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TRANSITION METALS AND OLEFINS. A PROMISING LAND: A PERSONAL ACCOUNT

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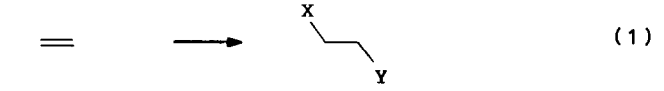
Whereas the chemistry of the carbonyl group as a functional group for structural elaboration is extraordinarily well developed, the ability to use the olefin in a similar way has been much more restricted. Two types of reactions may be considered, additions (eq. 1) and allylic substitutions (eq. 2).



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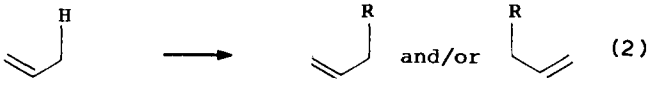
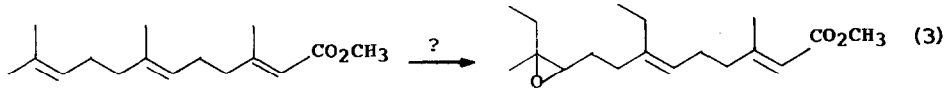


(2)

Heteroatom additions and allylic oxidations are well appreciated but the ability to form carbon–carbon bonds by additions or allylic insertions was limited, especially in a chemoselective fashion. We confronted this problem in our work on juvenile hormone (**1**) in which we posed the question whether such an unusual terpene might



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be available from the common terpenes such as methyl *E,E*-farnesoate by a bis-allylic alkylation. A problem arises in systems like methyl farnesoate in terms of chemoselectivity. Normally, reactions of the enoate end of the molecule can be performed selectively; functionalization of the isolated double bonds without protecting the enoate is a challenge. The ability of transition metals to select for less polarized unsaturation such as an isolated double bond over polarized unsaturation such as a carbonyl group led us to embark on a search for synthetically useful ways to elaborate olefins in a highly chemoselective fashion, especially with respect to a carbonyl group.

While we had been planning our assault on this broad problem of allylic substitution, we began our first foray into transition metal reactions by considering

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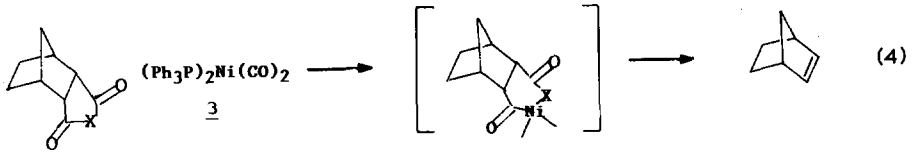
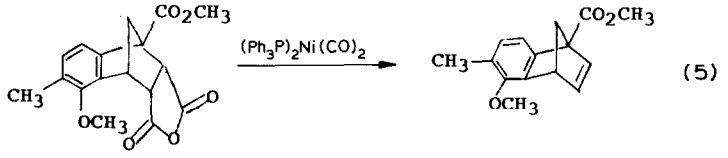


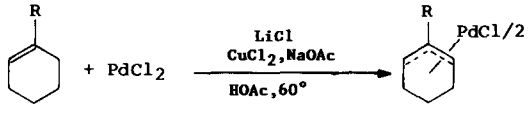
2 a) X=S
b) X=O

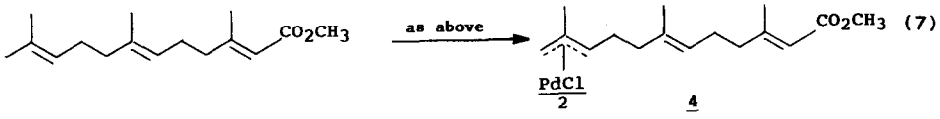
the problem of converting a 1,2-dicarboxylic acid to an olefin, a continuing perplexing problem. Our notion was to use the thioanhydride **2a** because nickel might have a high affinity for sulfur. Indeed, using **3** as the reagent, norbornene can be distilled from the reaction mixture (eq. 4). The affinity of nickel for sulfur was found not to be a requirement; even the anhydride **2b** undergoes equally facile elimination [1]. Our new method has subsequently found many applications such as serving as a key reaction in the synthesis of the aconite alkaloids (eq. 5) [2].



A palladium mediated allylic alkylation of olefins

The preparation of π-allylpalladium complexes by numerous routes has been reported. Of special interest was the reaction of palladium chloride complexes with olefins to form the π-allylpalladium chloride dimers, especially studied by Huttel [3]. Only simple olefins had been explored and, even among these, many, such as the cyclohexenes, failed to react satisfactorily. We developed a modification of the procedure in which high chloride ion concentration was maintained and an oxidant, cupric chloride, prevented formation of palladium(0) [4,5]. Most importantly, it proved applicable to cyclohexenes (eq. 6) and was chemoselective (eq. 7).





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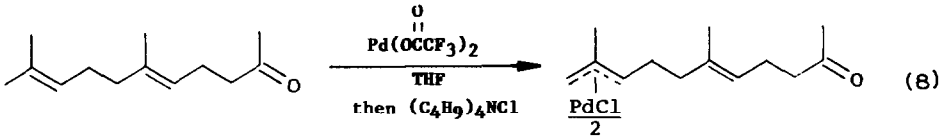
A search for milder conditions was deemed necessary to apply this method to more highly functionalized organic molecules and to ultimately develop a catalytic system. Use of more electrophilic palladium salts such as palladium acetate in the absence of chloride ion required sufficiently high temperatures that allylic oxidation dominated. Palladium trifluoroacetate resolved this dilemma by allowing reaction to proceed at sufficiently low temperatures (room temperature) to lead to the π-allylpalladium trifluoroacetates, which, because of their lability, were metathesized to



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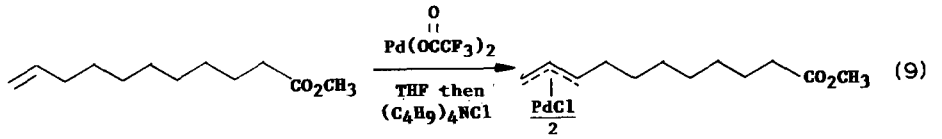
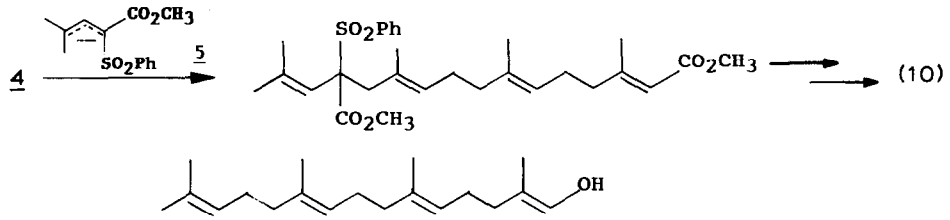
the chlorides for isolation (eq. 8) [6]. This method succeeds even with the relatively unreactive monosubstituted olefins (eq. 9).



