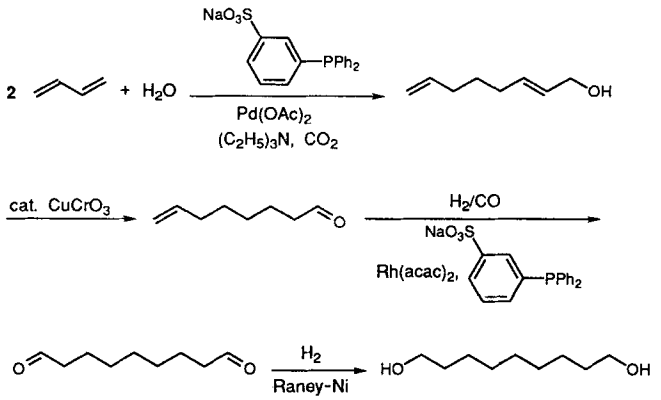
Scheme 34.

may obtained in 88% yield and 28:1 regioselectivity [catalyst $(o\text{-}C_7H_7O)_3P$, $Pd(OAc)_2$][52] served as a useful intermediate for the synthesis of the fragrance ingredient muscone[53] and the macrolide diplodialide.[54] The branched product is a convenient source of octa-1,7-dien-3-one, which by a simple sequence is converted into a useful steroid intermediate (Scheme 35).[55]



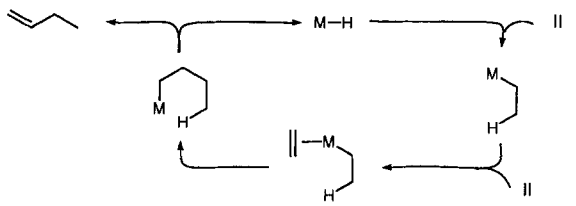
Scheme 35.

Since all the reactions are either simple additions or involve only water as a by-product, this strategy becomes rather atom economical. The commercial synthesis of 1,9-nonanediol (Scheme 36) that combines a prototropic addition and isomerization of the telomer 2,7-octadien-1-ol with hydroformylation and hydrogenation is an ideal synthetic strategy for this commercial target.[56]



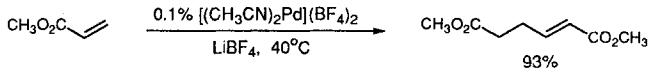
Scheme 36.

The employment of nonacidic reaction partners for additions to π-electron systems requires initiation by a metal hydride (Scheme 37). The dimerization of olefins by complexes of the



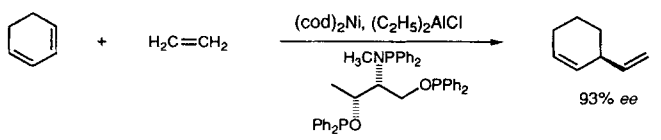
Scheme 37.

later transition metal complexes illustrates this approach. Whereas nickel is normally the preferred catalyst with nonfunctionalized olefins, a "naked" Pd^{2+} catalyst is recommended for the dimerization of methyl acrylate (Scheme 38).[57] Cross-cou-



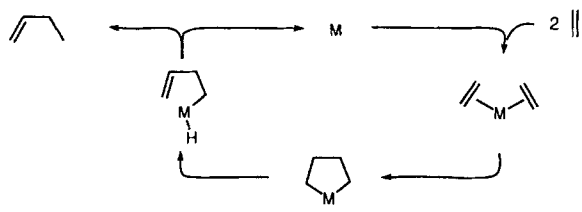
Scheme 38.

pling can occur between simple olefins (e.g. ethylene) and olefins activated either by strain (e.g. norbornene)[58] or electronic factors (e.g. styrene).[59] Alternatively, a diene is an excellent partner for hydrovinylation for which the advantage of transition metal catalysis for asymmetric induction may be exploited (Scheme 39).[60]



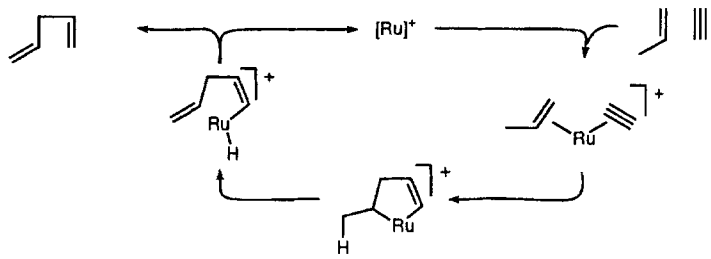
Scheme 39.

An alternative mechanism to that in Scheme 37 invokes a metallacycle (Scheme 40). This pathway requires a geometrically difficult β-hydride elimination in the metallacyclopentane, because the dihedral angle between the C–M and β C–H bonds



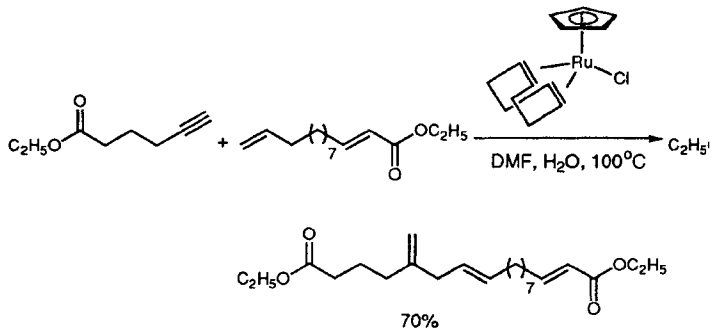
Scheme 40.

cannot readily become 0° as required for such eliminations.[61] On the other hand, such a mechanism seems to operate in a ruthenium catalyzed addition, which obviates the above problem by an elimination exocyclic to the ring according to Scheme 41. Thus, heating an internal or terminal alkyne with



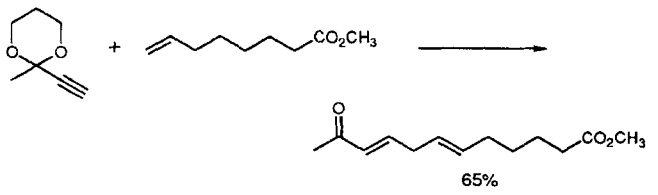
Scheme 41.

a monosubstituted olefin in the presence of a ruthenium complex gives rise to the equivalent of a highly selective Alder ene type reaction (Scheme 42).[62] The high chemoselectivity is exhibited by its compatibility with most functional groups (esters,

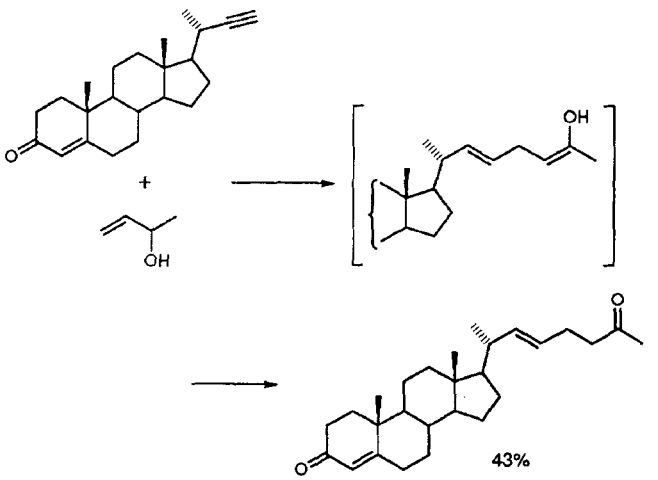


Scheme 42. DMF = dimethylformamide.

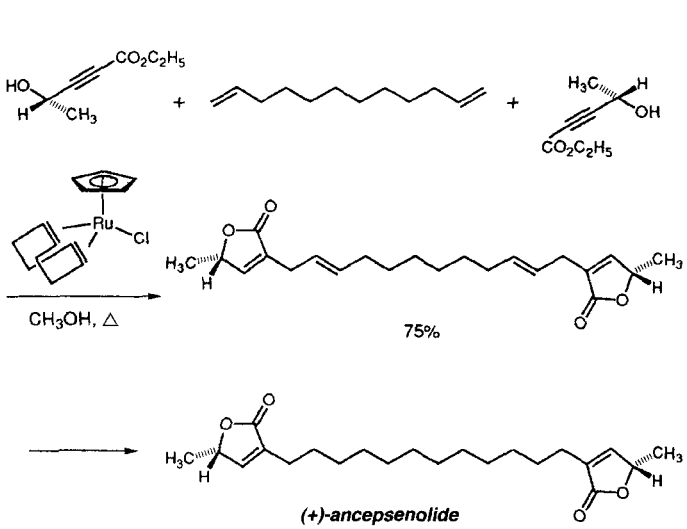
ketones, alcohols, ketals etc.): the "activated" olefin, that is, the conjugated ester, would normally be thought to be the site of reaction. The regioselective preference for formation of the "branched" product changes upon introduction of steric hindrance at the propargylic position (Scheme 43). A similar preference for the "linear" product also results from employment of an allyl alcohol in which the initial product, an enol, tautomerizes to give the γ,δ-unsaturated ketone (Scheme 44).[63] Employing a γ-hydroxybutynoate as the acetylenic partner (Scheme 45) leads to a surprising regioselectivity in which the alkylation occurs at the position α to the carbonyl group, a contra-elec-



Scheme 43. Reaction conditions as in Scheme 39.



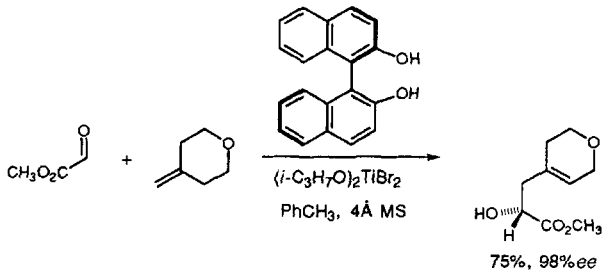
Scheme 44. Reaction conditions as in Scheme 39.



