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The Atom Economy—A Search for Synthetic Efficiency

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34. Thanks are due to my late friend and colleague, Y. Shiloh, for initiating this study, to the Geological Survey of Israel for supporting it, and to I. Perath, A. Horowitz, and Y. Kolodny for their constructive help in the preparation of the manuscript.

# The Atom Economy—A Search for Synthetic Efficiency

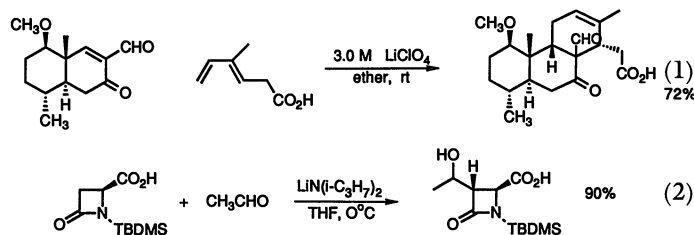
BARRY M. TROST

Efficient synthetic methods required to assemble complex molecular arrays include reactions that are both selective (chemo-, regio-, diastereo-, and enantio-) and economical in atom count (maximum number of atoms of reactants appearing in the products). Methods that involve simply combining two or more building blocks with any other reactant needed only catalytically constitute the highest degree of atom economy. Transition metal-catalyzed methods that are both selective and economical for formation of cyclic structures, of great interest for biological purposes, represent an important starting point for this long-term goal. The limited availability of raw materials, combined with environmental concerns, require the highlighting of these goals

THE CONTINUING SOPHISTICATION IN AND EVER CHANGING landscape of molecular targets for a myriad of applications ranging from biology to materials science requires a continuing evolution of synthetic methods. A key goal must be synthetic efficiency in transforming readily available starting materials to the final target. Selectivity—chemo- (functional group differentiation), regio- (orientational control of two reacting partners), diastereo- (control of relative stereochemistry), and enantio- (control of absolute stereochemistry)—has been the prime focal point because it defines the overall length of a sequence of reactions that constitutes a synthetic strategy (1). The success of the selective synthetic methods that have been developed is readily apparent by the ever more complex targets, exemplified by the successful synthesis of palytoxin, an extremely potent marine toxin of 128 carbons, 64 of which are stereogenic centers, that has more than two sextillion possible stereoisomers (2).

In the quest for selectivity, a second feature of efficiency is frequently overlooked—how much of the reactants end up in the

product, a feature we might refer to as atom economy. Consider regioselective methylenation with methyltriphenylphosphonium bromide, wherein a mass of only 14 out of 365 is transferred. The importance of this reaction cannot be overstated; we tolerate its uneconomical use of mass because it solves a selectivity problem we could not resolve otherwise. An alternative process that is both selective and atom economical remains a challenge. The ideal reaction would incorporate all of the atoms of the reactants. Major benefits that derive from such processes include more effective use of limited raw materials and decreased emissions and waste disposal. Such reactions do exist in our repertoire of synthetic methods. Most noteworthy among the classical reactions are the  $[4n + 2]$  electron cycloaddition, represented by the Diels-Alder reaction (Eq. 1; rt = room temperature) (3) and the aldol condensation (Eq. 2; TBDMS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran, *i*-C<sub>3</sub>H<sub>7</sub> = isopropyl) (4),

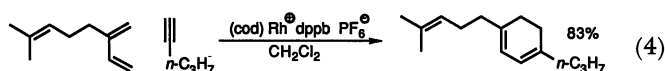
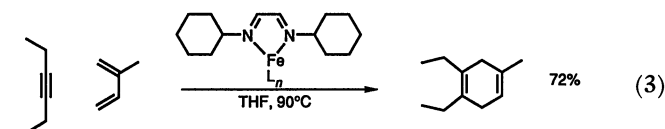


although the latter normally requires a stoichiometric amount of base "catalyst." A primary goal is the evolution of synthetic methods requiring only catalytic quantities of "activators." The ability of transition metal complexes to activate organic molecules makes them attractive prospects for developing catalytic processes with high atom economy. This concept is already embodied in important industrial processes such as Ziegler-Natta polymerization (5) and hydroformylation (6). However, little or no attention has been focused on developing such methods for the synthesis of complex molecular architecture or for intramolecular processes. This article examines these latter efforts with an emphasis on carbocyclic ring construction. All of the reactions involve simple summation of the reacting partners to form products, and any additional reagents are used only in catalytic quantities to serve as true catalysts, that is, substances that promote chemical change without being altered themselves.

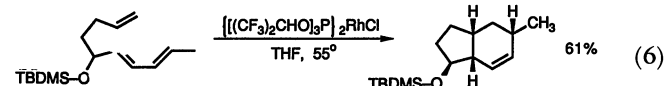
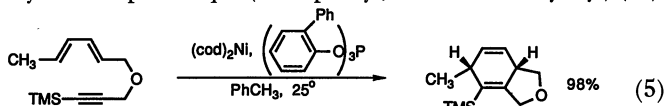
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## Cycloadditions

Polymerization and oligomerization of olefins, dienes, acetylenes, and so forth have been extensively studied but, in most cases, have proved to have little value for synthesis of complex molecules because of a lack of selectivity (7). Co-oligomerization of two or more unsaturated substrates through coordinative catalysis may provide important adjuncts to thermal cycloadditions involving transition states of  $[4n + 2]$   $\pi$  electrons. Consider Diels-Alder-type reactions that fail thermally for kinetic reasons, such as the reaction of dienes with unactivated acetylenes (8). This kinetic barrier can be overcome by coordinating the reacting partners onto iron (Eq. 3; L = ligand) (9) or rhodium [Eq. 4; cod = 1,5-cyclooctadiene, dppb = 1,4-bis(diphenylphosphino)butane] (10),