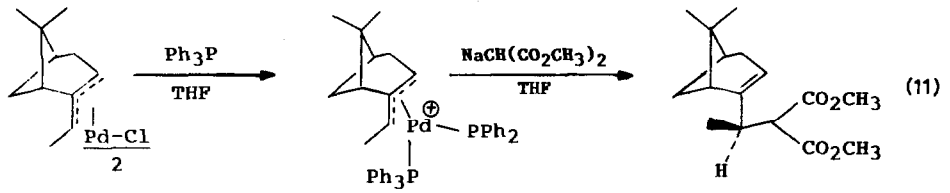
(9)

Having established the formation of the requisite complexes from olefins, their subsequent reactions became the challenge. Whereas, the reaction of the parent π-allylpalladium chloride dimer with nucleophiles in DMSO had been described [7], this reaction fails with almost every other complex. We believed we needed to increase the electrophilic characteristics to enhance susceptibility to nucleophiles. Additions of neutral ligands such as phosphines to the chloride bridged dimers which could (1) cleave the dimers to monomers and (2) ionize the remaining chloride did the trick [8–11]. Using triphenylphosphine or hexamethylphosphorus triamine to activate the chloride bridged dimer, the nucleophile **5** (eq. 10) smoothly alkylates



(10)

complex **4** (see eq. 7) [12,13]. The ultimate product of this sequence was geranylgeraniol; the overall result becomes a prenylation of a sesquiterpene, farnesol, to a diterpene, geranylgeraniol. We have formulated a mechanism based upon formation of a cationic intermediate and nucleophilic attack distal to the metal, as in eq. 11, a scheme for which much evidence has accumulated [14,15].



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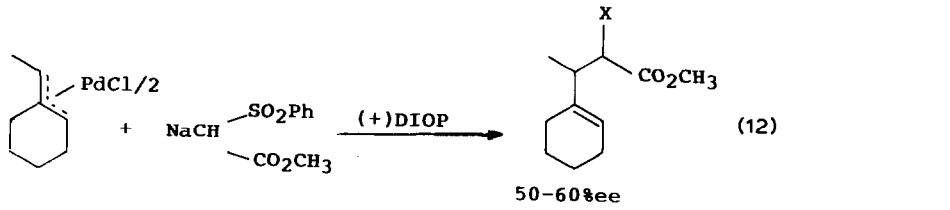
While our main emphasis was consideration of chemoselectivity, other problems of selectivity must also be addressed. Of particular significance is the question of enantioselectivity. Modest enantiomeric excess has been accomplished (eq. 12);

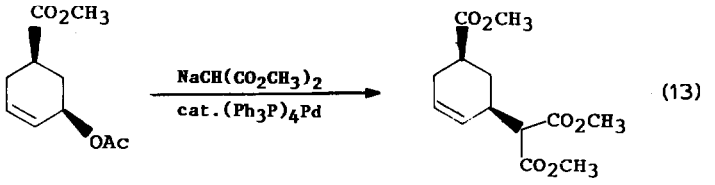


(12)

however, considering the reaction was performed at room temperature, a very practical operating temperature, it is quite significant [16].

A palladium catalyzed allylic alkylation

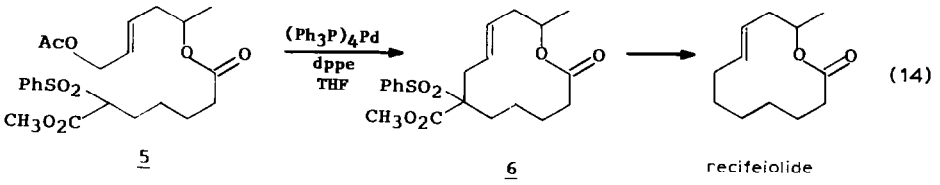
While the direct substitution of olefins at an allylic position met our first objective, we always had in mind a catalytic process. Our attention focussed on allylic carboxylates which form π-allylpalladium intermediates with a palladium(0) complex since, after alkylation, a Pd^0 complex reforms, thus a catalytic cycle results. We have established the generality and selectivity of this process [17,19]. As



(13)

illustrated in eq. 13, the reaction is chemoselective. Most importantly, its stereochemistry differs from traditional displacements where inversion is virtually synonymous with displacement. This metal catalyzed process results in a net retention of stereochemistry! It arises from two inversions: an inversion in the ionization step and an inversion in the displacement step. Thus, the transition metal reaction has two important implications. First, very poor leaving groups such as carboxylate are reactive enough to successfully participate. By avoiding highly reactive alkylating agents, much safer intermediates may be employed. They become reactive only in the presence of the transition metal. Furthermore, they can be incorporated into the substrate whenever convenient and carried through many steps without problems. Second, the palladium template enforces a stereochemical complement to the normally accepted displacements.

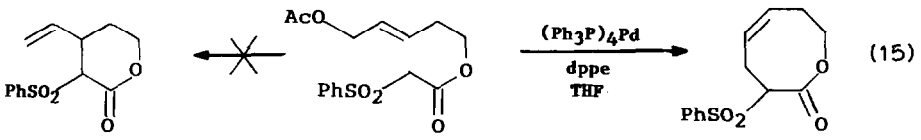
Having established the feasibility of the methodology, we set upon two parallel paths: (1) to explore the scope of the process and (2) to explore some applications. Whenever possible, we try to combine the two objectives in the same experiment. At the time we began, interest in formation of rings larger than six atoms, in particular macrolactonizations, was beginning. The notion that a transition metal template may impose a reactivity pattern to favor such a process led us to explore formation of macrolactones by C–C bond formation [20–23]. The cyclization of ester **5** using the standard catalysts led to an excellent yield of the macrolactone **6** which was transformed by decarbomethoxylation and desulfonylation to recifeiolide (eq. 14) [21,23]. An astounding result was the cyclization of ester **7** to give the eight-mem-



5 6 recifeiolide

(14)

bered ring when it could have given a much more favorable six-membered ring (eq. 15) [22,23]. In addition to recifeiolide, we illustrated this approach to various rings



(15)

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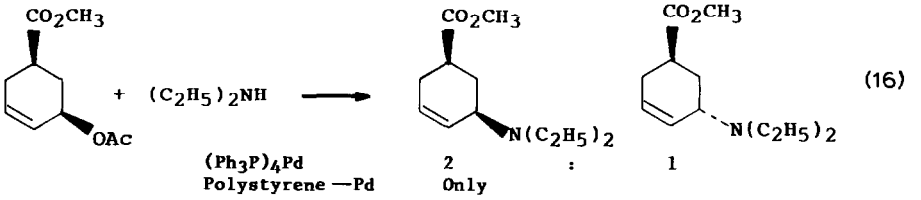
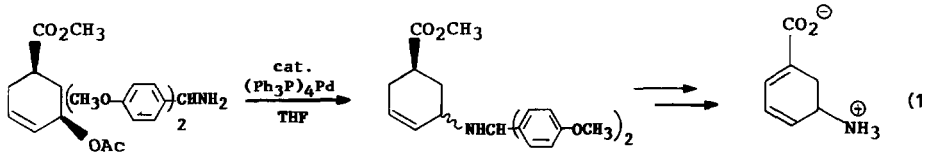
and included syntheses of exaltolide, phoracantholide I, and phoracantholide J [23].

