PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

Transition Metal Templates as Guides for Cyclizations [and Discussion]

B. M. Trost and M. T. Reetz

Phil. Trans. R. Soc. Lond. A 1988 **326**, 511-524
doi: 10.1098/rsta.1988.0103

Phil. Trans. R. Soc. Lond. A **326**, 511–524 (1988)
Printed in Great Britain

Transition metal templates as guides for cyclizations

By B. M. Trost

Department of Chemistry, Stanford University, Stanford, California 94305, *U.S.A.*

The improvement of synthetic efficiency requires the development of more chemo-, regio-, diastereo- and enantioselective methods. Transition metal templates form the equivalent of an 'active site' to impose selectivity upon reacting organic systems. Such effects will be examined within the context of cyclization reactions.

The first part examines cyclization reactions invoking intramolecular carbametallation. Catalytic reactions involving at least three different mechanisms and two different metals provide five- and six-membered rings from enynes and diynes.

A second strategy invokes transition metal templates to facilitate macrocyclization. Formation of macrocarbocycles, macrolactones and macrocyclic ethers and amines illustrates the versatility of this approach. Most importantly, many of the macrocyclizations proceed at normal concentrations of 0.25–0.50 M.

The third strategy invokes cycloadditions. A transition metal equivalent to the Diels–Alder reaction permits formation of odd membered rings by $[2n+3]$ cycloadditions for $n = 1$, 2 and 3.

The applicability that such methods have in devising new synthetic strategies towards biologically important natural products will be illustrated.

Introduction

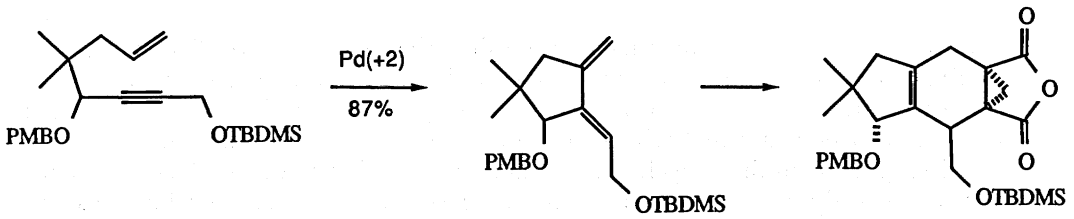
Enhanced chemo-, regio-, diastereo- and enantioselectivity provides a key to more effective routes for construction of complex organic structures. The widespread importance of cyclic structural units leads to a continuing search for effective reactions for their construction. The development of new types of reactivity with its corresponding selectivity offered by the ability of transition metal complexes to serve as 'activation sites' provides an opportunity to probe new approaches for ring formation.

Ring construction may occur by formation of one bond by using an acyclic precursor that bears reaction functionality at the termini to be joined. An important example is the cyclization of α,ω-dicarbonyl compounds via the aldol condensation: the second stage of the Robinson annulation. Cyclizations involving multiple-bond formation, as represented by the Diels–Alder reaction, represent particularly powerful tools for ring construction. We have undertaken an investigation of how transition metal chemistry may impact both of these strategies.

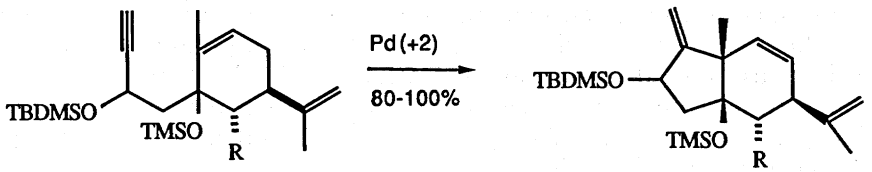
Intramolecular carbametallation

The addition of a carbon–metal bond across an unsaturated carbon–carbon bond is called a carbametallation. In most cases, such reactions involve stoichiometric amounts of highly reactive organometallic intermediates, which limits their chemoselectivity. Coordination of transition metal templates to unsaturated carbon–carbon bonds activates relatively stable functional groups in the presence of most other functional groups, most noteworthy carbonyl and hydroxy (Nugent & Calabrese 1984; Negishi *et al.* 1987; Negishi 1987).

We have found that 1,6-enynes undergo remarkably facile cyclizations to create either 1,3-dienes (scheme 1) or 1,4-dienes (scheme 2) (Trost & Lautens 1985*a*). As shown in scheme 1 (Trost & Chung 1985), the 1,3-dienes are important reaction partners for the Diels–Alder reaction and serves as a very short entry into the isolactaranes. The latter example (Trost & Jebaratnam 1987) illustrates the construction of the picrotaxane skeleton, a growing class of natural products whose high bioactivity has led to great interest in their construction.

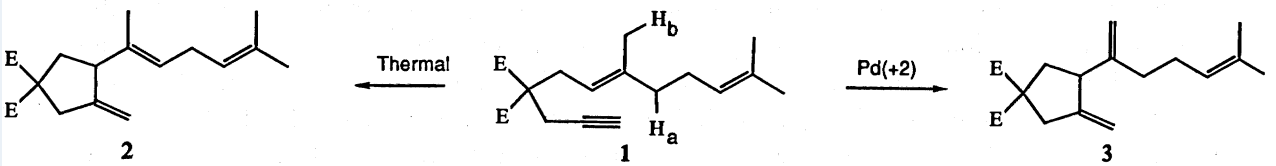


Scheme 1



Scheme 2

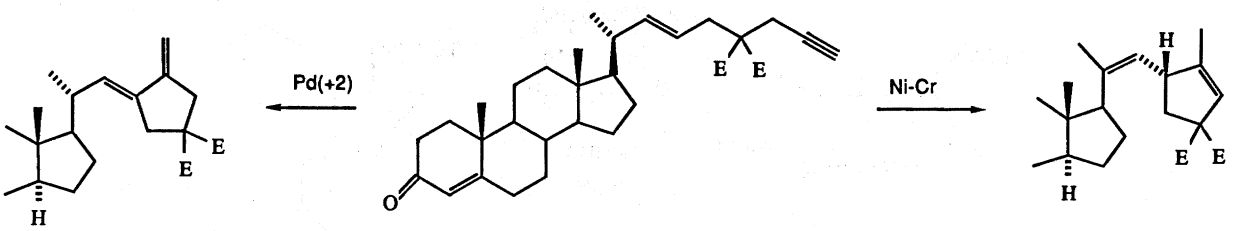
An intriguing feature of this metal templated approach is its ability to exercise control of subtle selectivities. For example, cyclization of the enyne **1** (scheme 3) proceeds thermally to produce the cyclopentane **2** in which H_a transferred but involves transfer of H_b with production of the regioisomeric olefin **3** under metal catalysed conditions (Trost & Lautens 1985*b*). Competitive studies reveal that the remote double bond is critical in establishing the regioselectivity of the metal-catalysed reaction. As in enzymatic reactions, the presence of a remote binding site alters the reaction conformation and, ultimately, the selectivity.