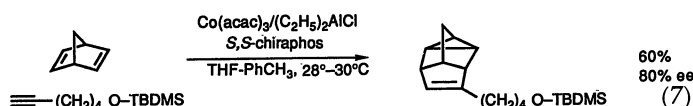


the latter giving a product involving subsequent hydrogen shift of the formal Diels-Alder adduct, a type of process that frequently accompanies transition metal-catalyzed reactions. The question of regioselectivity may be addressed by tethering the two reacting partners, thereby effecting a cycloisomerization as in the nickel-catalyzed example of Eq. 5 (Ph = phenyl; TMS = trimethylsilyl) (11).

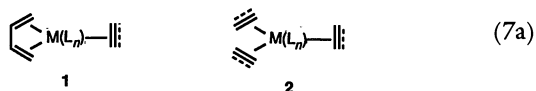


An electrophilic rhodium catalyst extends the reaction to unactivated olefins (12).

A skipped diene, norbornadiene, has participated in a cobalt-catalyzed cyclooligomerization with acetylenes (13). When chiral phosphine ligands are used, good asymmetric induction is observed (Eq. 7; acac = acetylacetonate, ee = enantiomeric excess) (14).

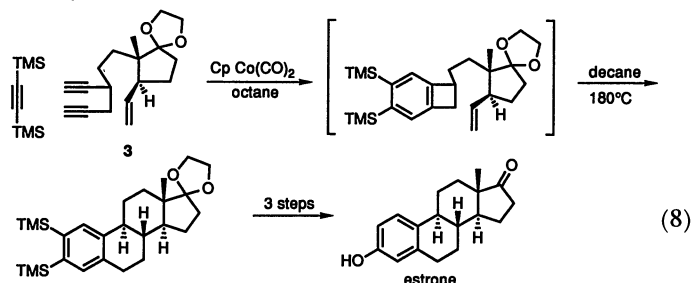


Although the mechanisms of these reactions are only sketchily known and undoubtedly vary with different transition metals, conceptually we can envision that templating the reactants on the metal complex as in 1 promotes the reaction.

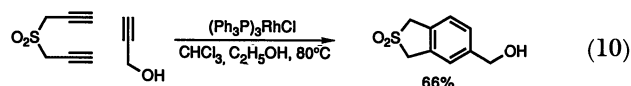
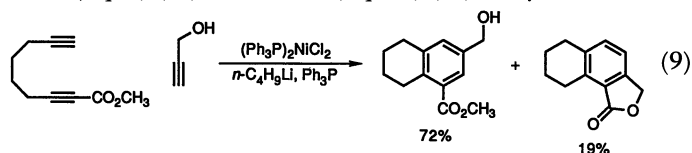


A priori, such complexation should not require bonding as in a 1,3-diene. In principle, we can envision a cyclooligomerization of any three  $\pi$  systems as in 2. Limited utility of this type of reaction stems from the problem of chemoselectivity. Syntheses of substituted benzenes are possible by homocyclotrimerization of a single acetylene (15), but cotrimerization of different acetylenes has been much more restricted. Tethering two of the three acetylenes and using an external acetylene that does not homooligomerize provides a useful solution to this problem. An extremely short synthesis of estrone derives from the cobalt-catalyzed cyclooligomerization of

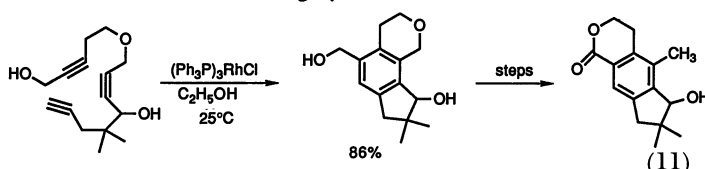
the diyne 3 and bis(trimethylsilyl)acetylene (Eq. 8; Cp = cyclopentadienyl) (16, 17).



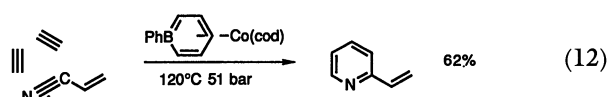
Propargyl alcohol condenses with  $\alpha, \omega$ -diynes in the presence of nickel (Eq. 9) (18) or rhodium (Eq. 10) (19) catalysis.



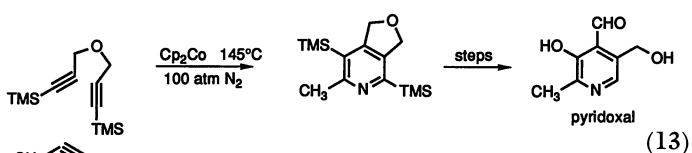
The regioselectivity problems that complicate the intermolecular process (see Eq. 9) are resolved by tethering all three acetylenes. An effective synthesis of the illudalane sesquiterpene calormelanolactone uses an ether linkage as a cleavable tether (Eq. 11) for the regiocontrolled construction of the highly substituted aromatic nucleus (20).



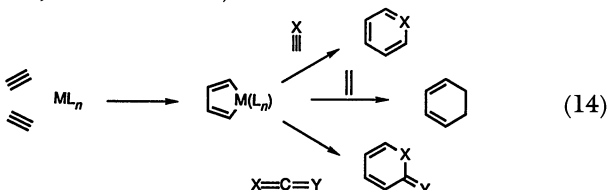
Replacement of an acetylenic linkage by other triple-bond functional groups is feasible. The cobalt-catalyzed cycloaddition allows the use of a nitrile with two acetylenes to create an effective pyridine synthesis (21). A practical synthesis of 2-vinylpyridine illustrates the chemoselectivity of the process (Eq. 12) (22).



