Palladium-Catalyzed Cycloisomerizations of Enynes and Related Reactions

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Received September 5, 1989 (Revised Manuscript Received December 11, 1989)

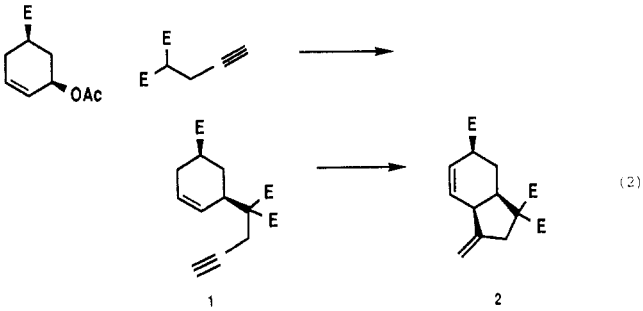
Cyclization reactions that involve a simple isomerization of an acyclic substrate provide the most effective utilization of material. A classical example is the intramolecular Diels–Alder reaction.[1,2] The related intramolecular Alder–ene reaction (eq 1) had much more

(1)

limited use, in part because of the rather high temperatures and restricted range of substrates.[2,3] The evolution of a catalyst for this process might extend its scope as well as permitting additional types of processes that are not available in the thermal reaction. This Account reviews the development of such catalytic systems. For simplicity, it is not noted but it is to be assumed that, unless otherwise specified, transition-metal complexes have been employed catalytically (typically 1–5 mol %).

A Catalytic Alder–Ene Reaction

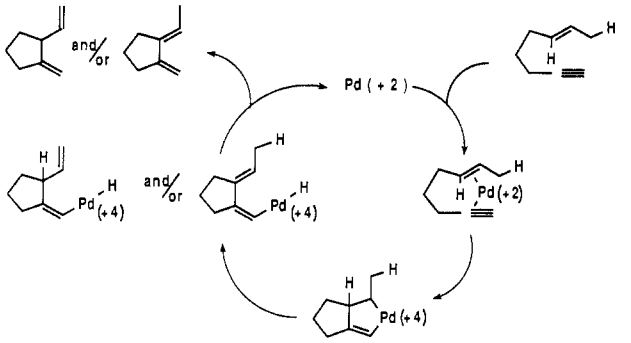
Our investigation of a tandem palladium(0)-catalyzed alkylation–Alder–ene cyclization[4] according to eq 2 revealed that the bicyclic product **2** was the direct result of a Pd(2+) catalyzed cyclization of the initial product **1**. Thus, a novel cyclopentane annulation of an allyl



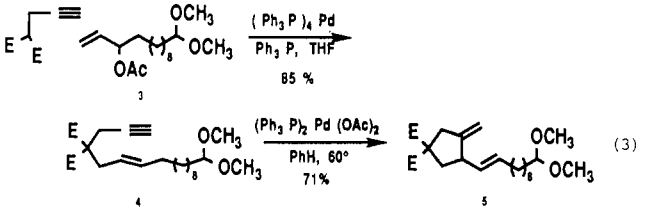
(2)

carboxylate results in which the formation of the first bond is catalyzed by Pd(0) and, by a simple electronic switch to Pd(2+), the formation of the second bond is catalyzed. The dramatic nature of this result is revealed by the fact that at no temperatures (up to 600 °C, no

Scheme I
Cyclopalladation as a Reaction Pathway

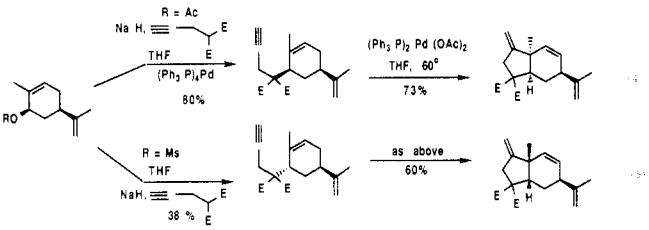


reaction, and above, only decomposition) does this substrate undergo a thermal reaction, but a catalytic amount of palladium acetate effects cyclization within 1 h at room temperature![5] The high activity of this catalyst limits the yields due to competing product decomposition. Attenuating the activity of palladium acetate by using its bis(triphenylphosphine) complex in benzene requires higher temperatures (66 °C) but improves the yield to 85%. A similar sequence converts the allyl acetate **3** via the enyne **4** to the cyclopentane **5** in which the acyclic double bond is exclusively *E* (eq 3). By choosing the appropriate alkylation method of



(3)

an allyl ester, either a Pd(0)-catalyzed alkylation which proceeds with net retention of configuration (eq 4) or a noncatalyzed alkylation which proceeds with inversion of configuration (eq 5), the stereochemistry of the overall cyclopentane annulation of an allyl alcohol may be controlled.[6]



The palladium-catalyzed cyclization of 1,6-enynes may provide a regioselectivity that complements the

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(2) Taber, D. F. *Intramolecular Diels–Alder and Alder Ene Reactions*; Springer-Verlag: Berlin, 1984.
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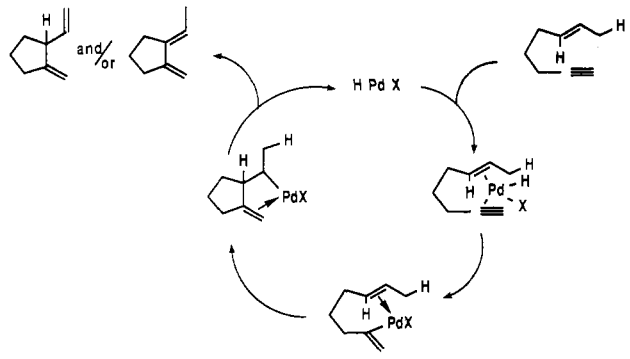
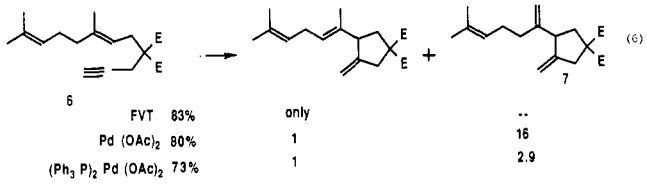
Scheme II
Hydropalladation Reaction Pathway



thermal reaction (eq 6). In this case, the presence or absence of phosphines has a dramatic effect on the selectivity.[7]

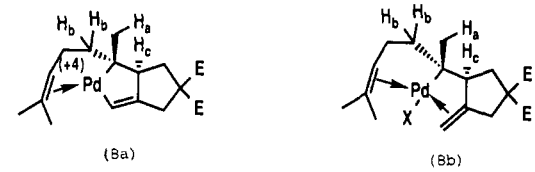


Mechanistic Possibilities

To understand the above reactions and to make predictions of other transformations require some insight into the mechanism of such reactions. Schemes I and II present two reasonable working hypotheses. Strong support for a cyclopalladium pathway derives from the related formation of metallocyclopentanes in cobalt,[8,9] zirconium,[10] and titanium[11] chemistry.[12] On the other hand, the involvement of a Pd(2+)–Pd(4+) cycle is not well presented in organopalladium catalytic cycles.[13]

An alternative pathway envisions the in situ formation of a hydridopalladium acetate by reaction of palladium acetate with the substrates. The well-documented reactions of hydro- and carbopalladation of olefins and acetylene[14] and the needlessness to invoke a Pd(4+) species lend credence to this pathway.