Scheme 45.

tronic orientation with respect to the normal preference in an Alder ene reaction. The *Z* juxtaposition of the hydroxy and ester groups leads to spontaneous lactonization with the expulsion of ethanol under the reaction conditions and thus to a facile synthesis of α-alkylated-γ-butyrolactones. A short route to the acetogenin (+)-ancepsenolide employs a double ruthenium catalyzed addition and establishes the absolute configuration of this natural product (Scheme 45).[64] The regioselectivity is consistent with the metallacycle intermediate proposed in (Scheme 40) in which 1) steric hindrance is minimized and 2) substituents that may coordinate to ruthenium are preferentially proximal to the metal.

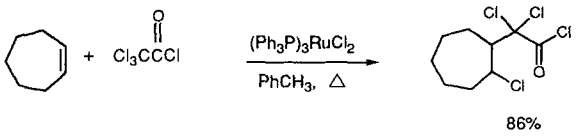
When the enophile is replaced by a carbonyl group, the reaction corresponds to the oxaene reaction. Such reactions have been catalyzed by standard Lewis acids including those of the early transition elements. Chiral titanium complexes as catalysts in these reactions have afforded high enantiomeric excess in selected cases (Scheme 46).[65]



Scheme 46. MS = Molecular sieves.

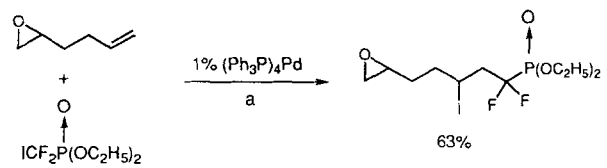
4. Intermolecular Heterotropic Additions

Halotropic additions of polyhalides to olefins have been catalyzed by ruthenium (Scheme 47)[66] and palladium



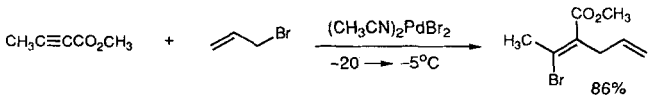
Scheme 47.

(Scheme 48).[67] Such reactions have characteristics very similar to those of radical reactions. The role of the metal may be mainly to serve as an electron shunt. On the other hand, the *cis*



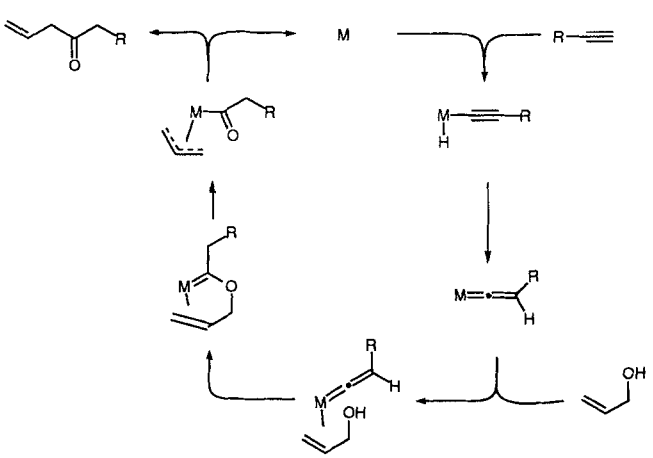
Scheme 48. a: Neat, at room temperature.

addition of allyl chlorides and bromides to alkynes (Scheme 49) appears to involve a halopalladation followed by carbametalation and dehalopalladation, in accord with the observed regioselectivity.[68]



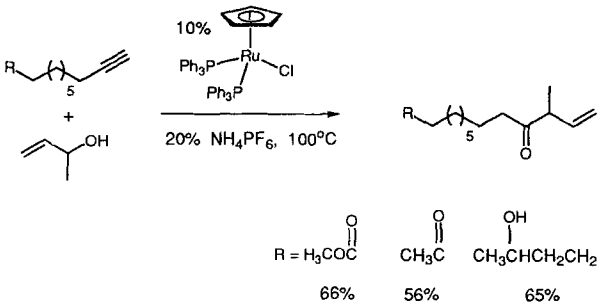
Scheme 49. The reaction was performed without solvent.

Novel transition metal complexes offer a particularly promising approach to new reactions involving heterotropic shifts. The ease of formation of vinylidene complexes from terminal alkynes suggested the catalytic cycle outlined in Scheme 50. Use of



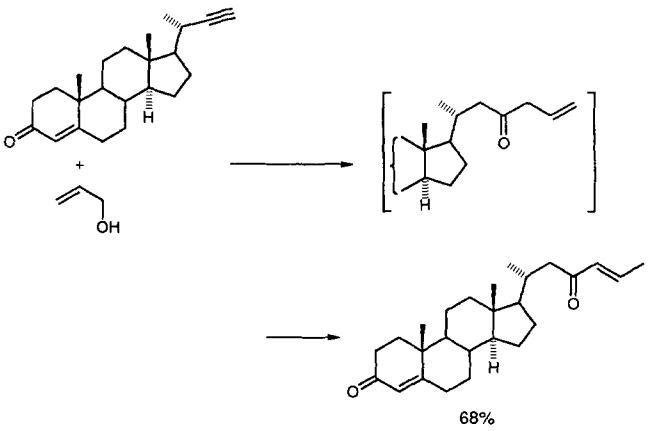
Scheme 50.

an allyl alcohol as the second component promotes a normally sluggish nucleophilic addition by precoordination. The resultant 1-metalla-3-oxa-1,5-hexadiene undergoes a metalla-Claisen rearrangement to set the stage for reductive elimination to form a β,γ-unsaturated ketone. The net result is the conversion of a terminal alkyne and an allyl alcohol into the simple adduct, and involves an oxytropic rearrangement. This process is realized with a ruthenium catalyst in a reaction that exhibited excellent chemo- and regioselectivity (Scheme 51).[69, 70] The dramatic



Scheme 51.

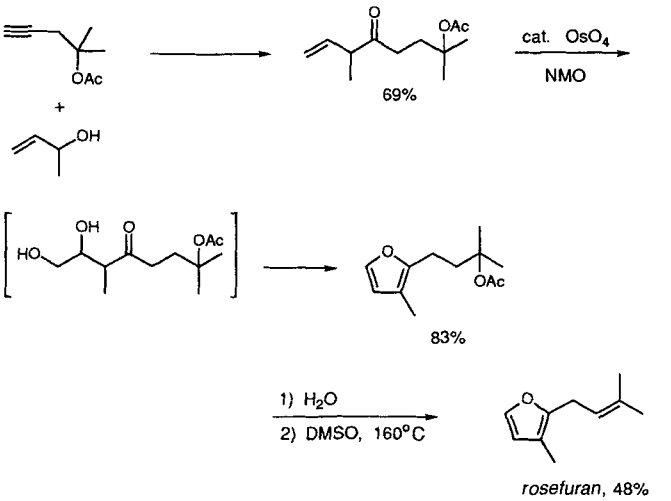
effect of the ligands on the course of the reaction can be seen by comparing Schemes 44 and 52. This latter example illustrates the utility of this methodology for the construction of functionalized steroid side chains such as that of the ganoderic acids, which function as ACE inhibitors.[71] By introducing phosphanes ligated to ruthenium, the pathway switches completely from the metallacycle pathway, which requires coordinative unsaturation, to the vinylidene pathway, which requires an electron-rich ruthenium center. The phosphanes both block coordination sites and enhance the electron-richness of the metal. Thus, from the same two reaction partners, addition may result



Scheme 52. Reaction conditions as in Scheme 48.

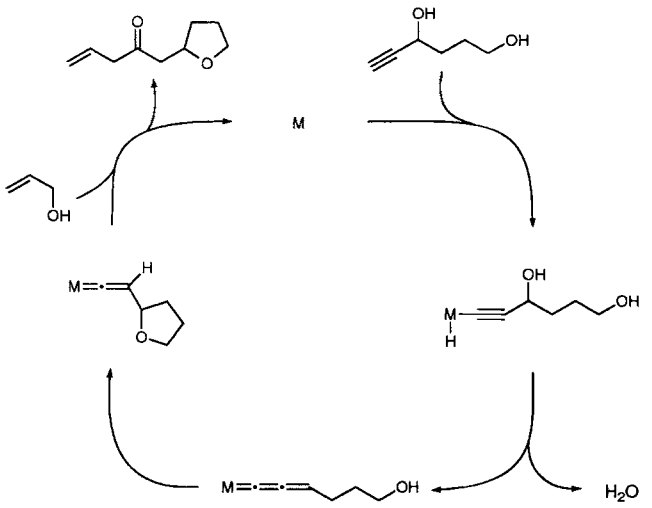
in a γ,δ-unsaturated ketone with no oxytropic rearrangement[63] or a β,γ-unsaturated ketone with oxytropic rearrangement.[69, 71]

The β,γ-unsaturated ketones also function as convenient furan precursors displaying atom economy. The synthesis of rosefuran (Scheme 53) exemplifies this methodology in which the recyclability of the *N*-methylmorpholine-*N*-oxide and acetic acid enables this sequence to be performed with only water as a by-product.[72]

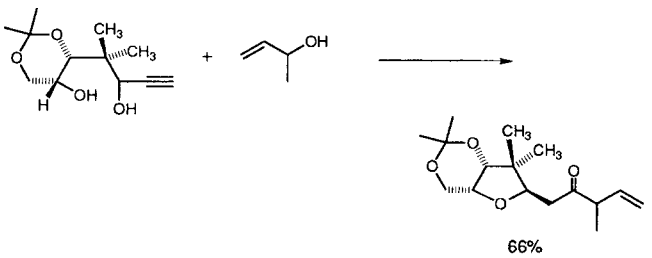


Scheme 53. Reaction conditions for the first step as in Scheme 48. DMSO = dimethylsulfoxide, NMO = *N*-methylmorpholine-*N*-oxide.