Scheme 3

The choice of metal catalyst may also affect the selectivity of this reaction. As shown in scheme 4, a polymeric Ni–Cr bimetallic catalyst also effects cyclization, but the cyclization product is regioisomeric to the one obtained in the Pd^{2+}-catalysed reaction (Trost & Tour 1987).

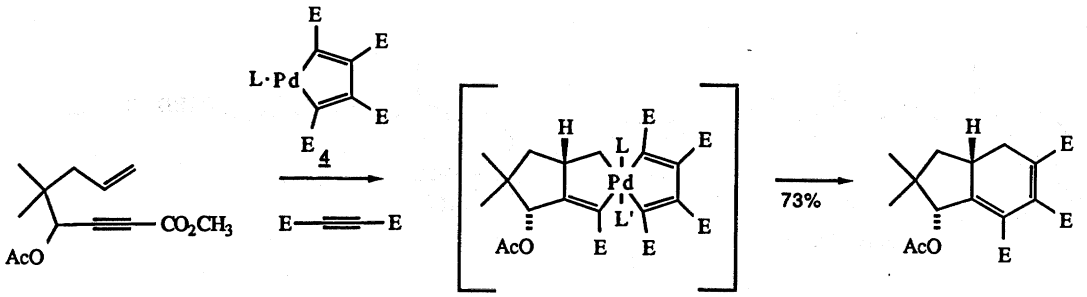
Understanding the mechanism of these reactions will undoubtedly enlighten us as to the source of such intriguing differences. Indeed, attempts to probe the mechanism of the Pd-catalysed reactions reveal that several pathways are clearly feasible and that more than one



SCHEME 4

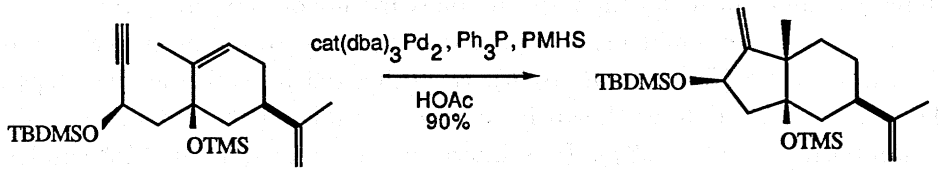
mechanism may be operating simultaneously. It has led to a rational design of new catalysts and the development of new reactions.

For example, the notion that a Pd^{4+} intermediate, as illustrated in scheme 5, may be involved led to the exploration of a Pd^{2+} catalyst such as **4** whose donor ligands on Pd may stabilize such an unfavourable oxidation state of the metal. Not only did this new catalyst prove efficacious in effecting our desired enyne cyclizations, but it also led to a catalytic [2+2+2] cycloaddition (Trost & Tanoury 1987).



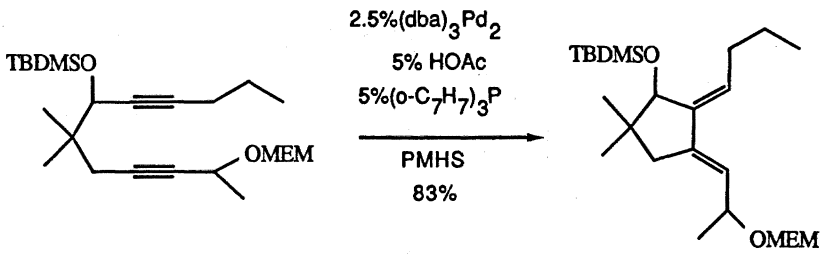
SCHEME 5

An alternative mechanism invokes the adventitious formation of a hydridopalladium complex as the active catalyst. Deliberate generation of such a catalyst by adding acetic acid to dibenzylideneacetone (DBA) palladium (0) not only catalyses the normal enyne cyclization, but it also led to the development of a reductive cyclization as shown in scheme 6 (Trost & Rise 1987). This reaction applies to diynes (scheme 7) and has led to a novel dicyclization (scheme 8) (D. C. Lee, unpublished results 1987).

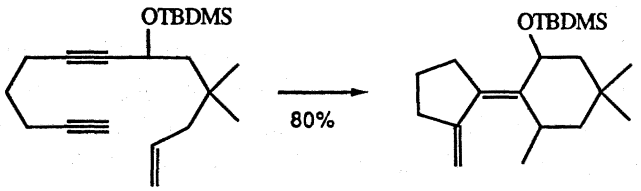


SCHEME 6

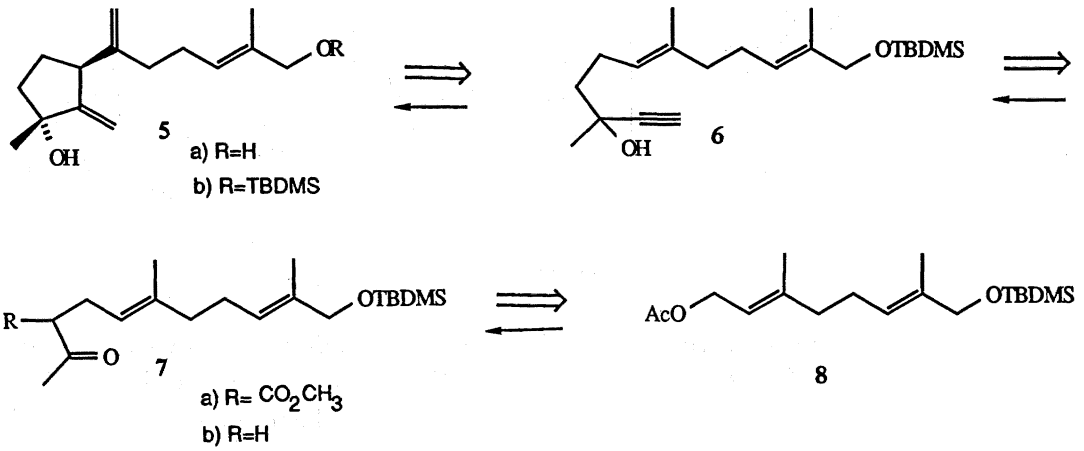
Two simple targets illustrate the ability to evolve short routes to natural products. Dehydrochokol C (**5**), an unsaturated analogue of the antifungal agent chokol C (Yoshihara *et al.* 1985), becomes available in only six steps from the hydroxylated geranyl acetate **8** (C. Chan, unpublished results 1987). Indeed, Pd^0-catalysed allylic alkylation proceeds with excellent regio- and stereocontrol to give only **7a** (87%). Addition of lithium trimethyl-