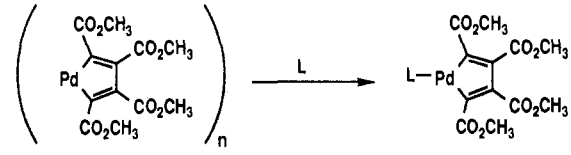
An attractive feature of both of these mechanistic possibilities is their ability to rationalize the regioselectivity of eq 6. Examining the proposed intermediates **8a** and **8b** reveals that coordination of the remote double bond to palladium fixes the conformation of the chain such that the dihedral angle between C–Pd and C–H_b is >90°. For optimum β-H insertion, this angle



must be as close to 0° as possible.[15] Thus, only H_a and H_c can achieve this geometry. Again, the palladacyclopentene ring of **8a** and pseudopalladacyclopentene ring of **8b** make the dihedral angle with H_c approach 90°, thereby favoring insertion in C–H_a and formation of diene **7**. Thus, this catalytic reaction has some features of enzymatic reactions. By recognizing more than just the sites on the molecule undergoing reaction, the palladium affects the conformation of the reacting molecule and thereby its selectivity. Other less likely mechanistic possibilities also exist.[16,17]

Palladacyclopentenes: A [2 + 2 + 2] Cyclotrimerization and a Cyclorearrangement

The ability to intercept metallocyclopentenes of cobalt,[8,9] zirconium,[10] and titanium[11] suggested a similar process to demonstrate the validity of Scheme I. Unfortunately, all attempts to trap a palladacyclopentene using palladium acetate as a catalyst failed. If the failure resided in the acetate groups destabilizing a Pd(4+) species, their replacement by more electropositive groups as present in the palladacyclopentadiene TCPC[18] might stabilize the palladacyclopentene sufficiently to permit its interception. The insolubility of



TCPC requires a ligand, either TPP or TPPO, to depolymerize it and thereby solubilize it. Both of the formed complexes catalyzed the normal enyne cyclization.[19] Most significantly, remarkably effective [2 + 2 + 2] cyclotrimerizations can occur with excellent diastereoselectivity when excess dimethyl acetylenedicarboxylate (DMAD) is used, as shown in eq 7.

A high-energy Pd(4+) metallocyclopentene may be envisioned to suffer a 1,1-reductive elimination, although such a process would generate the highly strained bicyclo[3.2.0]hept-5-ene. Interestingly, substrate **9a** under the above conditions but in the presence of only an equivalent amount of DMAD produces only

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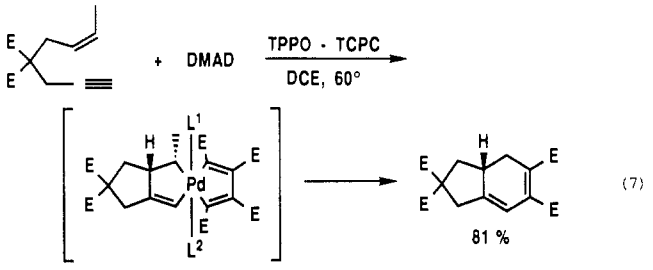

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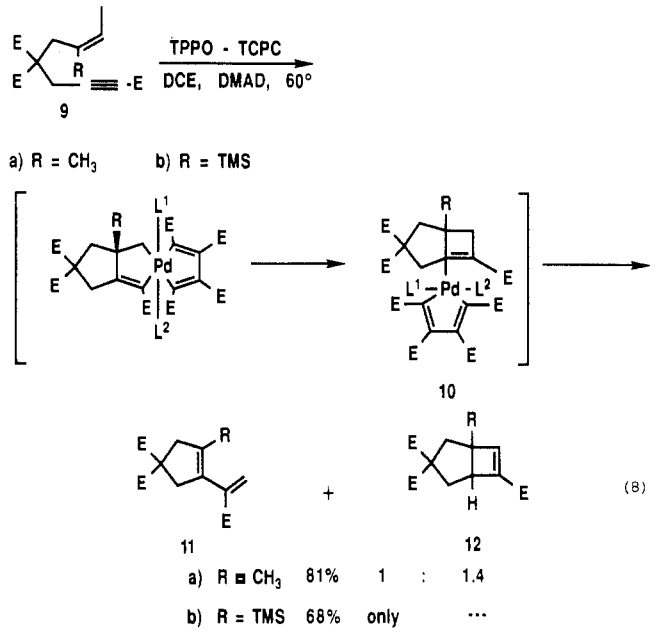
the two novel cycloisomerization products **11a** and **12a** (eq 8).[20,21] A most reasonable interpretation invokes



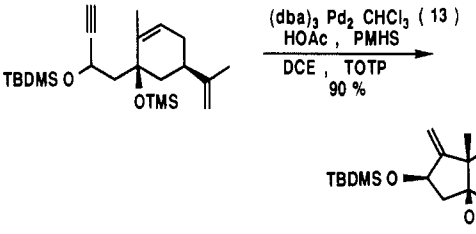
(8)

the formation of the 1,1-reductive elimination product **10**, which undergoes either conrotatory opening to diene **11** or hydrogen migration to form cyclobutene. Replacing the vinylic methyl group by a trimethylsilyl group enhances electrocyclic ring opening and produces the rearranged diene **11** as the exclusive product. The potential utility of dienes like **11** in synthesis makes this novel cyclorearrangement quite an interesting new route into such compounds.

