Transition metal templates as guides for cycloadditions

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Abstract - Cycloaddition reactions, represented by the Diels-Alder
reaction, set a standard of chemo-, regio-, diastereo-, and enantio-
selectivity for the development of new synthetic reactions. Cycloadditions
to carbocyclic rings other than six members becomes an important objective.
Palladium templates convert the novel bifunctional conjunctive reagents,
2-trialkyl (or trialkoxy) methylallyl carboxylates, into reactive inter-
mediates that transfer a trimethylenemethane or substituted trimethyl-
enemethane unit to suitable acceptors. In direct analogy to the Diels-
Alder reaction, typical Diels-Alder dienophiles undergo smooth cyclo-
additions in chemo-, regio-, and diastereoselective fashion. A novel
cyclopentenone annulation has evolved. Using co-catalysts, carbonyl
groups also become acceptors. Transfer of substituted trimethylenemethane
fragments to both types of acceptors can be controlled to provide regio-
complementary products derived from kinetic or thermodynamic reactive
intermediates. Such a reaction can be generalized into [2n + 3]
cycloadditions in which seven and nine, as well as five membered rings
may be formed. Application of this methodology in natural products
synthesis is probed.

INTRODUCTION

New synthetic reactions must meet the challenges posed by chemo-, regio-, diastereo-, and
enantioselectivity.[1] Of the many existing reactions, few succeed in meeting such challenges
as do cycloadditions, most notably the Diels-Alder reaction (eq 1). It would appear most
fruitful to seek processes that mimic the Diels-Alder reaction to achieve high levels
of selectivity but to generate rings other than six membered.

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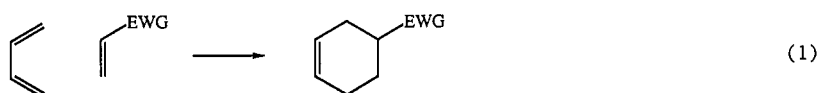
A cycloaddition to form five membered rings formally requires a reaction between a 1,3-
dipole and a suitable acceptor (eq 2). Use of trimethylenemethane zwitterion is attractive

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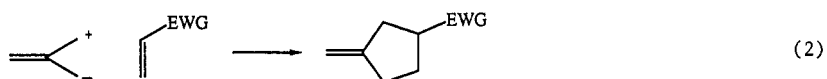
since (1) physical chemical studies have provided some information on trimethylenemethane
as a short-lived reactive intermediate, and (2) the exocyclic methylene group in the
product should prove to be a useful functionality for further structural elaboration in
the same fashion as the double bond of the Diels-Alder adducts. Unlike the dienes in
Diels-Alder reactions, trimethylenemethane cannot be stored as a reagent in a bottle,
but must be generated during the cycloaddition. Transition metal catalysts offer the
opportunity of generating reactive equivalents of trimethylenemethane for cycloaddition.[2]
A potential benefit from using a catalytic method is the evolution of a general [2n + 3]
cycloaddition (eq 3).

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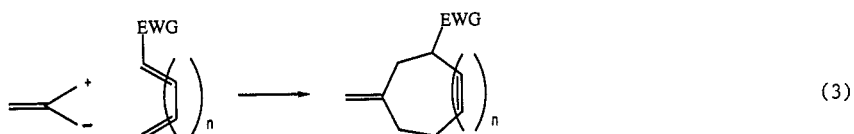
STEREOCHEMISTRY AND MECHANISM

The silyl carboxylate $\underline{1}$ represents a synthon for the dipole of trimethylenemethane in which the reactivity of the carbanion and carbocation equivalents are so chosen to avoid self-

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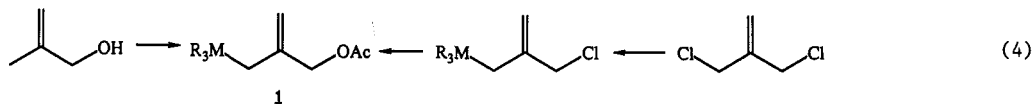
annihilation. Two approaches (eq 4) make this bifunctional conjunctive reagent readily available -- (1) metalation-silylation followed by 0-acylation of methallyl alcohol[3]; or (2) trichlorosilyl anion displacement with 2-chloromethylallyl chloride, replacement of the silyl chloride by alkyl or alkoxy groups, and nucleophilic displacement of the remaining allyl chloride by acetate.[4] Both procedures have been employed on large scale.

Eq 5 and 6 illustrate the basic process.[5] Equimolar amounts of the silyl carboxylate and

$$\text{(5)}$$

$$\text{(6)}$$
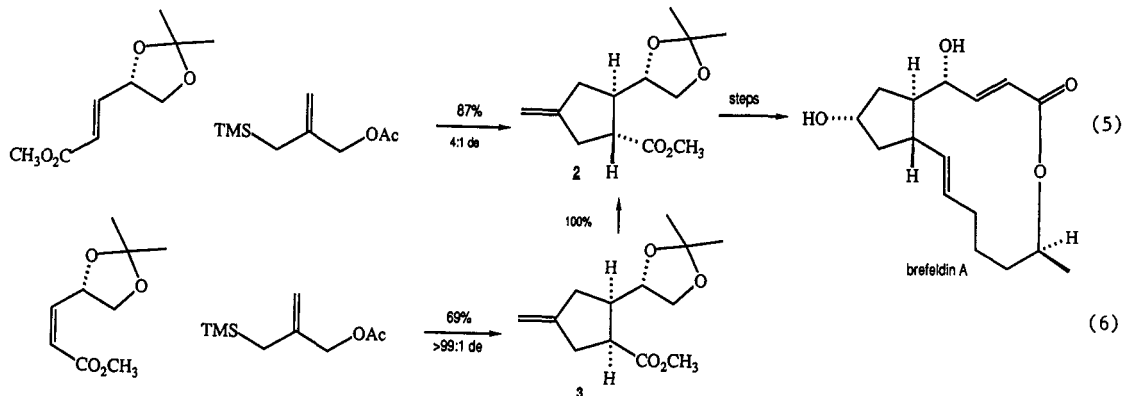
the substrate are heated with a Pd(0) catalyst prepared from 0.1 - 5 mol% of palladium acetate and a six-fold amount (relative to Pd) of triisopropyl phosphite with or without an additional reducing agent such as n-butyllithium. With this E,Z olefin pair, the reaction is stereospecific although the Z isomer shows a much higher diastereofacial selectivity than the E isomer. The high facial selectivity observed for the $\underline{Z}$-acceptor translates into production of adduct $\underline{2}$ with complete stereochemical control since adduct $\underline{3}$ quantitatively equilibrates to the trans-cyclopentane upon exposure to warm methanolic methoxide.[6] Thus, via the cycloaddition of eq 6, the stereochemical control of our earlier synthesis[6] of brefeldin A becomes complete. Trisubstituted double bond acceptors also show excellent stereospecificity (eq 7 and 8).