Scheme 7



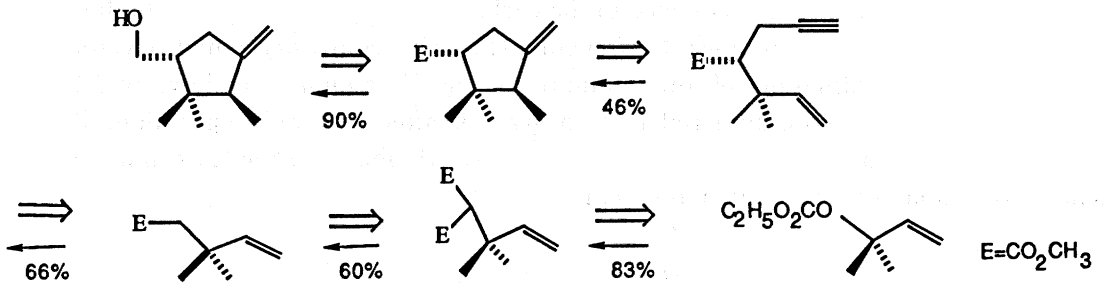
Scheme 8



Scheme 9

silylacetylide and desilylation gives the cyclization substrate **6**. Palladium acetate regio- and diastereoselectivity provides the requisite dehydrochokol C in 55% yield.

β-Necrodol, a cyclopentanoid monoterpenoid constituent of the defensive secretion of the red-lined carrion beetle (Eisner *et al.* 1986), is synthesized in as few as five steps from α,α-dimethylallyl ethyl carbonate as shown in scheme 10 utilizing the reductive cyclization (R. Braslau, unpublished results 1987). It is interesting to note that an Mo^0-catalysed allylic alkylation (Trost & Lautens 1982) was required to obtain the proper regiochemistry in the first step. Reductive cyclization with 2.5 mol% $(dba)_3Pd_2$:$CHCl_3$, 10 mol% tri-*o*-tolylphosphine, 2 equivalents of acetic acid and 10 equivalents of trimethylsilane in benzene at 0 °C gave predominantly (5:1) the *E*-isomer, which, upon LAH reduction, completed the necrodol synthesis. This templated cyclization provided the ability to control the diasteroselectivity of non-adjacent stereogenic centres.

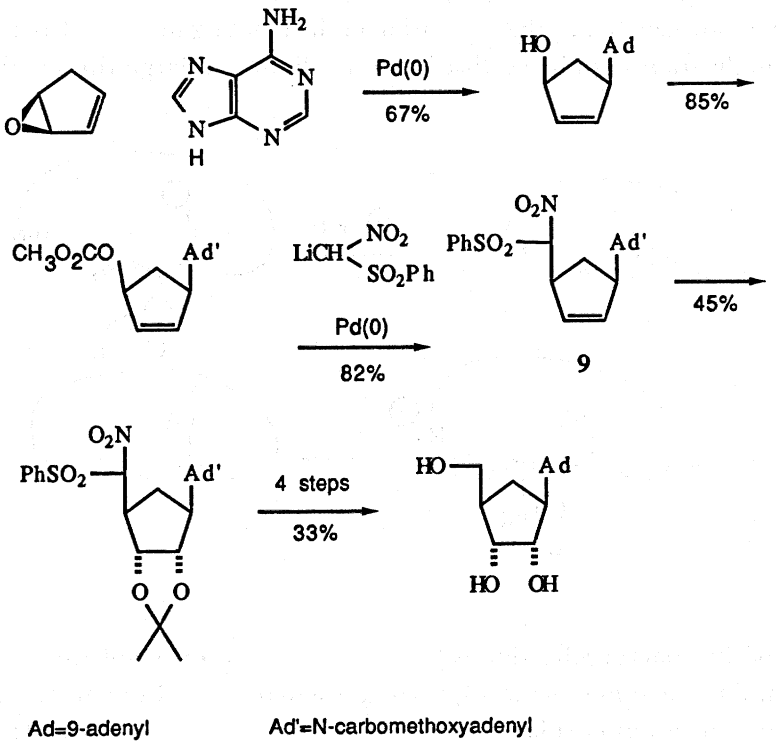


Scheme 10

An alternative cyclization via isomerization

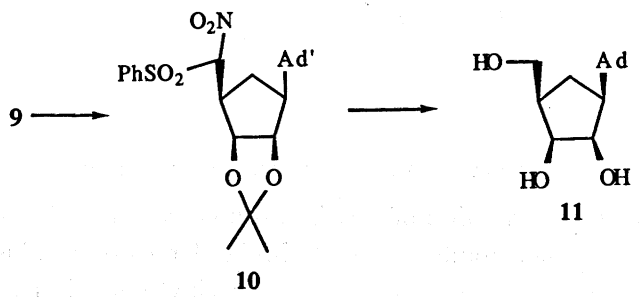
An intriguing strategy for formation of new bonds involves the Pd^0-catalysed condensation of vinyl epoxides with pro-nucleophiles (Trost & Molander 1981) as illustrated in scheme 11 (Trost *et al.* 1988). In this reaction, activation of the vinyl epoxide by the transition metal template generates the reactive electrophile and simultaneously a base. The latter, by deprotonation of the pro-nucleophile, creates the nucleophilic partner. The example of scheme 11 demonstrates how this totally neutral condensation reaction permits the fusion of cyclopentadiene monoepoxide and adenine on the way to the important antiviral and antitumor carbanucleosides, in this case aristeromycin.