Hydridopalladation Catalyst: Reductive Enyne Cyclizations and Semihydrogenation of Acetylenes

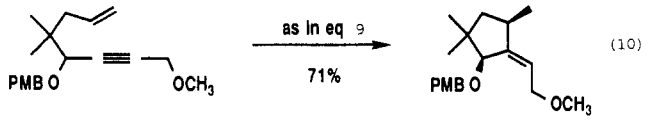
A test for Scheme II requires an independent generation of the supposed hydridopalladium acetate. Although the oxidative addition of hydrochloric[22] and trifluoroacetic[23] acids to some palladium(0) complexes is known, attempts to observe an analogous reaction with acetic acid failed. Nevertheless, addition of dimethyl geranylpropargylmalonate **6** (eq 6) to a catalytic amount of tris(dibenzylideneacetone)dipalladium–chloroform complex (**13**), acetic acid, and tri-*o*-tolylphosphine (TOTP) produces the same cyclized product **7** with even higher regioselectivity in 69% yield and in 86% yield in the absence of the phosphine ligand.

Interception of the σ-bonded palladium intermediates of Scheme II would validate the proposed catalytic cycle. Since interception after ring formation would represent a particularly useful synthetic transformation, efforts were directed toward a reductive cyclization in which a hydride is a trap. Among the various possible hydride donors, a silicon hydride (polymethylhydrosiloxane, PMHS) proved most efficacious, as shown in eq 9.[24]



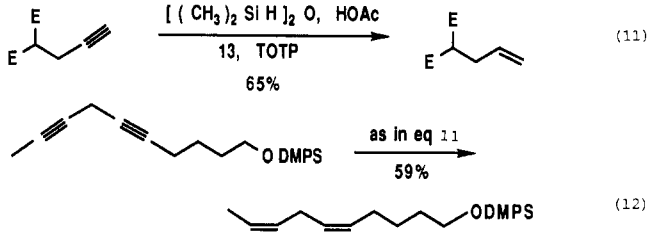
(9)

This reductive cyclization proved general and can show good 1,3-diastereoselectivity (eq 10), but surprisingly showed little 1,2-diastereoselectivity.[25] Deuterium labeling established a sequence in accordance with Scheme II.[24]



(10)

In the absence of the possibility of cyclizing, a simple 1,2-reduction of acetylenes should be possible. Indeed, both terminal (eq 11) and internal (eq 12) acetylenes undergo rapid semihydrogenation in what should prove to be a very convenient general laboratory procedure.[26]



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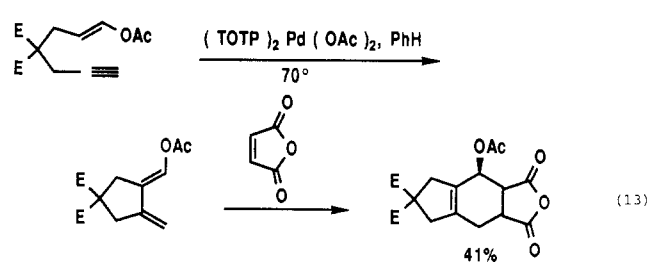
(12)

1,3-Diene Syntheses

An interesting prediction of both reaction mechanisms is the suggestion that 1,3- and 1,4-dienes may result from this metal-catalyzed cycloisomerization by migration of a vinylic rather than allylic hydrogen (see Schemes I and II). The utility of such intermediates as partners in Diels–Alder reactions makes this possibility particularly attractive. To test the feasibility of this approach, a substrate that lacked a vinylic hydrogen was subjected to a catalytic amount of bis(tri-*o*-tolylphosphine)palladium acetate (eq 13) and the resultant diene immediately subjected to maleic anhydride, which produced the tricycle in a very simple protocol.[27] The palladium-catalyzed cycloisomerization



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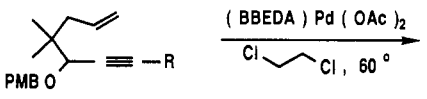
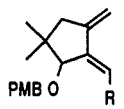
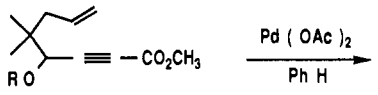
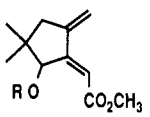
proves to be a very efficient and general diene synthesis. Cyclization of substrates bearing substituents on the acetylene terminus benefits by the employment of *N,N'*-bis(benzylidene)ethylenediamine (BBEDA) as ligand (eq 14). Substituents ranging from strong





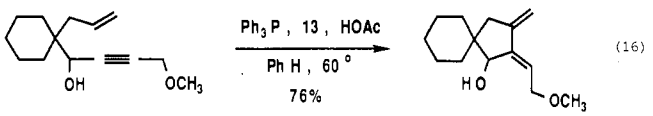
a)	R= $COCH_3$	67%	
b)	R= TMS	89%	
c)	* R= CH_2OCH_3	77%	(14)
d)	R= $CH_2CH_2OCH_3$	96%	
e)	R= CH_3	88%	
f)	R= OC_2H_5	32%	



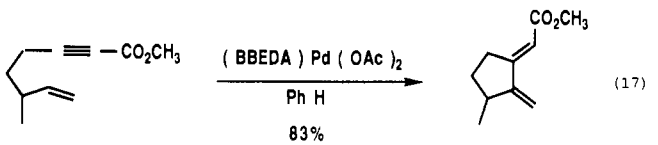


a)	R = H	50%	
b)	R = TMS	70%	
c)	R = TBDMS	71%	(15)
d)	* R = Ac	57%	

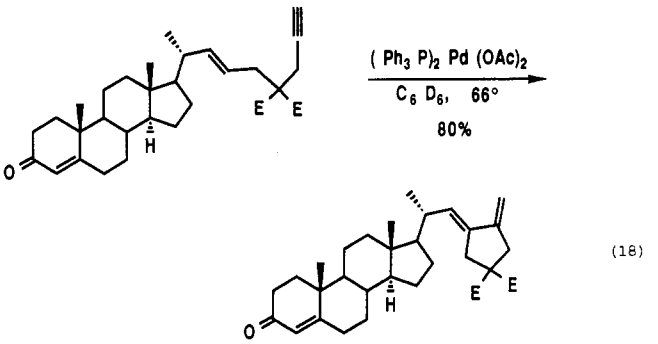
electron-withdrawing to electron-donating groups, as shown in the series **14a–f**, do not perturb the reaction.[28] The sensitivity of the reaction to alcohol functionalities was examined in the related substrate **15** (eq 15) for which palladium acetate itself was normally the preferred catalyst.[29] The compatibility with everything from the free alcohol to a propargyl carboxylate attests to the high chemoselectivity of this process. It is interesting to note that the use of the palladium(0) complex **13** in conjunction with acetic acid fails to effect any reaction with substrates like **15**. Thus, at least in this case, palladium acetate cannot effect this reaction via a hydropalladation mechanism. Nevertheless, the palladium(0)-based catalyst systems do effect cyclizations to 1,3-dienes, as the formation of the spiro fused ring system of eq 16 attests.[30] While synthetic con-