$$\text{(7)}$$

$$\text{(8)}$$
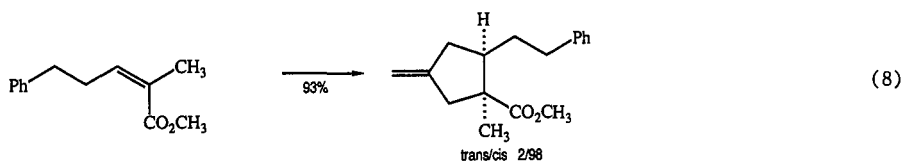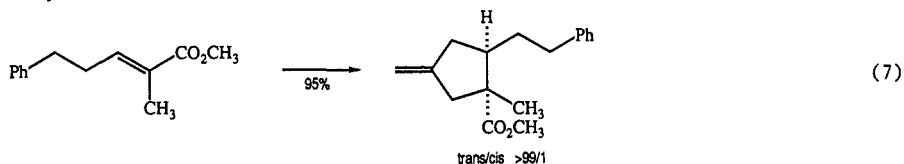
The above examples imply a concerted cycloaddition. Because we want to compare this process to a Diels-Alder reaction and because the stereochemical criterion of concertedness can be flawed, we decided to probe the question of concertedness by the kinetic criterion of Huisgen, who states that "the ratio of the trans-cis rates offers an elegant and theoretically clear criterion for concerted additions leading to five and six membered rings."[7,8] The $\underline{E},\underline{Z}$ acceptor pair $\underline{4}$ and $\underline{5}$ shows excellent second order kinetics at $66°$ with $k_{trans} = 7.09$ x $10^{-4} M^{-1} sec^{-1}$ and $k_{cis} = 1.50$ x $10^{-4} M^{-1} sec^{-1}$. The k_{trans}/k_{cis} of 4.72 compares to the ratio of 2.6 determined by Huisgen for the 1,3-dipolar cycloaddition of diphenyldiazomethane with the $\underline{E}$ and $\underline{Z}$ isomers of ethyl crotonate. The kinetic criterion also suggests concertedness.

$$\text{4} \xrightarrow[90\%]{} \quad 97 \quad\quad 3 \tag{9}$$

$$\text{5} \xrightarrow[89\%]{} \quad 22 \quad\quad 78 \tag{10}$$
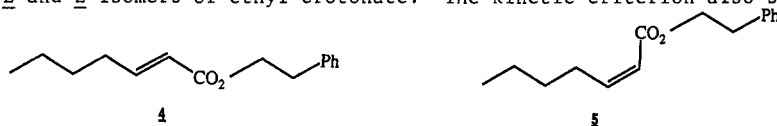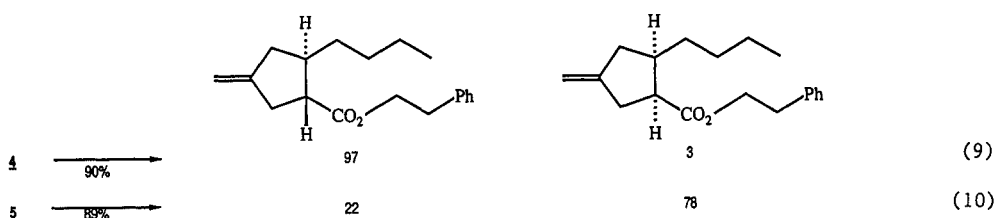
In contrast to the kinetic criterion in the cycloaddition of acceptors 4 and 5, the stereo-chemical criterion revealed by the product analysis (eq 9 and 10) questions a conclusion of concertedness in this case. The loss of stereospecificity for the Z-acceptor 5 requires that some isomerization to 4 must be occurring simultaneously with cycloaddition to be consistent with a concerted mechanism. The absence of any build-up of E-acceptor during cycloaddition and the constancy of the *trans* to *cis* product ratio as a function of percent completion of reaction rules out such a possibility. The results are best in accord with the scheme depicted in eq 11. From a synthetic point of view, enhanced stereospecificity


$$(11)$$
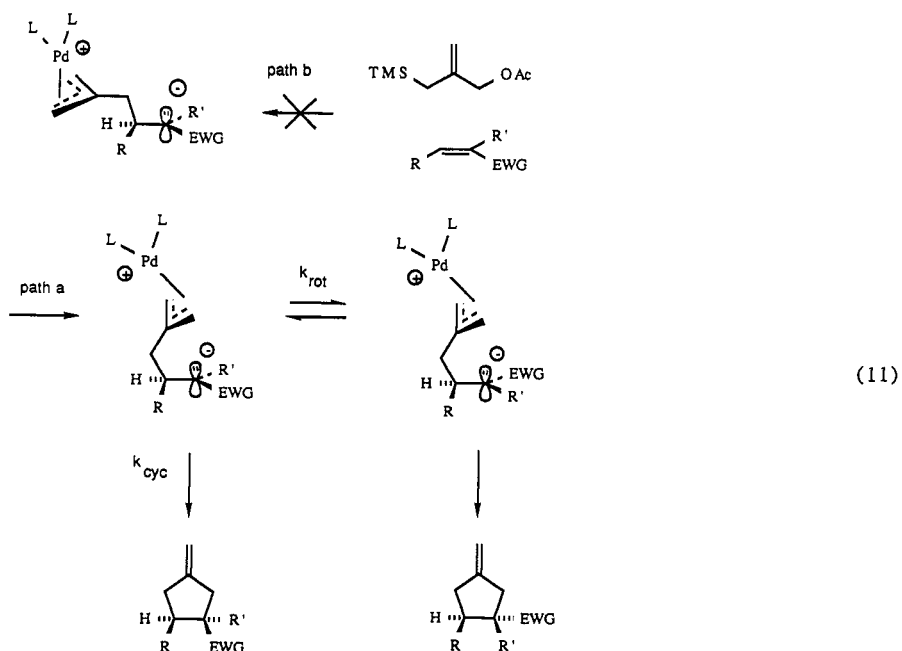
for Z-acceptors can be accomplished experimentally by performing the cycloaddition at room temperature. The silyl chloride 6 in conjunction with tetra-n-butylammonium acetate permits cycloadditions to proceed under such mild condition. The stereospecificity of the

$$(12)$$
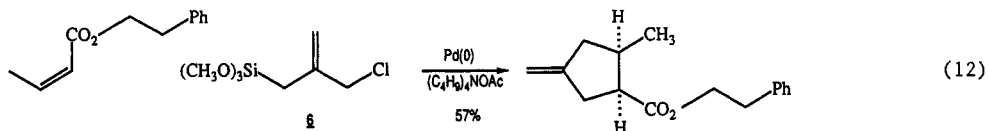
cycloaddition of the Z-crotonate, which shows the greatest loss of stereospecificity under our normal conditions, improves to a reasonable 7.6:1.