If the alkyne partner is a propargylic alcohol, the initial acetylide metal intermediate may undergo dehydration rather than protonation to form an allenylidene complex. Scheme 54 outlines a cyclization accompanying reconstitutive addition in which the only by-product is water.[73] In a model study which culminated in the synthesis of the spiroketal unit of the phosphatase inhibitor calyculin A, an alkyne derived from (*R*)-pantolactone condensed with 1-buten-3-ol to give the highly functionalized tetrahydrofuran unit with exclusive 2,5-*trans* configuration (Scheme 55).[74]



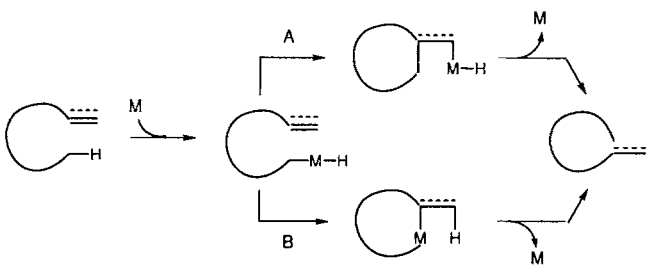
Scheme 54.



Scheme 55. Reaction conditions as in Scheme 48.

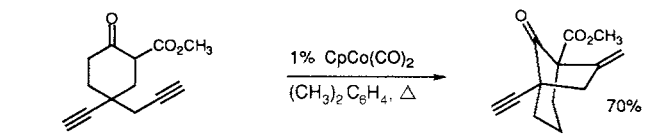
5. Prototropic and Related Cycloisomerizations

When the reactions described in Sections 2–4 are performed intramolecularly, the reaction constitutes a cyclization by isomerization as illustrated in Scheme 56 for a proton shift. Con-

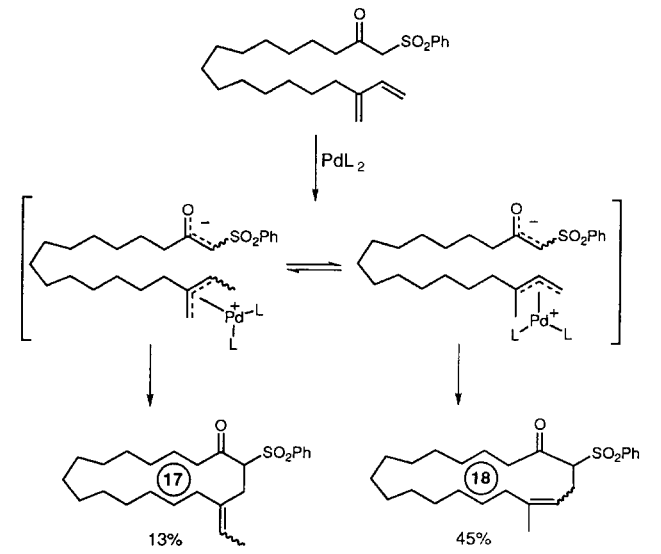


Scheme 56.

sidering the potential in this approach to cyclization, there are relatively few examples. For highly acidic compounds like β-keto esters, a cobalt complex effects addition to an alkyne (Scheme 57), presumably by a mechanism resembling path A in Scheme 56.[75] Additions of similar pronucleophiles to dienes occur with a palladium catalyst (Scheme 58).[76] This process probably involves initial hydropalladation to form π-allylpalladium intermediates (Scheme 56, path B), which undergo cy-

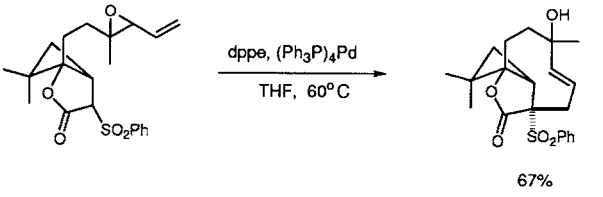


Scheme 57.



Scheme 58.

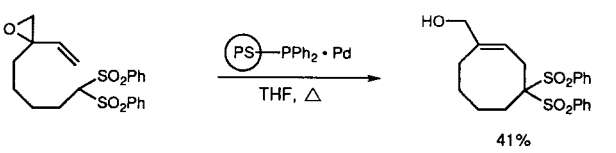
clization. The formation of macrocycles by this process is noteworthy. Initiating the cycloisomerization by deprotonation of the pronucleophile by the initial adduct between the Pd^0 catalyst and the vinyl epoxide has proven a powerful approach to macrocyclizations even for the formation of medium-sized rings.[77, 78] This reaction is a key step in the synthesis of punctaporonin B (Scheme 59).[79] With a polymeric catalyst cycliza-



Scheme 59. dppe = bis(diphenylphosphino)ethane.

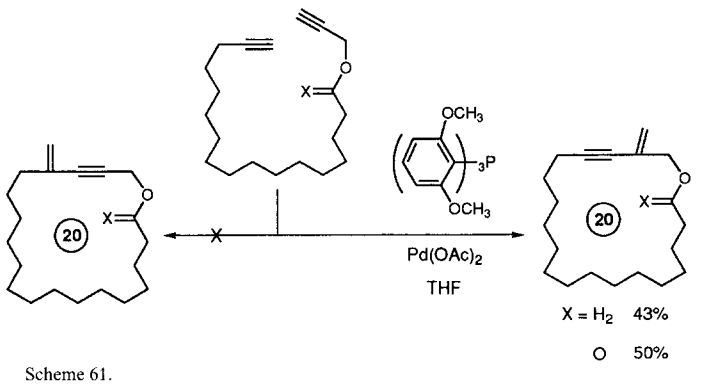
tions to medium as well as large rings can be performed at 0.5 M substrate concentration (Scheme 60).[80]

The ease of insertion of Pd^0 into acetylenic C–H bonds permits macrocyclizations also by a mechanism analogous to path



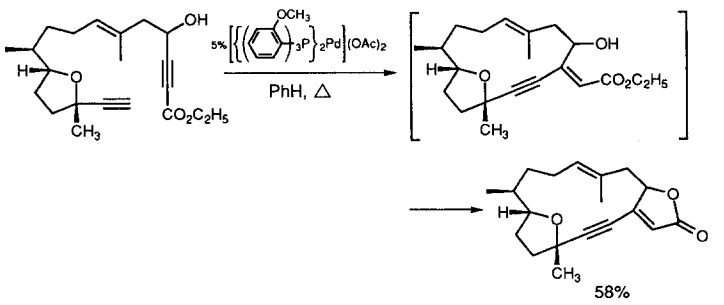
Scheme 60. PS = polystyrene.

B in Scheme 56. In the example of Scheme 61, although cyclization could occur in either direction, it is completely chemoselective: the acetylenic linkage proximal to the electronegative substituent serves as the acceptor.[81] In this reaction an activated



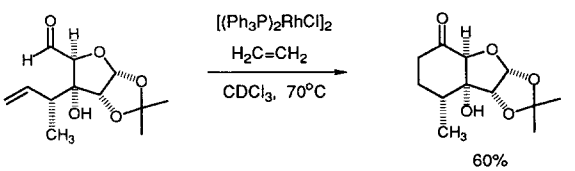
Scheme 61.

alkyne as in Scheme 62 results in cycloisomerization and concomitant butenolide formation.[82] This macrocyclization serves as a key step in a projected synthesis of the cembranoid pachiclavulanolide.



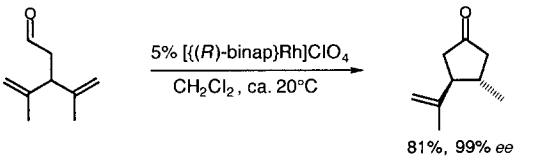
Scheme 62.

If the ability to insert into an aldehydic C–H bond (Scheme 26) is applied to intramolecular additions to unsaturated C–C bonds (intramolecular version of Scheme 12), the result is a novel cycloalkanone synthesis.[83] Although the formation of cyclopentanones proceeds most readily, cyclohexanones may also form (Scheme 63).[84] Excellent asymmetric induction may be observed (Scheme 64).[85]

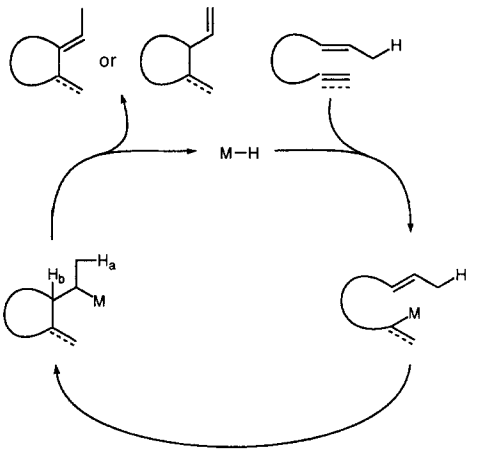


Scheme 63.

Initiating the reaction by hydrometalation and terminating the sequence by β-elimination (Scheme 65) opens a variant on Scheme 56 for cyclization that is a transition metal analogue of the intramolecular Alder ene reaction.[86] A further feature

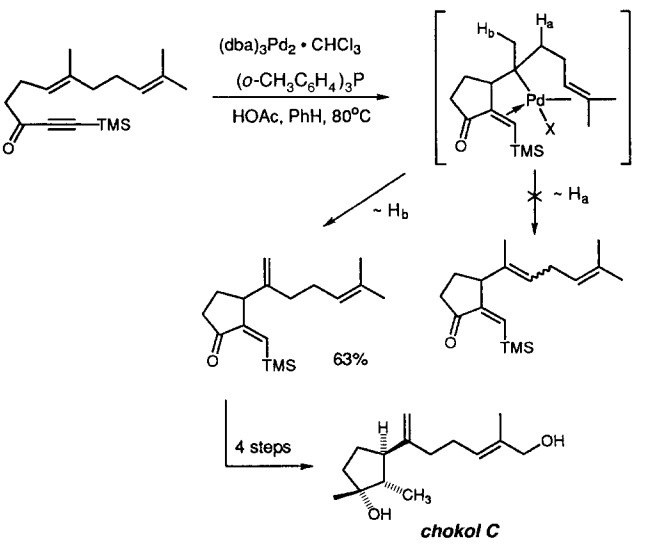


Scheme 64.