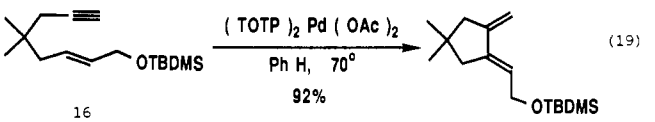
venience has frequently led to the substrates containing geminal substituents in the trimethylene chain, eq 17 emphatically demonstrates that such substitution is not required for successful cyclization.[31]



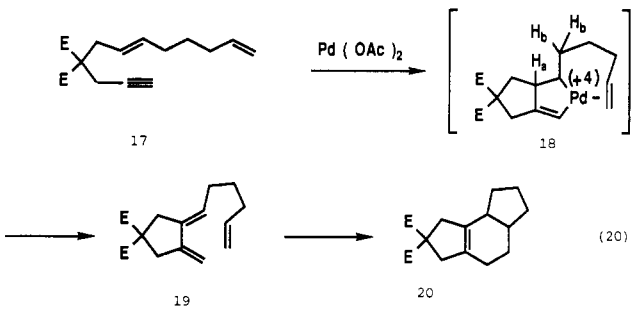
An important broadening of this synthesis arose because of the effect of substituents on the regioselectivity even when an allylic hydrogen, whose migration can lead to the 1,4-dienes, was present. A branch at this allylic position totally directs the reaction to form the 1,3-dienes (eq 18).[5] Even more dramatic is the effect



of a single oxygen substituent, as in **16** (eq 19).[32] The origin of this regioselectivity most reasonably derives from an inductive effect of oxygen and not by its coordination to palladium, since inserting an additional methylene spacer creates a substrate that strongly favors the 1,4-diene over the 1,3-diene.[33]



A most intriguing alternative mechanism for regiocontrol derives from the effect of a remote binding group, as in substrate **17**. Adopting the mechanism of Scheme I suggests that the palladacycle **18** would bind to the remote site of unsaturation, whereby fixing the conformation such that the >90° dihedral angle between C–H_b and C–Pd precludes formation of the 1,4-diene and only permits insertion into C–H_a to form the conjugated 1,3-diene **19**. Indeed, this product can be isolated in 76% yield.[21] Since it is ideally set up for an intramolecular Diels–Alder reaction, thermolysis provides the tricycle **20** (eq 20). From a practical point of view, a one-step conversion of acyclic precursor **17** into tricyclic **20** occurs in 72% yield simply by heating the former with 5% palladium acetate in toluene at 110 °C.



An alternative strategy for the synthesis of 1,3-dienes devoid of any structural ambiguities extends the palladium-catalyzed reductive cyclization to 1,6-diynes. The choice of silane determines the timing of the hydride transfer and, therefore, the success of the reaction. For this application, triethylsilane has proven to be superior.[34,35] Equation 21 and 22 illustrate that virtually unsubstituted as well as heavily substituted substrates cyclize in excellent yields. Considering the likely mechanism of this reaction suggested the feasi-

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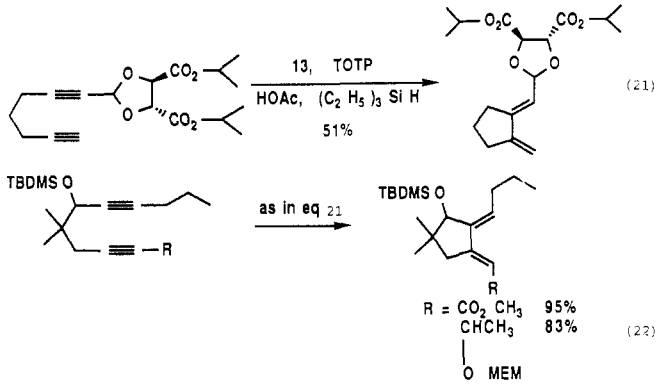
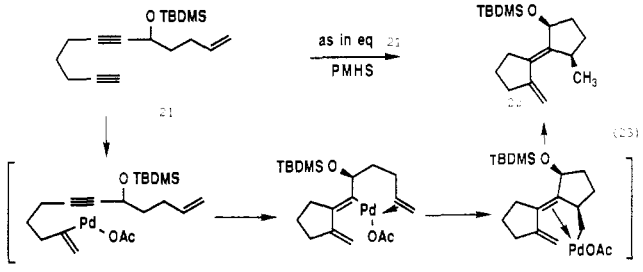
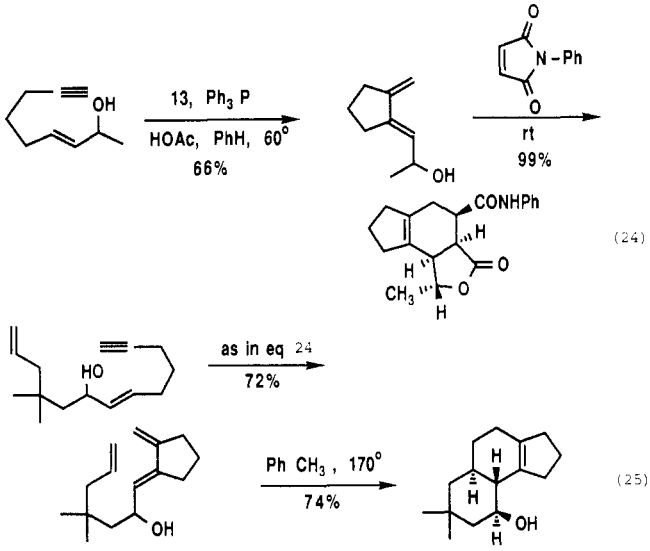
(30) Trost, B. M.; Lee, D. C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651.
(31) Trost, B. M.; MacPherson, D. T. *J. Am. Chem. Soc.* **1987**, *109*, 3483.
(32) Trost, B. M.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1985**, *107*, 4586.
(33) Trost, B. M.; Chan, C. To be published.
(34) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 7255.
(35) Cf.: Burns, B.; Grigg, R.; Sridharan, V.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 4325.