In the course of this study, we uncovered a most interesting directive effect in the hydroxylation of the olefin of cyclopentene **9**. Hydroxylation of **9** with catalytic osmium



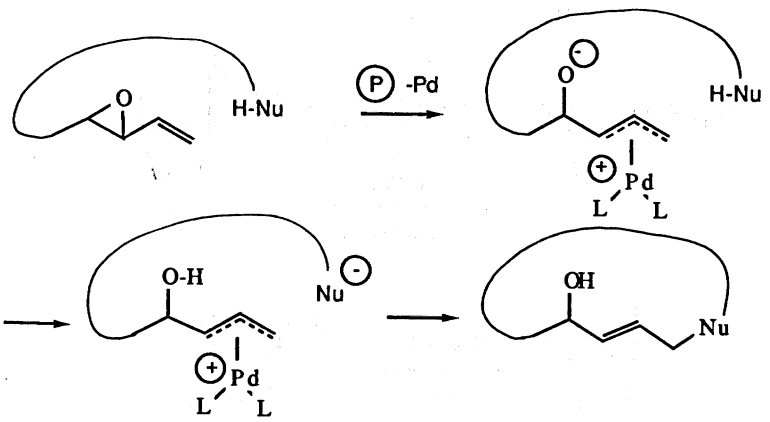
Scheme 11

tetraoxide and completing the sequence to the carbanucleoside did not generate the expected aristeromycin but its lyxo isomer **11** (scheme 12). The contrasteric hydroxylation arises because of the coordination of the osmium to the nitrosulfonyl moiety, which directs hydroxylation to the more-hindered face to give **10** after acetonide formation. Potassium permanganate hydroxylation permits a normal hydroxylation from the least-hindered face of olefin **9** to ultimately lead to aristeromycin.



Scheme 12

This type of reaction provides an excellent opportunity to resolve the problems of macrocyclizations as outlined in scheme 13 (Trost & Warner 1982, 1983). Because the cyclization involves simply an isomerization and since all the reactive functionality simply lies dormant until energized by the 'activation site', we can compartmentalize the reaction into a storage site and a reaction site by supporting the catalyst on an insoluble solid support. The substrate must first transfer from the bulk solution (its storage site) to an adsorbed phase on the solid support and then encounter a catalytic site (the activation site) before the events leading to cyclization can proceed. Thus, the separation of the reacting molecule from the bulk solution by compartmentalization permits cyclization to medium and large rings without resorting to high dilution.



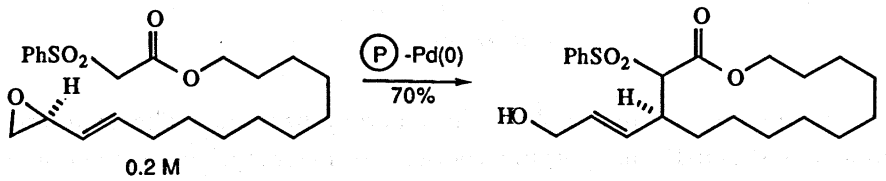
Scheme 13

An example of this macrocyclization is the creation of the 14-membered macrolide by C–C bond formation. As shown in scheme 14, a 70% isolated yield of the macrolide was obtained even at 0.2 M concentration of substrate (A. Dalla Cort, unpublished results 1987).

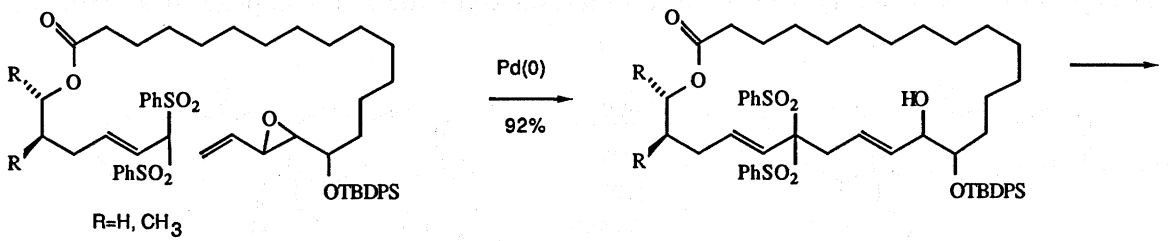
Very large rings can also be formed by this strategy. In studies directed towards the

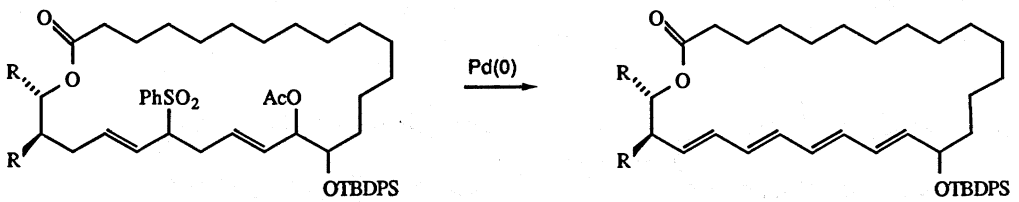
antifungal and antibiotic polyene macrolides, the 26-membered ring of scheme 15 was produced in 92% yield (Trost *et al.* 1986*a*). The juxtaposition of functionality created in this macrocyclization nicely sets up a final Pd^0-catalysed double elimination to generate the polyene of the macrolide.