A diastereoselective cyclopentenone annulation

The excellent diastereoselectivity associated with this process can translate into a stereocontrolled annulation.[9] Gamma-alkoxy-alpha, beta-unsaturated sulfones such as 7, which may readily derive from an allylic sulfide by exhaustive oxidation using MCPBA followed by base catalyzed ring opening with DBU,[10] represent a particularly versatile type of acceptor. Using our standard conditions in toluene at 80°, cycloaddition proceeds with good diastereoselectivity (9:1). The versatility of the sulfone arises from its ease of reductive cleavage, which generates the parent bicycle, and its propensity to be a leaving group. For example, ozonolysis of the exocyclic methylene group creates a ketone which

(13)
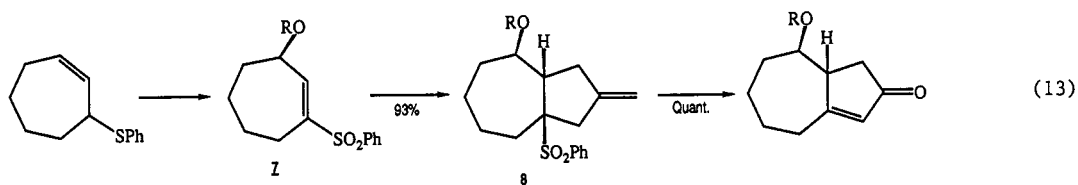
simultaneously acidifies the alpha-hydrogens and, consequently, facilitates the elimination of the elements of benzenesulfinic acid. The overall sequence becomes a versatile cyclopentenone annulation.

The excellent acceptor properties of gamma-alkoxy-alpha, beta-unsaturated sulfones is highlighted by the ability of the fully substituted acceptor 9 to participate in cycloaddition,


(14)
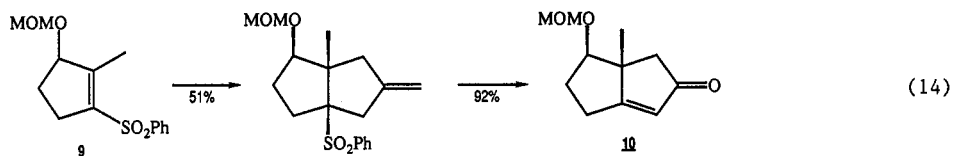
albeit at 150° in toluene in a sealed tube. The high temperature led to a diminished diastereoselectivity (2:1). The utility of this particular example stems from the accessibility to the bicyclic enone 10, a bis-nor Wieland-Miescher ketone analog of importance as a building block to polyquinanes.[11]

The availability of enantiomerically pure gamma-alkoxy-alpha, beta-unsaturated sulfones converts this sequence into an enantiocontrolled cyclopentenone annulation. The glucose derived aldehyde 11 undergoes a smooth E-selective olefination. Cycloaddition proceeds

(15)
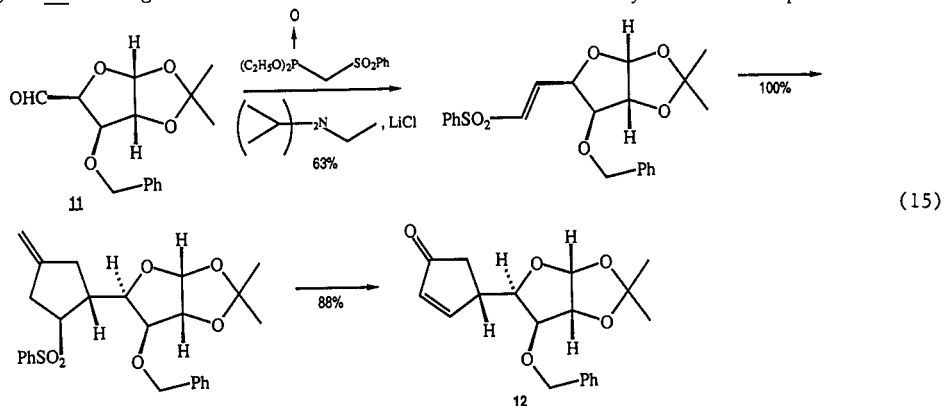
quantitatively with good diastereoselectivity (7.5:1) and provides the enantiomerically pure cyclopentenone 12 after ozonolysis (eq 15).

An alternative strategy employs an enantioselective reduction of an enone (eq 16). Treating 3-phenylthiocyclohex-2-enone (13) with LAH modified by methylephedrine and N-ethyl-2-


(16)
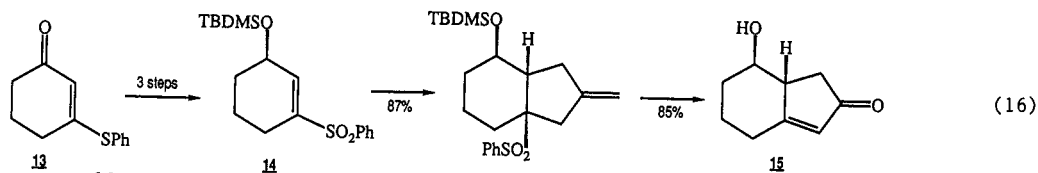
aminopyridine[12] ultimately provides the sulfone 14 of 95% ee. Carrying out the normal sequence of diastereoselective cycloaddition and ozonolysis now provides the cyclopentenone 15 of 93% ee. Use of substituted TMM intermediates also[13] leads to excellent results as illustrated in eq 17 with an enantiomerically pure acceptor.