We deemed the range of nucleophiles that could serve in such reactions to be important to the development of the methodology. Foremost among the possible non-carbon nucleophiles is nitrogen [24–27]. The lack of complete stereospecificity in such reactions led us to develop an interest in polymer bound catalysts which, for steric reasons, fully restored the stereospecificity (eq. 16) [25]. Primary and sec-



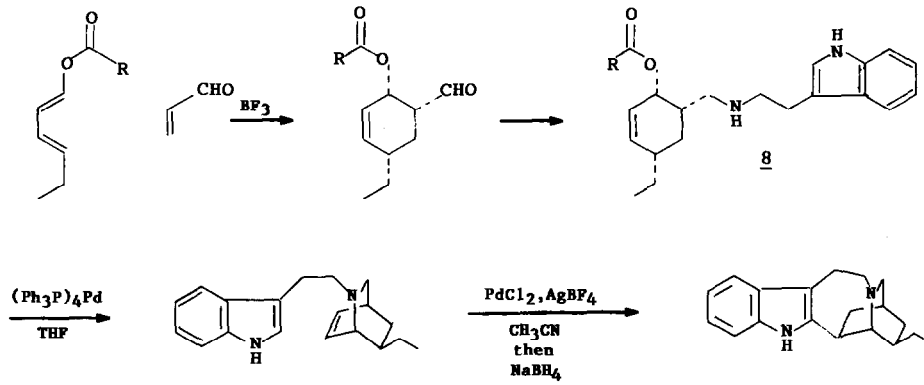
(16)

ondary amines react nicely but ammonia fails. A synthon for ammonia, *p,p'*-dimethoxybenzhydrylamine, resolved this problem [26]. A synthesis of gabaculine illustrates the sequence (eq. 17). The removal of the dimethoxybenzhydryl group proceeds chemoselectively and in high yields simply by dissolving in warm formic acid.



(17)

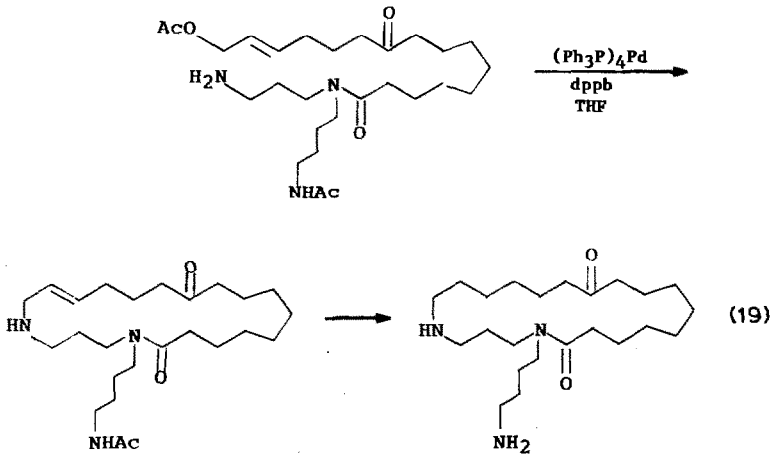
Cyclizations with amines as the nucleophiles was explored as a route to nitrogen heterocycles, especially for the synthesis of alkaloids [24]. Considering the stereochemistry of the Diels–Alder reaction and of the Pd catalyzed displacement reaction, a very simple strategy to the iboga family of alkaloids evolved (eq. 18) [28,29]. By using a chiral ester in the diene, excellent asymmetric induction occurs in



(18)

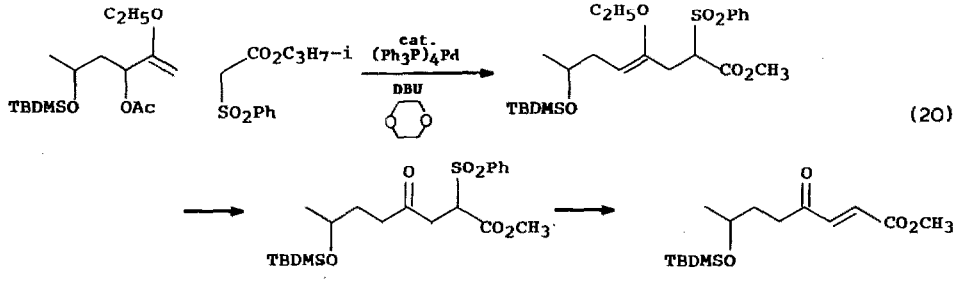
the Diels–Alder reaction, a fact that makes this route an asymmetric synthesis as well. The critical intermediate **8** requires the displacement of the leaving group by the secondary amine on the same face of the allyl unit (i.e. with retention of configuration but with allyl inversion). Indeed, palladium templates perform such a task. The final step also required development of a new palladium based reaction which we derived from consideration of the Heck reaction [30]. In addition to ibogamine, catharanthine was synthesized using a similar approach [29].

Much later, we considered the use of such amine nucleophiles in macrocyclization [31]. In developing such chemistry, we tackled the intriguing problem of the synthesis of the macrocyclic spermidine alkaloid inandenin-12-one (eq. 19) in which a 21-membered ring forms in 80–90% yields in a highly chemoselective fashion.



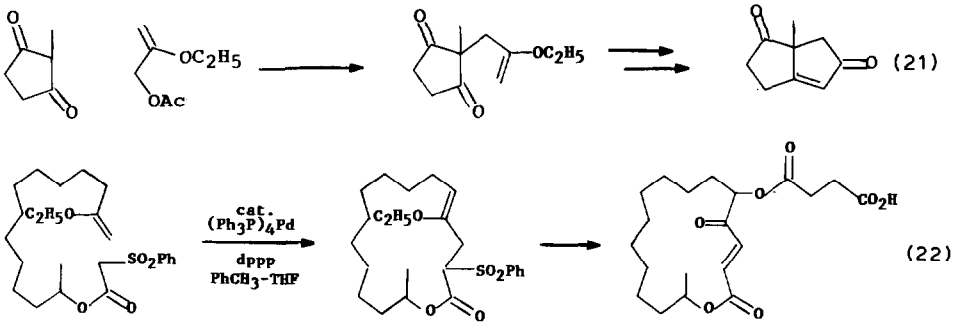
(19)

Concurrent studies concerned ourselves with the range of substituents possible on the allyl acetate moiety, in particular on the vinyl carbon atoms. Since the initiation of the process is believed to involve formation of an olefin palladium(0) complex, such a first step would be destabilized by strong electron donating groups. We felt that oxygen substituents, which are of particular utility in further synthesis, would be a good test of this extreme. While higher temperatures are necessary, such oxygen substitution does not prevent reaction as illustrated in eq. 20 [32]. The recognition of



(20)

the enol ether as a ketone equivalent facilitates elimination of the elements of benzenesulfinic acid to give **9**, the monomer corresponding to the macrodiolide, pyrenophorin. A cyclopentenone annulation resulted in the synthesis of the bis-nor-Wieland-Miescher ketone (eq. 21) [33]. Four years after the pyrenophorin applica-

