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ORGANOPALLADIUM INTERMEDIATES IN ORGANIC SYNTHESIS

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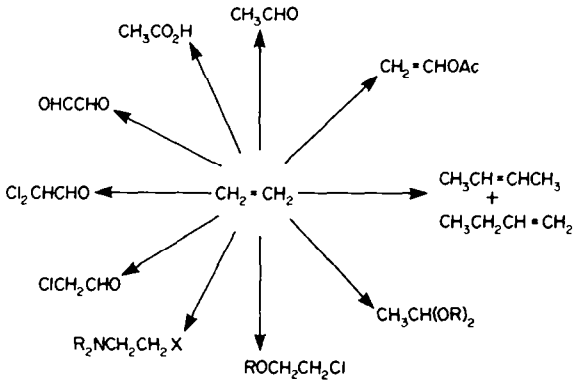
INTRODUCTION

The stimulus to more thoroughly explore the organic chemistry of palladium stemmed from the development of an efficient industrial process for the conversion of ethylene to acetaldehyde using soluble palladium catalysts (the Wacker process).[1,2] The early studies focusssed heavily on the ability to oxidize olefins and to understand the mechanism of these reactions. Scheme 1



Scheme 1. Additions to olefins catalyzed by palladium.

illustrates many of the transformations of olefins catalyzed by palladium salts.[2,3] This scheme demonstrates the versatility as well as one of the problems of palladium catalyzed reactions, i.e. how does one control the reaction course among several competing and closely related processes. On the other hand, the subtle effects achievable by the change of reaction conditions, mainly choice of ligands, allows for a chemoselectivity not easily attainable by any other methods. This aspect provides a strong motivation to develop the area of organopalladium chemistry especially in terms of the synthesis of complex organic molecules.

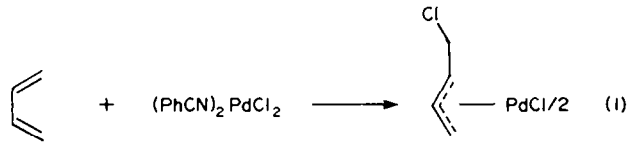
The explosive growth of organopalladium chemistry is attested to by the large number of reviews[1,2,4-18] and the appearance of a two volume set.[3] It is not the purpose of this account to update these comprehensive surveys. This account focusses on only a limited number of the reactions of organopalladium chemistry that appear to the author to have greater potential to serve the organic chemist in designing more efficient reactions and consequently synthetic strategy. The review is organized according to the type of organopalladium intermediate. Frequently much is learned from studying reactions that are stoichiometric in palladium with the desire that eventually they will be convertible into a catalytic process. Sometimes such a desire may not be realized. Even so, the ease with which palladium can be recycled makes the stoichiometric processes of interest in the syntheses of fine organics. Mechanism will be treated only in the context of providing sufficient understanding to make use of or further develop a reaction. In most instances, a few suggested mechanisms are proven but are presented since they allow a rationalization of a vast body of information.

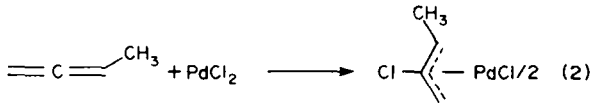
π-Allylpalladium intermediates

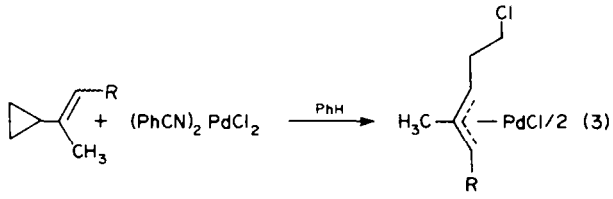
Formation. The first π-allylpalladium complex was prepared by the addition of palladium chloride to butadiene although the structure was not originally recognized as that of a π-allyl complex.[19-21] Addition of nucleophiles to dienes (eqn 1),[20,22] allene (eqn 2),[23] and vinylcylopropanes (eqn 3)[24] lead initially to π-allylpalladium complexes which can be isolated. Such complexes are normally crystalline, air stable materials that can be handled with ease. Unlike many organometallics, they can be easily purified by crystallization or by using chromatography. In these three cases, good yields are obtained with heteroatom nucleophiles.

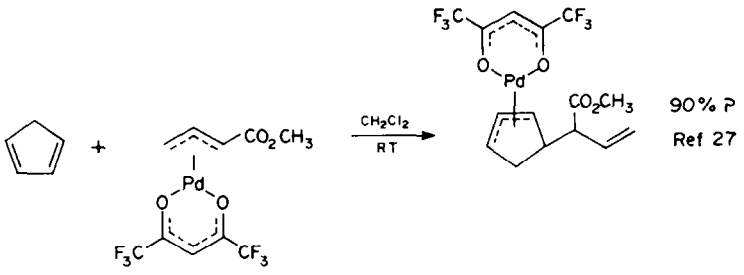
These reactions can be rationalized as involving nucleophilic attack by the chloride or alcohol (if performed in alcoholic solvents) on an olefin palladium complex. A neighboring double bond can compete with the external nucleophile. Thus, ocimene undergoes the expected simple addition, whereas, myrcene undergoes cyclization concommittant with addition.[25]

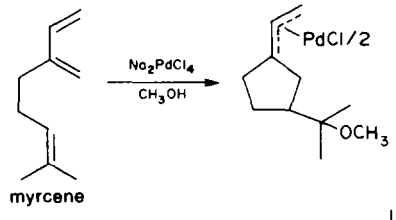
The analogy to the addition of heteroatom nucleophiles to olefins is apparent (*vide infra*). While in such cases the σ complexes are unstable and decompose, in the case of dienes, the stability associated with π-allyl complexes allows their isolation. A major reaction in the case of simple olefins is the Heck arylation (*vide infra*). Application of this reaction to dienes proceeds in moderate yields to give the isolable π-allyl complexes.[26] A most interesting chain extension occurs upon treatment of a preformed π-allylpalladium complex with a diene.[27-30] The reaction involves complexation to the less hindered double bond of an unsymmetrical diene followed by sigmatropic rearrangement and constitutes *cis* addition to the more substituted double bond.

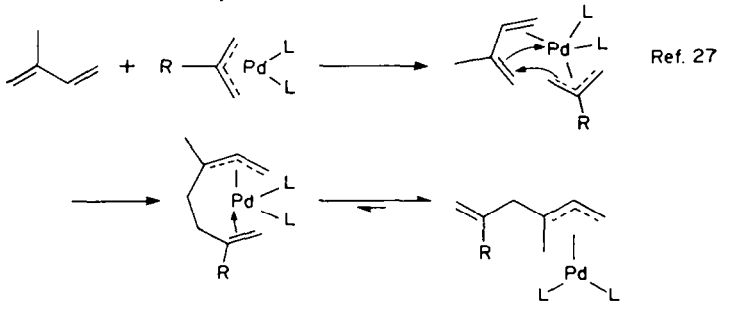

Cl
+ (PhCN)2 PdCl2
PdCl/2 (1)

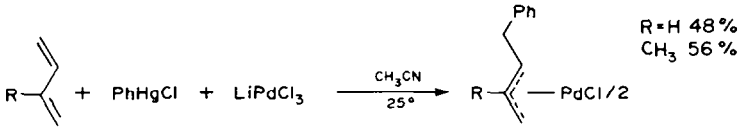

CH3
+ PdCl2
Cl
PdCl/2 (2)


Cl
R
+ (PhCN)2 PdCl2
PhH
H3C
PdCl/2 (3)
CH3
R


F3C
CF3
O
Pd
O
CO2CH3
90% P
Ref 27
CH2Cl2
RT
+
CO2CH3
Pd
O
O
F3C
CF3
ocimene
Na2PdCl4
CH3OH
OCH3
PdCl/2


Na2PdCl4
CH3OH
PdCl/2
OCH3
myrcene


+ R
Pd
L
L
L
Pd
L
R
Ref. 27
Pd
L
L
R
R
Pd
L
L
R = Cl
= CH3

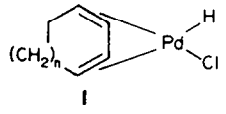

R
+ PhHgCl + LiPdCl3
CH3CN
25°
Ph
R
PdCl/2
R=H 48%
CH3 56%

Reduction of dienes to π-allylpalladium complexes occurs with palladium chloride in aqueous acetic acid.[22b] An intermediate such as **1** which can arise by the excess diene serving as a reducing agent accounts for the success of this reaction. Allylations of amines, alcohols, and active methylene and methine compounds (e.g. β-ketoesters, 1,3-diketones, etc.) by butadiene (*vide infra*) presumably involve a similar first step.

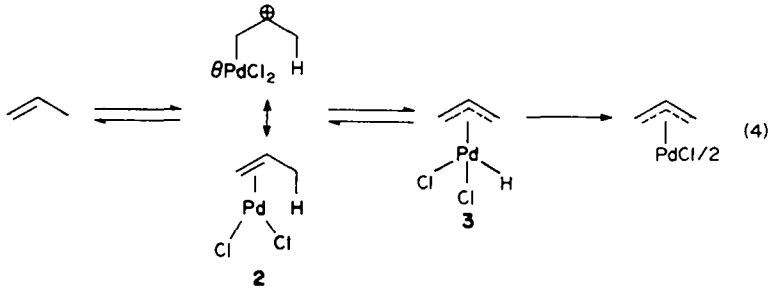
Synthetically, a major advance arose by the direct conversion of olefins to π-allylpalladium complexes since it allows the direct and chemoselective substitution at an allylic position of a simple olefin. The reaction presumably involves a π-olefin complex **2**[31] and a palladium hydride species **3**.[32-34] It is the fate of these two intermediates that determine the success of this approach.

Many different conditions have been employed. Early conditions involve palladium chloride[35-41] or a soluble form, either as sodium or lithium tetrachloropalladate[42-45] or bis-benzonitrilepalladium chloride[46,47] in solvents such as an alcohol or aqueous acetic acid (e.g. eqns 5–7). The use of palladium acetate in the presence of tetra-n-butylammonium chloride in methylene chloride has also been recommended.[49] The sensitivity of the product and/or starting material to redox reactions under these conditions limits the usefulness of such an approach. With nonconjugated polyenes, cyclization (*vide supra*) and/or addition to the double bond (as in the case of dipentene **4**) complicate the reaction.[50]

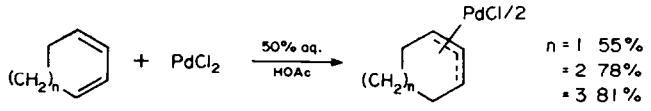
Use of anhydrous acetic acid, a dipolar aprotic or an aprotic solvent in the presence of a weak base[42,53] improved the generality of the reaction. Most importantly,

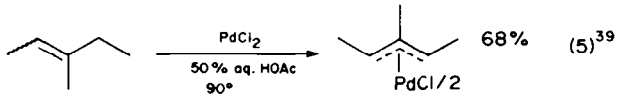


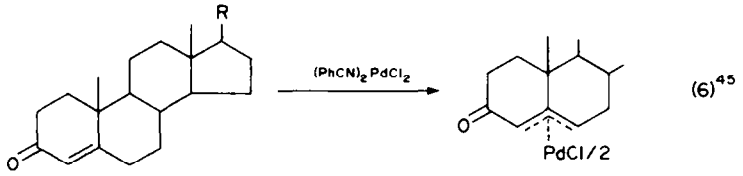
1

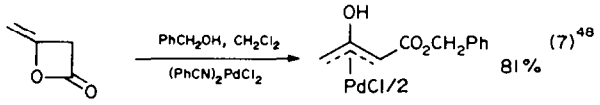


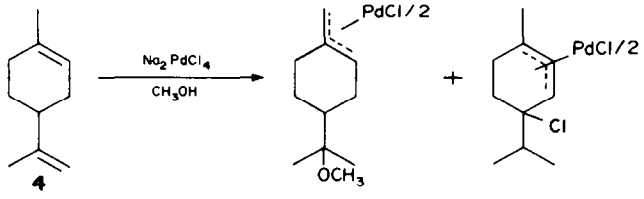
2 **3**



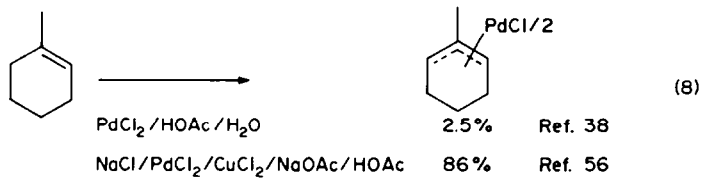


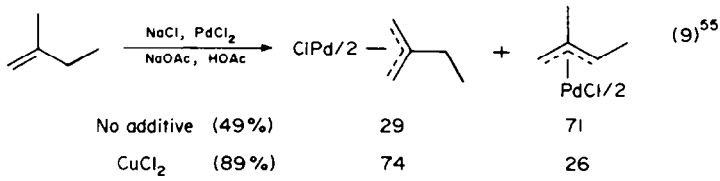


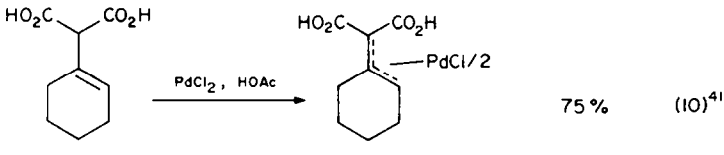




4







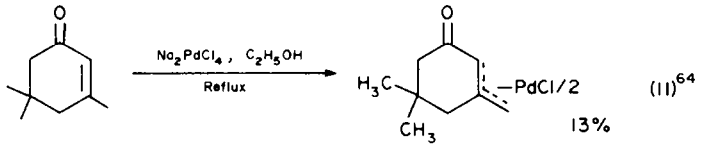


Table 1. Palladation of olefins to form π-allylpalladium complexes[a]