(17)
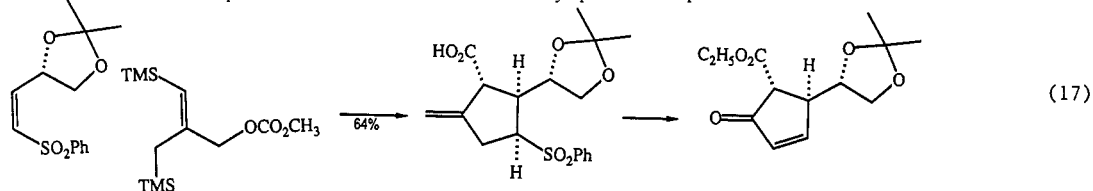
Regioselectivity with substituted TMM units

Introduction of a substituent on the TMM fragment destroys the threefold symmetry and opens the question of regioselectivity.[14,15] Eq 18 outlines the nature of the problem. Based upon the presumed mechanism of generating the TMM-palladium complexes, the substituted bifunctional conjunctive reagent **16** should kinetically form the TMM-complex **18** via the pi-allylpalladium cationic intermediate **17**. Based upon the two step mechanism initiated by a nucleophilic attack of the TMM-PdL$_2$ complex on the acceptor, the complex **18** may give rise

(18)
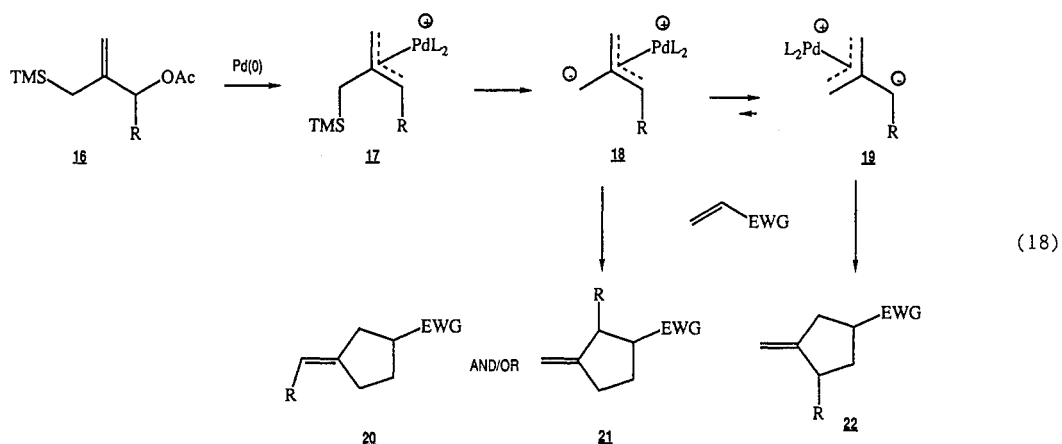
to two regioisomeric cycloadducts, **20** and/or **21**.[16] On the other hand, we have demonstrated that the parent TMM-PdL$_2$ is a fluxional species. Equilibration of **18** with **19** raises the possibility of a third regioisomeric product **22** arising from cycloaddition.

Our early results demonstrated that excellent regioselectivity is observed with both electron withdrawing (eq 19)[17] and electron donating (eq 20)[15] substituents. The regioselectivity is consistent with the product determining complexes being **23** and **24**. Such a

(19)

(20)
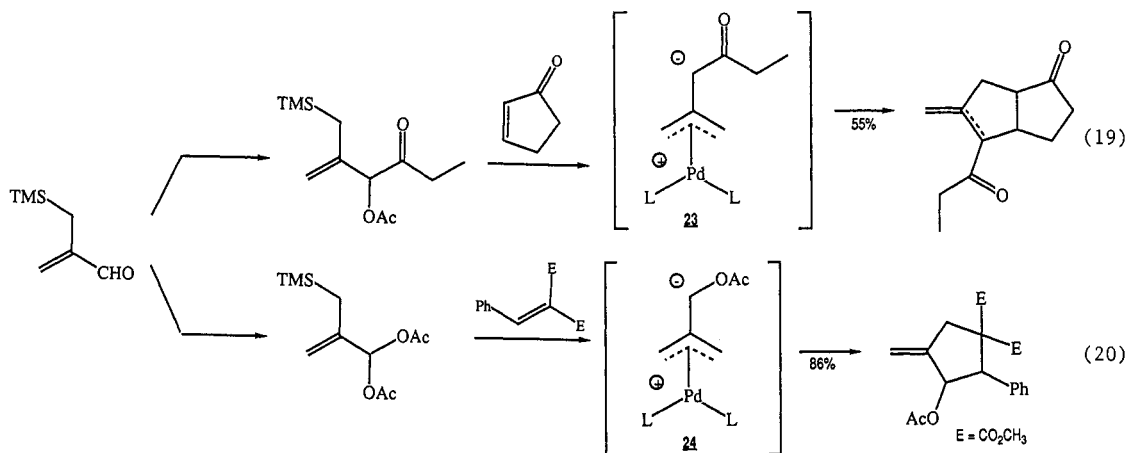
regioselectivity requires that the kinetically generated complex **18** must equilibrate with the alternative regioisomer **19** prior to cycloaddition. The present studies do not differentiate between two explanations -- (1) **19** being the kinetically more reactive regioisomer, or (2) the cycloaddition reflecting the equilibrium in which **19** greatly dominates.[18] Credence to the latter explanation derives from theoretical studies.

Being able to effect cycloadditions from the kinetic complex **18** would expand the scope of this methodology. In order to do so, we must increase the rate of the bimolecular condensation at the expense of the unimolecular rearrangement. Pressure offers an opportunity to affect these two rates in the desired sense. Indeed, with the excellent acceptor, dimethyl

(21)

R=OAc 56%
CH$_3$ 73%
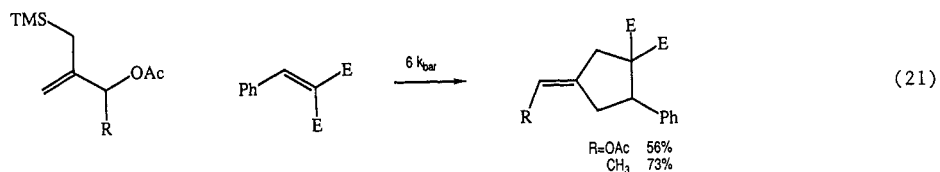
benzylidenemalonate, the regioisomeric products derived from the kinetic complex are produced with good (R = OAc produces 15% of the normal product in addition) to excellent (R = CH$_3$) selectivity by running the reaction at 6 kbar.[19] The feasibility of exercising full regiocontrol in cycloadditions is clearly indicated.