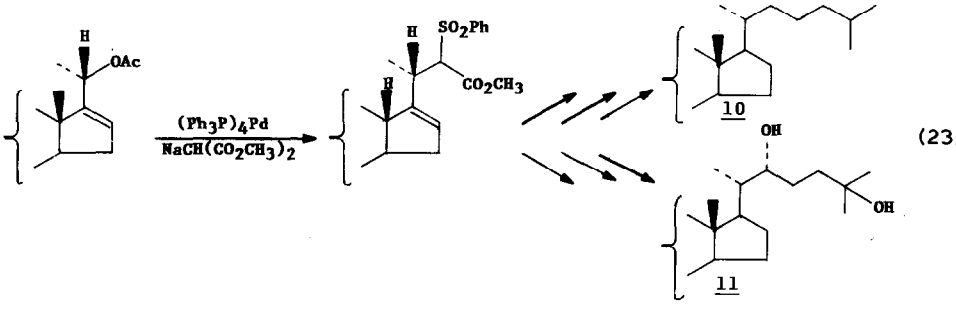


(21)

(22)

tion, we deomonstrated the feasibility of this approach in a synthesis of antibiotic A 26771 B (eq. 22) [34]. In this case, the virtue of the enol ether is illustrated by direct hydroxylation to unmask the ketone which creates the very important δ-hydroxyenedione system which is a common structural feature of the cytochalasins.

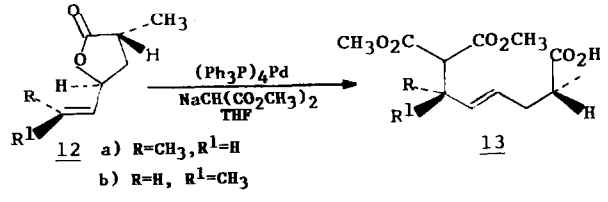
The presence of substituents on the non-vinyl carbons in non-cyclic systems raises the question of diastereoselectivity in creating a stereocontrolled approach to acyclic systems. Our first efforts concerned us with introduction of the steroid side chain [35–37]. As illustrated in eq. 23, the Pd catalyzed alkylation at the acyclic carbon



(23)

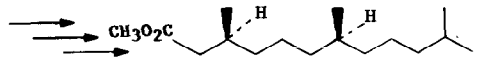
(C(20)) proceeds with complete retention, a fact that eventually translated into the cholesterol side [37] chain as in **10** or the ecdysone side chain as in **11** [36].

We wondered how much conformational control the palladium template could exert on an acyclic chain in order to achieve acyclic diastereoselectivity. For success in the case of substrate **12**, the following criteria must be met: (1) palladium initiated ionization of **12** must occur from only one of the several possible conformers, (2)



12 a) R=CH_3, R^1=H
b) R=H, R^1=CH_3

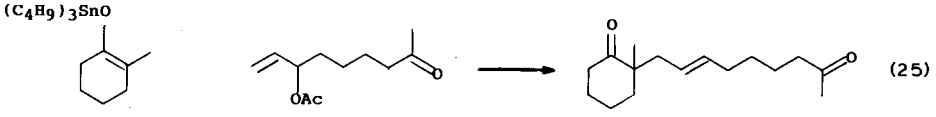
13



(24)

scrambling of the π-allylpalladium intermediate by well known $\pi \rightarrow \sigma$ interconversion must be slower than alkylation, and (3) alkylation must proceed with high regioselectivity. All of these requirements have been met by the palladium catalyzed allylic alkylation in that **13** is the exclusive product [38]. Stereocontrolled formation of **13a** translates into a stereocontrolled synthesis of the side chain of Vitamin E. Using glucose as a starting material, a similar route created the Vitamin E side chain with control of absolute as well as relative stereochemistry [39].

At approximately the same time, we returned to consider the range of carbon nucleophiles. Our early work with simple enolates had led to polyalkylation and with organolithium reagents, to attack at the metal with subsequent products involving disproportionations. Tin compounds seemed like they would "soften" the more reactive nucleophiles while maintaining sufficient reactivity. Indeed, the enol stannane (eq. 25) [40] or, later, a tin "ate" complex [41] resolved the problem of polyalkylation. Furthermore, the first case of palladium mediated cross coupling with allyl stannanes was developed by us (eq. 26) [42].



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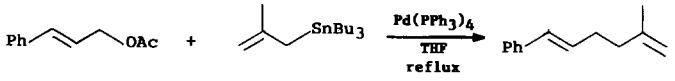
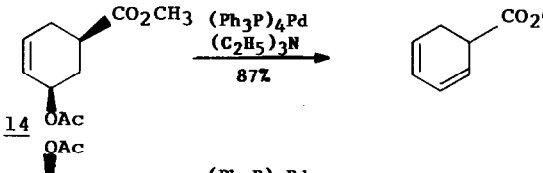


(26)

In an ancillary study, we considered the effect of no added nucleophile. In a case such as **14**, insertion into an adjacent proton *cis* to the metal occurs to form a diene with the net loss of the elements of acetic acid (eq. 27) [43]. By using a carboxylic acid such as **15**, a totally different course ensues wherein the elements of carbon dioxide and acetic acid are extruded to give the diene (eq. 28) [44]. Acyclic olefins can be generated with high *E*-selectivity as in the synthesis of Vitamin A ester (eq. 29) [45].



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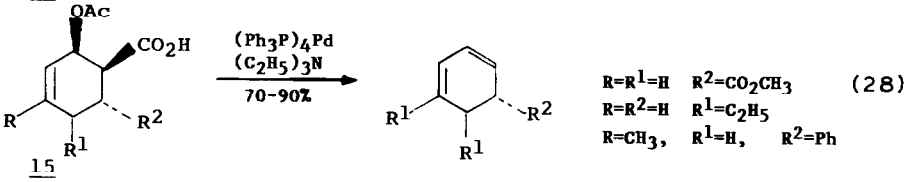

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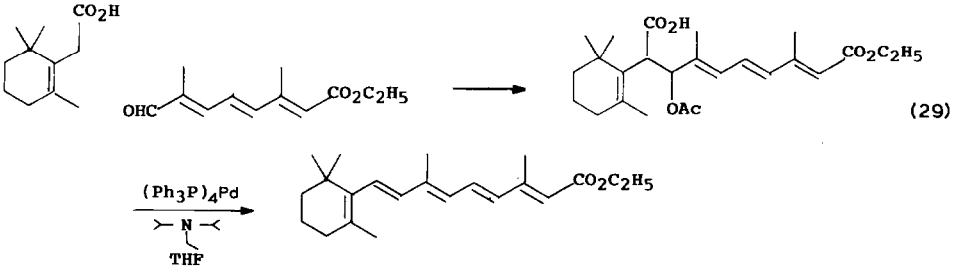
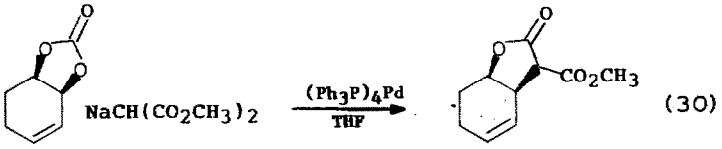