Tethering the two acetylenes simplifies the protocol (23) and has been used in a strategy for the synthesis of vitamin B6 (Eq. 13) (24).

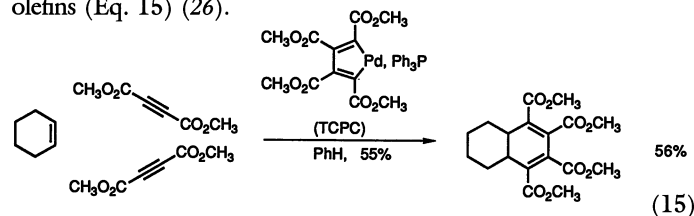


Reasonable evidence exists that a metallacyclopentadiene, as in Eq. 14, is involved in the above cycloadditions (X = carbon or heteroatom, Y = heteroatom).

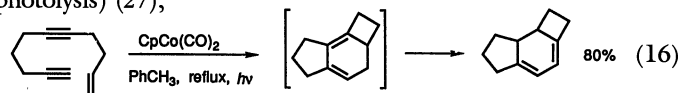


Involvement of this intermediate suggests that some other unsaturation may compete with an acetylene for the final cyclotrimerization stage. Indeed, the co-oligomerization with a nitrile appears to

involve just such a successful competition. In the case of palladium and dimethyl acetylenedicarboxylate (DMAD), 2,3,4,5-tetramethoxycarbonylpalladocyclopentadiene (TCPC) can be isolated (25) and utilized as a catalyst for the co-oligomerization of DMAD and olefins (Eq. 15) (26).

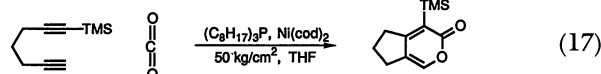


A more general reaction uses a cobalt catalyst (Eq. 16;  $h\nu$  = photolysis) (27);

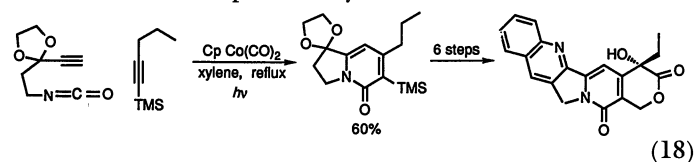


unfortunately, in most cases the strong coordination of the product diene with cobalt (in contrast to the aromatic products of acetylene cyclotrimerization) prevents this reaction from being catalytic in cobalt; therefore, it is usually not as atom efficient.

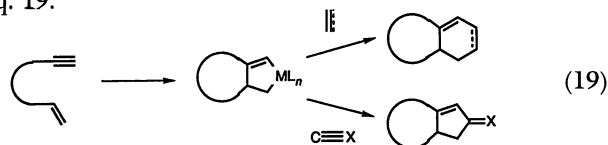
Cumulative heteroatom  $\pi$  systems may intercept the metallacyclopentadiene (see Eq. 14). Carbon dioxide co-oligomerizes with acetylenes, notably a 1,6-diyne, in a nickel-catalyzed synthesis of  $\alpha$  pyrones (Eq. 17) (28).



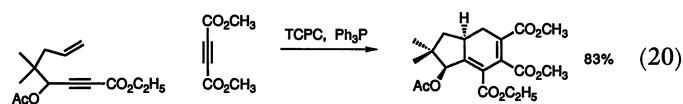
An isocyanate co-oligomerized with two acetylenes in the synthesis of an  $\alpha$  pyridone (Eq. 18) (29) that served as an important intermediate in a camptothecin synthesis.



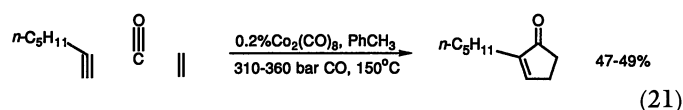
The proposal that a metallacyclopentadiene forms very efficiently from two acetylenes even in the presence of other types of unsaturation precludes co-oligomerizations involving only one acetylene except in special circumstances. One such case involves tethering an olefin and acetylene to promote formation of a metallacyclopentene as in Eq. 19.



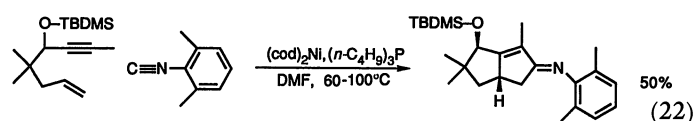
TCPC promotes the equivalent of a  $[2 + 2 + 2]$  cyclooligomerization, whereby a 1,6-enyne undergoes cycloaddition with dimethyl acetylenedicarboxylate in a highly diastereoselective fashion (Eq. 20; Ac = acetyl) (30).



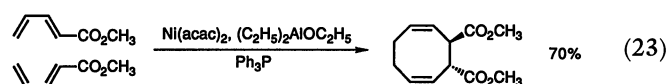
Depending on the metal, a novel type of interception may occur with carbon monoxide as the external two-electron partner. Through cobalt catalysis, a  $[2 + 2 + 1]$  cyclopentenone synthesis results (Eq. 21) (31).