CARBONYL GROUP CYCLOADDITIONS

The reactivity profile of the TMM-PdL$_2$ species suggests it requires polarized unsaturated groups as suitable acceptors. Carbonyl groups clearly represent one such possibility. The feasibility of this option for this type of cycloaddition compared to the Diels-Alder reaction is indicated by the cycloadditions of the glucose derived enones 25 and 26.[20] Whereas, 25 participates beautifully in Diels-Alder reactions, the partner 26 does not.
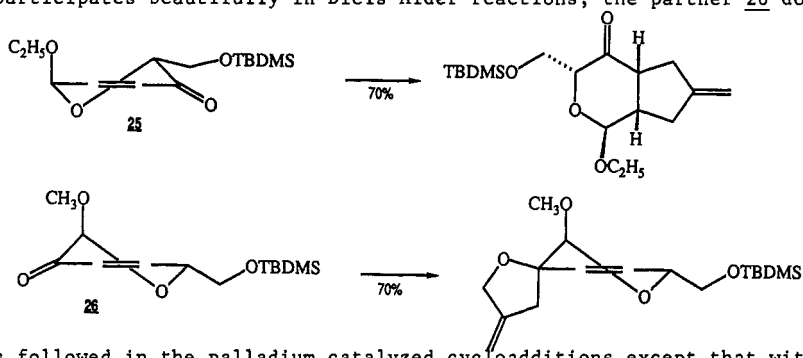

This trend is followed in the palladium catalyzed cycloadditions except that with 26 an alternative exists -- addition to the carbonyl group.[21]

Such additions proceed in good yield with both aldehydes (eq 22) and some ketones (eq 23 and 24) in the presence of a co-catalyst, tri-n-butyltin acetate.[22-24] The failure to undergo cycloaddition to the acetylene in deference to addition to the carbonyl group in the last example is striking. While cycloadditions to acetylenic acceptors have not yet been

(22)

(23)

(24)
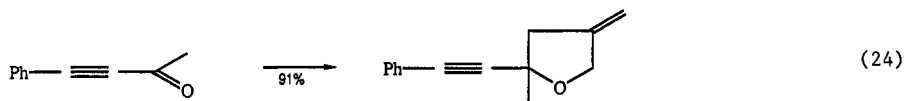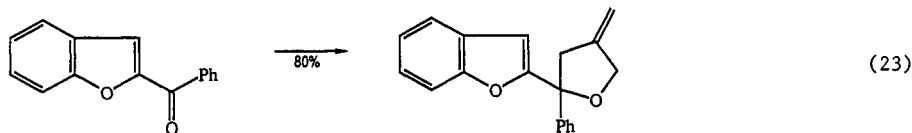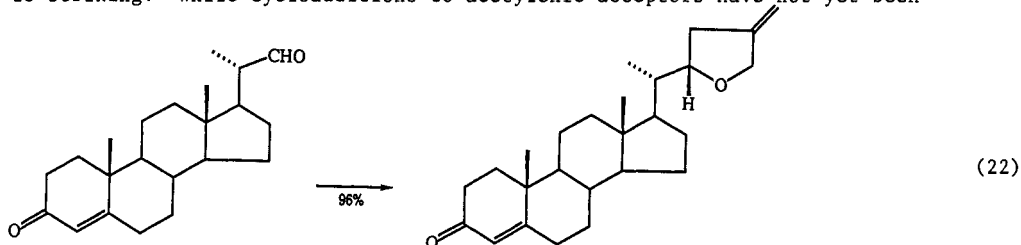
successful, this example suggests that variation of catalysts may affect the chemoselectivity of the cycloaddition with enones. Two systems test this concept (eq 25 and 26).[23] Performing the cycloadditions under our standard conditions with tri-isopropylphosphite leads


(25)

(26)
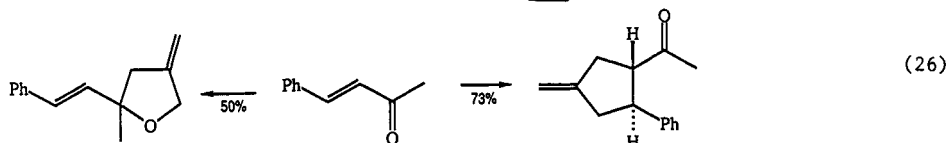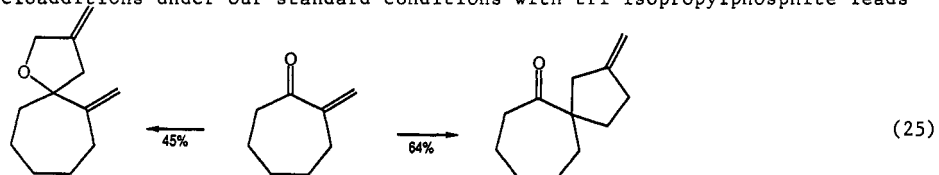
to the normal addition to the electron deficient double bonds. On the other hand, using triphenylphosphine as a ligand and a co-catalyst, tri-n-butyltin acetate in the case of 2-methylenecycloheptanone and indium acetylacetonoate in the case of benzalacetone, the principal cycloadducts involve addition to the carbonyl group. Such cycloadditions can also be achieved intramolecularly (eq 27), but this reaction does not appear to be general.[25]


(27)
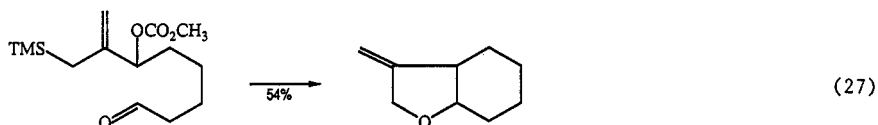
This particular example generates the ring system of the important antitumor agent phyllanthocin.