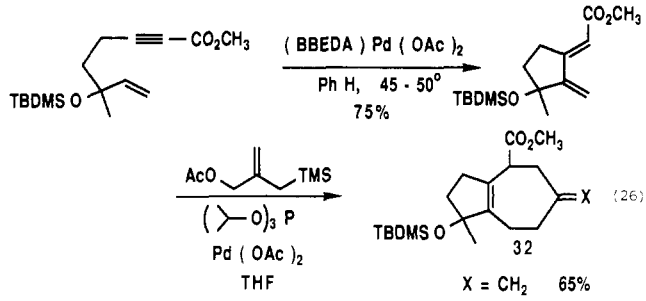
bility of a cyclization cascade to form polycycles. Indeed, the simply constructed enediyne **21** cyclizes to the bicycle **22** with good diastereoselectivity (diastereomeric ratio 7:1) (eq 23), presumably through the sequence of intermediates depicted.



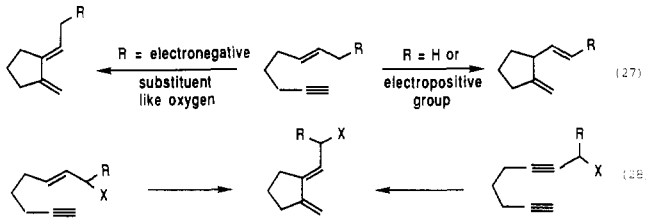
A major feature of these dienes is their potential for further structural elaboration. Most obvious is their employment in both intermolecular (eq 24) and intramolecular (eq 25) Diels–Alder reactions in which the



hydroxyl group plays the role of a regiochemical control element for the enyne cyclization and a diastereochemical control element for the Diels–Alder reactions.[36] Alternatively, a palladium-catalyzed [4 + 3] cycloaddition permits rapid construction of a polyhydroazulene **23** (X = CH_2, eq 26).[31] Chemoselective oxidative cleavage of the exocycle double bond with benzyltriethylammonium permanganate to ketone **23** (X = O) equates the sequence to an equivalent of a 2-oxyallyl dipolar cycloaddition. Thus, in two steps, complex polycyclic systems derive from totally acyclic

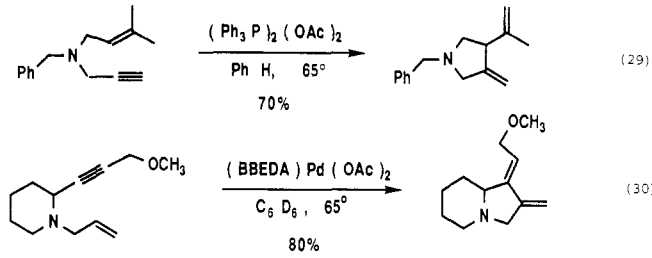


ones. Equations 27 and 28 exemplify the generalizations with respect to regioselectivity in these palladium-catalyzed reactions.

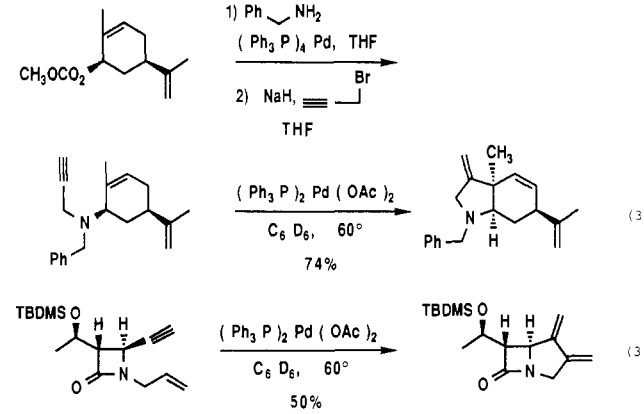


Heterocycle Synthesis

The incorporation of heteroatoms, which frequently has been the Achilles' heel of many metal-catalyzed reactions, in the intervening chain provides a novel strategy toward usefully functionalized heterocycles. Equation 29 and 30 illustrate that incorporation of a nitrogen does not affect the regioselectivity rules exemplified in eqs 27 and 28.[37] The ability of amines to



participate as nucleophiles in Pd(0)-catalyzed allylic alkylation combined with the Pd(2+) cycloisomerization creates a versatile heterocycle annulation (eq 31). Formation of a carbapenem highlights the high intrinsic selectivity and the ability to form a strained ring (eq 32), as well as generate an important ring skeleton.

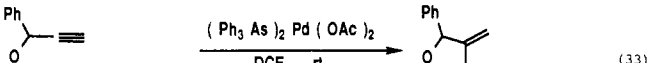


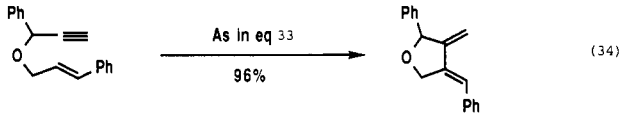
Extension to the formation of tetrahydrofurans proved surprisingly capricious, in part due to the sensitivity of the products. Nevertheless, with appropriate

(36) Trost, B. M.; Lee, D. C. *J. Org. Chem.* **1989**, *54*, 2271.

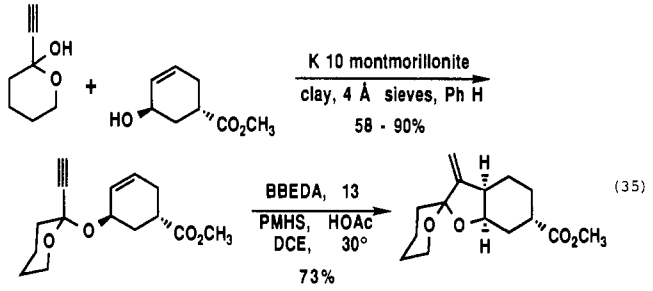
(37) Trost, B. M.; Chen, S. F. *J. Am. Chem. Soc.* **1986**, *108*, 6053.

ligands, good to excellent yields of both types of diene products (eqs 33 and 34) are obtained.[38] The latter should prove to be a particularly useful strategy toward such varied biologically active natural products as the furofurans and podophyllotoxins.



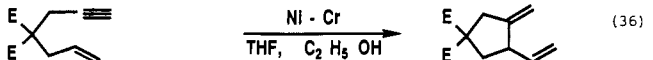


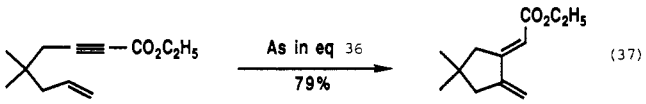
The reductive cyclization extends to heterocycle construction. In a study directed toward the antitumor agent phyllanthocin, a highly convergent strategy emerges in which the requisite substrate derives from a transacetalization and the final bond of the complete phyllanthocin ring system from the reductive enyne cyclization (eq 35). The stereochemistry of the anomeric center equilibrates to that corresponding to the natural product under thermodynamic conditions.