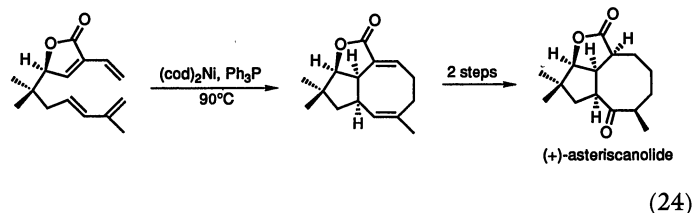
Unfortunately, almost all of the current examples require stoichiometric amounts of the cobalt catalysts (8). In spite of this fact and the frequently modest yields, the reaction has drawn wide attention because it accomplishes so much in one step. Improvements, foremost among which should be increasing the generality of the catalytic version, remain a challenge. On the other hand, replacing carbon monoxide with an isonitrile does permit a catalytic process using a nickel complex (Eq. 22; DMF = dimethylformamide) (32).



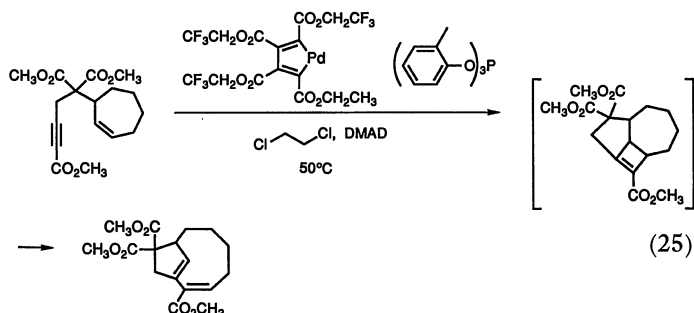
Whereas thermal cycloadditions are normally restricted to transition states involving  $[4n + 2]$   $\pi$  electrons because of the large differences in energy between concerted and nonconcerted reaction pathways, such restrictions do not apply to transition metal-catalyzed processes. Quite the contrary—because so many competing pathways lie close in energy in transition metal-catalyzed reactions, selectivity frequently becomes a problem, and the lack of selectivity renders such reactions synthetically nonviable. To the extent that selectivity can be imposed, such reactions can become important. The metal-catalyzed oligomerization of 1,3-dienes highlights this issue. In addition to the question of the degree of oligomerization, there is the question of the regioselectivity. For example, dimerization of 1,3-butadiene can generate four-, six-, or eight-membered rings (7). The great difficulty of constructing eight-membered rings by conventional methodology imparts special significance to the ability to achieve both an iron- (33) and a nickel- (Eq. 23) (34) catalyzed  $[4 + 4]$  dimerization of a diene.



Although the intermolecular version appears restricted at present to homocoupling, effecting such reactions intramolecularly allows two different 1,3-dienes to cross-couple (35). A very efficient synthesis (13 steps) of (+)-asteriscanolide uses this process as a key step (Eq. 24) (36).



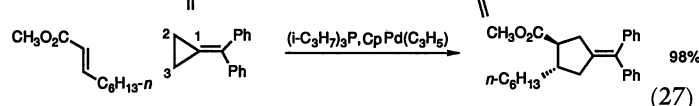
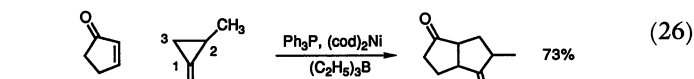
Except for cumulated unsaturation, thermal  $[2 + 2]$  cycloadditions are rare (37). On the other hand, such a cycloaddition of an enyne occurs in the presence of the palladium catalyst TCPC (38). Creating a second-generation catalyst in which the methyl ester is replaced with an ester derived from trifluoroethanol greatly expands the scope of the reaction (Eq. 25).



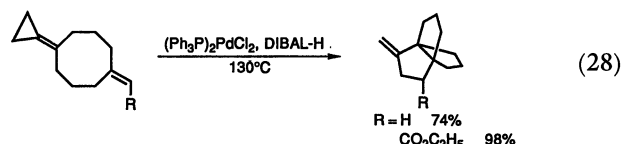


Most interestingly, the initial strained cyclobutene products suffer in situ cycloreversion to the bridged bicyclic structures in a formal metathesis reaction (39). Such difficultly obtained bridged bicyclic structures constitute the core of biologically important molecules such as the clinically useful taxanes (40).

The pi character associated with cyclopropane bonds permits them to complex with transition metals and thereby be activated for unprecedented types of reactions such as novel cycloadditions. Methylene cyclopropanes have been particularly interesting because of their participation in [3 + 2]-type cycloadditions for the construction of five-membered rings (41). The behavior depends on the nature of the catalyst. The 1,3-bond participates in the equivalent of a cycloaddition using a nickel complex as a catalyst (Eq. 26) (42), but the 2,3-bond is cleaved in a palladium-catalyzed cycloaddition (Eq. 27) (41).

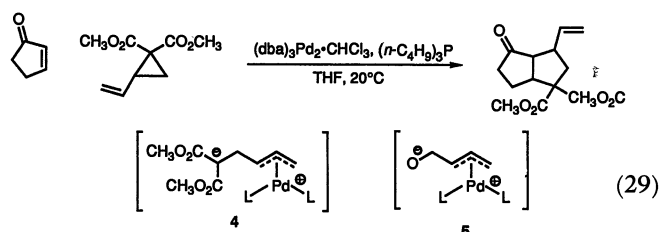


An intramolecular version of the latter reaction has also been observed (Eq. 28; DIBAL-H = diisobutylaluminum hydride) (43).