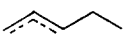
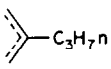
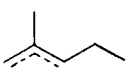
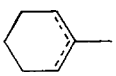
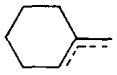
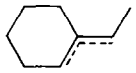
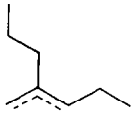
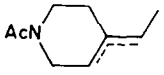
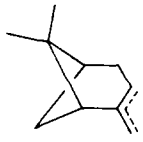
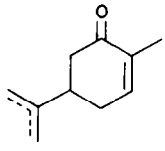
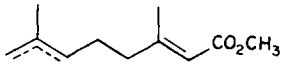
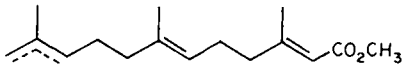
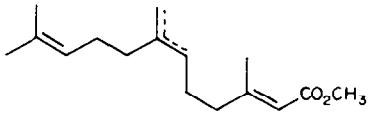
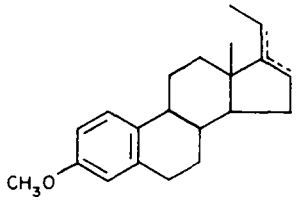
Entry	Olefins	Complex	M.P. (dec)	Yield	Ref.
1	cis-2-pentene		160°	72%	57
				10%	
2	1-methylcyclopentene		129°-132°	66%	56
3	cyclohexene		92°-65°	100%	56
4[b]	1-methyl-1-pentene			65%	55
				12%	
5	1-methylcyclohexene		88°-90°	86%	56

Table 1. (*Contd*)

Entry	Olefin	Complex	M.P. (dec)	Yield	Ref.
6	methylenecyclohexane		131-8°	92%	56
7	ethylidenecyclohexane		123-9°	57%	56
8	2-n-propyl-1-pentene		130-1°	95%	44
9	N-acetyl-4-ethylidene piperidine		142-152°	71%	58,59
10	β-pinene		161-8°	66%	59,60
11	4-t-butyl-1-methylene cyclohexane		165-70°	90%	61
12	carvone		152-6°	52%	59
13	methyl geraniate		117-8°	68%	62
14	methyl farnesoate		oil[c]	34%	62
			114-121°	4%	
15	3-methoxy-cis-19-norpregna-1,3,5(10),17(20)-tetraene		161-182°[d]	67%	63

(a) All reactions were performed in the presence of cupric chloride, sodium chloride, palladium chloride, and sodium acetate in acetic acid unless otherwise noted. (b) In this case, sodium chloride was omitted from the reaction. (c) Crystallization occurs at -78°. The oil analyzes properly (Calc'd: C, 49.12; H, 6.44; Cl, 9.06. Found: C, 49.09; H, 6.36; Cl, 9.14). (d) Although decomposition range is unusually large, nmr analysis (3.74, 1H; 3.56, 1H; 1.26, d, 3H; 1.00, s, 3H) indicates a stereohomogeneous complex and elemental analysis (Calc'd: C, 57.84; H, 6.18; Cl, 8.06. Found: C, 57.68; H, 6.22; Cl, 8.11) indicates chemical purity.

more rapid conversion of **3** to the π-allyl complex (eqn 4) by the addition of a weak oxidizing agent like cupric chloride not only improved the generality of the approach (cf. eqn 8) but also affected the regiochemistry (cf. eqn 9).[54-56] Table 1 lists some of the complexes that have been made in this way.

The reactions involve a Markownikoff orientation in that the proton abstracted is allylic to the more substituted end of the olefin (see eqn 4). In the absence of conformational or neighboring group effects, kinetic deprotonation is preferred in the order $CH_3 > CH_2 \gg CH$. The observation that 2,3-dimethyl-1-butene produces bis(1,1,2 - trimethyl - π - allylpalladium chloride) with palladium chloride in aqueous acetic acid may be a result of thermodynamic control since such conditions are equilibrating.[36]

Conformational control is illustrated by entries 2 and 5, Table 1, in which the exocylic and endocyclic complexes are obtained in the 5- and 6-membered ring cases respectively. Reaction conditions, acidity of the hydrogen being abstracted, and steric hindrance also affects this selectivity (eqns 10 and 11). While reaction occurs preferentially at nonconjugated double bonds (Table 1, entries 12, 13 and 14), conjugated double bonds react well too (eqns 6 and 11).[65]

The chemoselectivity of this reaction is well illustrated by the examples shown in Table 1. Consideration of the use of the aprotic methods, such as *bis*-benzonitrilepalladium chloride, allows these methods to be extended to acid sensitive substrates such as acetals or ketals.[66] Unreacted double bonds are normally not affected under these conditions as suggested by entries 13 and 14 and proven in the case of the **E** and **Z** isomers of geranylacetone.[67] In formation of the terminal π-allylpalladium complexes **4** and **5**, the integrity of the internal double bond remains intact.

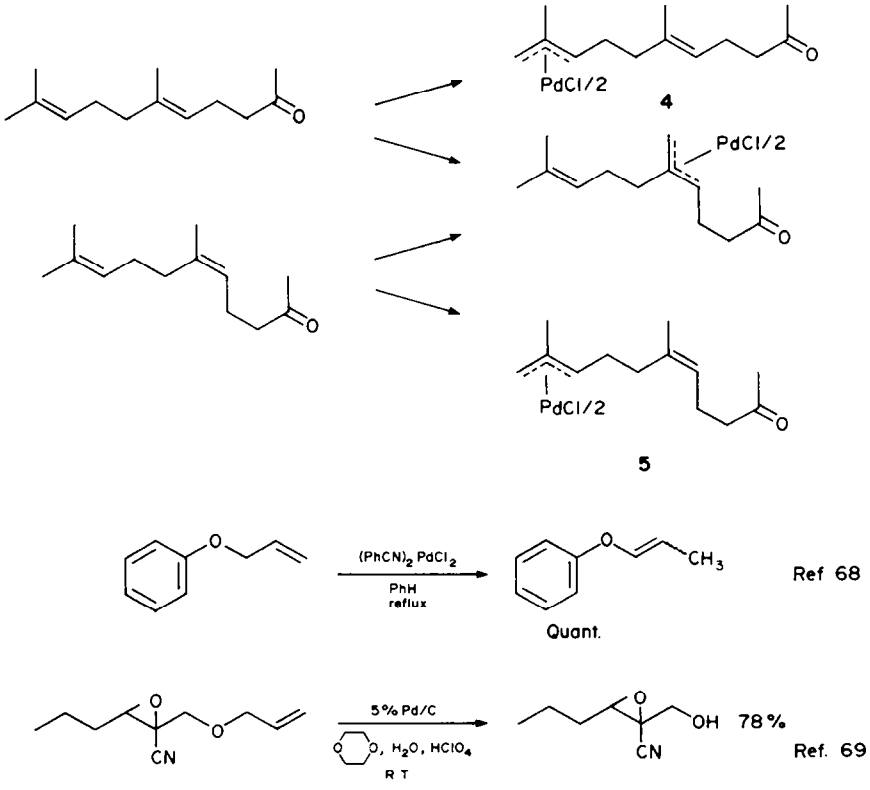
That such reactions in their early stages can be reversible can be utilized to migrate double bonds. The ability to convert an allyl ether to a vinyl ether which can easily be hydrolyzed allows the allyl group to be used as a protecting group for alcohols.[68,69]

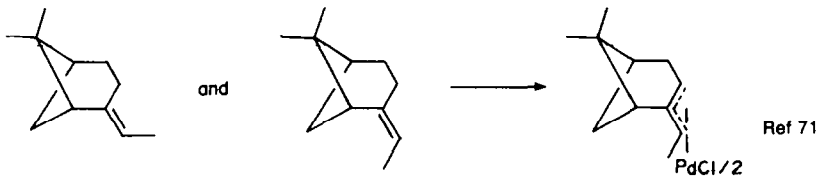
The stereochemistry of the π-allylpalladium complex is independent of the stereochemistry of the starting olefin and reflects the thermodynamic stability of the resultant complex. Since the *syn* complexes are normally more stable than the *anti* complexes,[70] the reaction does show a high degree of stereoselectivity. The bulk of the palladium chloride portion normally places this group on the less hindered face of the π-allyl unit (see Table 1, entry 15). Starting with a mixture of the two geometric isomers of 2-ethylidenenorpinane only a single π-allylpalladium complex is obtained which possessed the *syn* configuration and the palladium *trans* to the *gem* dimethyl bridge.[71]

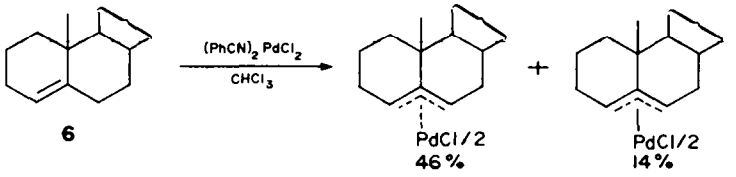
With a $\Delta^{4(5)}$ steroid a mixture of the α and β complexes are obtained; whereas, only the α complex resulted from the $\Delta^{5(6)}$ isomer.[47] The unexpected observation of appreciable amounts of the β isomer from **6** follows the same trends seen in catalytic hydrogenations in which the amount of 5β dihydro product is formed in larger amounts from the $\Delta^{4(5)}$ compared to the $\Delta^{5(6)}$ isomer.

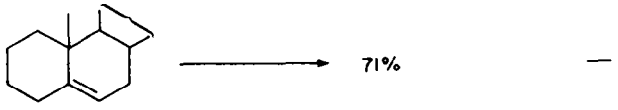
Additions of alkynyl- or vinylpalladium (generated *in situ* from the corresponding organomercury) compounds to olefins lead to π-allylpalladium complexes after hydrogen rearrangement.[72] Since the vinylmercury compounds have their origin from the acetylenes, it becomes an interesting disubstituted olefin synthesis.

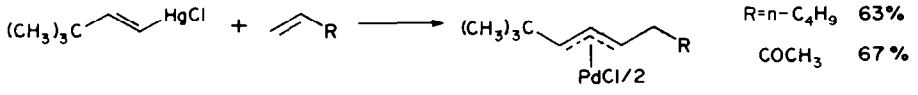
While the direct conversion of olefins to π-allyl complexes can be viewed as a formal oxidation of the organic fragment and reduction of the metal in the formation of **3**, the reverse situation can also be envisioned—i.e. the oxidative addition of an allylically ox-