Substituted TMM systems add regioselectively to aldehydes under normal cycloaddition conditions.[21] For example, the bifunctional conjunctive reagent **27** kinetically generates the


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(29)
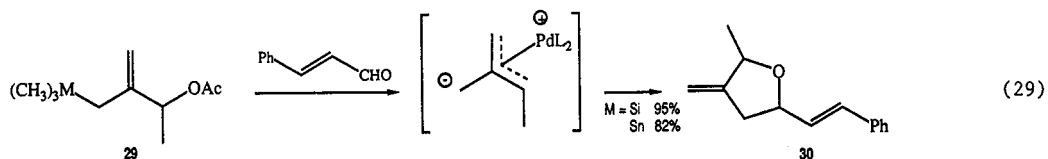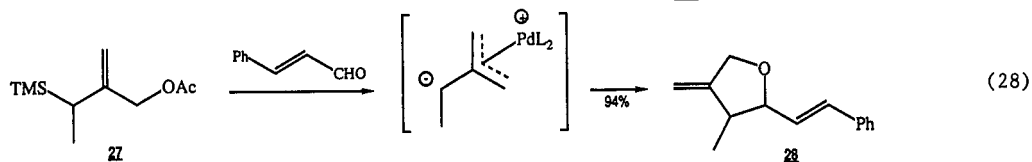
thermodynamically more stable regioisomeric TMM-PdL$_2$ complex (eq 28). Its cycloaddition with cinnamaldehyde in the presence of trimethyltin acetate gives the tetrahydrofuran **28** with >200:1 regioselectivity. On the other hand, the isomeric reagent **29** (M=Si) kinetically generates the thermodynamically less stable TMM-PdL$_2$ complex (eq 29). Its cycloaddition with the tin catalyst produces the isomeric tetrahydrofuran **30** with lower regioselectivity (**30**:**28**, 7:1). The **30**:**28** ratio increases to 31:1 by using **29** (M=Sn) and trimethyltin tosylate as the co-catalyst. A more elaborate bifunctional conjunctive reagent **31** shows complementary regioselectivity depending upon the donor properties of the ligand for palladium (eq 30).


(30)
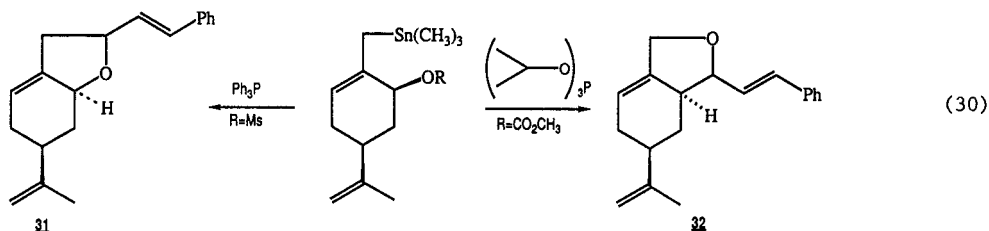
Increasing the donor properties of the ligand increases capture of the kinetically formed TMM-PdL$_2$ intermediate leading to **31**; whereas, the better acceptor ligand leads to predominant capture of the thermodynamically favored TMM-PdL$_2$ intermediate.
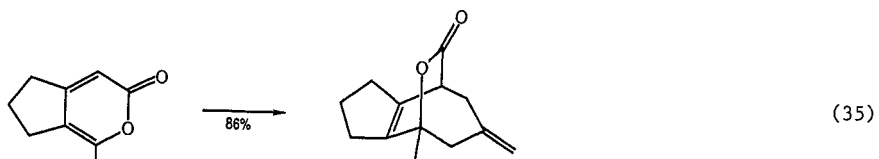
(4+3) CYCLOADDITIONS

At the outset of our program, our goal was to establish a family of cycloadditions to a variety of ring sizes. Our discovery of a particularly facile cyclization to dialkylidene cyclopentanes[26] led us to explore a strategy for the synthesis of the polyhydroazulene ring system (eq 31).[27] Indeed, this rigid cisoid dienoate provides the [4+3] cycloadduct in excellent yield.


(31)
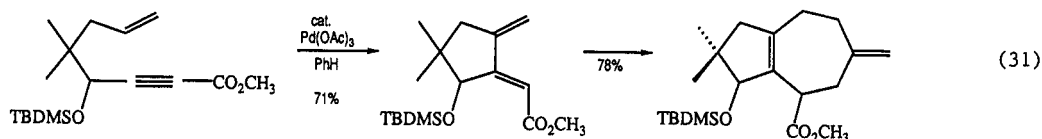
In considering other acceptors for [4+3] cycloadditions, our attention focussed on pyrones represented by methyl coumalate (33, eq 32).[28] Cycloaddition with 33 under our standard conditions proceeds smoothly to give a 1:1 mixture of the [3+2] and [4+3] adducts. By positioning the carbomethoxy group at C(2) of the pyrone, exclusive formation of the [3+2]

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\text{(32)}
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\text{(33)}
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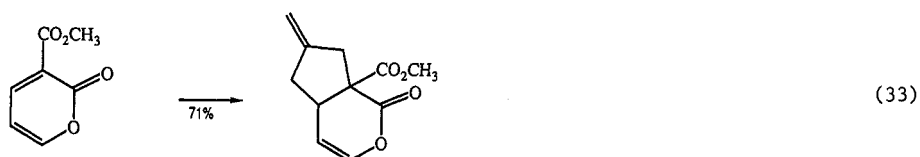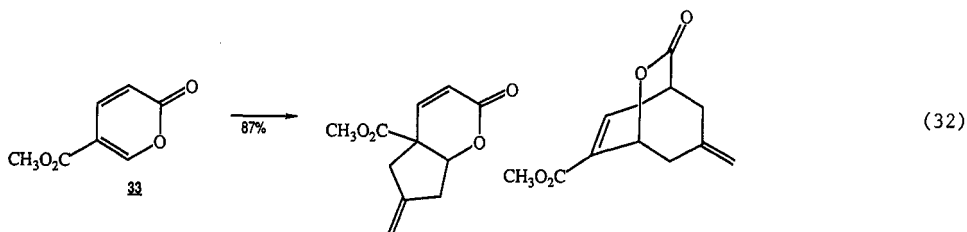
adduct occurs (eq 33). On the other hand, the absence of any additional activating group as in the case of the parent pyrone leads only to the [4+3] adduct (eq 34). The exceptionally fine acceptor properties of pyrones allows smooth cycloaddition even with a highly

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\text{(34)}
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\text{(35)}
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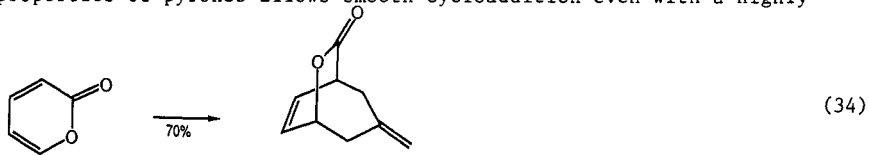
substituted pyrone (eq 35). Substituted TMM systems participate in these cycloadditions as summarized in eq 36 and 37.[19]