This [3 + 2] cycloaddition highlights one of the major advantages of such transition metal-catalyzed reactions, whereby complementary selectivity, in this case regioselectivity, is achievable simply by switching the transition metal catalyst. Although the mechanisms of both of these reactions remain to be established, the palladium-catalyzed reaction can be thought to involve a trimethylenemethane palladium complex. Trimethylenemethane is a reactive intermediate of sufficient instability that it cannot be effectively captured by intermolecular cycloadditions. Complexation to a palladium template imparts some stability, yet sufficient reactivity is retained for cycloaddition (44). The ability of transition metal complexes to interact with reactive intermediates in similar fashion is an exciting area of activity. Prospecting for new efficient cycloadditions using this concept is a challenging endeavor.

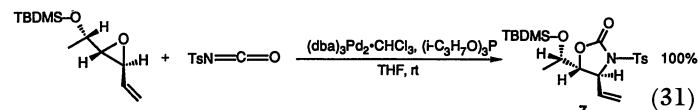
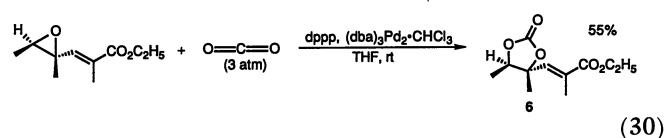
Palladium catalysts promote cycloadditions of vinylcyclopropanes to electron-deficient olefins (Eq. 29; dba = dibenzylideneacetone) (45).



This reaction may involve a nonconcerted cycloaddition initiated by a 1,4-addition of the "soft" carbon nucleophile of the pseudo-1,3-dipole 4 to the enone.

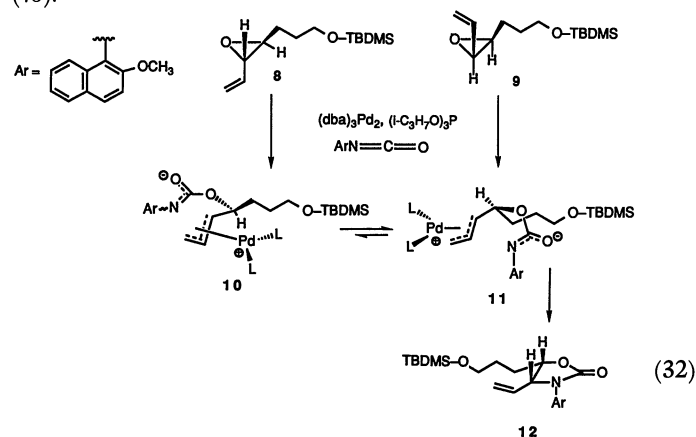
Vinyl epoxides open in analogous fashion to the dipole 5 in the presence of palladium catalysts, but the "hardness" of the resultant oxyanion precludes conjugate additions. On the other hand, cumulative unsaturated partners such as carbon dioxide [Eq. 30; dppp = 1,3-bis(diphenylphosphino)propane] (46) and isocy-

anates (Eq. 31; Ts = *p*-toluenesulfonyl) (47)



effectively capture this intermediate to give the cyclic carbonate 6, an intermediate toward (+)-citroviral and consequently (+)-citroviridin, a potent adenosine triphosphate synthetase inhibitor, and oxazolidin-2-one, 7, an intermediate toward the aminosugar (–)-acosamine, an important carbohydrate conjugate of anthracycline antibiotics.

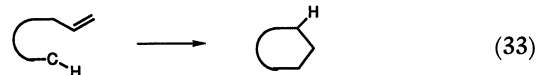
The transition metal template can impose its imprint on the reacting substrate and thereby direct formation of a contrathermodynamic product. Thus, both the *E* and *Z* epoxides 8 and 9 condense with 2-methoxy-1-naphthyl isocyanate to give only the *Z*-oxazolidin-2-one 12 (Eq. 32) (48).



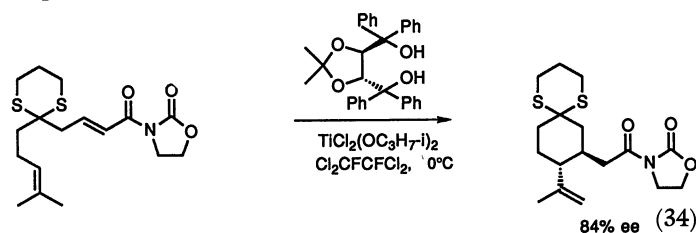
The steric interactions between the  $\pi$ -allyl substituents and the transition metal template in the intermediates 10 and 11 outweigh the unfavorable steric interactions in the developing *cis* product. The generalization of the ability of a transition metal template to dictate the stereochemistry of the product regardless of its relative thermodynamic stability can become a powerful tool for stereochemical control (49).

## Prototropic Cycloisomerizations

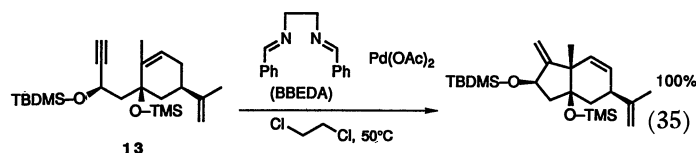
A very atom-economical way to effect ring closures involves converting a  $\pi$  unsaturation to a ring unsaturation accompanied by a hydrogen shift (Eq. 33).