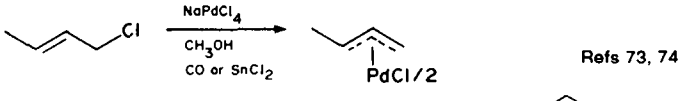


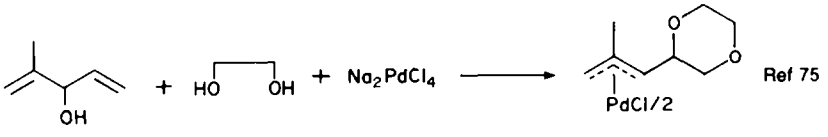

and
PdCl/2
Ref 71

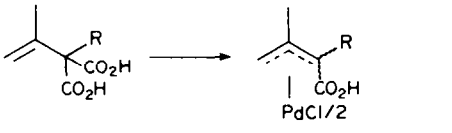

(PhCN)2 PdCl2
CHCl3
6
PdCl/2
46%
PdCl/2
14%
Ref 47

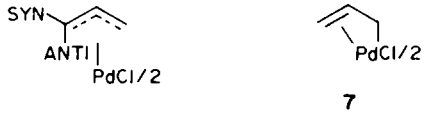

71%
—

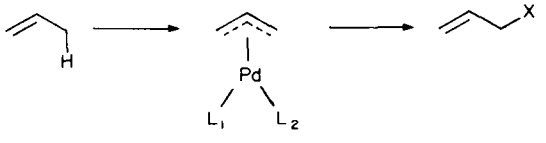

(CH3)3C
HgCl
R
PdCl/2
R=n-C4H9 63%
COCH3 67%

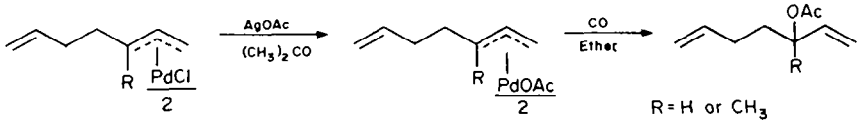

NaPdCl4
CH3OH
CO or SnCl2
PdCl/2
Refs 73, 74

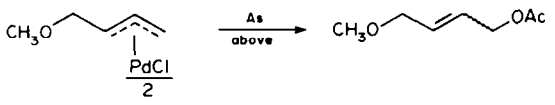

OH
HO
OH
Na2PdCl4
O
O
PdCl/2
Ref 75


R
CO2H
CO2H
PdCl/2
Ref 41


SYN
ANTI
PdCl/2
PdCl/2
7


H
Pd
L1
L2
X


R
PdCl
2
AgOAc
(CH3)2CO
R
PdOAc
2
CO
Ether
OAc
R
R=H or CH3

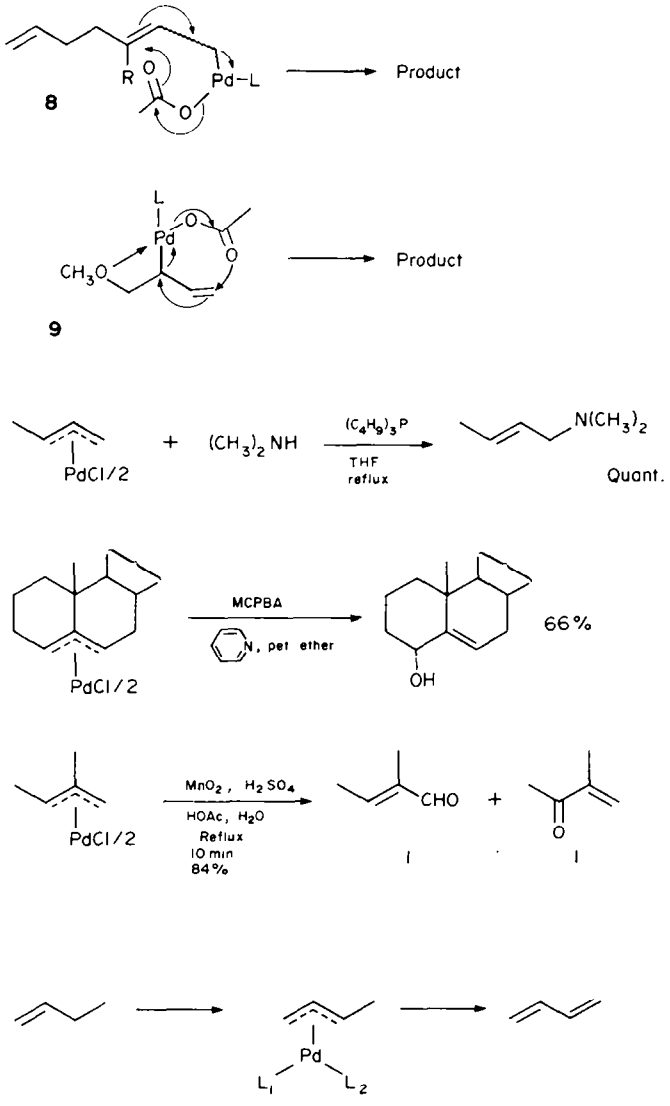

CH3O
PdCl
2
As
above
CH3O
OAc

idized compound (e.g. allylic halide, carboxylate, etc.) to palladium (0). Thus, crotyl chloride is converted to its corresponding complex in the presence of a reducing agent such as carbon monoxide[73] or stannous chloride.[74] Divinyl carbinols undergo a similar reaction concommittant with vicinal ether formation of the uncomplexed double bond.[75] A further interesting variant is the decarboxylation of vinylmalonic acids.[41]

The stereochemistry of the π-allylpalladium complexes is ascertainable via NMR spectroscopy in that an *anti* proton normally absorbs approximately 1–2 ppm to higher field than a similarly situated *syn* proton.[76] These complexes have also been characterized by ^{13}C NMR spectroscopy.[77] The formulation as a π-allyl complex rather than a σ complex such as **7** is supported by the spectroscopic and X-ray crystallographic data.[3] Variation of the ligands at palladium can favor the formation of such σ complexes.[78]

Stoichiometric reactions. Redox reactions of π-allylpalladium complexes are among the first studied. Attack of heteroatom nucleophiles (e.g. O, N, etc.) leads to the products of net allylic oxidation considering the availability of the complexes from olefins. Such reactions gained interest from a study of the mechanism of allylic acetoxylation catalyzed by palladium salts. Addition of a ligand such as carbon monoxide to a π-allylpalladium acetate dimer leads to migration of acetate from palladium to carbon.[79] The regiochemistry may be rationalized on the basis of σ-complexes as intermediates. Thus, the less substituted complex **8** should dominate and if decomposition occurs with allylic inversion, as in the case of the corresponding mercury system, the product involves addition to the more substituted carbon. However, the presence of the internal coordination site in **9** leads to an abnormal regiochemistry in this case. This approach to allylic acetates may serve as a useful approach to the thermodynamically less stable allylic acetate. Lead tetraacetate in acetonitrile[26] and mercuric acetate in acetic acid[80] also convert these complexes to their corresponding allylic acetates. The greater lability of the π-allylpalladium acetates to migration of acetate from Pd to C suggests the importance of high chloride ion concentration in the reactions to synthesize the π-complexes without decomposition.[81]

Substitution with retention of configuration has been shown with *m*-chloroperbenzoic acid (MCPBA).[82] Metal oxidants like chromic acid, manganese dioxide, and even excess palladium chloride in aqueous acid solvent converts these complexes to the carbonyl derivatives.[37] Amines attack π-allylpalladium chloride complexes ac-



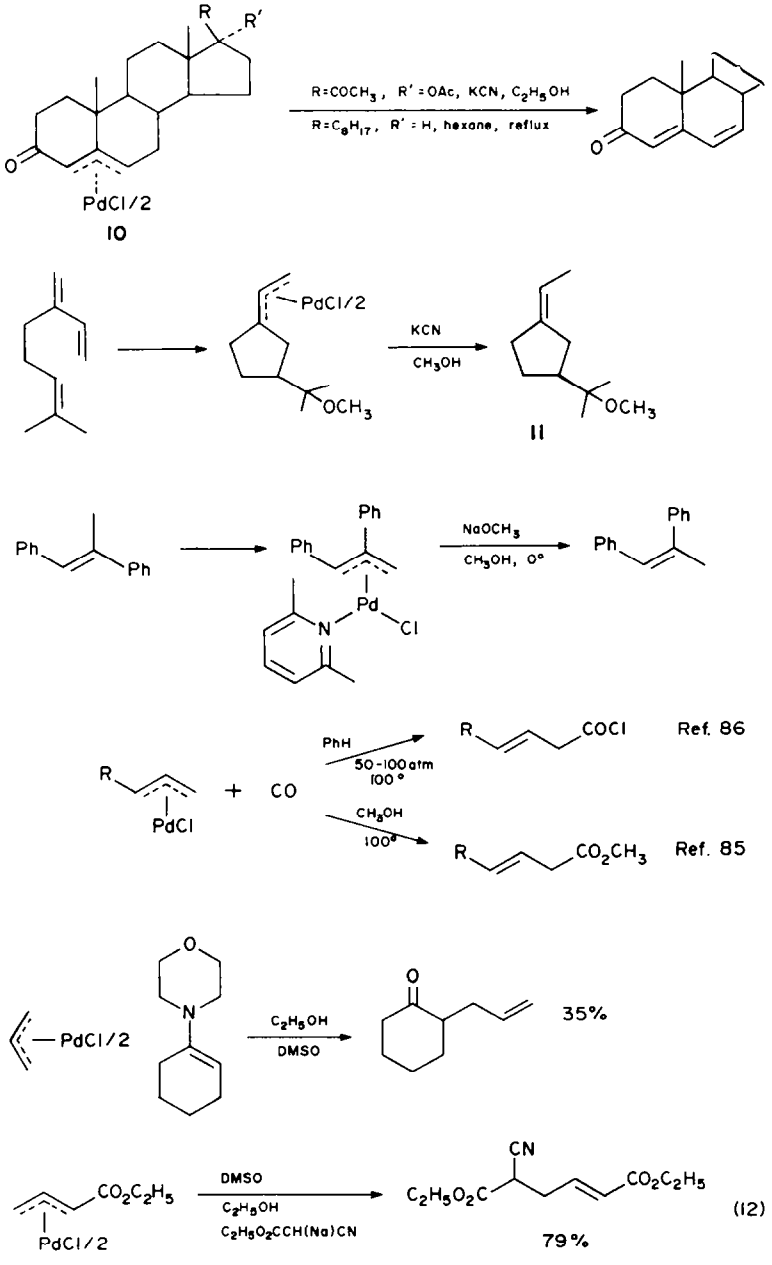
tivated by phosphines (*vide infra* for a discussion of this effect) to give allylic amines with addition to the less substituted carbon.

A net dehydrogenation results upon deprotonation of a π-allyl complex and may be considered the reverse of the formation of π-allyl complexes from dienes. Complex **10** is particularly prone to decomposition to the diene either thermally[50] or in the presence of cyanide ion.[51]

Simple π-allylpalladium complexes undergo reduction in basic alcoholic solvents. Thus, ocimene is converted to the ethylidenecyclopentane **11** by a two step process and thus comprises a useful cyclization method.[25] An interesting olefin isomerization of **E**-α-methylstilbene to **Z**-α-methylstilbene made use of the thermodynamically more stable *syn* complexes to control olefin geometry.[84] This reaction suggests that reduction is stereospecific.

The most interesting reactions involve the formation of new carbon–carbon bonds. The earliest studies examined insertion of carbon monoxide to generate β,γ-unsaturated carboxylic acid derivatives. Isonitriles behave similarly to carbon monoxide in which case the β,γ-unsaturated imino ether is the product.[87] However, these reactions have been most studied in a catalytic process and thus further discussion is postponed to that section.

Bis-(π-allylpalladium chloride) has been shown to be attacked at carbon by carbon nucleophiles like the anions derived from diethyl malonate and ethyl acetoacetate[88] or enamines.[88,89] This type of reaction fails with any but the parent π-allylpalladium complex except when the π-allyl unit bears a strong electron withdrawing group (eqn 12).[90] This example illustrates the utility of this approach for γ-alkylation of α,β-unsaturated carbonyl systems.

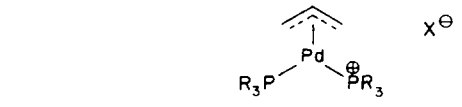


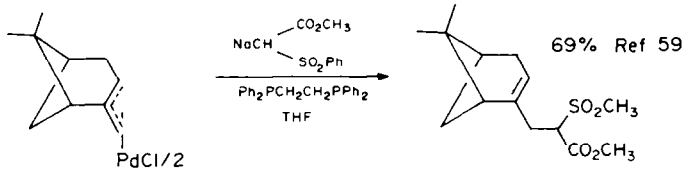
The requirement for a solvent that could also serve as a ligand[91] suggests the need to dissociate the π-allyl complexes in order to achieve substitution. In fact, a general alkylation procedure for virtually all π-allylpalladium complexes in ethereal solvents like THF or DME is available upon addition of a trivalent phosphorus derivative—phosphines, phosphites, phosphorus-triamides, etc.[44,56-59,61-63] The optimum stoichiometry, 2 P per Pd, suggests the intermediacy of cationic complexes. Indeed, subjection of such complexes to these reactions leads to identical results.[59,61] The nature of the activating ligand determines the range of nucleophiles that can be utilized. With the most stabilized anions like those derived from diethyl malonate, methyl methylsulfonylacetate, or methyl phenylsulfonylacetate, triphenyl phosphine (TPP) or 1,2-bis(diphenylphosphino)ethane (DIPHOS) may be employed. With harder anions like those derived from phenylthioacetone, methyl phenylthioacetate or methyl phenylsulfinylacetate, hexamethylphosphorustriamide (HMP) is preferred. With the last nucleophile, a useful alkylative elimination allows a direct synthesis of dienoates from olefins.[93]

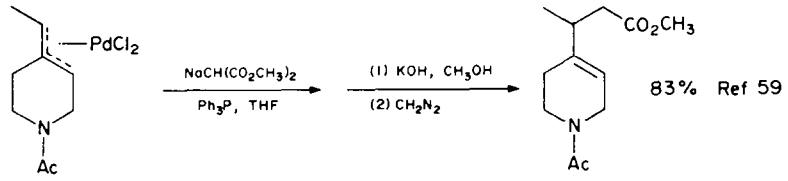
In some of these cases, activation by the use of the phosphine and DMSO as solvent may be desireable. Attempts to extend the alkylation to harder anions such as organometallics (derivatives of magnesium, lithium, zinc or copper), anions of thioacetals, or enolates of simple ketones or esters failed. Since the complexes are ambident electrophiles, nucleophiles can attack at carbon or palladium. Successful alkylation involves direct attack at carbon (*vide infra*). Attack at palladium by the harder anions leads mainly to disproportionation. Arylmercury compounds have been reported to lead to C-arylation.[26] Since the transfer of aryl groups from mercury to palladium is well documented[26] and since the reaction of arylthallium compounds does lead to isolable π-allylarylpalladium complexes,[94] these reactions may involve transfer from palladium to the allyl unit.