Scheme 65.

of this process is the ability to direct regioselectivity.[87] For example, cycloisomerization of the enyne of Scheme 66 may produce two Alder ene type products. Thermal reactions of analogous substrates generally favor migration of H_a. A hydri-

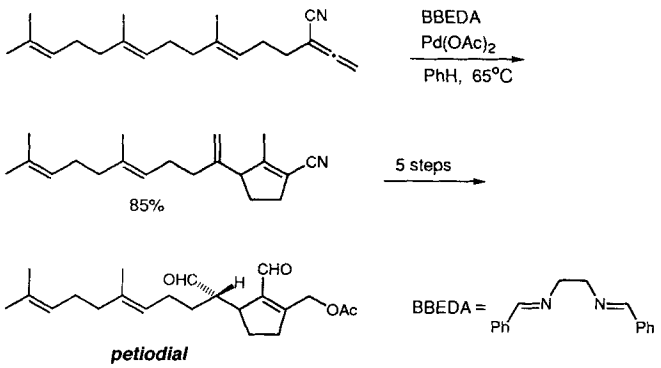


Scheme 66.

dopalladium catalyst, generated in situ from palladium (0) and acetic acid, yields the compound produced exclusively by migration of H_b.[88] This unorthodox regioselectivity derives from coordination of the remote double bond to palladium, thereby fixing the geometry of C–H_a to disfavor its β-elimination. The resultant product is easily converted into the cyclopentanoid antifungal agent chokol C. The total synthesis requires only

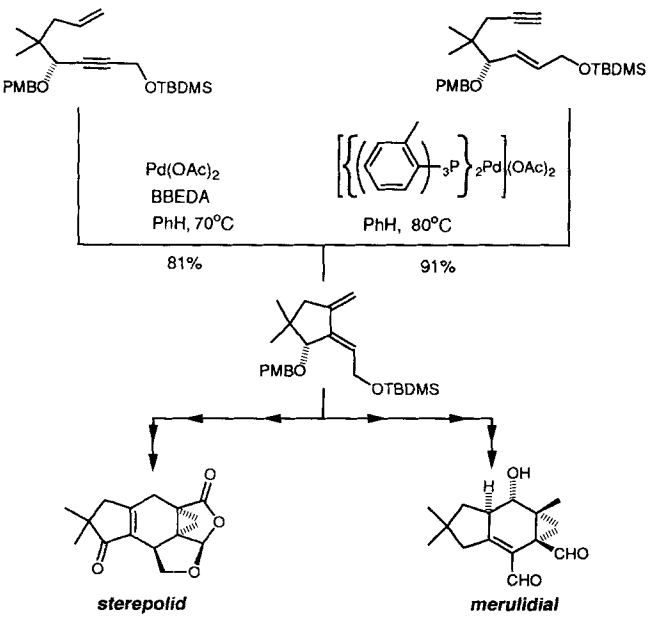
seven steps from commercially available geranyl bromide and *N*,*N*-dimethylacetamide. Syntheses of dendrobine[89] and picrotoxinin[90] utilized this cycloisomerization as a key step.

Replacing an alkyne by an allene may also lead to successful Alder ene type cyclizations. A synthesis of the marine antibiotic petiodial involves such a tranformation to create the properly substituted cyclopentenyl ring (Scheme 67).[91] A nickel-chromium catalyst supported on polystyrene[92] appears to be more general for cyclizations of enallenes.[93]



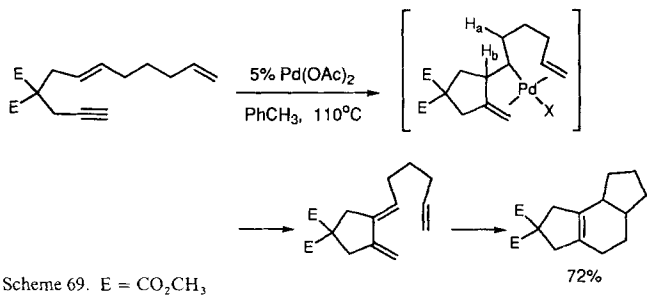
Scheme 67.

A major benefit of this type of transition metal catalyzed reation is the prospect of performing reactions not possible under thermal conditions. In Scheme 65 it is seen that the Alder ene type product derives from β-elimination of H_a in the primary cyclized product. Elimination of H_b to produce the synthetically versatile 1,3-dienes cannot be achieved thermally, but it can be envisioned to occur in this metal catalyzed version. Indeed, such a reaction proceeds in excellent yield[94, 95] and served as the key to a general strategy for the synthesis of the isolactaranes represented by sterepolide[96] and merulidial[97] (Scheme 68). The regioselectivity of the cycloisomerization of the enyne with the terminal triple bond reveals the effect of



Scheme 68. PMB = *para*-methoxybenzyl.

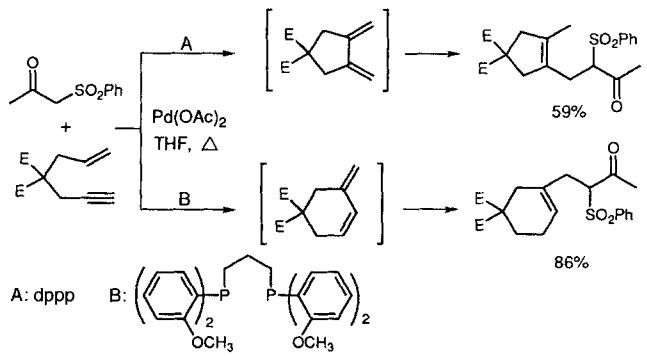
substitution at the allylic position: an alcohol or its derivative functions as a regiochemical control element directing the β-elimination to favor the 1,3-diene.[95, 98] The importance of this cycloisomerization stems from the ability of the 1,3-dienes to function in a second atom economical process, the Diels–Alder reaction. Tethering of remote substituents also favors 1,3-diene formation. Thus, cycloisomerization may be followed by cycloaddition to fold an acyclic polyenyne into a polycycle (Scheme 69).[94] While elimination of neither H_a nor H_b is particularly geometrically favorable, the C–H_b bond can



Scheme 69. E = CO_2CH_3

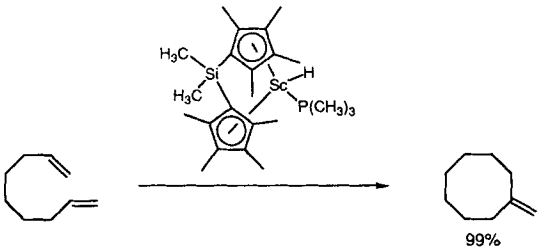
more nearly approach the requisite orientation and, being allylic, is weaker—two factors that favor formation of the 1,3-diene. The remote double bond then functions as the dienophile to form the tricycle. Similar reactions have also been catalyzed by a nickel–chromium complex, preferably supported on polystyrene.

The formation of 1,3-dienes by cycloisomerizations sets the stage for metal catalyzed additions of pronucleophiles as in Scheme 15 and path A in Scheme 16a. Since palladium can catalyze each step separately, finding the right ligand allows the steps to proceed successively in a one-pot reaction (Scheme 70).[99] Surprisingly, changing the ligand completely



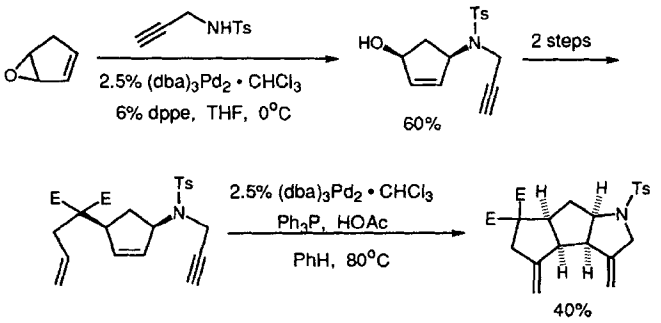
Scheme 70. The ligands for the routes A and B are listed separately. E = CO_2CH_3.

changes the regioselectivity of the initial cyclization from five- (Path A) to six-membered (Path B) ring formation. Path B normally is not observed in the simple cycloisomerizations. A scandium hydride catalyzes the cycloisomerization of α,ω-dienes by a similar mechanism.[100] Remarkably, medium and large rings form readily (Scheme 71), although the catalyst cannot tolerate Lewis basic sites. Other metals including palladium,[101] rhodium,[101] and nickel[102] are reported to cycloisomerize α,ω-dienes with varying success.



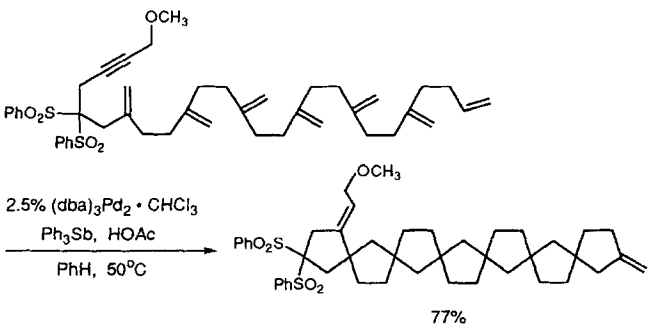
Scheme 71.