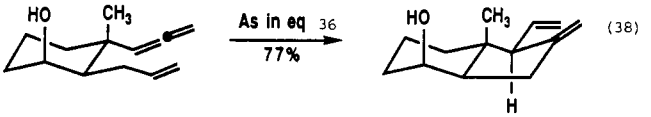
A Ni–Cr Catalyst System. Cycloisomerization of Enallenes

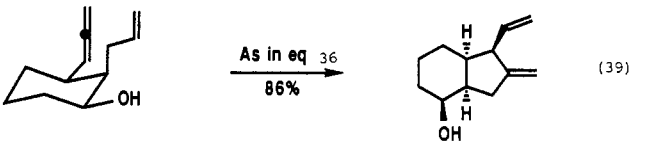
A search for alternative metal catlysts that can effect cycloisomerization to both 1,3- and 1,4-dienes led to the development of a novel nickel–chromium system.[39] To maintain catalytic activity, site isolation by heterogenizing the catalyst on an insoluble phosphinylated polymer is required. Both 1,4-dienes (eq 36) and 1,3-dienes (eq 37) are produced. The success of the cyclization of the ynoate (eq 37) parallels the reactions with palladium acetate and contrasts with the inability of the Pd(0)–acetic acid catalyst to effect such reactions.



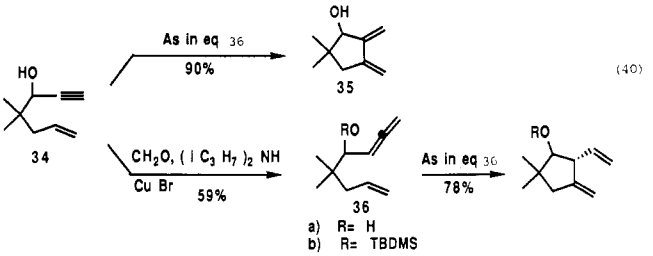


A key feature of this catalyst system is its ability to effect cyclization of enallenes which generate unambiguously the 1,4-diene-type ring systems with high diastereoselectivity (eqs 38 and 39).[40] In the latter case, the thermodynamically less stable isomer with the vinyl group preferring to be on the concave face of the molecule dominates (diastereomeric ratio 15:1).



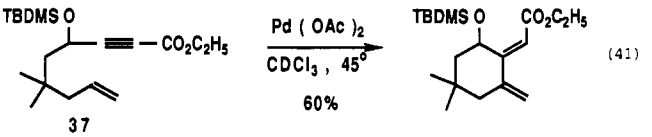


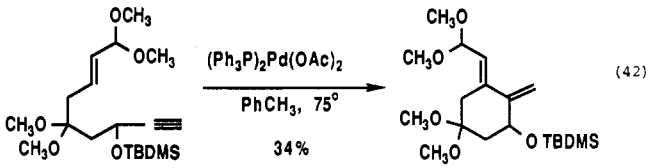
The availability of the enallenes by a novel one-carbon homologation[41] allows a single type of substrate to generate both 1,3- and 1,4-diene-type products. For example, direct cyclization of the enyne **24** produces the 1,3-diene **25** (eq 40). Alternatively, the corresponding allene **26a** is readily available by reacting with a Mannich reagent in the presence of cuprous bromide. While cyclization of the alcohol **26a** succeeds, higher diastereoselectivity (diastereomeric ratio >99:1) occurs upon using the silyl ether **26b** (eq 40).



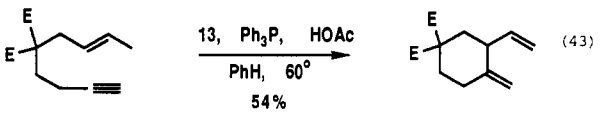
Cyclohexane Formation

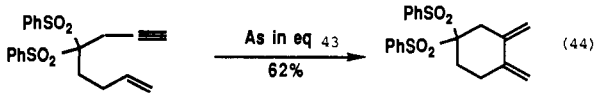
While the cycloisomerization proceeds most generally in the case of five-membered-ring formation, six-membered rings do form (eq 41).[42] In a program directed toward the synthesis of vitamin D metabolites, the synthesis of the A ring envisions the cyclization of eq 42.[43] The modest yield stems in part from the sensitivity of the substrate.





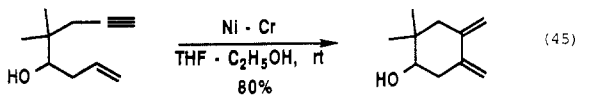
The Pd(0)–acetic acid catalyst proceeds somewhat better for the construction of six-membered rings to form both 1,4-dienes (eq 43) and 1,3-dienes (eq 44).[30]



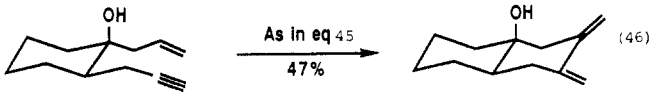


(38) Trost, B. M.; Edstrom, E.; Carter-Petillo, M. B. *J. Org. Chem.*, in press.
(39) Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 5268.
(40) Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 5231.
(41) Searles, S.; Li, Y.; Nassim, B.; Lopes, M. T. R.; Tran, P. T.; Crabbé, P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 747.
(42) Trost, B. M.; MacPherson, D. T. *Unpublished* observations.
(43) Trost, B. M.; Villa, M. Unpublished observations. Cf.: Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098.

The difficulty for formation of six-membered rings is ascribed to the poorer ability of 1,7-enynes to function as bidentate ligands to palladium. The development of the nickel catalyst was motivated by the notion that such coordination may be more facile and thereby may promote the cycloisomerization to six-membered rings. Indeed, the cyclization of eq 44 proceeds in 80% yield with the Ni–Cr catalyst in contrast to 62% with the palladium system.[39] Equations 45 and 46 further illustrate that, with the Ni–Cr system, six-membered rings form with equal facility to five-membered rings. The Ni–Cr system, however, cannot tolerate additional substitution on either the olefin or the acetylene.