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\text{(36)}
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\text{(37)}
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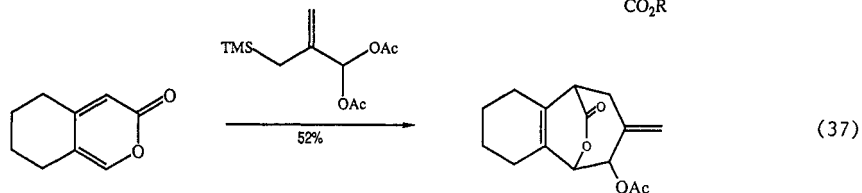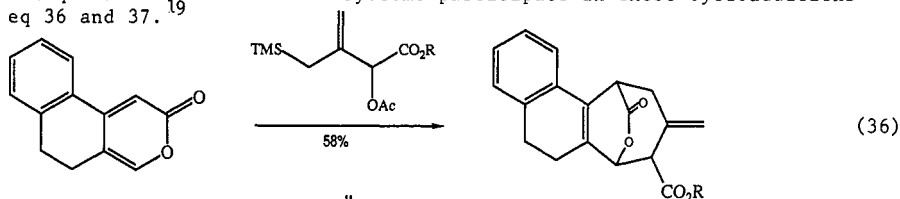
(6+3) CYCLOADDITION

The great success in construction of seven membered rings raises the question of how far such cycloadditions can be extended. Can we create a [6+3] cycloaddition for construction of nine membered rings? The ability of tropones to undergo [6+4] cycloadditions with electron rich dienes[29] suggests the feasibility of such acceptors being 6 pi electron partners toward the nucleophilic TMM-PdL$_2$. Indeed, tropone and even tropolone methyl ether undergo exclusive [6+3] cycloaddition (eq 38).[30]

$$
\begin{array}{c} \text{R=H} \quad 67\% \\ \text{OCH}_3 \quad 41\% \end{array}
\text{(38)}
$$
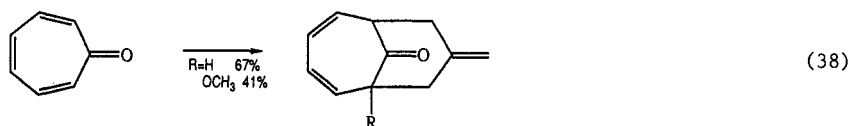
High regioselectivity accompanies this cycloaddition. The product arises from capture of the thermodynamically more stable substituted TMM-PdL$_2$ intermediate (eq 39 and 40). The

example of eq 40 illustrates the high regioselectivity with unsymmetrical tropones as well as unsymmetrical TMM units. We have just initiated the cycloaddition of disubstituted TMM


(39)

(40)
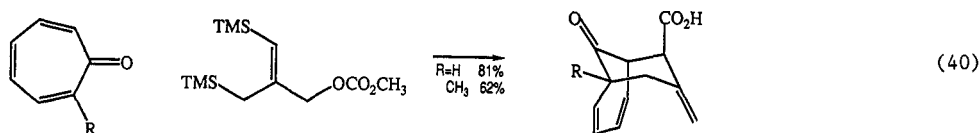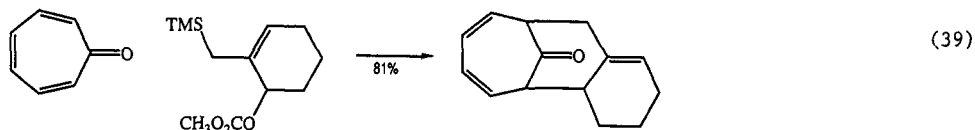
systems. A very preliminary observation shows that excellent selectivity for an unexpected regioisomer is observed (eq 41).[31] The general utility of disubstituted TMM systems is an exciting future direction.


(41)
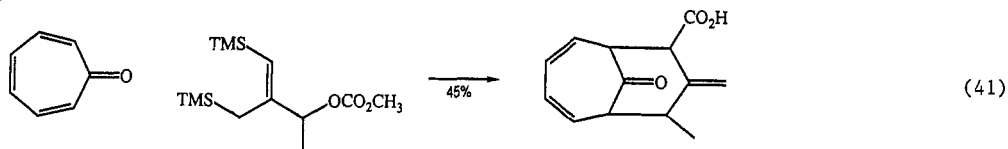
A SYNTHETIC STRATEGY TO ROCAGLAMIDE

The existence of a cycloaddition approach to odd membered rings opens new strategies for total synthesis. Rocaglamide (34), an antileukemic agent,[32] may be viewed as an example of a highly functionalized cyclopentane in which the proposed intermediate 35 possesses all

(42)
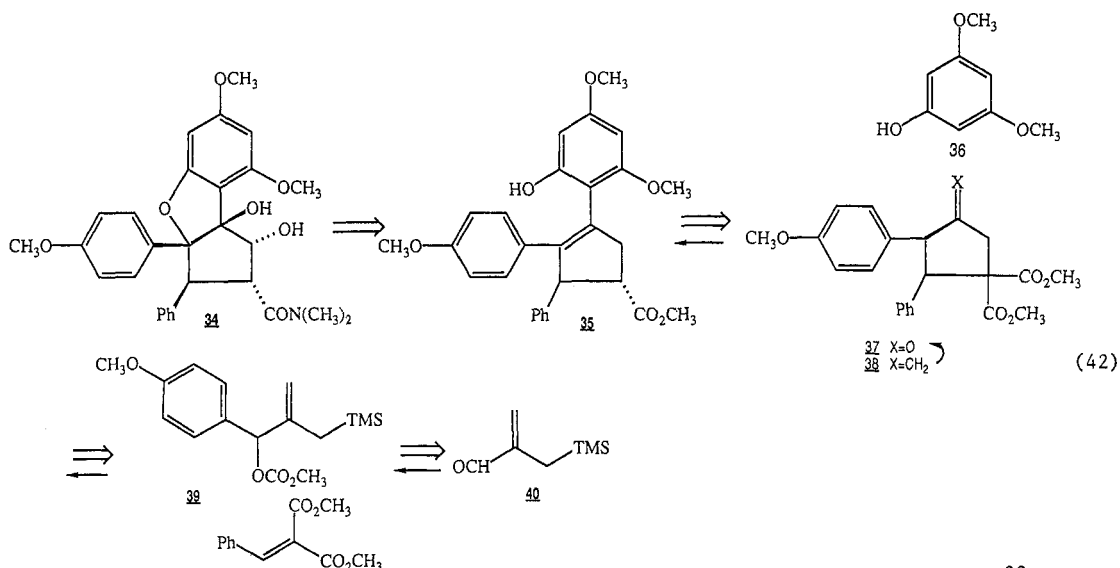
of the carbons of rocaglamide and only the oxidation pattern needs to be adjusted.[33] A condensation of the phloroglucinol derivative 36 with the cyclopentanone 37 followed by decarbomethoxylation should provide the key precursor 35. Taking advantage of the ready interconversion between a carbonyl group and an exocyclic methylene group allows the methylenecyclopentane 38 to be considered as an intermediate. Such a structure immediately evokes the notion of a cycloaddition using a substituted bifunctional conjunctive reagent 39 and dimethyl benzylidenemalonate. The aldehyde 40 provides easy access to a broad array of substituted reagents as shown in earlier sections of this report. Simple addition of the Grignard reagent derived from p-bromoanisole and capping of the alcohol with methyl chloroformate provides this reagent. Its cycloaddition to product 38 proceeds superbly and ultimately leads to the key precursor 35 as outlined.