Another prospect for invention is the interception of the initial monocycle of Scheme 65 by further unsaturated functional groups. Construction of quinanes and heteroquinanes involves capture by an additional double bond system (Scheme 72) in a



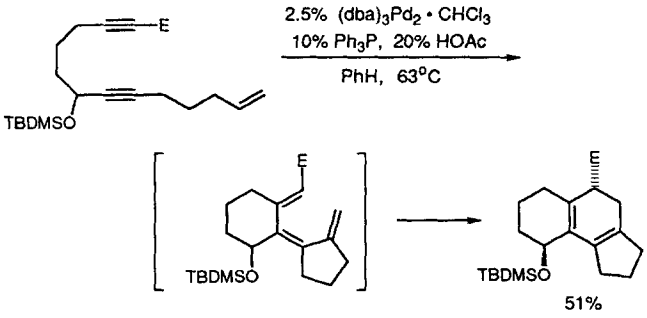
Scheme 72. Ts = *para*-tolylsulfonyl, E = CO_2CH_3.

sequence initiated by a palladium catalyzed addition of a vinyl epoxide and a pronucleophile.[103] The juxtaposition of the unsaturated bonds determines the nature of the ring system that will be created, as illustrated for a linear azatriquinane synthesis in Scheme 72. The number of rings that can be created equals the number of double plus triple bonds minus one. Thus, zipping up the heptaenyne in Scheme 73 with a palladium catalyst creates a heptaspirane that resembles a molecular rope.[104]



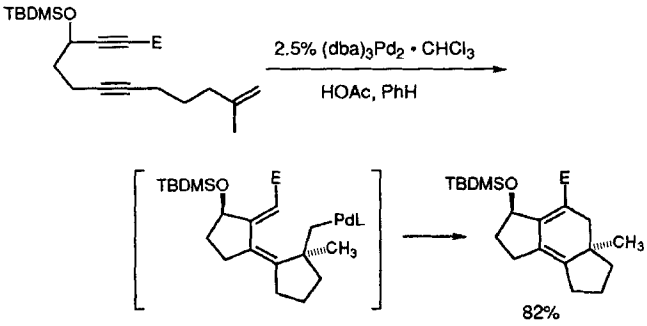
Scheme 73.

Replacing the internal double bond by another triple bond provides a novel strategy for the synthesis of 1,3,5-hexatrienes (Scheme 74). These intermediates further cycloisomerize by a rotoselective disrotation to form a single diastereomeric tricycle. Preclusion of the final β-elimination does not stop cyclization, since the intermediate with a terminal palladium moiety



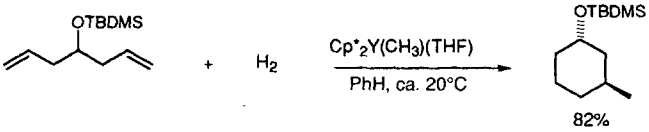
Scheme 74. E = CO_2CH_3.

may bite back on itself to produce a tricycle similar to that derived from electrocyclization of a hexatriene (Scheme 75). Other mechanisms also explain this efficient tricyclization.



Scheme 75.

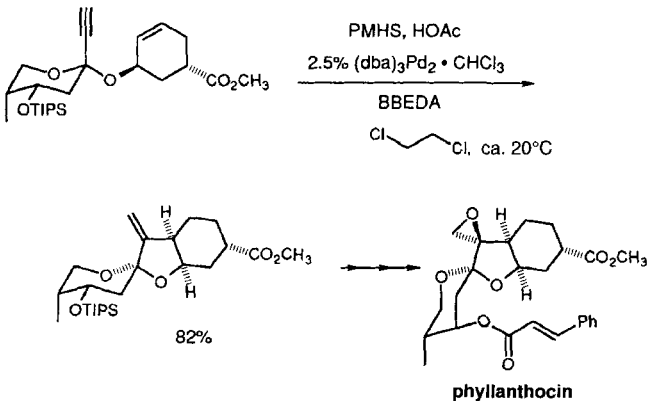
Another opportunity for innovation envisions interception of the C–M bond of the initial monocycle of Scheme 65 by an external trap such as hydrogen to effect a reductive cyclization. Indeed, an yttrium hydride formed in situ permits an atom economical addition of hydrogen with concomittant cyclization, which dominates over simple reduction with appropriate substrates (Scheme 76).[105] A more general but less atom econom-



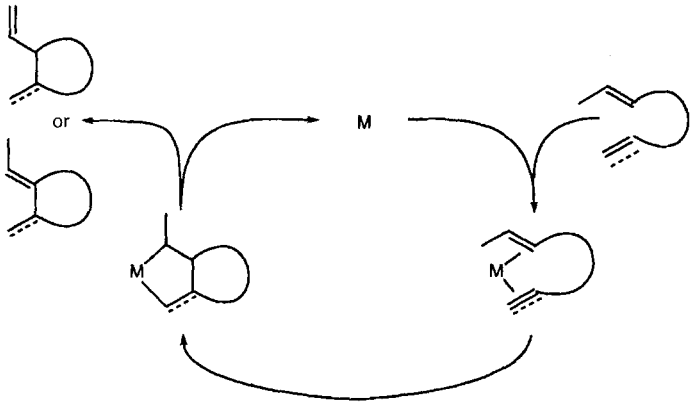
Scheme 76. Cp*.

ical reductive cyclization employs a proton and a hydride source as an equivalent of molecular hydrogen.[106] This palladium catalyzed reductive cyclization of an enyne served as a key step in a synthesis of the clinically useful phyllanthocin (Scheme 77).[107]

An alternative mechanism for cycloisomerization recognizes the chelating potential of α,ω-unsaturation (Scheme 78). In fact, some of the palladium catalyzed cyclizations of Schemes 66–69, 72–75, and 77 may proceed through such a pathway.[86b, 94] Use of "tetramethoxycarbonylpalladacyclopentadiene" (TCPC) as catalyst for such cycloisomerizations is

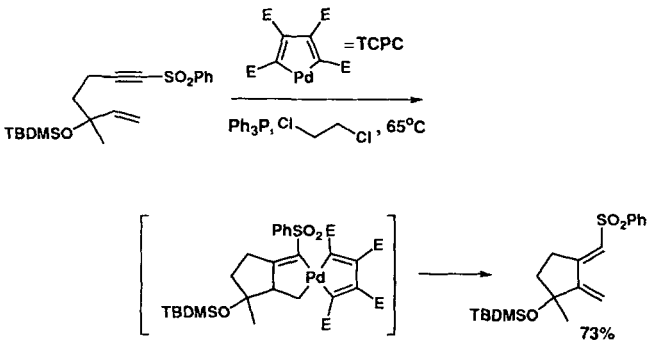


Scheme 77. PMHS = polymethylhydrosiloxane. TIPS = triisopropylsilyl.

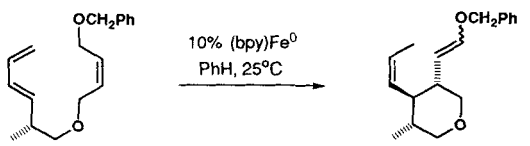


Scheme 78.

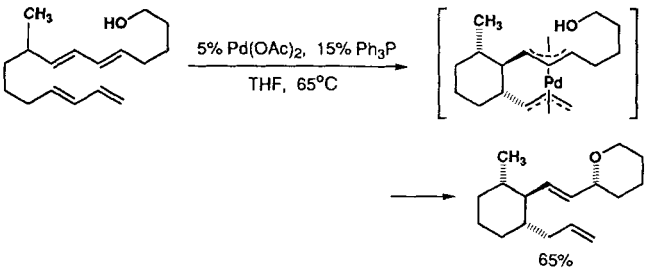
be lieved to involve such a pathway (Scheme 79).[108] The iron(0) catalyzed Alder ene type process (Scheme 80) appears to involve such a mechanism.[109] The intramolecular analogue of the diene telomerization reaction (Scheme 31)[110] also invokes a similar concept (Scheme 81) via a bis(π-allyl)palladium intermediate.



Scheme 79. E = CO_2CH_3.

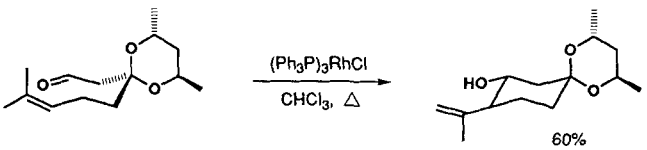


Scheme 80. bpy = bipyridine.



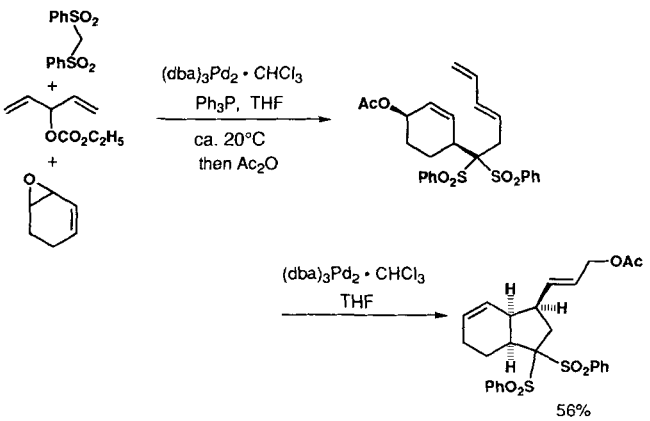
Scheme 81.

Replacment of an olefin by a carbonyl group leads to an oxaene reaction. While typical Lewis acids normally catalyze this reaction, such cycloisomerizations have also been reported with Wilkinson's catalyst (Scheme 82), although the mechanism of this catalysis is obscure.[111, 112]



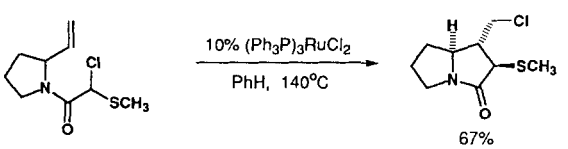
Scheme 82.

Cycloisomerizations can also involve heterotropic rearrangements. An oxytropic cyclization involving π-allylpalladium intermediates proceeds stereospecifically to the bicycle with an *endo*-oriented side chain (Scheme 83).[113] The ruthenium



Scheme 83.

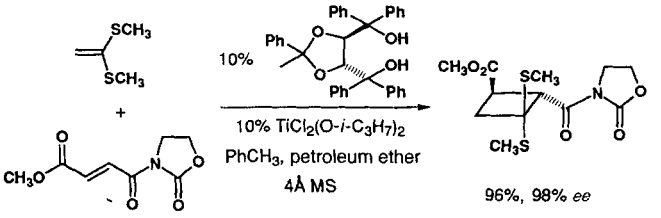
catalyzed halotropic addition occurs intramolecularly (Scheme 84).[114] This reaction may be extendable to form medium and large rings.[115]



Scheme 84. Only the major product is shown.