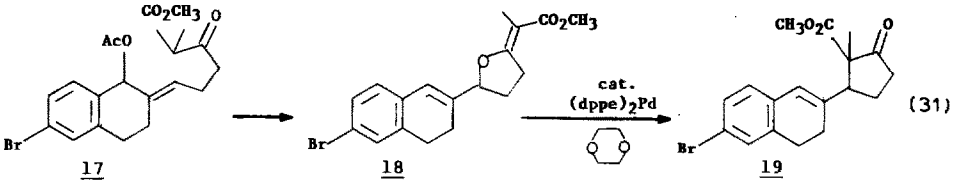
(29)

While we focussed our attention on allyl alcohol derivatives because of their ease of synthesis, we felt that major opportunities for selective construction of complex molecular architecture might result by considering the range of leaving groups. An early attempt focussed on cyclic carbonates such as **16** which participated very well as substrates and resulted in an unusual regioselectivity (eq. 30) [46]. The fact that a



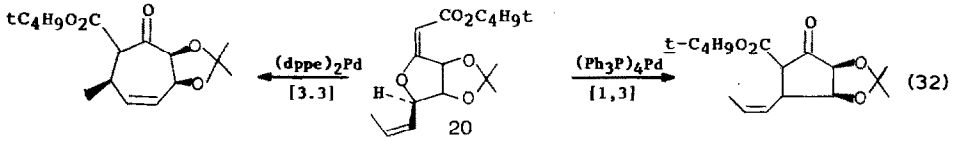
16

carbonate served as an exceptionally good leaving group led us to consider whether a vinylogous carbonate such as **18** would also serve as a leaving group [47–50]. In this case, the leaving group serves as an internal nucleophile to cyclize via *C*- rather than *O*-alkylation to give the cyclopentanone **19**. Thus, the classical problem of *O*- vs. *C*-alkylation of *β*-ketoesters such as **17** can now be resolved due to the fact that the



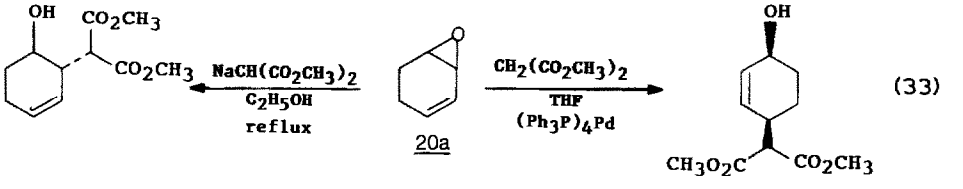
17 18 19

O-alkylation product is still reactive in the presence of a palladium(0) catalyst. An additional virtue of the use of transition metal templates is the ability to manipulate the regiochemistry of the *C*-alkylation. In the case of the vinylogous carbonate **20** either the 5- (1,3-rearrangement) or 7- (3,3-rearrangement) -membered ring is equally accessible by simply switching the ligands on the metal (eq. 32) [50].



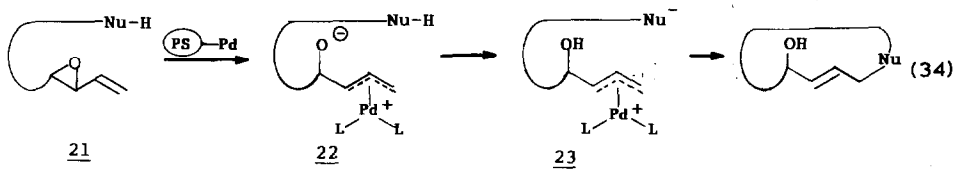
20

An alternative to a *cis*-1,2-cyclic-carbonate such as **16** is an epoxide such as **20a** [51]. The complementary chemistry available by using the transition metal compared to standard methods is nicely highlighted by this example (eq. 33). In addition to complementary regio- and diastereo-selectivity, the palladium catalyzed reaction proceeds under totally neutral conditions.



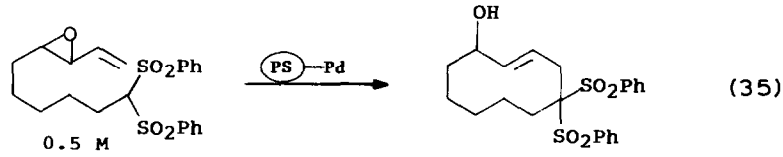
20a

The use of neutral substrates appeared to offer an exciting solution to another problem, cyclization to rings larger than six members. The idea that we had was to imbed our active catalyst in a solid phase support such as polystyrene to create a limited number of active sites. Absorption onto such a non-polar support would require a neutral substrate such as **21** which contains a pro-nucleophile and a pro-electrophile (eq. 34). After its absorption, it must migrate around the polymeric



21 22 23 (34)

matrix to eventually encounter an active site at which time ionization creates a reactive electrophile and a base as in **22**. Once in a while, the tether bearing the pro-nucleophile will bring this grouping close in space to the alkoxide at which point a proton can jump to unmask the nucleophile. Due to the fact that the newly created anionic nucleophile must be in close proximity to the π-allylpalladium cation at its moment of birth, by operating in a non-polar medium such as polystyrene prevents separation of charge and thereby inhibits the movement of the two ends of the molecule away from each other. Collapse to form the ring effects charge neutralization. Since the reacting substrate is in a phase apart from the bulk solution, this cyclization should be independent of the concentration of the substrate in solution. This idea proved to be spectacularly successful both in forming all carbon rings (eq. 35) [52] as well as macrolactones (eq. 36) [53]. The yields were excellent (60–80%) and were independent of substrate concentrations even up to 0.5 M.



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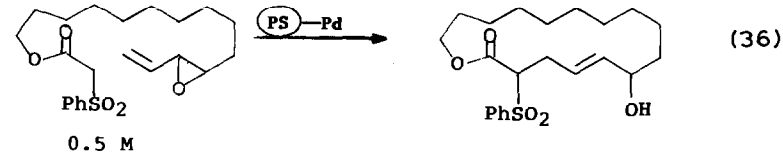
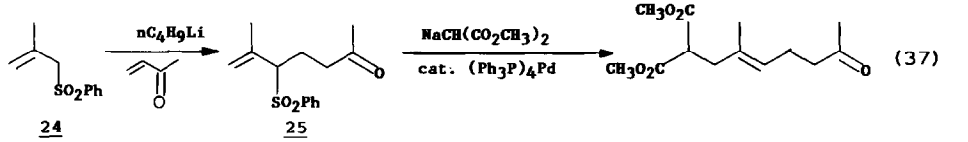