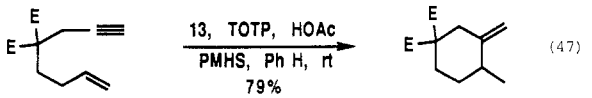


(45)



(46)

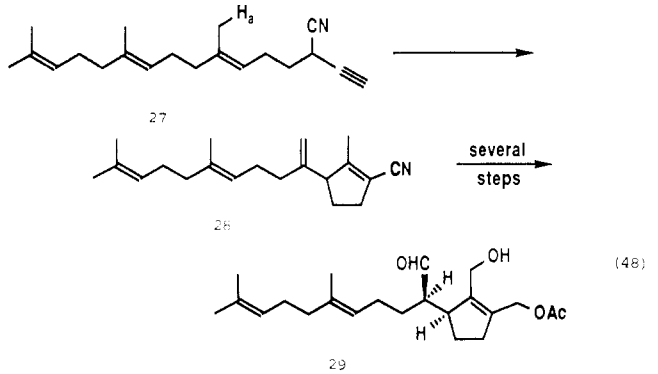
Reductive cyclization to form a six-membered ring is also possible, as illustrated in eq 47.[24] While at present six-membered-ring formation is not as general as that of five, it clearly is successful in many cases. Further improvement in catalyst design to broaden the scope of the reaction with respect to ring size continues as a major challenge.



(47)

Complex Molecule Synthesis

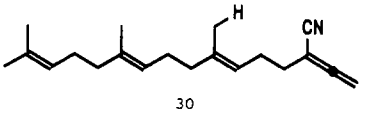
The ability to devise concise synthetic strategies toward complex molecules helps establish the utility of methodology. Petiodial (**29**),[44] a constituent of the extracts of a marine alga of the family Udoteaceae, which has shown antimicrobial, cytotoxic, and ichthyotoxic properties, represents an early target. While the carbon skeleton and olefin geometry were established, neither the relative nor absolute stereochemistry was known, the former becoming a goal of synthesis. Farnesyl bromide served as a convenient precursor to the requisite enyne **27**.[45] Regioselective cycloisomerization occurred with palladium acetate in warm benzene in which only the product of migration of H_a in **27** is observed (eq 48). The formation of the unexpected en-



(48)

29

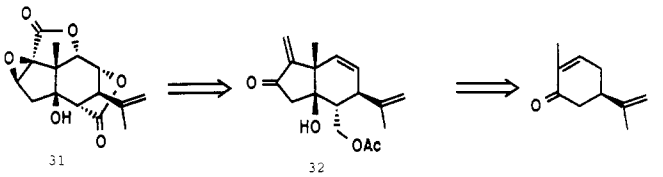
docyclic cyclopentyl olefin depicted in **28** occurs, not as a result of the anticipated exocyclic olefin isomerizing under the reaction conditions but because the starting material isomerizes to the allene **30**, which then



30

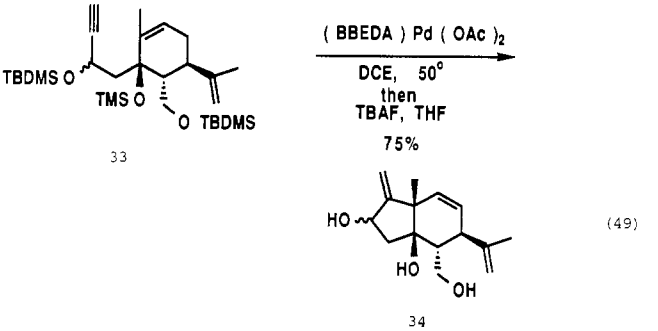
smoothly cyclizes directly to the illustrated product. This cycloisomerization is the only example of a palladium-catalyzed enallene cyclization. Subsequent work reaffirmed this relative stereochemistry and established the absolute stereochemistry as well.[46]

The picrotoxins constitute a more formidable challenge. In a recent synthesis of picrotin and picrotoxinin (**31**), the bicyclic compound **32** served as an interme-



31 32

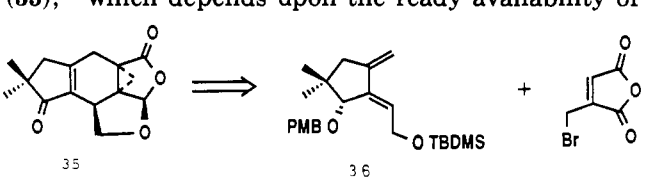
diate which the authors synthesized in 27 steps from carvone.[47] The cycloisomerization allows an alternative strategy involving enyne **33**, which is available in eight steps from carvone.[48] The development of the BBEDA ligand proved crucial for this cyclization, which proceeded virtually quantitatively. The yield for the two steps of eq 49, which included desilylation, reflects the



(49)

difficulty in isolating the very polar triol **34**. Allylic oxidation and acetylation completes the synthesis of intermediate **32** in a total of 12 steps, less than half the number of the literature route. It is important to note not only the mildness of the metal-catalyzed conditions but also the fact that thermal conditions for this Alder–ene reaction completely fail!

The 1,3-dienes available from the cycloisomerization prove to be equally, if not more, usful as synthetic intermediates. A particularly noteworthy example is the synthesis of the unusual sesquiterpene sterepolide (**35**),[49] which depends upon the ready availability of

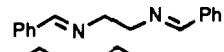
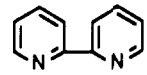
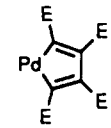
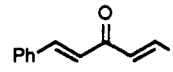
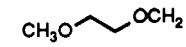
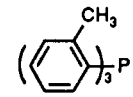
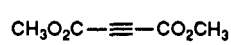
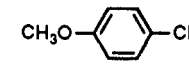
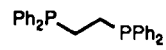


35 36

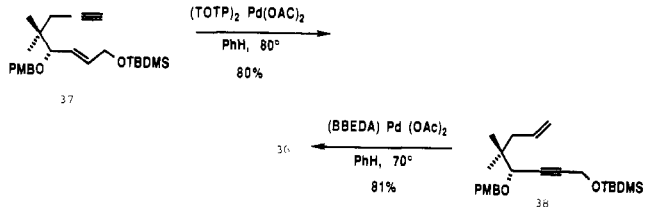
diene **36**, since its Diels–Alder reaction with (bromo-

(44) Paul, V. J.; Fenical, W. *Tetrahedron* **1984**, *40*, 2913. Fattorusso, E.; Magno, S.; Mayol, L.; Novellino, E. *Experentia* **1983**, *39*, 1275.
(45) Trost, B. M.; Matsuda, K. *J. Am. Chem. Soc.* **1988**, *110*, 5233.
(46) Isoe, S.; Ge, Y.; Yamamoto, K.; Katsumura, S. *Tetrahedron Lett.* **1988**, *29*, 4591.
(47) Miyashita, M.; Suzuki, T.; Yoshikoski, A. *J. Am. Chem. Soc.* **1989**, *111*, 3728.
(48) Trost, B. M.; Jebaratnam, D. J.; Thomas, A.; Haffner, C. D. To be published.
(49) Ayer, W. A.; Browne, L. M. *Tetrahedron* **1981**, *37*, 2199.