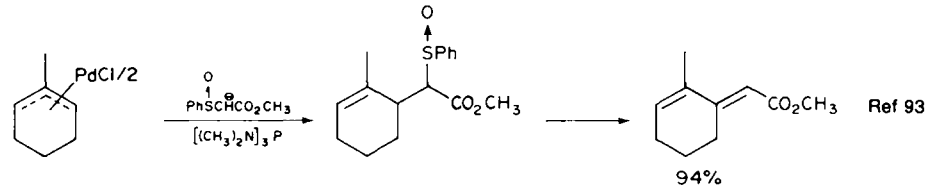
The regiochemistry in the case of 6-membered rings also depends upon the activating ligand.[61] While normally substitution occurs at the sterically most accessible end of the π-allyl unit, in the case of the complexes from methylenecyclohexanes reaction occurs either at the acyclic or cyclic end depending upon the steric bulk of the ligand. This phenomenon can be understood in terms of two competing effects—steric approach of the nucleophile and the relative stability of the initially formed π-olefin complexes **14** and **15**.[95] Sterically bulky ligands combined with the usual destabilization of the olefin complex by alkyl substitution on the olefin serve to make the stability of these intermediates the determining factor with tris-*o*-tolylphosphine (TOT).

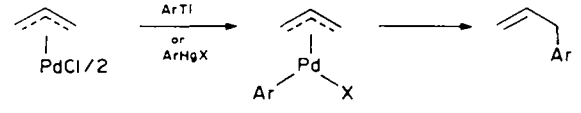
High stereochemical control is an important feature of this carbon-carbon bond forming reaction. In the cyclohexyl case **12** R = t-C_4H_9, ring substitution led to the axial product (cf. enolate alkylations[96]). At an acyclic

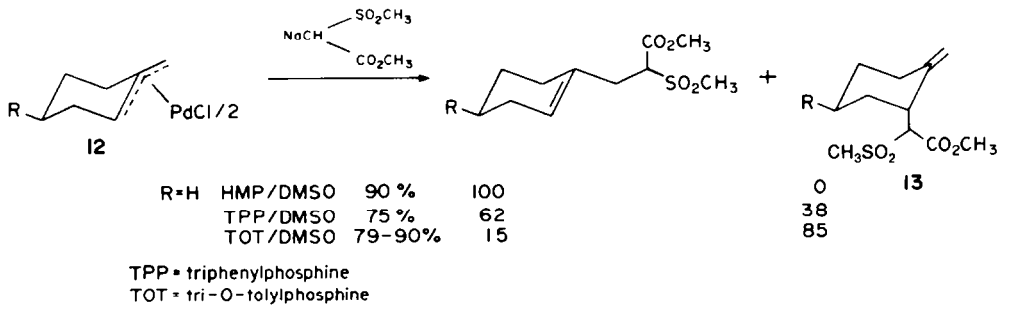


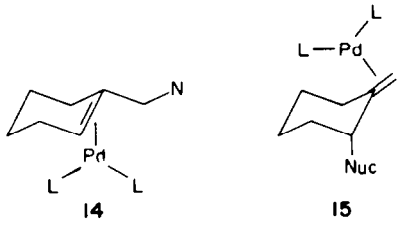


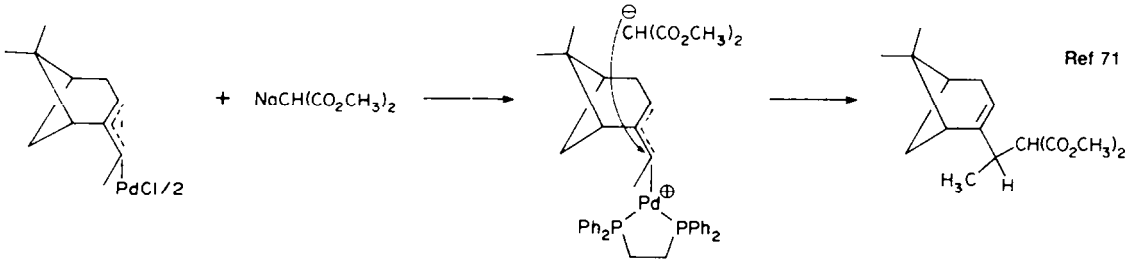


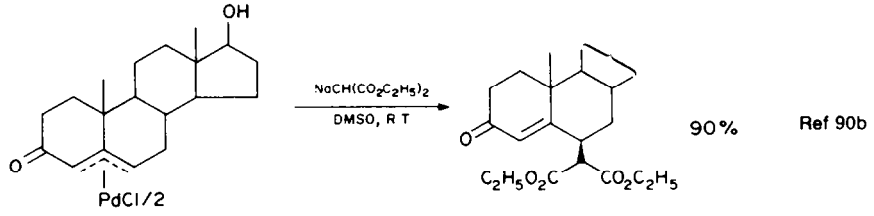


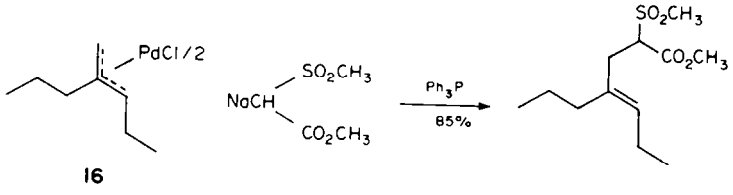








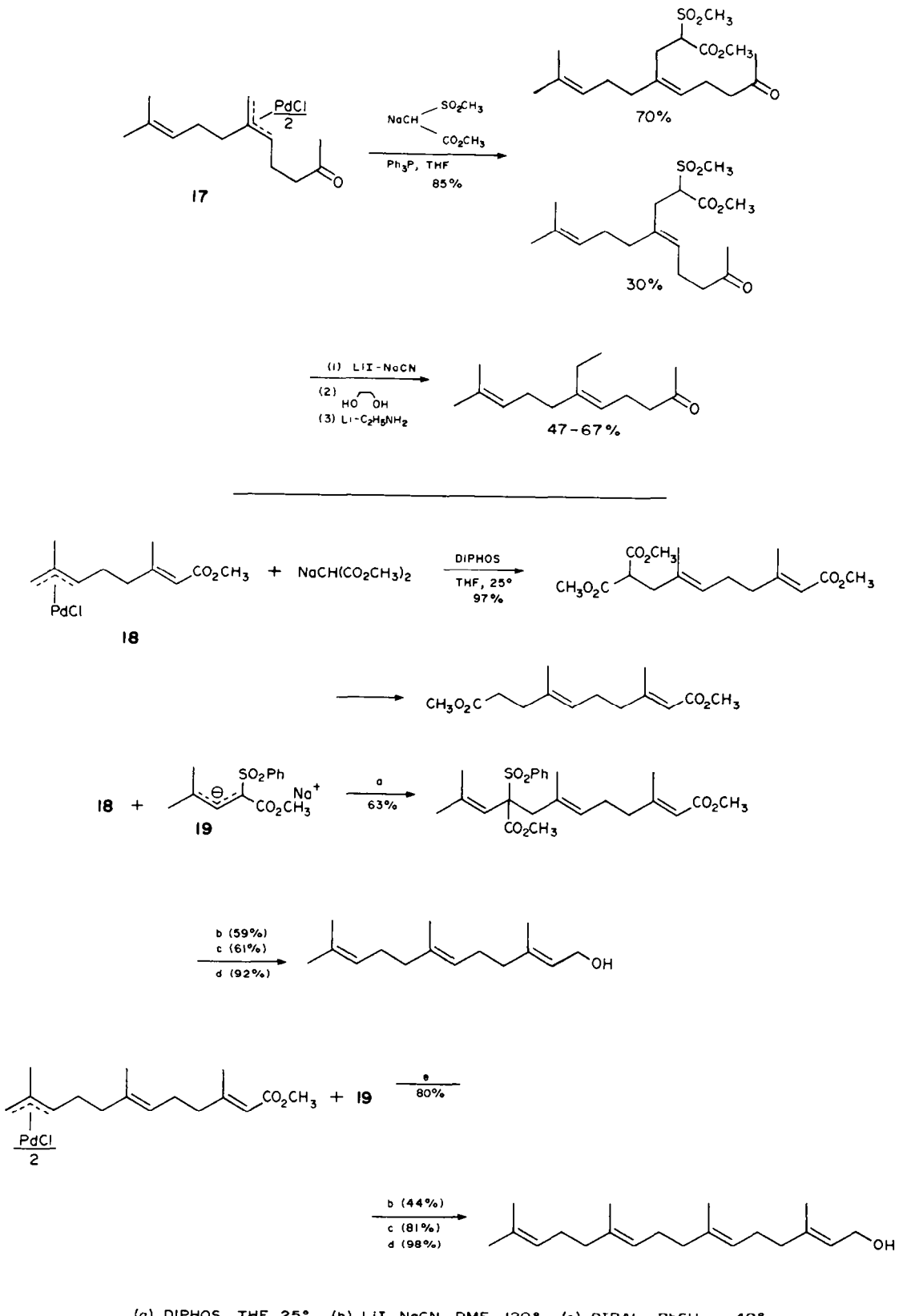




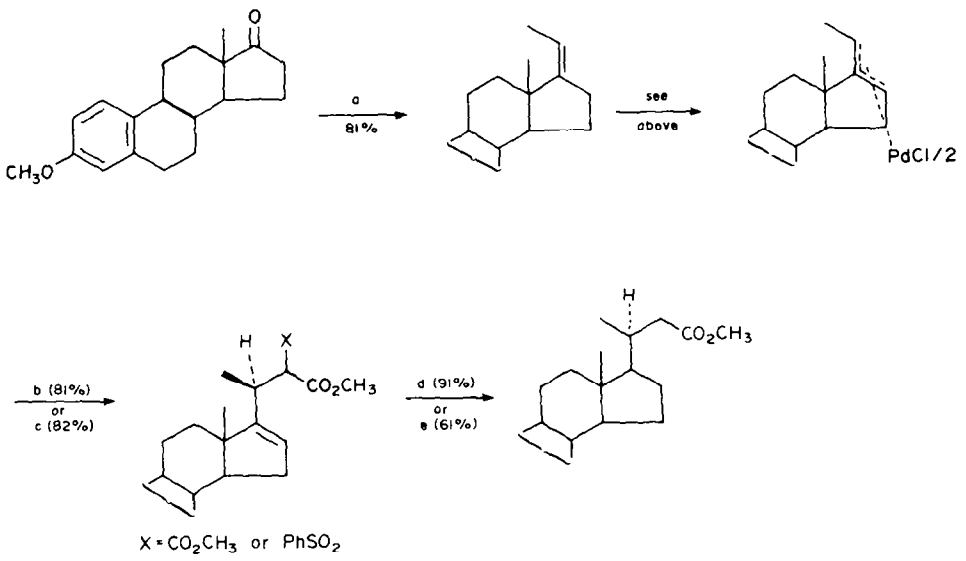
carbon, substitution occurs on the face opposite palladium.[71,90b] Since the starting π-complex is available from a mixture of olefin isomers and only a single stereoisomer is produced, this allylic alkylation represents a stereoconvergent approach.

The geometry of the olefin resembles the geometry of the starting π-allylpalladium complex. In these complexes, the preference for the *syn* rather than *anti* stereochemistry translates into a stereocontrolled olefin homologation independent of the stereohomogeneity or stereochemistry of the starting olefin. The degree of specificity does depend upon the substitution and nucleophile. The complex **16** which gave only a single product using the anion of the sulfone ester gave a mixture with dimethyl sodiomalonate. The complex **17** which bears bulkier groups began to produce more of the E olefin arising from the *anti* complex.[67] The use of the sulfone ester is highlighted by the ability to remove both activating groups to generate a simple alkyl homologation (i.e. methyl to ethyl).

Use of complex **18** allows the direct conversion of simple terpenes to more complex ones. Thus, alkylation with dimethyl sodiomalonate achieves a simple stereocontrolled synthesis of the dimethyl ester of a pheromone of the Monarch butterfly from methyl geraniate.[62] Scheme 2 illustrates a net prenylation of methyl geraniate to form farnesol and methyl farnesoate to form geranylgeraniol. In these cases, high regio- and stereospecificity are observed in the alkylation such that only the all *trans* isomers are observed.