One feature of this strategy is the establishment of the absolute stereochemistry by the cycloaddition. To probe this aspect, we examined the use of a chiral auxillary in this cycloaddition. Alkylidenemalonate 41 proves to be a particularly interesting acceptor since the products arising by conjugate addition appear to involve selectivity for the B-face;[34] whereas, intramolecular heteroatom Diels-Alder reactions appear to involve

41
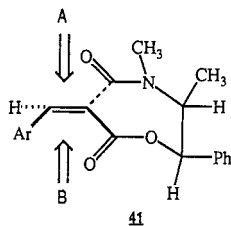
preferentially the A face.[35] Cycloaddition to **41**, Ar = Ph, gives a single diastereomer which is assigned as **42**.[36] This stereochemistry arises from attack on face B of the acceptor **41**. Removal of the chiral auxillary by simple basic hydrolysis, esterification,

$$(43)$$

42   **43**
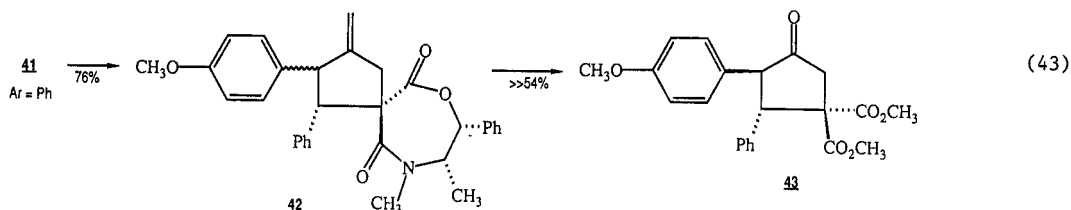
and ozonolysis generates enantiomerically pure cyclopentanone **43**. While the absolute stereochemistry of **43** is opposite to that needed for rocaglamide, use of the acceptor derived from the enantiomeric chiral auxillary **44** provides the cycloadduct **45** (eq 44) whose absolute stereochemistry should correspond to that required for rocaglamide.

$$(44)$$

44   **45**
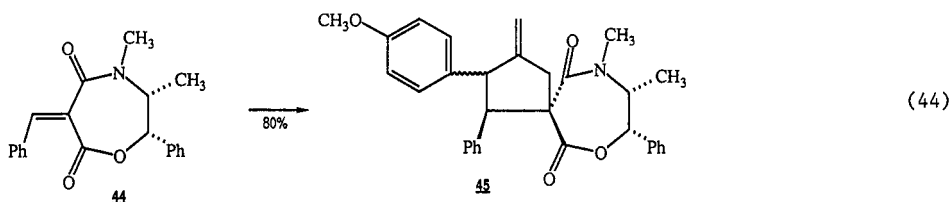
CONCLUSIONS

The metal catalyzed cycloaddition has a remarkable resemblance to a Diels-Alder reaction. As summarized in eq **45**, this reaction constitutes a chemo-, regio-, and diastereocontrolled approach to cyclopentanes and tetrahydrofurans. Use of chiral auxillaries may provide

$$(45)$$
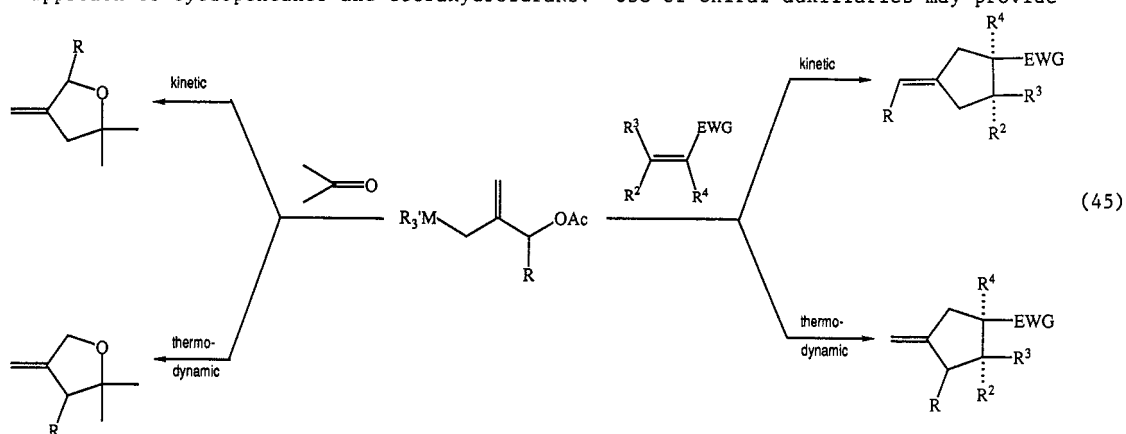
enantiocontrol. Moreover, this approach extends beyond five membered ring construction. With appropriate diene and triene acceptors, seven and nine membered rings are also available. The goal of a general [2n + 3] cycloaddition is approachable.

The transition metal catalyzed strategy offers unique future opportunities. Can variation of the electronic nature of the metal template vary the electronic nature of the acceptor? Can adjustment of the ligands adjust the diastereo- and enantioselectivity? Can we develop co-catalysts to extend the range of types of unsaturation that are suitable acceptors? Can we develop new open shell reactive intermediates -- for example oxa or aza analogues of trimethylenemethane or extend the pi system to create [2n + 5] cycloadditions? These few questions are just the beginning. The prospects for simplifying synthetic strategy by the development of cycloaddition creates a great excitement to such questions.

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