Non-carbon nucleophiles can also be used in Pd^0-catalysed macrocyclizations. Schemes 16 and 17 illustrate the use of oxygen in the form of a carboxylate and phenoxide (C. M. Brzezowski, unpublished results 1987). It is interesting to note that for the latter, good regioselectivity only occurs when ethanol is used as solvent. Whereas vinyl epoxides normally

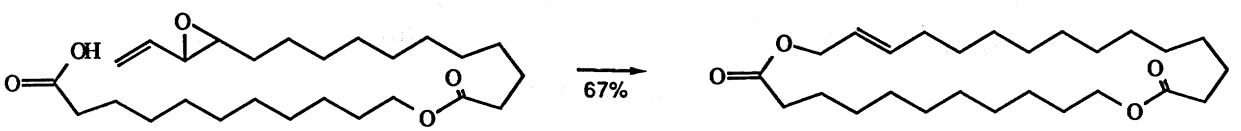


SCHEME 14

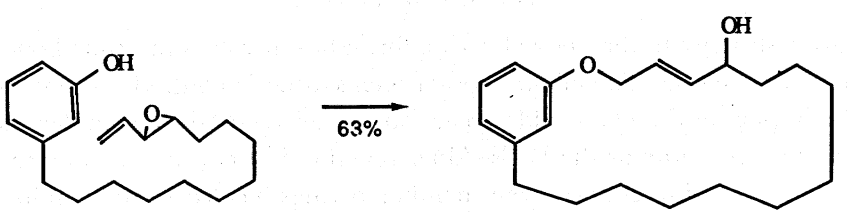




SCHEME 15

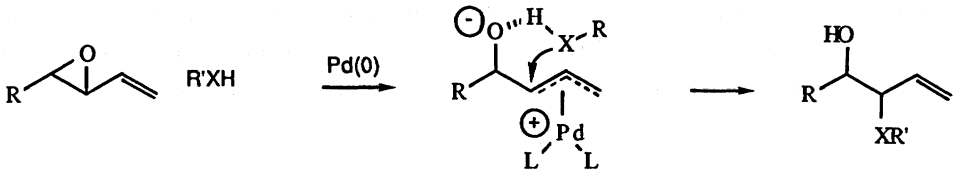


SCHEME 16



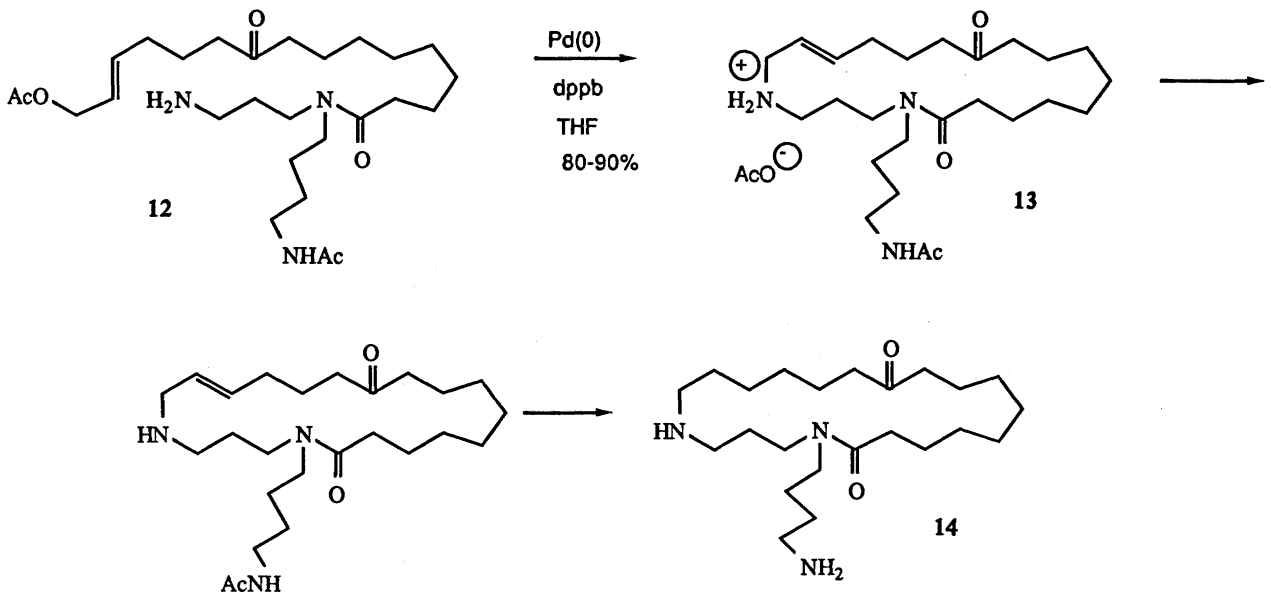
SCHEME 17

have an intrinsic preference for attack distal to the hydroxyl group, a hydrogen bond between the heteroatom nucleophile and the alkoxide directs such nucleophiles proximal to the oxygen in opposition to the electronic bias for distal attack (scheme 18). Use of an alcoholic solvent disrupts this templating effect and restores the intrinsic regioselectivity.



Scheme 18

Amines can also function as nucleophiles in macrocyclizations. The synthesis of the spermidine alkaloid inandenin-12-one (**14**) incorporates the macrocyclization via isomerization of **12**, which forms the isomeric salt **13** in excellent yields (scheme 19) (Trost & Cossy 1982). The susceptibility of this macrocyclic allylic ammonium salt to Pd^0-catalysed reactions makes this cyclization particularly delicate. Neutralization and hydrolysis completes this synthesis.



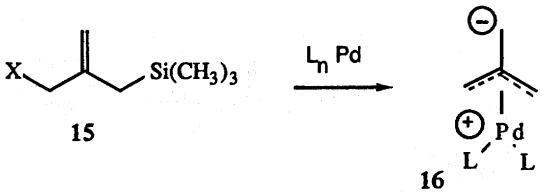
Scheme 19

Cycloadditions

An alternative strategy to the above for ring formation involves multiple bond formation in the act of ring construction. The advantages of such synthetic methods becomes obvious upon inspecting the impact of the Diels–Alder reaction on the synthesis of complex molecules. Can we invent reactions that mirror the Diels–Alder reaction but permit entries into different ring sizes? The importance of five- and seven-membered rings has led us to examine the role that transition metal templates may play in reaching such a goal.