Scheme 2. Prenylations.



Scheme 3. Synthesis of C-20 epimeric steroids.

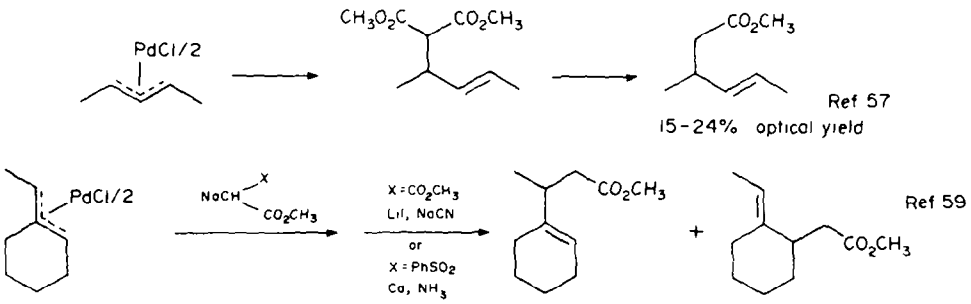
This stereochemical control can also be used to good advantage in steroid synthesis. As illustrated in Scheme 3, a side chain can be added to a 17-ketosteroid to give the C-20 epimeric series exclusively.[63]

The high stereochemical control in a relative sense suggested the possibility of chiral synthesis. Indeed, the use of chiral phosphines as the activating ligands has led to carbon–carbon bond formation of up to 74% optical yields, among the highest ever seen for such a "template-like" asymmetric carbon–carbon bond formation.[57,59]

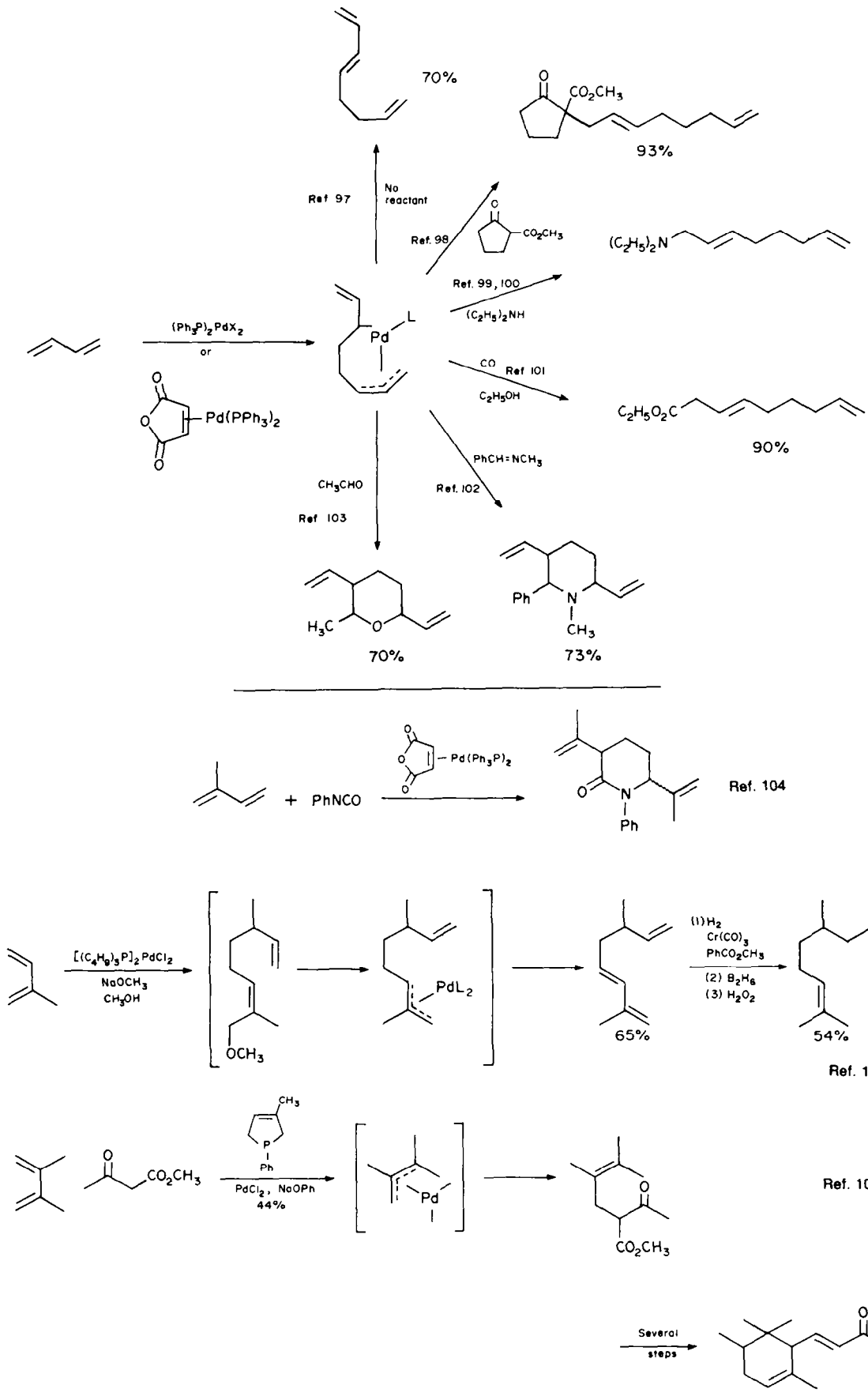
The above reactions illustrate the stereo- and chemoselectivity available for allylic substitutions via π-allylpalladium complexes. In each of the cases, the by-product is palladium (0) which can be easily recycled. While such a procedure makes this approach quite feasible and of general utility, a catalytic process would further enhance the utility of these reactions in synthesis.

In situ *Generation and catalytic reactions.* The oligomerization of dienes in the presence of X–H (alcohols, amines, malonates, etc.) catalyzed by palladium complexes represents some of the first examples of catalytic reactions involving nucleophilic attack on π-allylpalladium complexes (see equations on p. 2628).

The regiochemistry of this dimerization reaction with unsymmetrical dienes can be controlled by reaction



	Overall chemical yield	Optical yields	
X = CO_2CH_3			
(+) CAMPHOS	81%	25%	NP
(−) DIPAMP	49%	30%	33%
(+) DIOP	83%	26%	45%
X = $PhSO_2$			
(+) CAMPHOS	64%	66%	N.P.
(−) DIPAMP	49%	55%	74%
(+) DIOP	99%	63%	N.P.


70%
CO2CH3
93%
Ref 97
No reactant
Ref 98
CO2CH3
(C2H5)2N
Ref 99, 100
(C2H5)2NH
(Ph3P)2PdX2
or
Pd(PPh3)2
Pd
L
CO
Ref 101
C2H5OH
C2H5O2C
90%
PhCH=NCH3
Ref 102
CH3CHO
Ref 103
H3C
O
70%
Ph
N
CH3
73%
+ PhNCO
Pd(Ph3P)2
Ref 104
[(C4H9)3P]2PdCl2
NaOCH3
CH3OH
OCH3
PdL2
65%
(1) H2
Cr(CO)3
PhCO2CH3
(2) B2H6
(3) H2O2
OH
54%
Ref 105
CH3
P
Ph
CO2CH3
PdCl2, NaOPh
44%
Pd
O
CO2CH3
Ref 107
Several
steps
O

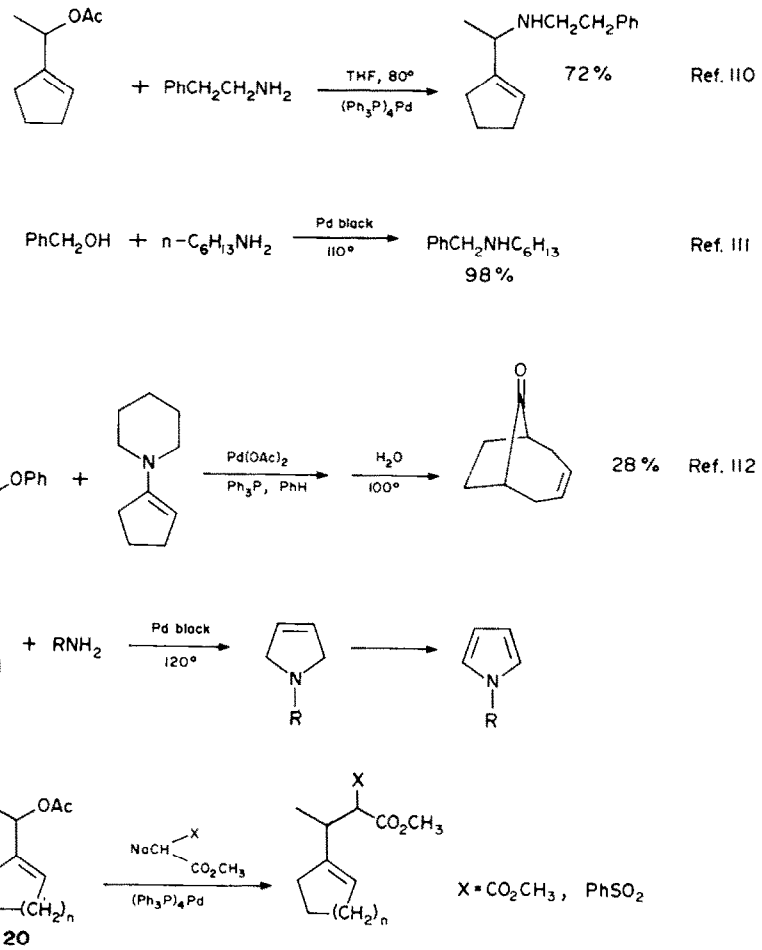
conditions. Thus, under the above conditions in the presence of phenyl isocyanate, a head to head coupling occurs;[104] whereas, in the presence of methanol a head to tail coupling occurs (see equation on p. 2628).[105] The latter probably involves the insertion of a second isoprene unit onto a π-allylpalladium complex formed by addition of methanol to a first isoprene unit. This latter sequence translated into a simple biomimetic synthesis of citronellol.

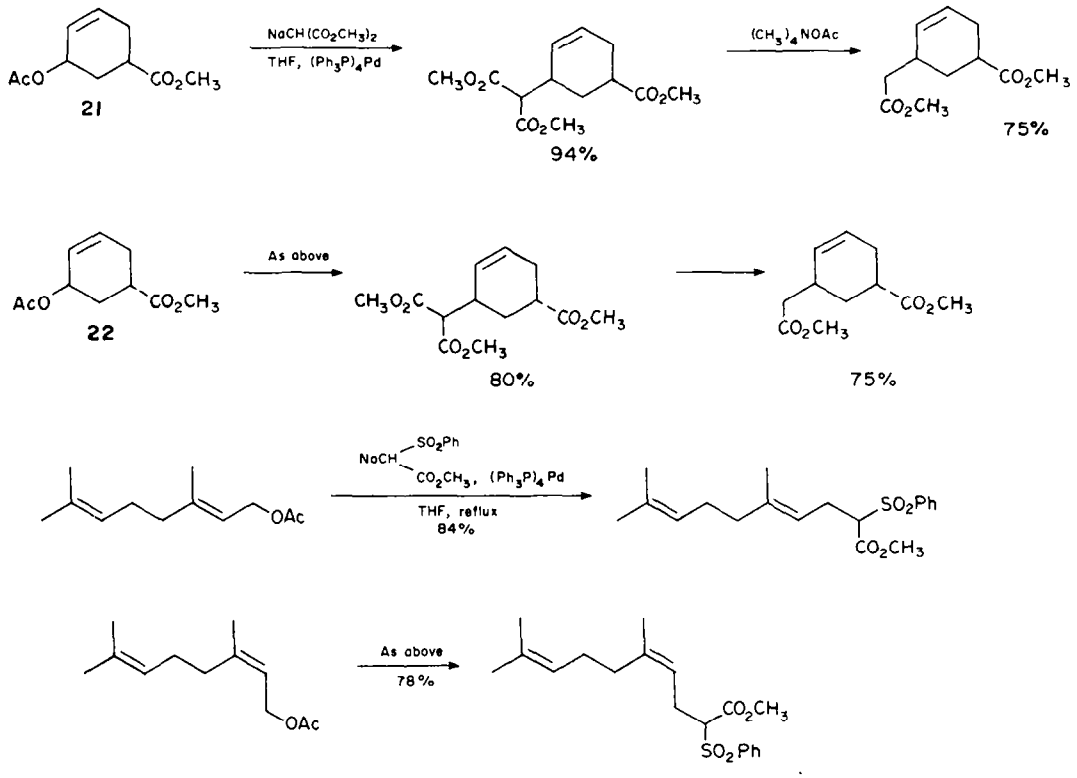
By using stronger phosphine ligands such as DIPHOS or 1 - phenyl - 3 - methylphosphol - 2 - ene, oligomerization of the diene is suppressed and direct addition of X–H to the diene is observed.[106] The initiation step involves formation of a π-allylpalladium complex by proton transfer from the HX group where the latter may be an amine, 1,3-diketone, or a β-ketoester. This method constitutes a synthesis of π-allylpalladium complexes when HX is hydrochloric acid (*vide supra*). A homologue of β-ionone was available from 2,3-dimethylbutadiene embodying this reaction as a key step.[107]

Since π-allylpalladium complexes are available from allylic chlorides, acetates, ethers, and even alcohols, etc. these substrates can serve as precursors for allylic alkylation catalyzed by palladium.[108,109] An interesting and potentially very useful pyrrole synthesis involves the allylic alkylation of amines by a *cis*-2-buten-1,4-diol in which the initially formed dihydropyrrole undergoes dehydrogenation *in situ*.[111] These reactions involve the oxidative addition of the allylic ether, alcohol, etc. to a palladium (0) species followed by the normal chemistry of the π-allylpalladium complexes. In those cases where a palladium (+2) salt is employed an *in situ* reduction must occur.