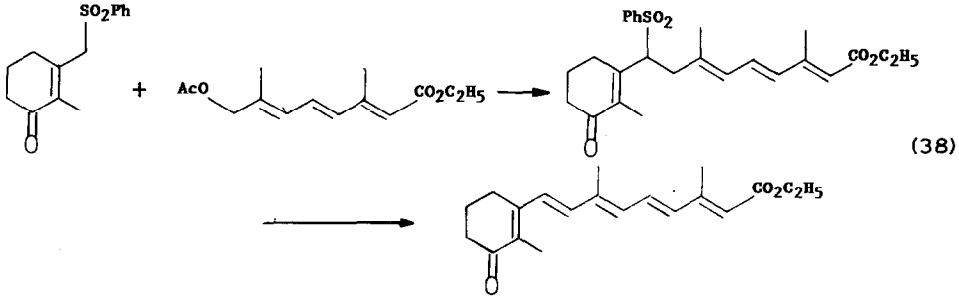
(36)

The fact that very poor oxygen leaving groups are such good reaction partners led us to consider whether non-oxygen groups which are normally not leaving groups in displacement reactions might also be substrates. Sulfones appeared to be particularly exciting because of the ability of this group to facilitate C–C bond formation via carbanion chemistry (eq. **24** → **25**, eq. 37). The allyl sulfone is indeed labile towards



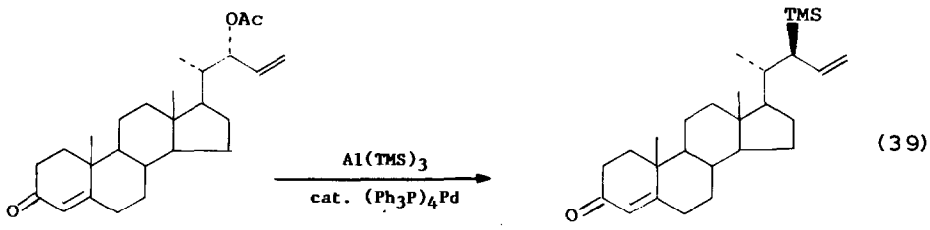
24 25 (37)

displacement reactions in the presence of a palladium(0) catalyst where the allyl sulfone moiety now represents an electrophilic equivalent [54]. Elimination reactions also succeed as illustrated in a one pot palladium catalyzed alkylation and elimination to give a Vitamin A ester analogue (eq. 38).



(38)

In all the chemistry developed so far, we have considered the allyl unit to be a synthetic equivalent to an allyl cation. We believed a useful new direction would be to invert the electronic sense of this system. A synthon for an allyl carbanion would be either an allyl silane or stannane. Indeed, using a silylaluminum [55] or stannylaluminum [56] reagent, allyl acetates can be chemoselectively converted into their allyl silanes or stannanes (eq. 39 and 40).



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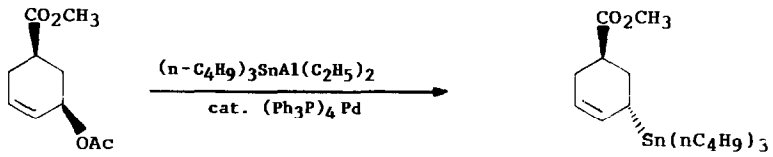
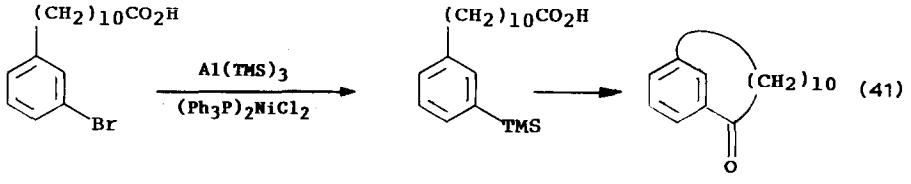


(40)

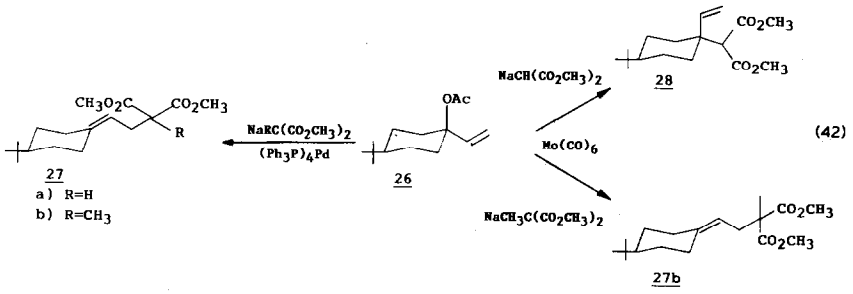
In an aside, we have shown that cross coupling of these aluminum metal systems with aryl halides using a palladium(+2) or preferably nickel(+2) catalyst can be useful to introduce regioselectivity control elements for electrophilic aromatic substitution. A *meta*- (eq. 41) or *para*-cyclophane synthesis ultimately resulted [57].



(41)

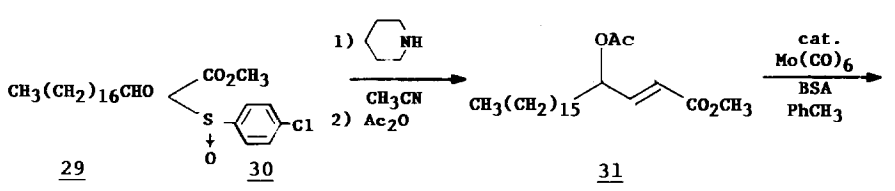
A molybdenum-catalyzed reaction

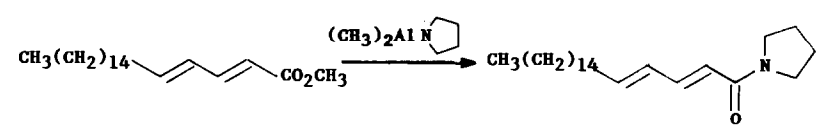
Our first efforts on metal-catalyzed allylic alkylation with palladium proved to be highly selective in many respects including regioselectivity. Normally, a single regioisomer resulting from alkylation at the less hindered allyl position but with some dependence on the substitution pattern of the allyl unit also exists. We wanted to find a way to be able to select for either regioisomer from the same substrate. Lets consider the simple case of allyl acetate **26**. Based upon a steric model with respect



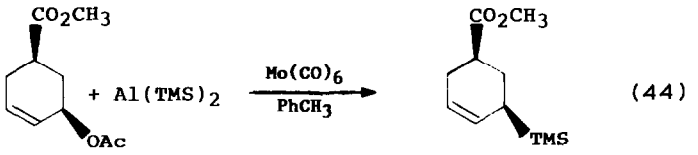
to the carbon fragments, attack should be preferred at the least hindered end of the allyl unit. Indeed, palladium templates generally, but not always, follow such a trend to give **27**. On the other hand, consideration of the steric and electronic biases of the metal template, the preference for lower electron density at the more substituted end of the allyl unit, and the larger coefficient in the LUMO of the allyl fragment at the more substituted carbon argues for preferential alkylation at the more substituted end. In order to achieve a transition state to favor such factors, we felt a more electropositive metal would be needed. Going from the right hand side to the left in a periodic table from palladium, we encounter molybdenum. As shown in eq. 42 a molybdenum catalyst indeed favors attack at the more substituted side to give **28**, even though we create a quaternary carbon [58–60]. Nevertheless, increasing the steric demands of the nucleophile by the simple act of introducing a methyl group as in dimethyl methylmalonate switches the reaction back to preferential attack at the less substituted carbon.