6. Cycloadditions

The fastest way to increase molecular complexity is to form more than one bond at a time as in cycloadditions. Orbital symmetry reveals that Hückel-like (4n + 2) transition states are favored whereas 4n transition states are forbidden in a geometrically favorable suprafacial conformation. However, metal catalysis may succeed in both cases since it opens a plethora of mechanistic possibilities beyond the concerted cycloaddition. The orbital-symmetry-forbidden [2 + 2] suprafacial cycloaddition is catalyzed by early transition metals which seem to function as Lewis acids. Chiral cyclobutanes (Scheme 85) and cyclobutenes form with excellent enantioselectivity.[116]

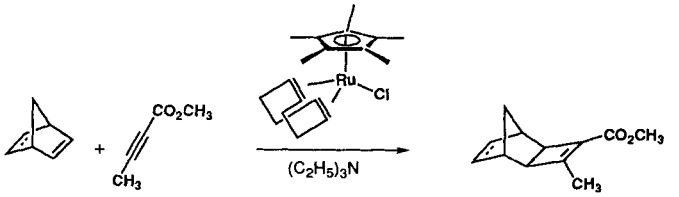


Scheme 85.

A more promising strategy involves reductive elimination of metallacyclopentenes that may form from alkynes and alkenes (Scheme 86). Such an intermediate has been invoked in the

Scheme 86.

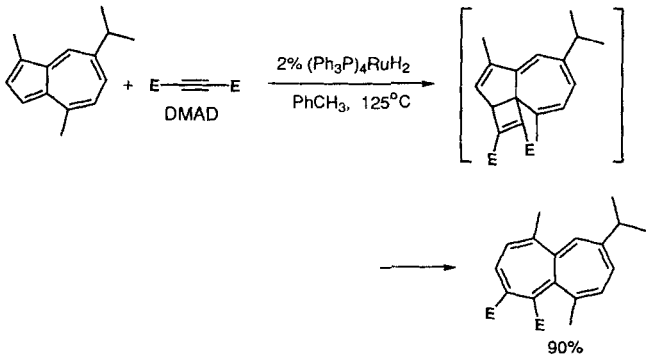
ruthenium catalyzed Alder ene reaction (Scheme 41). With a strained alkene partner such as norbornene or norbornadiene, such a [2 + 2] cycloaddition occurs in the presence of a coordinatively unsaturated ruthenium complex (Scheme 87).[117] In



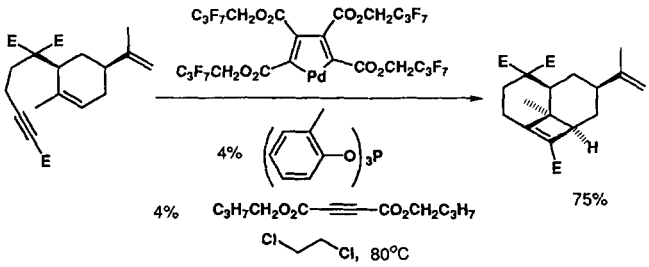
Scheme 87. The yield is 79% relative to norbornene and 87% relative to norbornadiene.

contrast to other diene reaction partners (vide infra), norbornadiene undergoes only [2 + 2] cycloaddition. Other catalysts have been reported to behave similarly.[118] This reaction expanded an azulene into a heptalene with dimethyl acetylenedicarboxylate (DMAD) (Scheme 88).[119]

Palladacyclopentadienes promote [2 + 2] cycloadditions of enynes (Scheme 89).[120] The resulting cyclobutenes undergo

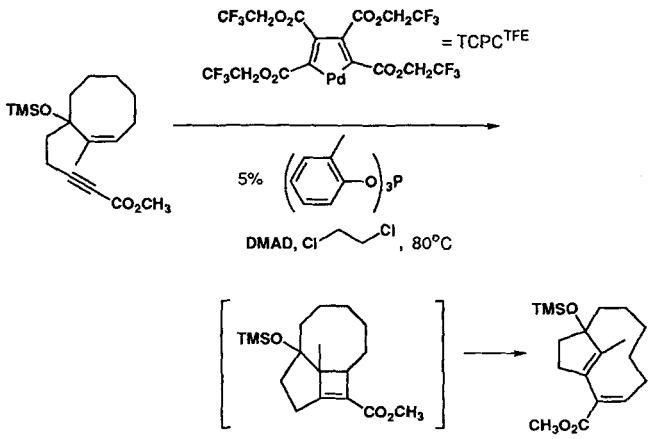


Scheme 88. E = CO_2CH_3.



Scheme 89.

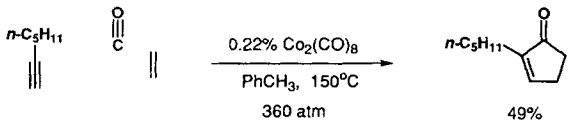
thermal conrotatory ring opening to form 1,3-dienes. Shortening the tether connecting the double and triple bonds of the substrate from four to three atoms lowers the temperature for ring opening so much that only the enyne metathesis product is observed (Scheme 90).[121] The presence of bicyclic structures like those depicted in Scheme 90 in many natural products makes this simple approach for their creation very attractive.



Scheme 90.

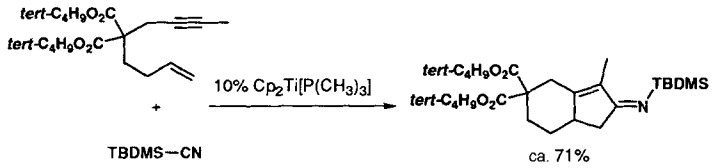
Intercepting the metallacyclopentene by carbon monoxide creates the structurally important cyclopentenones. Surrogates for CO such as isonitriles react analogously. With dicobalt octacarbonyl as the complex, this addition is known as the Pauson–Khand reaction and is an important synthesis of cyclopentenones.[122] Unfortunately, the reaction generally requires a stoichiometric amount of the cobalt complex, although a recent

example has illustrated the potential for a catalytic process (Scheme 91).[123] An analogous process catalytic in a titanium complex traps the cyclopentene with a silylisonitrile generated in



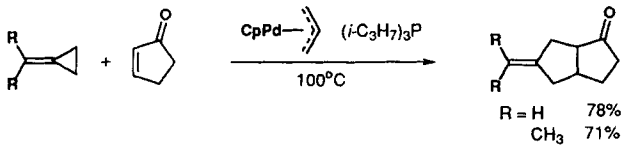
Scheme 91.

situ by isomerization of a silylcyanide (Scheme 92).[124] Ni^0 effects a similar reaction, which, however, requires a stoichiometric amount of the "catalyst."[125] These sequences constitute a [2 + 2 + 1] approach for five-membered ring construction.



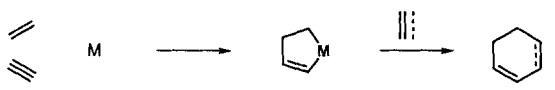
Scheme 92.

A [3 + 2] cycloaddition also generates five-membered rings. A cooligomerization of methylenecyclopropane with electron-deficient or strained alkenes produces methylenecyclopentanes even with substituted substrates (Scheme 93).[126] Whether the reaction involves ring opening to a trimethylenemethane complex or direct oligomerization through a metallacycle has not been elucidated.



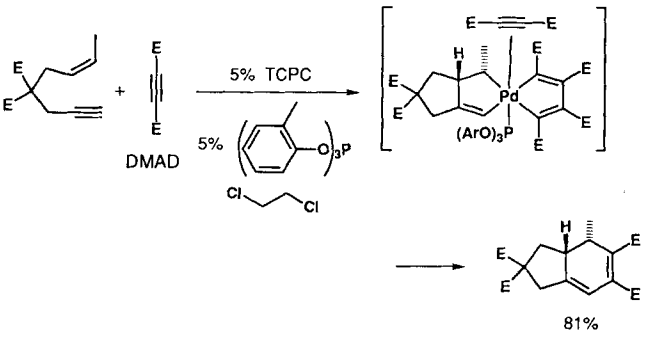
Scheme 93.

Intercepting the metallacycle of Scheme 86 with a two-carbon trap generates six-membered rings in a formal [2 + 2 + 2] type of cycloaddition (Scheme 94). Cycloisomerization of enynes

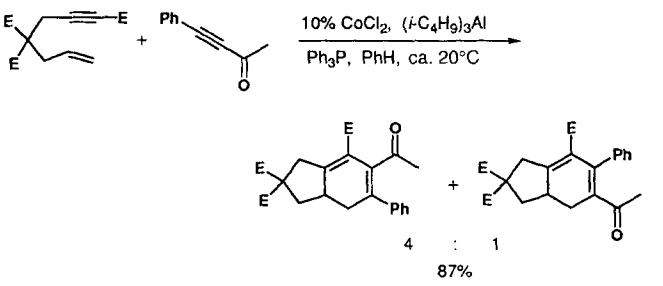


Scheme 94.

with TCPC in the presence of excess dimethyl acetylenedicarboxylate leads to the bicyclic derivative formed by trapping the purported palladacyclopentene intermediate (Scheme 95).[108] A low-valent cobalt complex generated in situ extends this reaction to monoactivated alkynes (Scheme 96),[127] whereas tethering all three unsaturated bonds permits [2 + 2 + 2] cycloaddi-

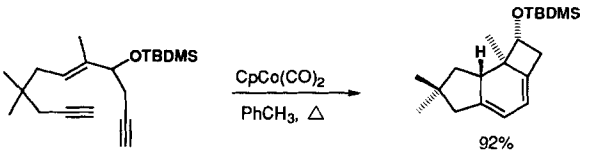


Scheme 95.



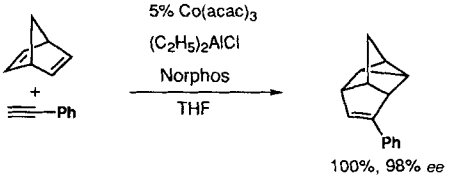
Scheme 96.

tion even without activating groups (Scheme 97),[128] although a stoichiometric amount of the cobalt "catalyst" is required because the product is strongly coordinated to cobalt.



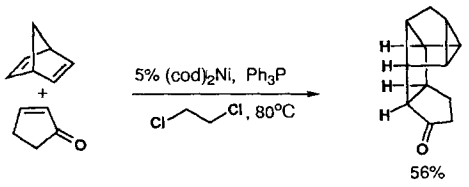
Scheme 97.