Chart I

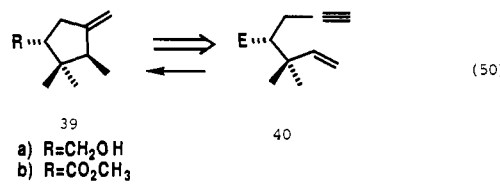
BBEDA		E	CO_2CH_3	TBAF	$(n\text{-}C_4H_9)_4N,F$
Bby		FVT	flash vacuum thermolysis	TBDMS	$(CH_3)_3C(CH_3)_2Si$
Cp		L	ligand	TCPC	
dba		MEM		TMS	$(CH_3)_3Si$
DCE		Ms	CH_3SO_2	TOTP	
DMAD		PMB		TPPO	$(PhO)_3P$
dppe		PMHS	polymethylhydrosiloxane		

methyl)maleic anhydride constructs the entire carbon skeleton with proper juxtaposition of functionality to allow easy completion of the synthesis of sterepolide. Indeed, the cyclization of enyne **37**, available in only three steps from isobutyraldehyde, exhibits the oxygen effect on regioselectivity and gives rise exclusively to the 1,3-diene **36**. The subsequent Diels–Alder reaction



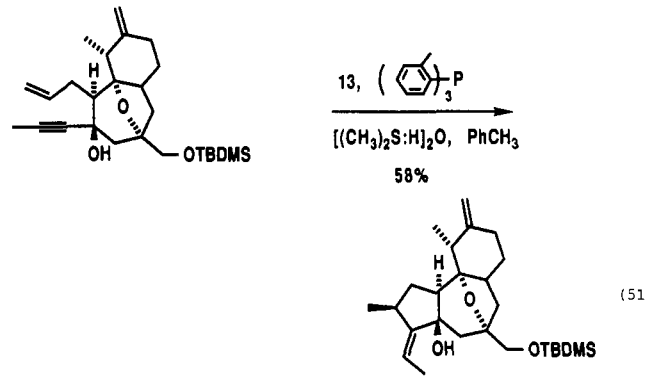
and minor structural modifications require five steps (overall nine steps from isobutyraldehyde) to complete this synthesis.[32] Approaching the synthesis of diene **36** by the cycloisomerization of enyne **38**, which requires the BBEDA ligand, provides a facile asymmetric synthesis[28] since **38** is available in enantiomerically pure form by the asymmetric reduction of the corresponding ketone.[50] This route proceeds in 10 steps from the known 2,2-dimethyl-4-pentenoyl chloride[51] with an overall yield of 34%!

The reductive cyclization has provided a strategy toward the phyllanthocin system,[52] the aglucon of the important antitumor agent phyllanthoside (vide supra). Exploration of the diastereoselectivity of this process provided a simple strategy toward the beetle pheromone β-necrodol (**39a**) (eq 50).[53,54] Trimethylsilane in conjunction with the standard catalyst system [TOTP, $(dba)_3Pd_2{\cdot}CHCl_3$, HOAc, PhH] gave the desired cyclized product in a 5:1 diastereomeric ratio in which the *E* isomer **39b** dominated. Simple LAH reduction completed the synthesis in a total of five steps.



(50)

The availability of the reductive cyclization, as applied in eq 51, permitted the design of a synthesis of phorbol myristate acetate[55] which shortened the previous route by 11 steps![56,57]



(51)

The syntheses completed begin to show the utility of this new methodology. Clearly, strategies that otherwise would not exist become possible, and from them enhanced efficiency. The high selectivity, especially regioselectivity by subtle electronic and conformational factors that mimic enzyme–like behavior, impart versatility and power to this method.

Some Alternative Processes

The cyclization of enynes and diynes with low-valent zirconium[10] and titanium[11] provides some similar processes but requires stoichiometric employment of metals and requires nonterminal acetylenes, as well as other applications such as cyclopentenone syntheses, the latter also possible via a related cobalt-based process (known as the Pauson–Khand reaction).[9,58] Cobalt-mediated cyclooligomerizations provide one-step

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transformations of acyclic molecules into polycyclic systems but at a higher oxidation level than the sequence of cyclization to a 1,3-diene followed by intramolecular Diels–Alder reaction.[59]

A metalloene reaction has proven to be an effective version of the Alder–ene process.[60] Catalytic versions using both palladium[60,61] and nickel[62] catalysts have been reported. Of special note is a cycloisomerization that employs the metalloene reaction as a key step.[63] Variations of the Heck reaction have triggered cyclizations.[64,65] Iron catalysts have effected vinylogous ene reactions of 1,7,9-trienes.[66] Among non transition metal catalyzed processes, free-radical reactions offer versions of cycloisomerizations.[67] Cyclization via an allyl radical onto an acetylene constitutes the radical version of forming an ene-type product.[68] An enyne cyclization initiated by addition of a tin radical to the acetylene complements the reductive cyclization catalyzed by palladium.[69] The rather high dilution required in these radical cyclizations detracts from their practicality.

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Future Prospects

Cycloisomerizations, represented by classical reactions like the intramolecular versions of the Diels–Alder and Alder–ene reactions, constitute the most economical use of material in ring-forming reactions. Catalysis of such processes offers the major benefits of faster reactions at lower temperatures. The palladium chemistry and nickel–chromium chemistry recorded herein clearly achieve this goal but also do much more. Reactions that fail thermally now succeed. Selectivity, using the same basic principles employed by enzymes, provides control not possible thermally. Most significantly, related reactions not achievable by the thermal method, such as 1,3-diene formation, are now possible. Opportunities for new inventions emanating from proposed mechanistic possibilities abound. New catalysts that extend the sequence to larger rings can provide a real opportunity for macrocycle formation at high concentration using pseudo-high-dilution techniques. Such a prospect provides major impetus to discover other candidates for cycloisomerizations.

Glossary of Abbreviations

To streamline the presentation, a variety of abbreviations have been employed, some quite standard and others not as common. A glossary is included in Chart I to aid all readers.

We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences Institute, for their generous support of our programs. A special appreciation goes to my collaborators, individually acknowledged in the references, for their many contributions, intellectual and experimental, to this exciting area.

Registry No. Pd, 7440-05-3.