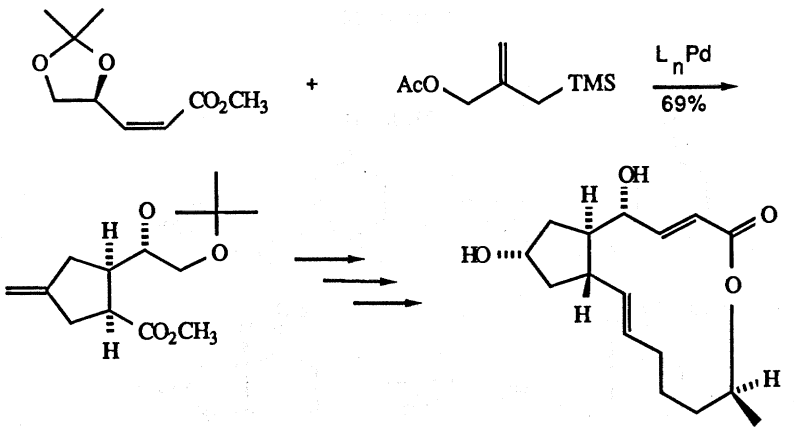
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

Trimethylenemethane would, at first glance, offer the possibility of cycloadditions to olefins to form five-membered rings, but initial experiments with iron complexes of such reactive intermediates proved extremely disappointing (Ehrlich & Emerson 1972). In considering ways to impart reactivity to such a species, the propensity of palladium to prefer a trihapto 16-electron state in the form of π-allylpalladium cations suggested that the palladium complex of trimethylenemethane would be polarized as depicted in **16** and thus more reactive (scheme 20). Furthermore, the easily available bifunctional conjunctive reagent **15** would provide a ready entry to such a complex in what would be a catalytic cycle (Trost 1986).



Scheme 20

In the event, we have established the cycloaddition of **15** to electron deficient olefins as illustrated in scheme 21 (Trost & Mignani 1986). It is to be noted that this cycloaddition proceeds with complete diastereoselectivity both in terms of faithfully translating olefin geometry into ring stereochemistry and facial selectivity. This particular cycloadduct proved to be a valuable intermediate towards a totally stereocontrolled synthesis of the antitumour macrolide brefeldin A (Trost *et al.* 1986*b*).

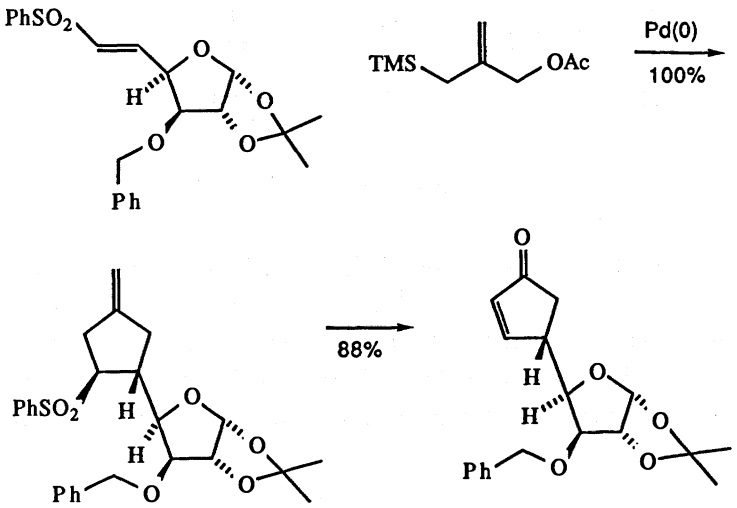


Scheme 21

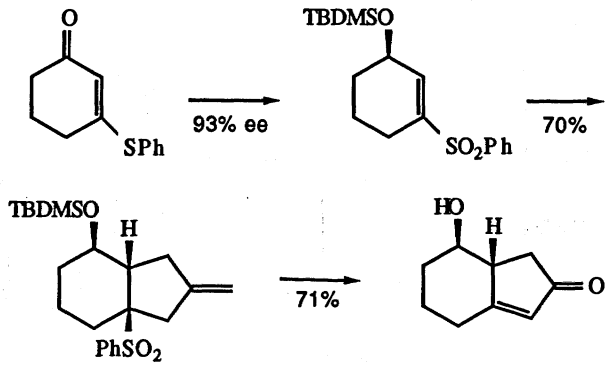
The stereospecificity of this reaction suggests a concerted reaction. Huisgen stated that a *trans/cis* rate ratio of greater than one was an unambiguous indication of a concerted cycloaddition (Huisgen 1963). The k_{trans}/k_{cis} rate ratio of 4.73 for the *E* and *Z* isomers of phenethyl 2-heptenoate compares favourably with other concerted cycloadditions (Huisgen *et al.* 1962; Sauer *et al.* 1962*a*, *b*).

The stereochemical control possible in this reaction permits the development of an asymmetric cyclopentenone annulation. The diastereoselective cycloaddition to a γ-alkoxy-

α,β-unsaturated sulfone as shown in scheme 22 simply transforms to a cyclopentenone annulation by oxidative cleavage of the exocyclic methylene group (P. R. Seoane, unpublished results 1987). The creation of a carbonyl group facilitates the elimination of the elements of benzenesulphinic acid to generate the cyclopentenone such that it occurs during workup. Because the acceptor in this example is enantiomerically pure, so is the final adduct. To the extent we can obtain enantiomerically pure acceptors from achiral starting materials, the excellent diastereoselectivity of the cycloaddition converts into an enantioselective cycloaddition. Scheme 23 outlines one such case. The high enantioselectivity associated with the carbonyl reduction of an enone transforms into an enantioselective annulation sequence.

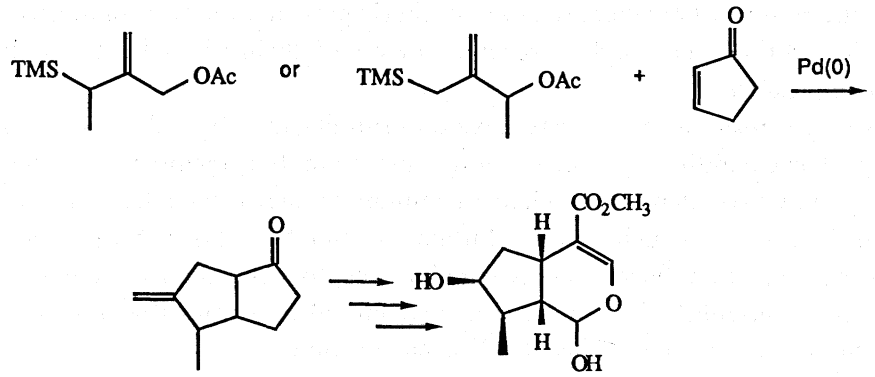


Scheme 22

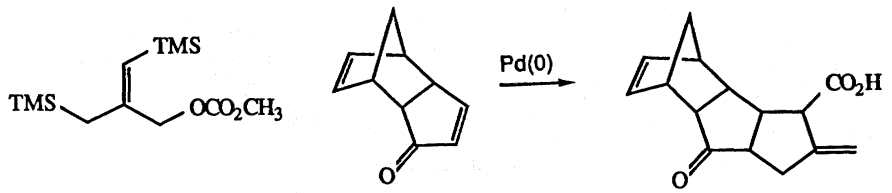


Scheme 23

A most intriguing aspect of this cycloaddition has been the effect of substituents. As schemes 24 (Trost & Chan 1981) and 25 (Trost *et al.* 1986*c*) show, both electron-donating and electron-withdrawing substituents show the same regioselectivity regardless of the location of the substituent on the precursor. The product of the cycloaddition of the methyl-substituted analogue constituted a critical intermediate towards loganin (Trost & Nanninga 1985). The latter reaction exemplifies an *in situ* carboxylation during the cycloaddition to generate a