Norbornadiene undergoes [2 + 2 + 2] cycloadditions (homo-Diels–Alder reactions) with alkynes in the presence of a cobalt catalyst.[129] Since norbornadiene functions as a bidentate ligand to direct the initial cobaltacycle to the *endo* face, deltacyclenes (Scheme 98) rather than cyclobutenes (Scheme 87)[130]



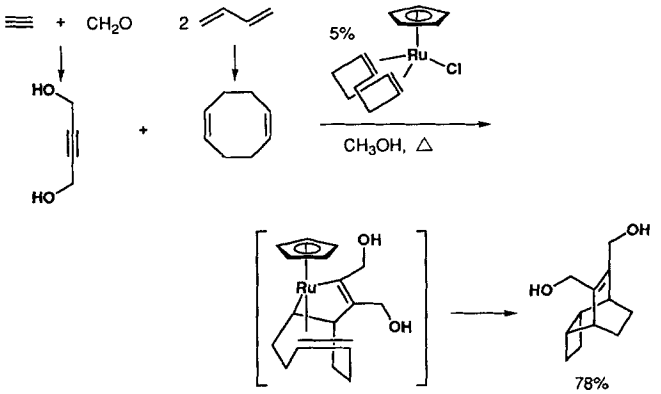
Scheme 98. Norphos = 5,6-bis(diphenylphosphino)norbornene.

result. As illustrated, placing the metal in a chiral ligand environment may impart high enantioselectivity. Using a nickel catalyst enables enones to be used as the "homodienophile" (Scheme 99),[131] which suggests that the course of reaction in Scheme 94 may be applicable to metallacyclopentanes. 1,5-Cy-



Scheme 99.

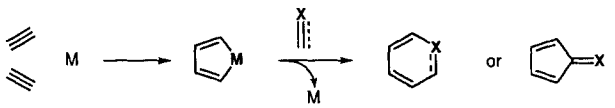
clooctadiene participates efficiently in [2 + 2 + 2] cycloadditions (bis-homo-Diels–Alder reaction) with alkynes in the presence of a ruthenium catalyst in which a ruthenacyclopentene may be postulated as an intermediate (Scheme 100).[132] The



Scheme 100.

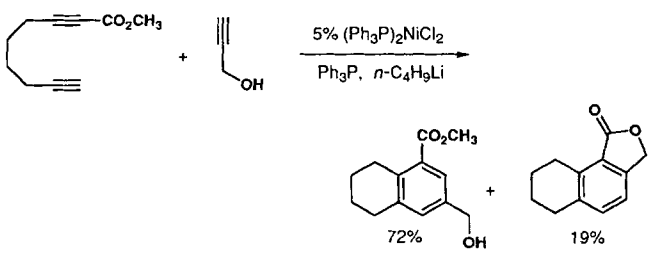
atom efficiency of this process for construction of the energy-rich tricycle becomes evident when it is realized that both reaction partners are synthesized by simple addition reactions. Thus, by a series of three additions, acetylene, formaldehyde (or other aldehydes or ketones), and butadiene combine to form the tricyclo[4.2.2.0^{2,5}]dec-7-enes. All other are used catalytically.

The formation of metallacyclopentadienes (Scheme 101) appears to be even more facile than that of metallacyclopentenes.

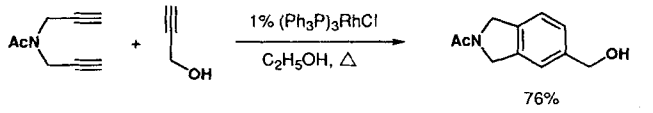


Scheme 101.

The classical example is the construction of benzenoid arenes by cotrimerization of alkynes.[133] Many metals catalyze this process, but nickel (Scheme 102),[134] rhodium (Scheme 103),[135]

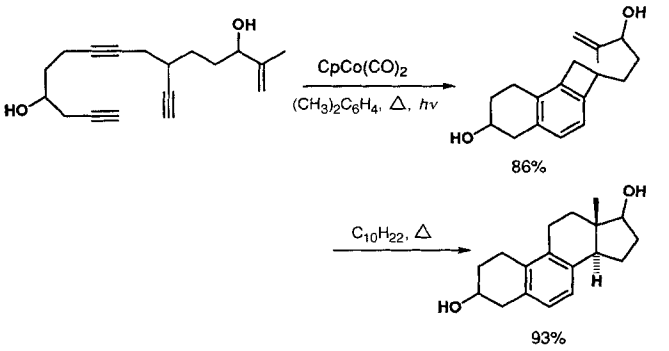


Scheme 102.



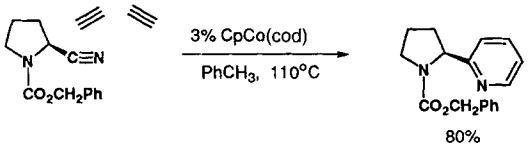
Scheme 103.

and especially cobalt (Scheme 104)[136] have proven particularly effective. In contrast to the reaction in Scheme 97, the cobalt dissociates easily from the arene, and the reaction is truly cata-



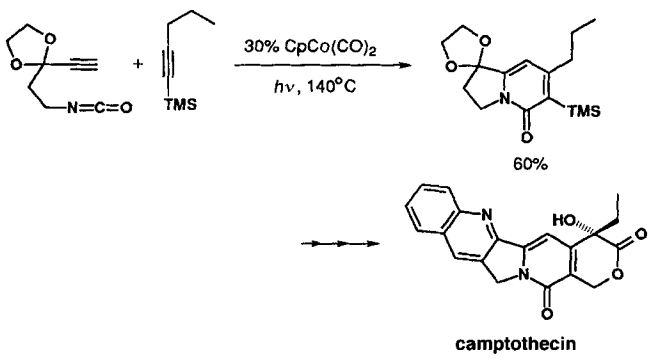
Scheme 104.

lytic in cobalt. This example illustrates the strain that may be incorporated into the cycloaddition product, which is released in a subsequent thermal electrocyclic reaction to set the stage for a final [4 + 2] thermal cycloaddition. Thus, by a series of simple cycloisomerizations, an acyclic precursor is folded into the entire steroid skeleton. Replacing an alkyne by the isoelectronic nitrile leads to a very efficient pyridine synthesis (Scheme 105).[137, 138] Cumulative unsaturation represented by



Scheme 105.

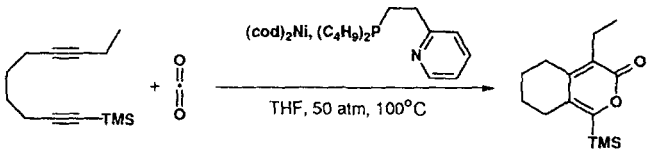
an isocyanate effectively captures the cobaltacyclopentadiene (Scheme 106)—an important step for the synthesis of the antitumor agent camptothecin.[139] Alkenes also function as effective



Scheme 106.

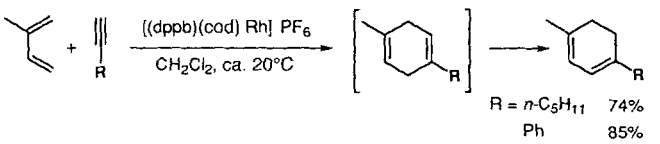
traps. Since the resultant cyclohexadienes coordinate extremely well to cobalt, normally stoichiometric amounts of the "catalyst" are required in such cases. Niobium complexes also initiate [2 + 2 + 2] cycloadditions of alkynes.[140]

With carbon monoxide, capture of the metallacyclopentadiene normally generates the cyclopentadienone rather than pyran derivatives. However, since cyclopentadienones are excellent ligands, the products are normally metal complexes, and thus the reactions require stoichiometric amounts of the metal.[141] On the other hand, carbon dioxide participates in a [2 + 2 + 2] type cycloaddition under the influence of a nickel catalyst (Scheme 107).[142] Aldehydes may function in similar fashion to produce pyrans.[143]



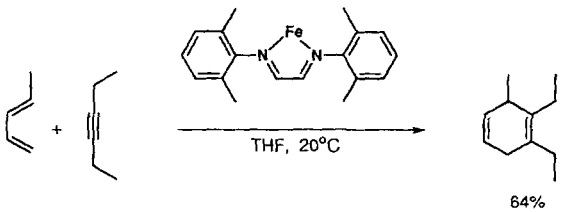
Scheme 107.

Precoordination onto a transition metal promotes [4 + 2] cycloadditions that might not occur thermally or occur only at unacceptably high temperatures. On use of a coordinatively unsaturated electrophilic rhodium complex, dienes react with unactivated alkynes (Scheme 108) to give the adduct in which



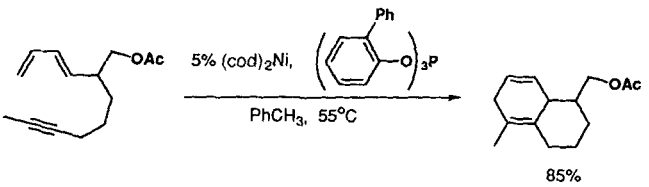
Scheme 108. dppb = 1,4-bis(diphenylphosphino)butane

isomerization of the double bonds to the thermodynamically more stable conjugated isomer accompanies cycloaddition.[144] With an iron(0) complex, catalysis of the cycloaddition occurs without isomerization of the double bonds (Scheme 109).[145]

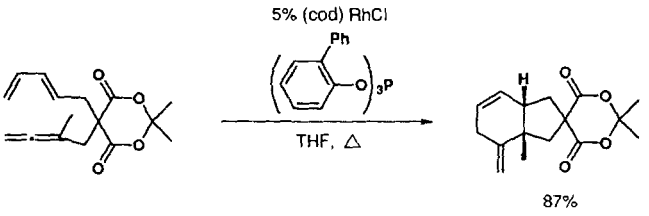


Scheme 109.