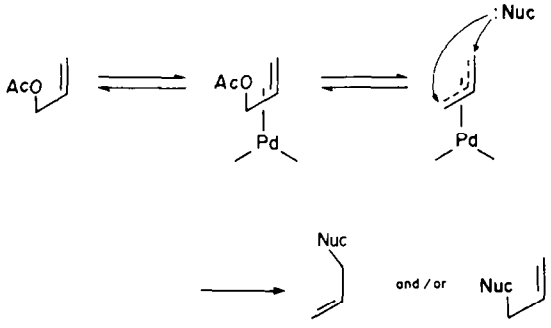
The best substrate for these reactions appears to be the allylic acetates and with these substrates the best catalyst appears to be tetrakis - (triphenylphosphine)palladium. Satisfactory quantities of catalyst range from 0.01 to 10 mol%. The ratio of attack on the ring carbon versus the acyclic carbon in allylic acetates like **20** resembles this ratio for the stoichiometric reaction. In particular, for $n = 1$ or 3 only attack at the acyclic carbon is observed and for $n = 2$ this ratio varies with the choice of phosphine. The rate of this reaction is highly dependent upon ring size with it decreasing in the order $n = 1 > 3 \gg 2$—an observation suggesting a useful chemoselectivity.[59]

The stereochemistry of this process has been investigated both with respect to the carbon bearing the acetoxy group and the double bond.[113] Subjecting the *cis* (**21**) and *trans* (**22**) isomers of 3 - acetoxy - 5 - carbomethoxycyclohexene to alkylation with dimethyl sodiomalonate catalyzed by palladium led to a net S_N2 reaction with retention of configuration. With trisubstituted allylic acetates, the stereochemistry of the double bond is also completely retained. In this case, regioselectivity for attack at the primary end of the allyl unit is maximized by using methyl sodiophenylsulfonylacetate. With disubstituted allylic acetates, appreciable loss in stereospecificity occurs such that this approach is only practical for the stereocontrolled synthesis of trisubstituted double bonds.[114]



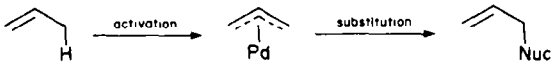


This process can be understood in terms of an initial olefin–palladium (0) complex followed by expulsion of acetate on the face opposite to palladium. Attack of the nucleophile also on the face opposite to palladium leads to the net retention of configuration. The position of bonding of the nucleophile is not determined by the



original location of the acetate but by the usual factors that dictate the regiochemistry of attack of π-allylpalladium intermediates. The chemical and stereochemical stability of allylic acetates, the selectivity for C versus O attack in 1,3-dicarbonyl compounds, and the minimization of elimination versus substitution also constitute advantages of this approach.

In considering the allylic alkylation procedure, two stages are involved—activation and substitution. In the stoichiometric sequence, palladium achieves both chemo-

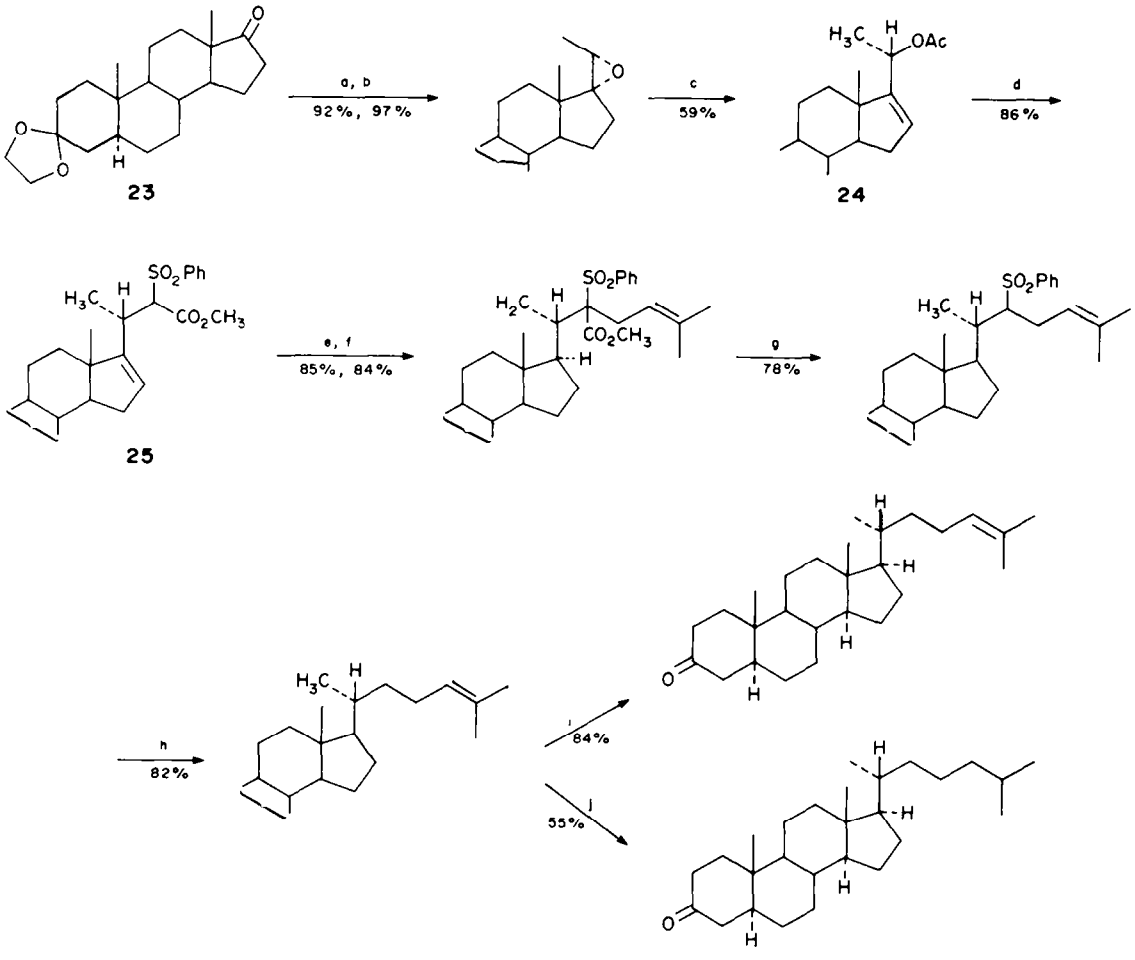


selectively. The foregoing discussion illustrates the ability to achieve a catalytic process if an alternative activation step can be achieved. Scheme 4 outlines such a sequence and demonstrates the feasibility of adding a steroid-like side chain to a carbonyl group.[114]

The ketal **13**, available from testosterone, was converted to the Z-olefin by the normal Wittig reaction. Introduction of the allylic acetate in a stereodefined fashion (activation step) involved epoxidation and base catalyzed ring opening. The key step is the conversion of allylic acetate **24** to sulfone ester **25** with complete retention of configuration which establishes the correct configuration at C(20) and thus complements the approach utilizing stoichiometric amounts of palladium. The remaining steps illustrate the utility of the sulfonylacetate group but fall outside the scope of this review.

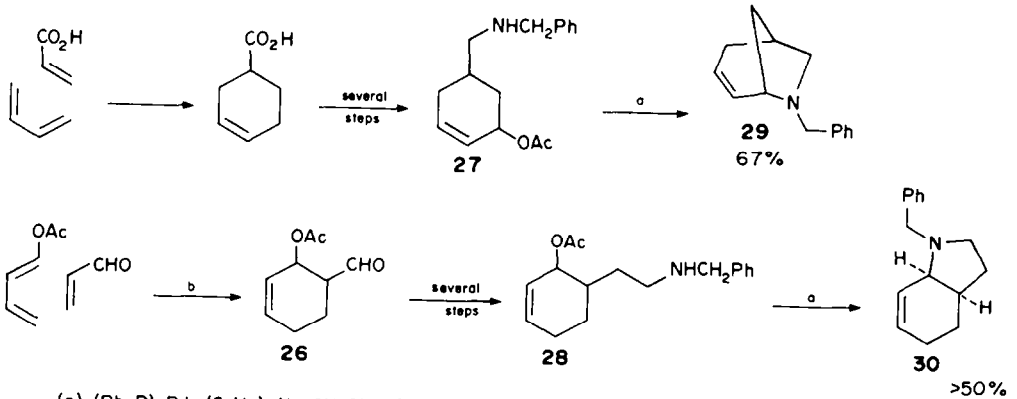
The ability to achieve net S_N2 displacements with retention of configuration allows one to take advantage of the endo selectivity in Diels–Alder reactions in synthetic design. Thus, nucleophilic centers can be easily created *cis* to an acetoxy group to allow cyclizations as illustrated in Scheme 5.[115] Treatment of the amino acetates **27** and **28** with a catalytic amount of tetrakis(triphenylphosphine)palladium in THF or acetonitrile containing triethylamine gave the desired cyclized amines **29** and **30**, respectively, which represent the basic ring skeletons of actinobolamine and mesembrine.

The isoquinuclidine synthesis summarized in Scheme 6 demonstrates the efficiency of this type of approach.[115] The positional selectivity, i.e. azabicyclo[4.2.0]octane (**31**) versus isoquinuclidine (**32**) formation, reflects the relative thermodynamic stability of the two ring systems and indeed may be the result of an isomerization of the former to the latter catalyzed by palladium.[116] Use of tryptamine in the reductive amination followed by cyclization (Scheme 7) produces an excellent precursor



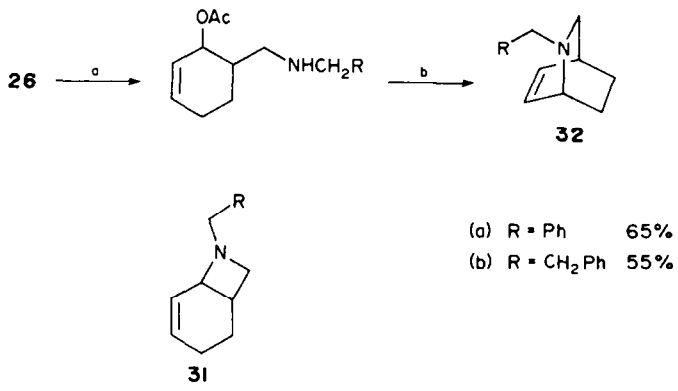
(a) $Ph_3P=CHCH_3$, THF, reflux (b) MCPBA, $CHCl_3$, 0° (c) $LiN(C_2H_5)_2$, hexane, RT, then CH_3COCl, −78° (d) $(Ph_3P)_4Pd$, $NaCH(PhSO_2)CO_2CH_3$, THF, reflux (e) 3 atm H_2, C_2H_5OAc, C_2H_5OH, 5% $Pd/BaCO_3$, RT (f) NaH, HMPA, $(CH_3)_2C=CHCH_2Br$, RT (g) $(CH_3)_4NOAc$, HMPA, 100°, (h) 6% Na(Hg), Na_2NPO_4, CH_3OH, DME, RT (i) PhH, H_2O, HCl, reflux, (j) 3 atm H_2, C_2H_5OH, 5% $Pd/BaCO_3$, RT then HCl, H_2O, acetone, PhH, reflux.

Scheme 4. Synthesis of cholestanone.