Like in the case of palladium, in the absence of a nucleophile, elimination of the elements of acetic acid occurs. The ready availability of γ-acetoxy-α,β-unsaturated esters in two steps from aldehydes and α-sulfinylesters (**29** + **30** → **31**) led to a very simple synthesis of trichonine from stearyl aldehyde (eq. 43) [61]. The molybdenum





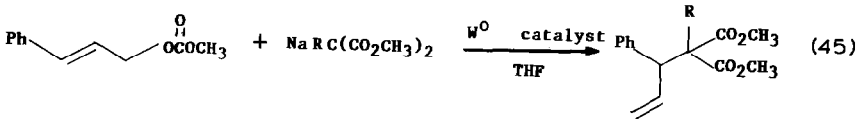
catalyst also effects coupling of the allyl acetates with tris(trimethylsilyl)aluminum but with net retention (eq. 44) rather than inversion of configuration as happens with the palladium catalyzed reaction [55].



(44)

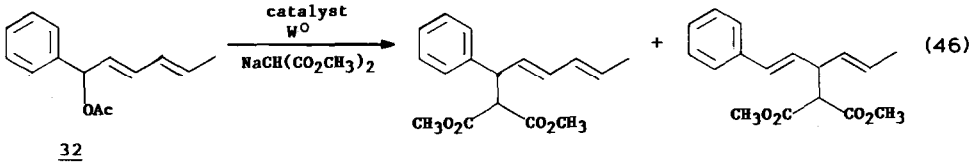
A tungsten-catalyzed reaction

In trying to generalize the regioselectivity to favor attack at the more hindered position, we thought we could increase the steric demands of the catalyst by going from molybdenum to tungsten. An active catalyst could be generated by treating $(CH_3CN)_3W(CO)_3$ with 2,2′-bipyridyl. Indeed, a substrate like cinnamyl methyl-carbonate reacts selectively at the more substituted benzylic position regardless of the steric demands of the nucleophile (eq. 45) [62]. This catalyst very much reflects



(45)

the charge distribution and LUMO coefficients which predict a 1/1 mixture of attack at C(1) and C(3) in the alkylations of dienyl acetate **32** (eq. 46) but strongly favoring attack at C(3) in the case of the pyridyl substrate **33** (eq. 47) [63]. Experiment verifies both predictions.



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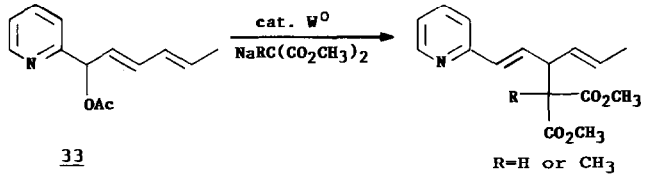
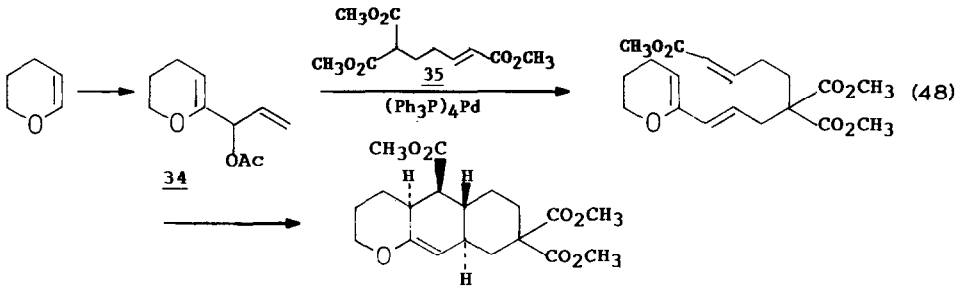
32



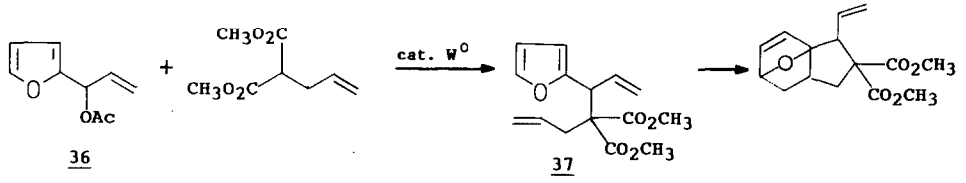
(47)

33

One virtue of such methods is the types of products that result. For example, it is easy to create a 1,3-diene by regiocontrolled alkylation of a dienyl carboxylate. If a dienophile is incorporated into the nucleophile, a subsequent Diels–Alder reaction permits rapid creation of polycyclic systems [64]. For example, creation of a 1,3-diene by alkylating **34**, available in a one pot operation from dihydropyran, requires alkylating at the terminal carbon, a regioselectivity ideal for palladium(0) templates. Thus, even sensitive nucleophiles like the acrylate **35** participate without



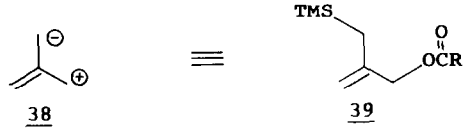
difficulty in these reactions. Alternatively, alkylation of **36**, available in one pot from furfural, must proceed at the more substituted position in order for the product **37** to



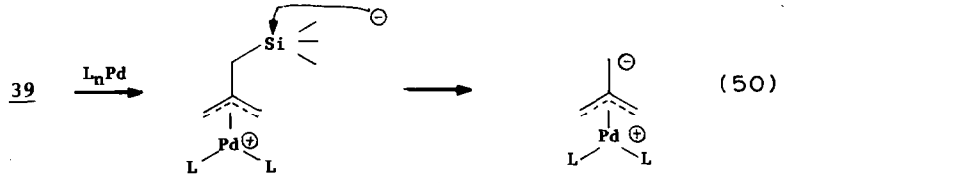
undergo an intramolecular Diels–Alder reaction. For such a regiochemistry, we choose a tungsten catalyst.

A cycloaddition to cyclopentanes

The ability to ionize poor leaving groups with transition metals suggested an approach to a problem that had concerned us for sometime, a selective cyclopentannulation. In trying to design a synthetic equivalent of a dipolar form of trimethylenemethane **38**, we envisioned that a carboxylate could be a synthon for a carbocation

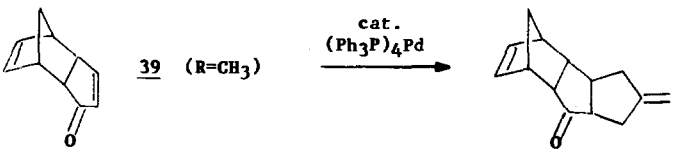


and a trimethylsilyl group as a synthon for a carbanion, both of whose reactivities are such that they may coexist. The lack of reactivity of **39** thereby requires a specific activation which may be initiated by ionization of the leaving group with a palladium(0) catalyst as in eq. 50. The presence of the electron deficient π-allyl



cation should weaken the C–Si bond such that a weak silylophile like acetate would effect cleavage to give the TMM unit as its palladium complex.