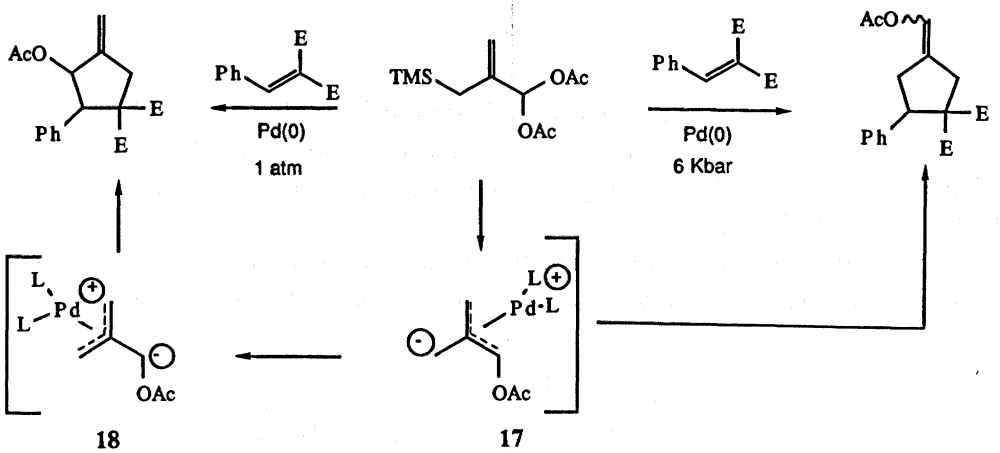


SCHEME 24



SCHEME 25

carboxytrimethylene methane palladium complex. That two different species are responsible for the regioisomeric products as outlined in scheme 26 for the acetoxy substituted trimethylenemethane is illustrated by the effect of pressure on the regiochemistry (O. Achmatowicz, unpublished results 1987). Whereas the normal regiochemistry wherein the substituent is located on the carbon of the trimethylenemethane fragment in the cycloadduct that becomes bonded to the β-carbon of the acceptor is followed at atmospheric pressure, presumably through the intermediate **18**, an isomeric product that might arise through the reactive complex **17** is obtained at 6 kbar.† The high pressure speeds up trapping of the



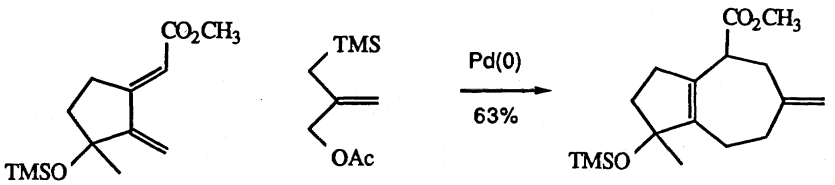
SCHEME 26

† 1 kbar = 10^8 Pa.

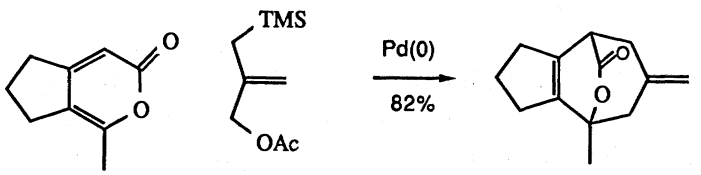
presumed kinetic complex **17**; whereas, at atmospheric pressure, the two complexes equilibrate faster than cycloaddition occurs and the reaction preferentially involves the thermodynamically more stable complex **18**.

The effects that transition metals may have on orbital symmetry led to an investigation of the feasibility of cycloaddition to form rings other than five membered. Indeed, a facile approach to polyhydroazulenes, a skeleton common to many bioactive natural products, emerged from the success of such a cycloaddition (scheme 27) (Trost & MacPherson 1987).

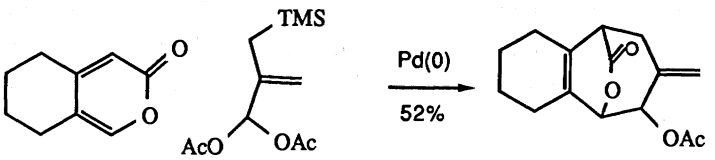
Pyrones have proven to be exceptionally reactive acceptors of trimethylenemethane (scheme 28) (S. Schneider, unpublished results 1987). Scheme 29 illustrates that the regioselectivity follows the same trends as seen in the [3+2] cycloaddition.



SCHEME 27



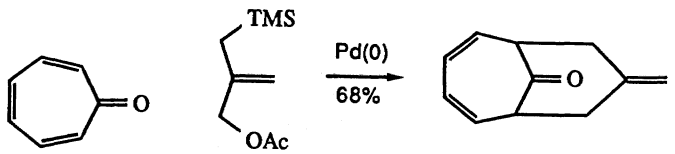
SCHEME 28



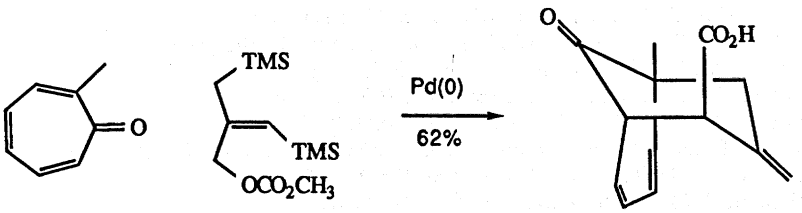
SCHEME 29

Emboldened by the success of the [4+3] cycloaddition, we also examined the possibility of a [6+3] cycloaddition. Indeed, both the parent and substituted trimethylenemethane donors react solely by a [6+3] mode with tropone and substituted tropone as shown in schemes 30 and 31 (Trost & Seoane 1987).