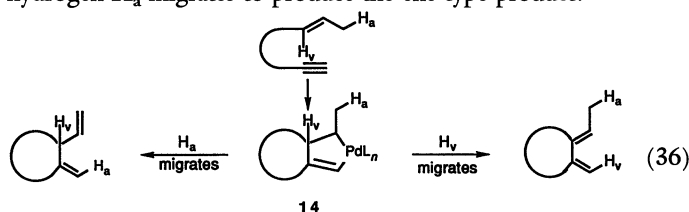
A thermal version of this reaction is known as the Alder ene reaction (50), which, like its more famous relative the Diels-Alder reaction, may be catalyzed by Lewis acids with high selectivity, even enantioselectivity (Eq. 34) (51).



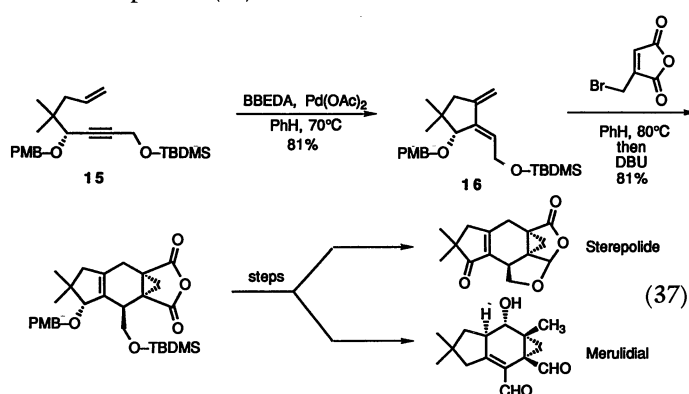
The high temperatures required in the thermal process and the structural restrictions of the Lewis acid-catalyzed reaction limit the applicability of this process, as in the case of the acetylenic substrate **13**:



The discovery that palladium catalyzed the ene reaction of acetylenic substrates (**52**) converted the failure of the thermal reaction of **13** into a quantitative cyclization that was used for the synthesis of picrotoxins (Eq. 35) (**53**). The mechanism of the catalysis may be envisioned to involve a metallacyclopentane **14** in which the allylic hydrogen  $H_a$  migrates to produce the ene-type product:

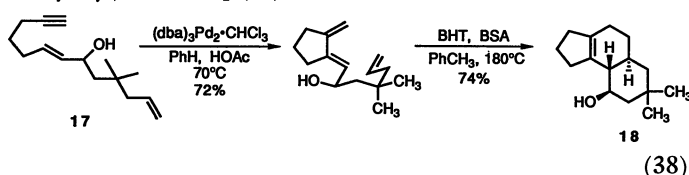


Examination of this intermediate suggests that an alternative path involving migration of what was originally the vinylic hydrogen  $H_v$  can generate an even more exciting type of product, a 1,3-diene, that cannot be generated by the thermal or Lewis acid protocols (see Eq. 36). Indeed, the enyne **15**, which can only react by migration of a  $H_v$ , smoothly cycloisomerizes to the 1,3-diene **16**, an excellent Diels-Alder partner (**54**):



Equation 37 (PMB = *p*-methoxybenzyl, DBU = 1,8-diazabicycloundecane) exemplifies this cycloisomerization-cycloaddition approach for polycyclic construction in a highly efficient and general strategy for isolactaranes (**55**), two members of which, sterepolide (**56**) and merulidial (**57**), have been synthesized by this methodology.

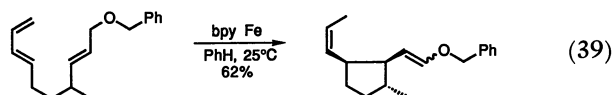
Using a dienyne such as **17** permits these two steps to be performed in tandem; an acyclic substrate is ultimately folded to the tricycle **18** with high chemo-, regio-, and diastereoselectivity [Eq. 38; BHT = 2,6-di-*tert*-butyl-4-methylphenol, BSA = *O,N*-bis(trimethylsilyl)acetamide] (**58**).



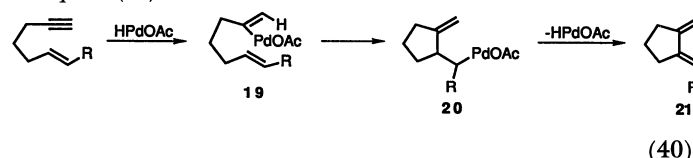
In this case, the hydroxyl group plays a dual role—as a regiochemical control element for the palladium-catalyzed cycloisomerization to the 1,3-diene and as a diastereochemical control element for the Diels-Alder cycloaddition.

The iron-catalyzed Alder ene-type reactions of dienes with olefins

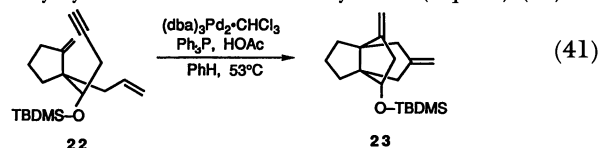
(**59**) have been extended to cycloisomerizations for diastereocontrolled cyclopentane formation (Eq. 39; bpy = 2,2'-bipyridyl) (**60**).



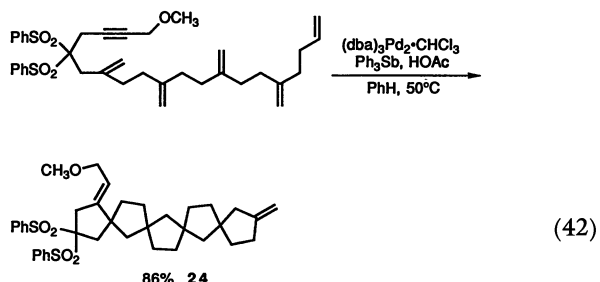
The catalyst conditions for the cycloisomerization to the 1,3-diene used in Eq. 38 differ from those used in the earlier examples, suggesting that another mechanistic pathway may operate in which a hydridopalladium acetate is a catalytically active species according to Eq. 40 (**61**).