This hope was satisfyingly realized by heating **39** ($R = CH_3$) with an olefin bearing an electron-withdrawing group as in **40**. This reaction proved to be general with respect to the acceptor (the olefin), the only requirement being that it bear at least one electron-withdrawing group [65–71].



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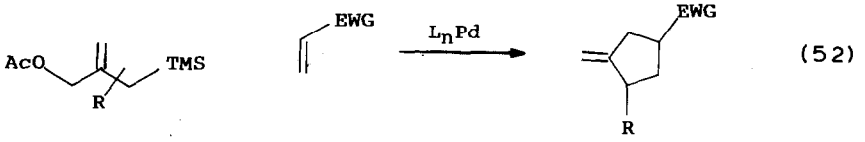
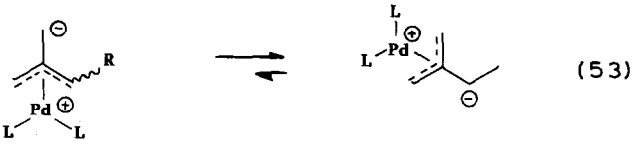
Our next goal was to focus on the substituent compatibility on the trimethylenemethane fragment. Indeed, electron-withdrawing, neutral, and electron-donating substituents can all be tolerated [72,73]. As eq. 52 summarizes, all of these reactions



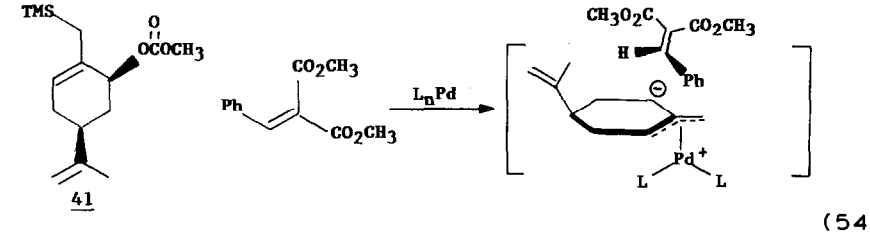
R = COC_2H_5, $CH{=}CH_2$, Ph, CH_3, OAc

are regioselective. To determine the source of this regioselectivity, we turned to computational methods which suggested that equilibria of the type represented by eq. 53 lie to the right, regardless of whether the substituent is electron donating or



electron withdrawing, a heresy in organic chemistry [74]. As we delved into these calculations, it appeared that increased stability due to enhanced bonding energy to the metal accounts for the position of the equilibrium in the cases of electron-donating ligands; whereas, anion stabilization accounts for the effect of electron-withdrawing groups.

In order to probe the possibility for asymmetric induction, we needed to establish



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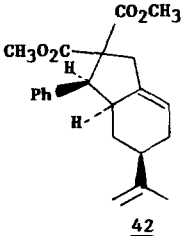
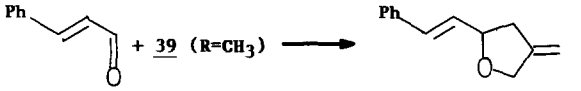


42

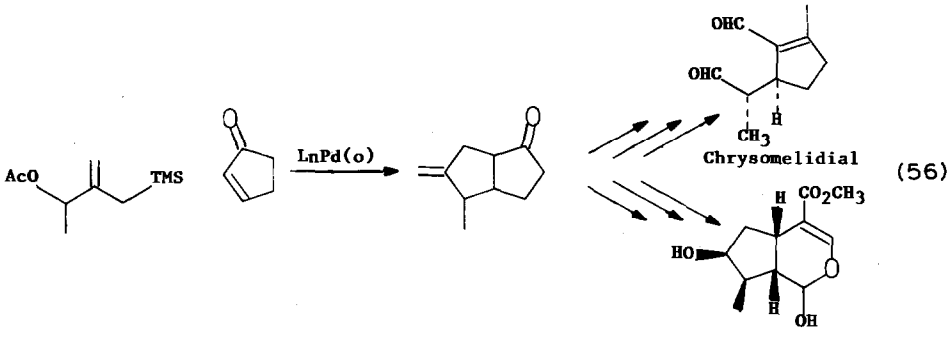
the stereochemistry of approach of the acceptor to the trimethylenemethanepalladium. At first glance, such a process is akin to metal-catalyzed cooligomerizations and would be anticipated to arise by binding the acceptor to the metal followed by ligand reorganization to lead to the cycloaddition product. Such an analogy proved misleading since the new C–C bond in the annulation product **42** forms on the same face of the π-allyl unit from which the carbonate of the bifunctional conjunctive reagent departs (eq. 54) [75]. Since we have previously shown that the ionization of allylic carboxylates proceeds with inversion of configuration, then the acceptor must approach on the face of the trimethylenemethane that is opposite to that of the metal to give the net retention of configuration, a new mechanistic type.

Having established the ability of electron-deficient olefins to participate in cycloadditions, we wanted to see whether the parallel to the Diels–Alder reaction would extend to carbonyl partners. In fact, cinnamaldehyde preferentially undergoes carbonyl addition to give the methylenetetrahydrofuran (eq. 55), a reaction that appears to be general for aldehydes [76].



(55)

After we established the general feature of this cycloaddition, we explored the implications for retrosynthetic analysis of complex molecules. We have completed three syntheses: that of chrysomelidial [72], loganin aglucone [77] and albene [78] for which the cycloadditions appear in eq. 56 and 57.



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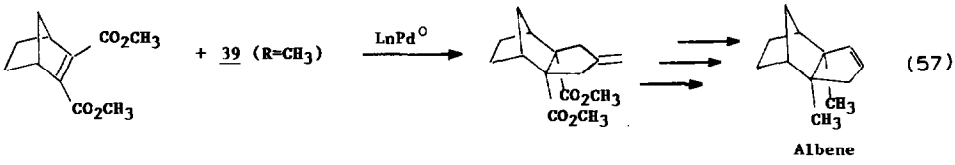

(57)

Conclusions

We have learned a great deal by our venture into the use of transition metals as catalysts. Frustration arises because a single "recipe" which the organic chemist treasures is frequently not possible. Each substrate has its own requirements that make optimization of reaction conditions necessary for each case. Furthermore, experimental rigor becomes more important due to the ease by which minor

components may poison the catalyst. On the other hand, elation derives from the opportunities presented for changing selectivities by appropriate modification of the reaction conditions and especially the nature of the catalyst. The ultimate goal becomes to design a catalyst for a specific purpose that can be made in a very short time. For formation of C–C bonds at allylic positions, we are having some success in doing just that.

Acknowledgement

I wish to especially acknowledge my outstanding coworkers who have been so much a part of the evolution of this field in our laboratories. I am indebted to the National Science Foundation and the National Institutes of Health for their generous support of our programs.

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