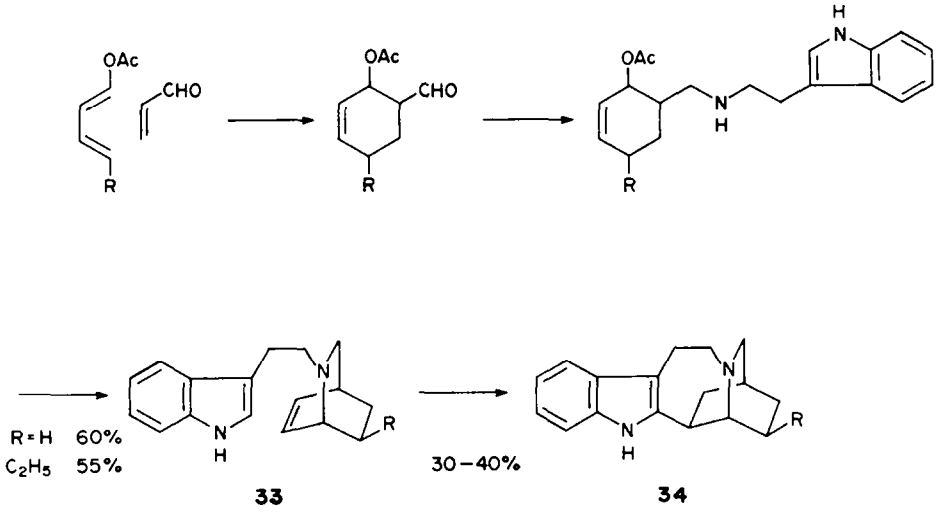
(a) $(Ph_3P)_4Pd$, $(C_2H_5)_3N$, CH_3CN, 55°–70° (b) neat, RT → 95°, hydroquinone

Scheme 5. Intramolecular cyclizations.



(a) RCH_2NH_2, $PhCH_3$, -25° to 0°, $MgSO_4$ then $NaBH_4$, CH_3OH (b) $(Ph_3P)_4Pd$, $(C_2H_5)_3N$, CH_3CN, 70°

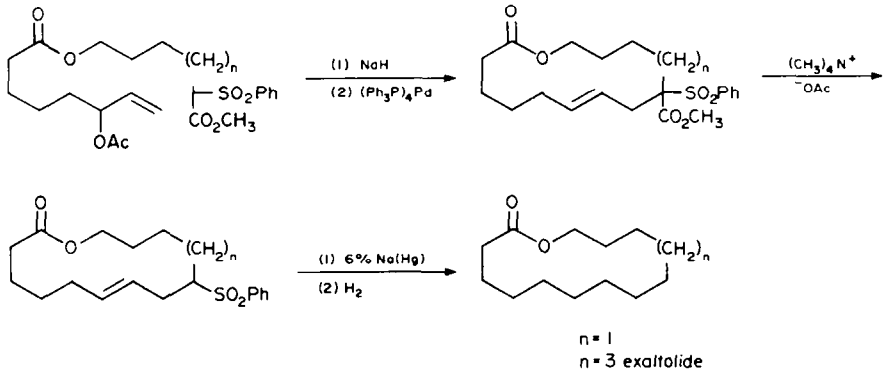
Scheme 6. Isoquinuclidine syntheses.



Scheme 7. Desethylibogamine and ibogamine synthesis.

of the iboga skeleton.[110,115] The isomerization of **33** to **34** was achieved utilizing palladium catalysis as well and was based upon the Heck–Fujiwara reaction (*vide infra*).[12] It is envisioned to involve palladation of the indole ring and *in situ* cyclization. Work-up of the reaction with sodium borohydride completes the sequence. This approach is particularly well-suited to a stereocontrolled synthesis of ibogamine since the stereochemistry of the ethyl group is established in the initial Diels–Alder reaction. The chemoselectivity of the two palladium reactions creates a simple four step total synthesis.

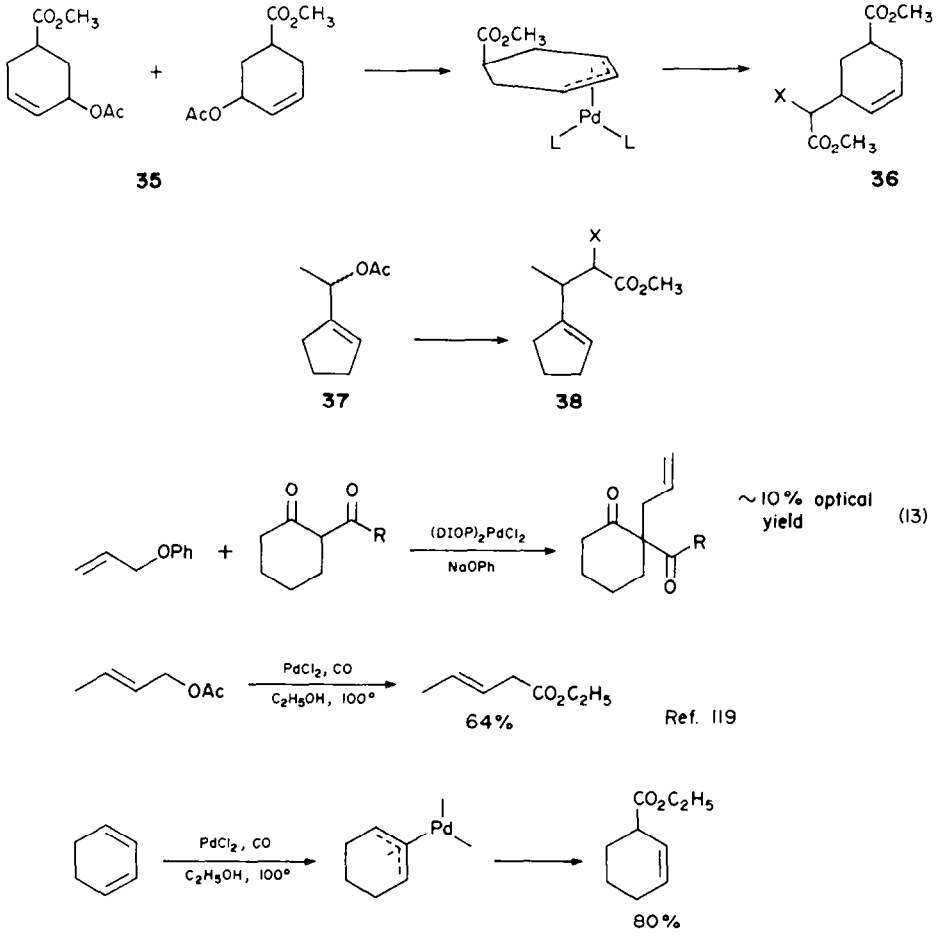
Intramolecular alkylations using carbon nucleophiles constitutes an interesting new cyclization method. While normal ring sizes are easily formed, formation of 14- and 16-membered lactones in 50–55% yields indicates the regioselectivity of this template approach to carbon–carbon bond formation and suggests a new approach to the macrolide antibiotics.[114] A synthesis of exaltolide has been achieved using this reaction as a key step.



The demonstration of high optical yields in the stoichiometric approach also carries over to the catalytic reaction.[117] Treatment of racemic **35** in the presence of 0.75 mol% of tetrakis-triphenylphosphinepalladium and 10 mol% of (+)-DIOP with methyl sodiophenylsulfonylacetate leads to **36** X = $PhSO_2$ (77% yield) which after desulfonylation gives **36** X = H consisting of 62% 3*R*, 5*S* (depicted) and 38% 3*S*, 5*R*. Alkylation of racemic **37** as above with either dimethyl sodiomalonate or methyl sodiophenylsulfonylacetate leads to **38** X = H of up to 46% optical purity.[117] The ability to achieve such high asymmetric induction in a catalytic process at normal operating temperatures holds promise for this approach to chiral C–C bond formation. Inducing chirality at the nucleophilic center has been less successful. Thus, allylation of 1,3-dicarbonyl systems (eqn 13) gives optical yields on the order of 10%.[118]

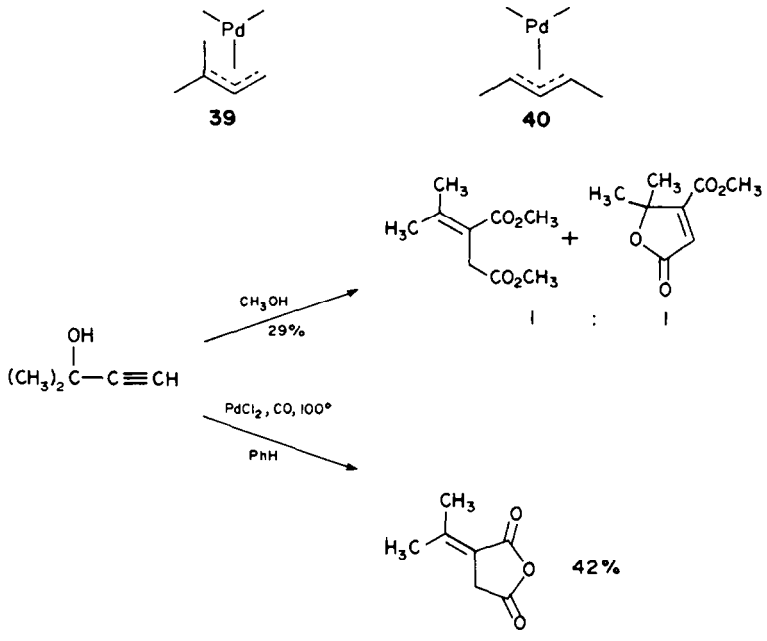
carbonylation. Thus, isoprene and 1,3-pentadiene form predominantly ethyl 4-methyl-3-pentenoate and ethyl 2-methyl-3-pentenoate respectively through complexes **39** and **40** respectively.[121] Propargyl chlorides or alcohols produce mainly products of bis carbonylation, itaconic derivatives.[122]

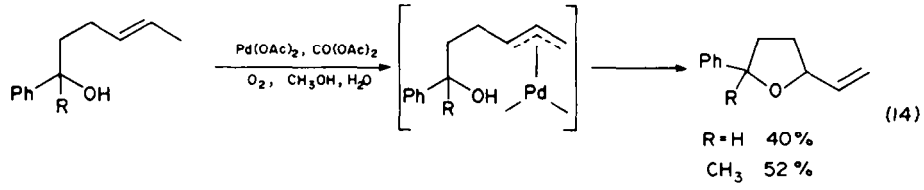
Trapping a π-allylpalladium complex generated from an olefin with an oxygen nucleophile can form a catalytic allylic oxidation. Indeed, the conditions for forming π-allylpalladium chloride dimers from olefins can lead to allylic oxidation by decreasing chloride ion concentration and increasing reaction temperature and time.[1,3,15] The complexity of the reaction mixtures in catalytic allylic oxidation utilizing palladium salts has not made it a viable synthetic method to date.[32] With an internal oxygen nucleophile, a potentially useful oxidative cyclization did occur (eqn 14).[123] In the absence of any



Other reactions of π-allylpalladium complexes can be envisioned in a catalytic sense. In terms of carbon–carbon bond formation, carbonylation stands out. Allyl halides, alcohols, and derivatives of the latter produce β,γ-unsaturated esters in the presence of alcohols in which carbon monoxide adds to the less substituted end of the π-allyl system.[119] The known conversion of dienes to π-allylpalladium complexes (*vide supra*) translates into a catalytic process for synthesis of β,γ-unsaturated esters.[120] The stability of the intermediate π-allylpalladium complexes dictate the regiochemistry of the reasonable nucleophiles, a net dehydrogenation can occur. Thus, a novel synthesis of 9,10-anthraquinones employs *in situ* generation of dienes from monoenes.[124] The dehydrogenation of a β,γ-unsaturated ester, the product of carbonylations, to an $\alpha,\beta,\gamma,\delta$-dienoate has also been reported.[125]

Oxidation reactions involving π-allylpalladium complexes normally are performed utilizing catalytic quantities of palladium. One potentially useful variant that is stoichiometric in palladium is the dehydrogenation of saturated ketones[126] which can be envisioned to involve



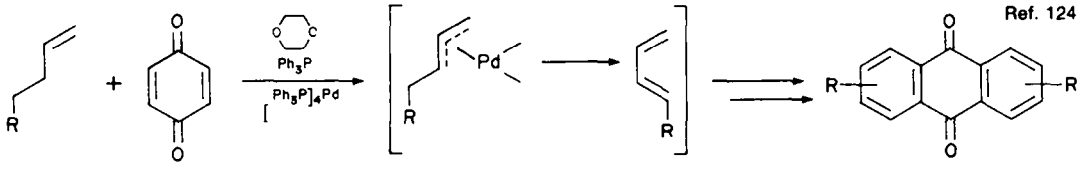


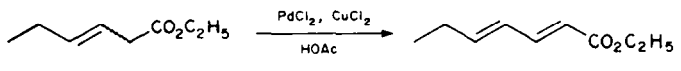
an oxa-π-allyl intermediate.[127] Ring size does not appear to have a significant effect; on the other hand, steric factors do. While 2-t-butylcyclohexanone gives only 6-t-butylcyclohex-2-enone, 2-methylcyclohexanone gives a 1:1 mixture of the two regioisomers. *In situ* formation of oxa-π-allyl and aza-π-allyl complexes has led to flavone[128] and isoxazole[129] syntheses.