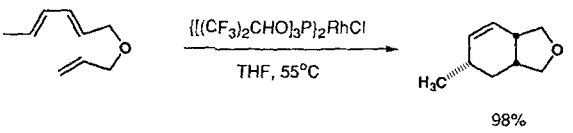
While the "para" type product dominates, other isomers also form. Tethering the partners overcomes the regioselectivity problem, and catalysis may be accomplished both with rhodium[146] and nickel (Scheme 110)[147] complexes. Rhodium catalysts enable both allenes (Scheme 111)[148] and simple olefins (Scheme 112)[148] to serve as "dienophiles." The ability of transition metals to promote ring opening of strained rings has led



Scheme 110.

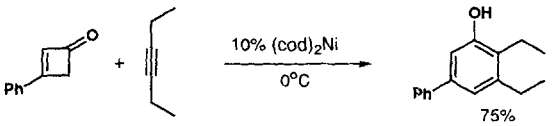


Scheme 111.



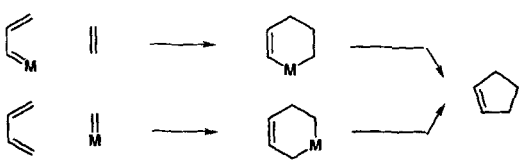
Scheme 112.

to a novel Diels–Alder type cycloaddition of cyclobutenones with alkynes, presumably involving a vinylketene coordinated to the metal as the diene partner (Scheme 113).[149] Unsymmetrical alkynes show no regioselectivity.



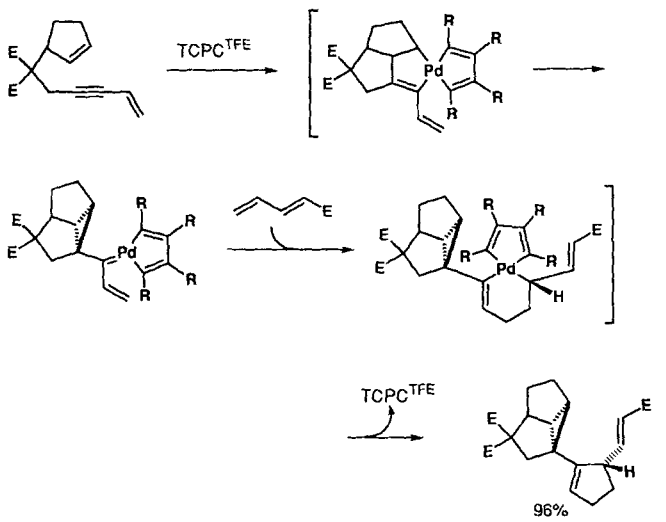
Scheme 113.

A new type of approach for cycloaddition proposes the use of a metalladiene or metallaenophile as reaction partner (Scheme 114). Although such carbenes normally participate in [2 + 2] cycloadditions leading to metathesis type products, the potential for creation of unusual ring systems not directly accessible by Diels–Alder reactions, such as cyclopentenes, make the search for such processes highly worthwhile. In the first example of a metalladiene participating in a cycloaddition, the vinylcar-



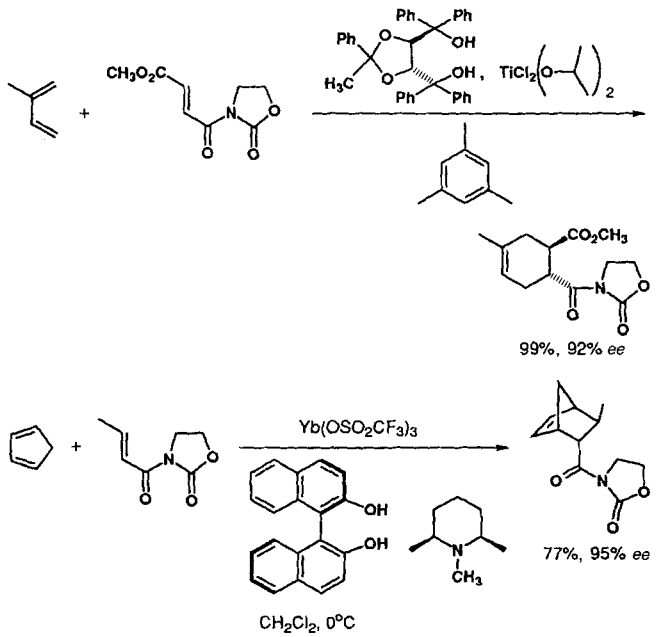
Scheme 114.

bene is generated in situ by a cycloisomerization of an enyne as in Scheme 115.[150] Trapping of the palladadiene intermediate requires a diene or enyne and proceeds with high regio- and diatereoselectivity.[151] Thus, simple metal catalyzed isomerization and addition convert simple building blocks into complex polycycles with high atom economy.



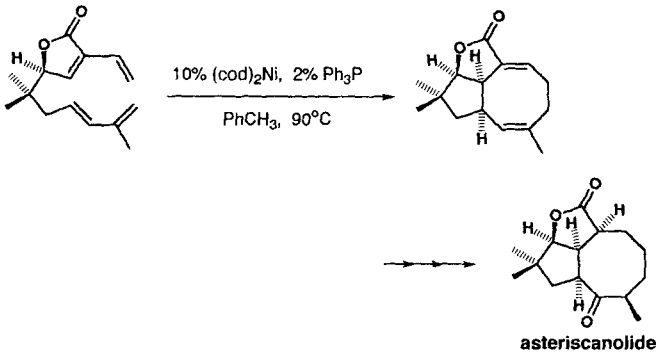
Scheme 115. E = CO_2CH_3, R = $CO_2CH_2CF_3$.

A more traditional catalysis of the Diels–Alder reaction utilizes the transition metal as a Lewis acid. These catalysts offer the advantage of imparting enantioselectivity as exemplified by titanium[152] and lanthanide (Scheme 116)[153] catalysts.



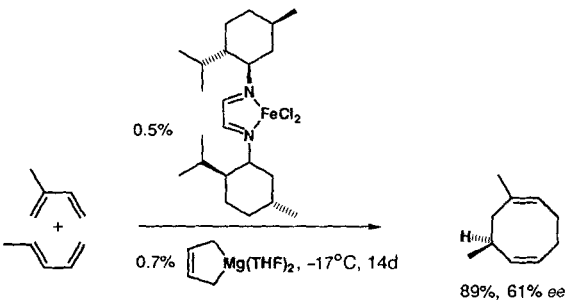
Scheme 116.

Higher order cycloadditions are also promoted by transition metals. The [4 + 4] cycloaddition to cyclooctanes catalyzed by nickel controls regioselectivity by tethering the two groups.[154–156] An effective synthesis of (+)-asteriscanolide highlights the practicality of this cycloaddition (Scheme 117).[157] While intermolecular homocoupling of dienes also



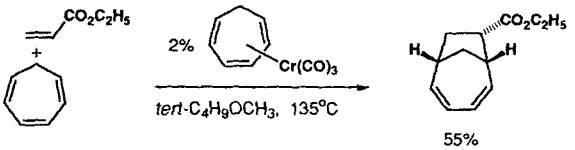
Scheme 117.

may be achieved with the nickel catalyst, an iron catalyst has effected selective cross-coupling of two different dienes asymmetrically (Scheme 118).[158] An alternative paradigm for eight-



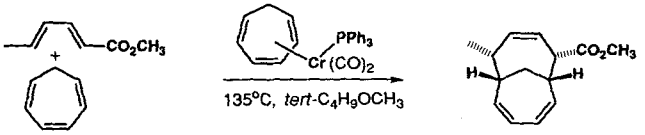
Scheme 118.

membered ring construction is [6 + 2] cycloadditions. On use of a chromium catalyst, cycloheptatriene (Scheme 119) and its heterocyclic variants form cycloadducts with typical dieno-



Scheme 119.

philes.[159] This reaction has been extended to [6 + 4] cycloadditions, which, however, proceed much slower (only 36% complete after 18 h, Scheme 120). Many further prospects for metal assisted cycloadditions not achievable otherwise abound.



Scheme 120.

7. Conclusion

The tremendous strides in organic synthesis in the last several decades have engendered the feeling that no target is too complex to tackle by synthesis. However, such notions founder if the practicality is questioned. It is not adequate only to complete a synthesis; the effectiveness of the route is critical. Improving the ability to design molecular structures more efficiently stems largely from enhancements in the selectivity of available reactions and reagents. Increasingly, transition metal catalyzed reactions are proving their value for such goals. No reaction better exemplifies this point than the transition metal catalyzed cross-coupling. However, in solving such problems of selectivity, the issue of atom economy is normally neglected. The scale-up of a complex synthesis from the research laboratory to the plant cannot ignore this fundamental question. This issue has long been recognized by the commodity chemical industry for obvious reasons. Only recently has the subject become an issue for the synthesis of smaller volume products. As the legitimate concerns of society for wise use of our limited resources with minimal environmental risk grow, the ability to produce the chemicals needed to improve the human condition will hinge on the inventfulness of chemists to design more efficient syntheses.

As a start, the repertoire of reactions that are highly atom economical must increase. The prospects for invention are vast. Clearly, the molecular gymnastics—even acrobatics—for organic molecules that transition metals direct represent promising opportunities for new invention.

Several themes become evident. Many reactive intermediates do not participate usefully in synthetic reactions either because of the harshness of the conditions required to generate them or because their high reactivity makes their trapping impractical. The ability of transition metals to create such "reactive" intermediates under mild conditions promotes specific further reactions with a selectivity tunable by the ligand environment. Precoordination imparts both selectivity and kinetic reactivity to otherwise unselective or unreactive systems. One additional benefit that emerges from this last concept addresses chemical safety. By imparting chemical reactivity only during the synthesis, the chemicals to be handled and/or stored can be more benign.

The reactions described herein represent only a beginning towards achieving these objectives. Clearly, the vastness of the territory to be explored assures exciting opportunities for generations. We still require "functional groups" to assist selective activation for new bond formation. An ideal for which we should strive is the elimination of such a requirement when the functional groups are absent from the ultimate target. We have barely begun to broach such a strategy, which today seems unattainable. Undoubtedly, such pessimism will fade as new breakthroughs emerge, especially those emanating from the domain of transition metal catalysis.

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