This rationale differs from that of Eq. 35 in that only one C-Pd bond exists at any one time. Significantly, this pathway suggests that the initial cyclization product **20**, which still retains a C-Pd bond, may undergo further cyclizations if  $\beta$ -hydrogen insertion can be suppressed. Indeed, the [3.3.3]propellane **23** is readily assembled by cycloisomerization of dienyne **22** (Eq. 41) (**62**).

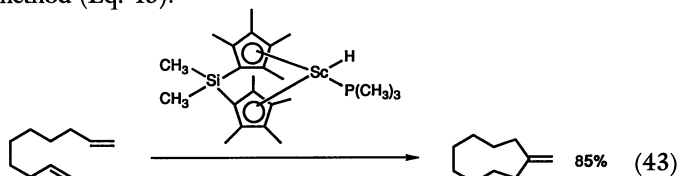


The process may continue, limited only by the number of double bonds. Six sites of unsaturation have been zipped together to generate the structurally novel polyspirocycle **24** in a one-step cycloisomerization (Eq. 42).

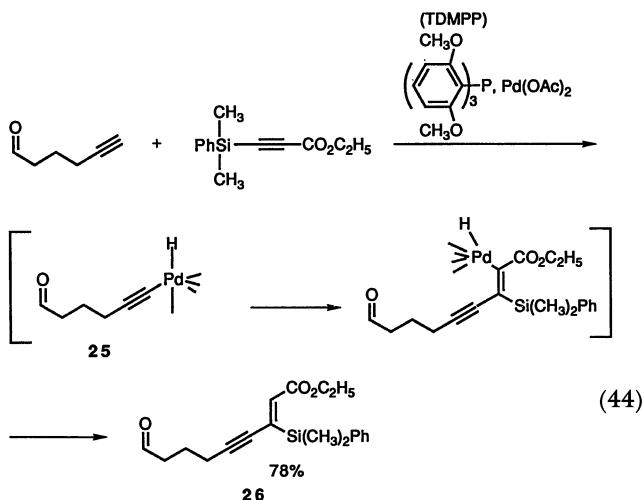


The nature of the ring system depends only on the juxtaposition of the unsaturation, in which the  $\pi$  orbitals are like the teeth of a zipper and the palladium serves as a tab; thus, this process is dubbed “a palladium-catalyzed zipper reaction.”

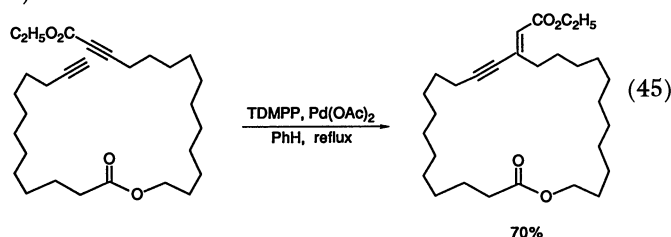
While the above palladium-catalyzed cycloisomerization requires an acetylenic linkage as an initiator, very limited cycloisomerizations of  $\alpha,\omega$ -dienes occur with the use of palladium (**63**), rhodium (**63**), nickel (**64**), and scandium (**65**). Spectacularly, a nine-membered ring formed with the use of scandium in high yield, although sensitivity of the catalyst to Lewis basic sites may limit the applications of this method (Eq. 43).



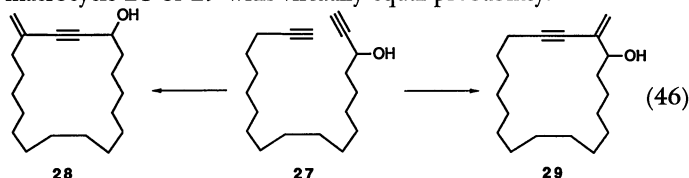
Acetylenes are particularly versatile substrates for transition metals. In addition to their excellent coordination properties, terminal acetylenes serve as hydrogen donors according to Eq. 44 (**66**).



The creation of a C-Pd bond in **25** then permits carbametalation of an acceptor acetylene, either another molecule of terminal acetylene or an electron-deficient acetylene, to give ultimately a simple addition product, **26**. Performing this reaction intramolecularly effects a cycloisomerization, even when very large rings are generated, such as the 26-membered macrolide of Eq. 45 (67).

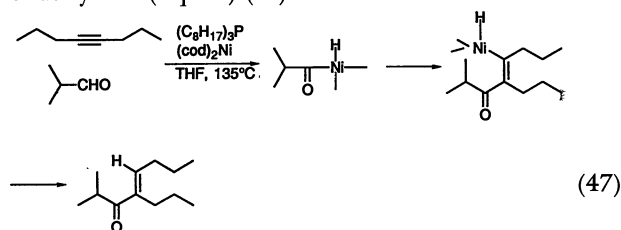


Cyclization of the bis-terminal diyne **27**, in principle, could form macrocycle **28** or **29** with virtually equal probability.

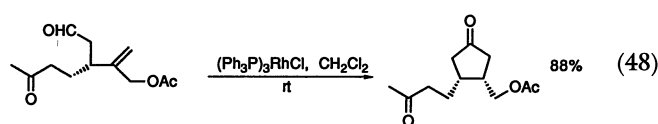


In contrast to such an expectation, cyclization proceeds chemoselectively to generate macrocycle **29**, in which the propargyl alcohol serves as the acceptor and the nonfunctionalized terminal acetylene serves as the donor (Eq. 46) (67, 68).