Indeed, the results verify the supposition that transition metals can promote the formation of reaction intermediates suitable for cycloaddition reactions. The flexibility that such metal



SCHEME 30



SCHEME 31

catalysis offers permits a breadth of cycloadditions of a [2*n*+3] variety. Although it will be important to establish the mechanisms of these cycloadditions, their potential in synthetic design is immense. The current success raises the hope that other cycloaddition approaches to yet additional ring systems will be possible.

CONCLUSION

The ability to approach complex cyclic systems depends upon our arsenal of reactions to create rings. The ever changing and ever more challenging structures that emerge, either from Nature or man's imagination, demand more sophisticated tools. Hammer and tongs must be exchanged for laser scalpels. The ability of transition metal complexes to selectively promote bond formation has the promise of becoming that fine scalpel for creation of new ring-forming methods. From such reactions, not only can the limitations that traditional methods have to be removed, but whole new strategies may emerge. For example, the cyclization via isomerization obviates the need for high dilution in creating large rings. The intramolecular carbametallation is a highly chemoselective process because it creates reactive sites for cyclization that do not exist in the absence of the catalyst. The catalytic approach also provides multibond-forming reactions that now allow cycloadditions to odd-membered rings. The invention of such methods provides strong impetus to finding many other strategies based upon these versatile catalysts.

I express my greatest appreciation to my collaborators who have made all of this chemistry possible. We gratefully acknowledge the financial support of the National Institutes of Health and the National Science Foundation.

REFERENCES

Ehrlich, K. & Emerson, G. F. 1972 *J. Am. chem. Soc.* **94**, 2464.
Eisner, T., Deyrup, M., Jacobs, R. & Meinwald, J. 1986 *J. chem. Ecol.* **12**, 1407.
Huisgen, R. 1963 *Angew. Chem.* **2**, 633.
Huisgen, R., Sturm, H. J. & Wagenhofer, H. 1962 *Z. Naturf.* **17b**, 202.
Negishi, E. 1987 *Acct chem. Res.* **20**, 65.
Negishi, E., Swanson, D. R., Cederbaum, F. E. & Takahashi, T. 1987 *Tetrahedron Lett.* **28**, 917.
Nugent, W. A. & Calabrese, J. C. 1984 *J. Am. chem. Soc.* **106**, 6422.
Sauer, J., Lang, D. & Weist, H. 1962*b* *Z. Naturf.* **17b**, 206.
Sauer, J., Weist, H. & Midert, A. 1962*a* *Z. Naturf.* **17b**, 203.
Trost, B. M. 1986 *Angew. Chem.* **25**, 1.
Trost, B. M. & Chan, D. M. T. 1981 *J. Am. chem. Soc.* **103**, 5972.
Trost, B. M. & Chung, J. Y. L. 1985 *J. Am. chem. Soc.* **107**, 4586.
Trost, B. M. & Cossy, J. 1982 *J. Am. chem. Soc.* **104**, 6881.
Trost, B. M., Hane, J. T. & Metz, P. 1986*a* *Tetrahedron Lett.* **27**, 5695.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES

Trost, B. M. & Jebaratnam, D. J. 1987 *Tetrahedron Lett.* **28**, 1611.
Trost, B. M., Kuo, G. H. & Benneche, T. 1988 *J. Am. chem. Soc.* (In the press.)
Trost, B. M. & Lautens, M. L. 1982 *J. Am. chem. Soc.* **104**, 5543.
Trost, B. M. & Lautens, M. L. 1985*a* *J. Am. chem. Soc.* **107**, 1781.
Trost, B. M. & Lautens, M. L. 1985*b* *Tetrahedron Lett.* **26**, 4887.
Trost, B. M., Lynch, J., Renaut, P. & Steinman, D. J. 1986*b* *J. Am. chem. Soc.* **108**, 284.
Trost, B. M. & MacPherson, D. T. 1987 *J. Am. chem. Soc.* **109**, 3483.
Trost, B. M. & Mignani, S. M. 1986 *Tetrahedron Lett.* **27**, 4137.
Trost, B. M., Mignani, S. M. & Nanninga, T. N. 1986*c* *J. Am. chem. Soc.* **108**, 6051.
Trost, B. M. & Molander, G. 1981 *J. Am. chem. Soc.* **103**, 5969.
Trost, B. M. & Nanninga, T. N. 1985 *J. Am. chem. Soc.* **107**, 1293.
Trost, B. M. & Rise, F. 1987 *J. Am. chem. Soc.* **109**, 3161.
Trost, B. M. & Seoane, P. R. 1987 *J. Am. chem. Soc.* **109**, 615.
Trost, B. M. & Tanoury, G. J. 1987 *J. Am. chem. Soc.* **109**, 4753.
Trost, B. M. & Tour, J. M. 1987 *J. Am. chem. Soc.* **109**, 5268.
Trost, B. M. & Warner, R. W. 1982 *J. Am. chem. Soc.* **104**, 6112.
Trost, B. M. & Warner, R. W. 1983 *J. Am. chem. Soc.* **105**, 5940.
Yoshihara, T., Togiya, S., Koshino, H. & Sakamura, S. 1985 *Tetrahedron Lett.* **26**, 5551.

Discussion

M. T. Reetz (*Fachbereich Chemie der Universität, Marburg, F.R.G.*). Why do oxygen nucleophiles (for example, in lactonization) require high dilution, in contrast to the carbon nucleophiles? Would Professor Trost also say something about the undesired polymerizations that he indicated?

B. M. Trost. For macrocyclization at high concentration, the rate of proton transfer and the nature of the nucleophile appear to be important. The low acidity of alcohols and the fact that hard nucleophiles like oxygen are relatively poor in attacking the soft π-allylpalladium electrophile may account for their inability to participate in the two-phase macrocyclization at high concentration. However, they cyclize very successfully under higher dilution conditions. By using homogeneous catalysts at high concentration, polymerization occurs. We have not examined optimizing this process for such an application.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY A MATHEMATICAL, PHYSICAL & ENGINEERING SCIENCES