Transition metal-carbon bonds also form readily by insertion into aldehydic C-H bonds, which now can promote carbametalations of olefins or acetylenes (Eq. 47) (69).

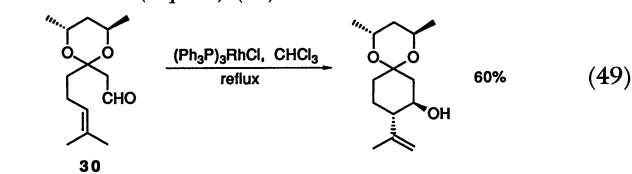


A rhodium complex (Wilkinson's catalyst) effectively catalyzes an intramolecular hydroacylation of an unsaturated aldehyde to effect a chemo-, regio-, and diastereoselective synthesis of cyclopentanones (Eq. 48) (70).

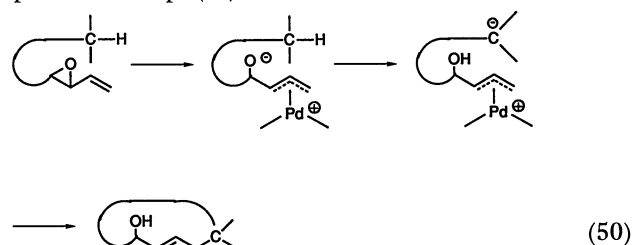


Ring size is critical. In a substrate that has one additional carbon in

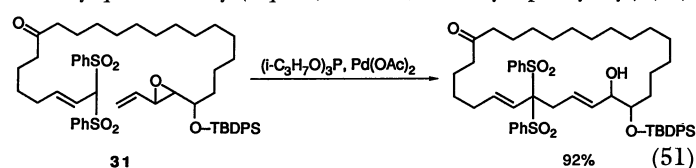
the tether joining the aldehyde and olefin as in **30**, the reaction completely changes course to an Alder ene-like process under very similar conditions (Eq. 49) (71).



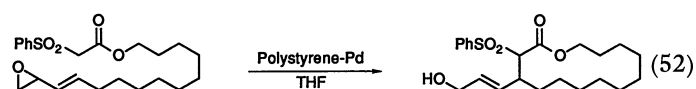
A different strategy for C-H activation for prototropic cycloisomerization involves removal of the hydrogen as a proton by a base generated in a transition metal-promoted ionization. The cycloisomerization of a vinyl epoxide with a palladium complex (Eq. 50) depicts the concept (72).



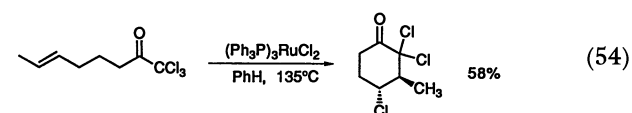
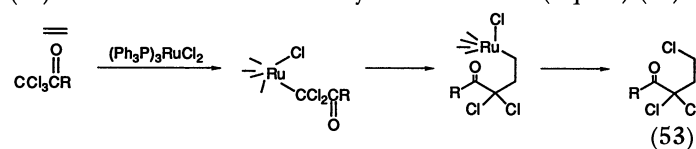
The cycloisomerization of the vinyl epoxide **31** directed toward an antifungal polyene macrolide provides a striking illustration of the success of this approach because the 26-membered ring formed virtually quantitatively (Eq. 51; TBDPS, *tert*-butyldiphenylsilyl) (73).



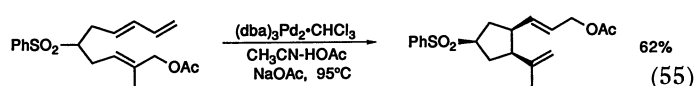
Anchoring the palladium to an insoluble polymer permits cyclizations to the unfavorable medium and large rings to proceed at high concentrations without competing polymerization (Eq. 52) (74, 75), an observation almost without precedent.



Transition metal-catalyzed cycloisomerizations should not be limited to proton shifts. A few examples of heterotropic cycloisomerizations have appeared. For example, the ruthenium-catalyzed additions of polyhalocarbonyl compounds to olefins (Eq. 53) (76) have been converted into a cycloisomerization (Eq. 54) (77).



The ability to add  $\pi$ -allylpalladium complexes to 1,3-dienes (78) and to generate such complexes from allyl acetates (79) has been transformed into a cycloisomerization involving the shift of an acetoxy group (Eq. 55) (80).



## Conclusion

The limitations of raw materials, combined with environmental concerns, necessitate our rethinking of strategies toward complex organic synthesis. Although some of the most important industrial processes already recognize the advantages of atom-economical reactions, most do not. Several reasons account for the current situation. First, the importance of this strategy has not been emphasized. Second, our repertoire of simple addition reactions is extremely limited. Third, of the currently existing examples, many reactions are difficult to perform selectively. The great development of our understanding of transition metal catalysis in organic chemistry has opened a major avenue for invention of new processes and improvement of existing ones. While such processes are of great importance for synthesis of acyclic as well as cyclic systems, focusing on the latter recognizes their importance and their higher probability of success, because many reactions that fail intermolecularly succeed intramolecularly. Furthermore, cycloisomerizations offer special opportunities for enhancing efficiency for construction of the more difficult medium (eight-, nine-, and ten-membered) and large (>ten-membered) rings. While we are at a very early stage of development, the value of the existing methods for construction of complex molecular architecture has been demonstrated. The ultimate goal must be to construct any molecule by a series of steps in which one building block is simply added to another until the edifice has been completed (81).

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