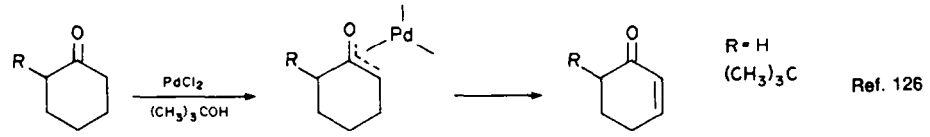
A reduction of allylic acetate by formic acid in the presence of tetrakis(triphenylphosphine)palladium has potential as a hydrogenolysis procedure.[130]

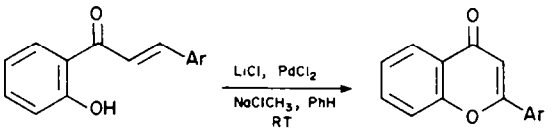
σ-Palladium intermediates

Additions to olefins. The basis for the conversion of ethylene to acetaldehyde (the Wacker process) involves the palladium catalyzed addition of a heteroatom to an olefin.[1,2] Applications of this concept to higher molecular weight compounds have remained limited but exceedingly promising. The conversions of terminal olefins to methyl ketones proceed in good yield in aqueous DMF[131] or sulfolane.[132] 1,4-Diketones, precursors to cyclopentenones, are readily available from the α-

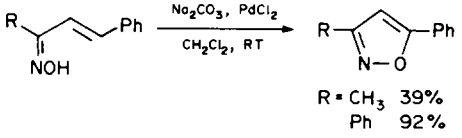




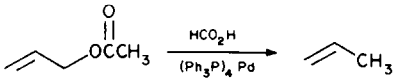




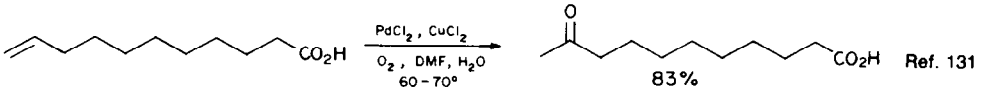
Ref. 128



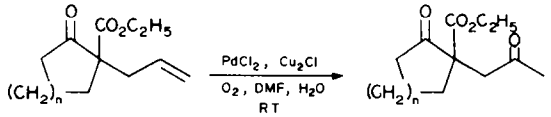
Ref. 129



Ref. 130



Ref. 131



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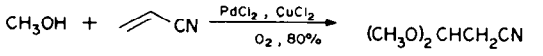

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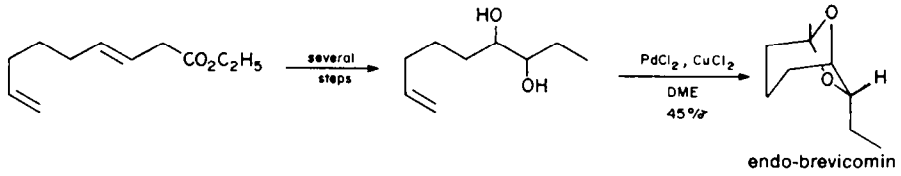
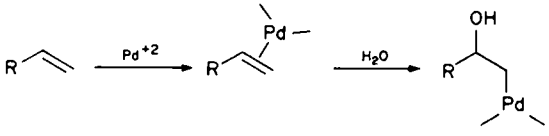
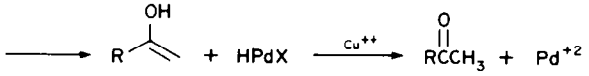
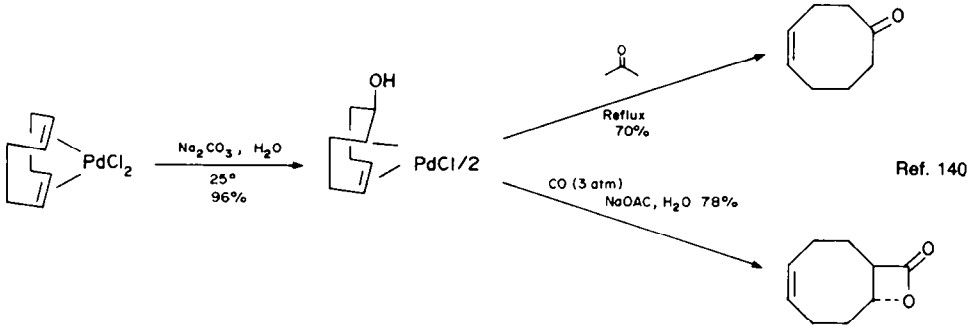




(15)





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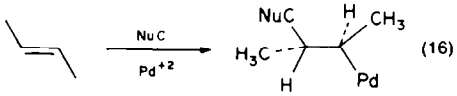
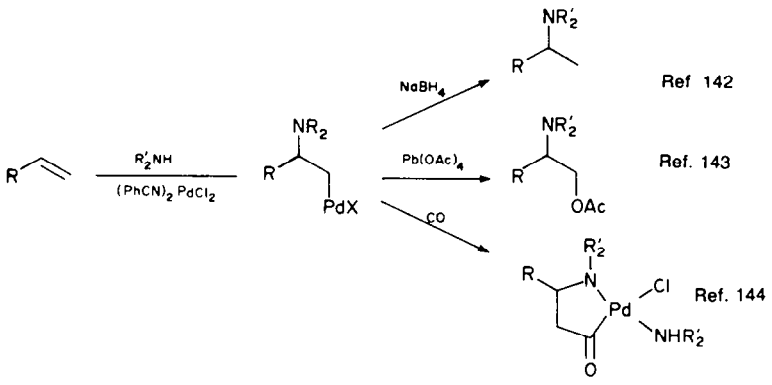
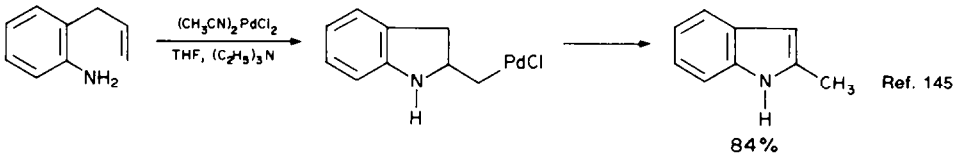
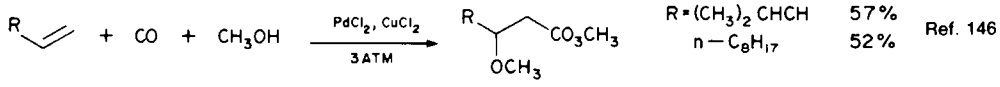
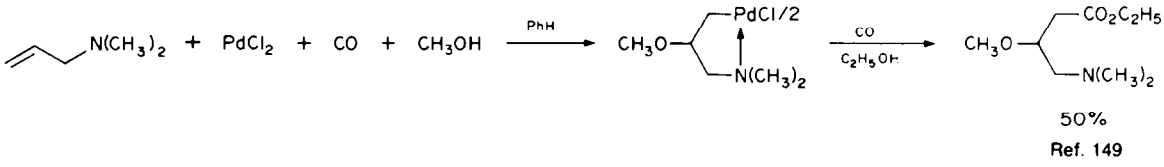
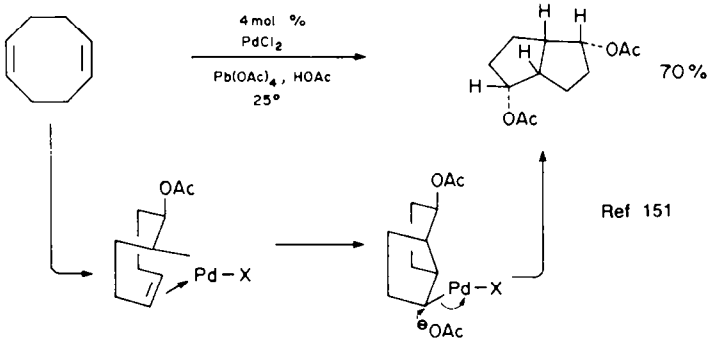

NuC
Pd+2
(16)

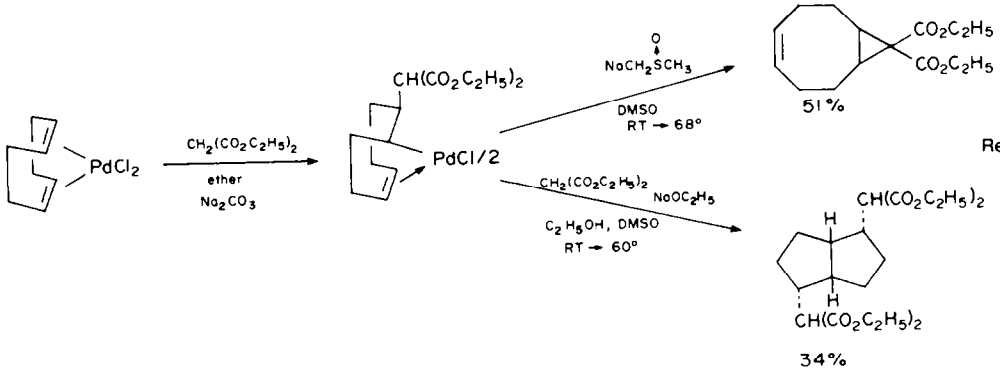

NaBH4
Ref 142
Pb(OAc)4
Ref. 143
CO
Ref. 144


(CH3CN)2PdCl2
THF, (C2H5)3N
Ref. 145
84%


PdCl2, CuCl2
3ATM
R=(CH3)2CHCH 57%
n-C8H17 52%
Ref. 146

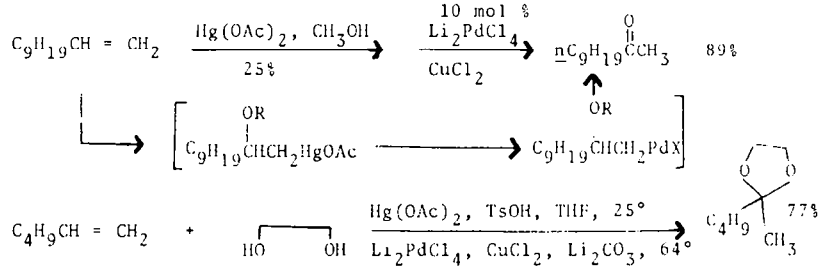

PhH
CO
C2H5OH
50%
Ref. 149


4 mol %
PdCl2
Pb(OAc)4, HOAc
25°
70%
Ref 151


CH2(CO2C2H5)2
ether
Na2CO3
NaCH2SCH3
DMSO
RT → 68°
51%
Ref. 154
NaOC2H5
C2H5OH, DMSO
RT → 60°
34%

allylated ketones.[133] In the presence of alcohols, ketals rather ketones are normally the initial products.[134]

An interesting synthesis of *endo*-brevicomin, a bark beetle pheromone, utilized this reaction as a key step in which the use of an intramolecular hydroxyl group (i.e. a cyclization) precluded the need for an aqueous medium.[135] The starting diol was available from ethyl 3,8-nonadienoate, itself obtained from the palladium catalyzed dimerization and carbonylation of butadiene (*vide supra*). Because of the high temperatures sometimes required for the hydroxypalladation reaction, an alternative that makes use of the facility of acetoxymercuration and of transfer of carbon from mercury to palladium (or replacement of thallium for mercury[136]) appears promising.[137] This reaction has also generated



ketals.[138] Application of this reaction to α,β-unsaturated acids leads to ketones with concommittant decarboxylation.[139]

Despite many studies, the course of these reactions is only partially understood. The gross features are outlined in eqn (15). To make the reaction catalytic in palladium, an oxidant such as cupric chloride or benzoquinone is utilized to reform Pd(+2) from a hydridopalladium species or its subsequent decomposition product. The main uncertainty is the stereochemistry of the hydroxypalladation step. While with simple olefins this question is still open, with a bidentate olefin *trans*-hydroxypalladation is clearly demonstrated.[140] A most interesting synthesis of a *trans*-fused β-lactone resulted from the hydroxypalladation and carbonylation of cyclooctadiene palladium dichloride.[140]

Addition of other heteroatom groups has been shown to be *trans* and can be viewed as an approach to reverse the normal polarity of an olefin (umpolung[141])—i.e. transform the nucleophilic double bond into an electrophile (see eqn 16). Amination of terminal olefins in THF followed by reduction,[142] oxidation,[143] or carbonylation[144] leads to selective addition of nitrogen at C(2). The most useful reaction involves an intramolecular version in which the σ-palladium intermediate eliminates palladium hydride to effect aromatization to an indole.[145] Other nucleophiles, such as alcohols, lead to similar results.[146–148] The presence of allylic substituents that can serve as a chelating agent to palladium potentially can expand the utility of these reactions.[149] Application of these reactions to any olefin except monosubstituted ones leads to low yields or extensive rearrangement (*vide infra*). Nonconjugated dienes (e.g. dicyclopentadiene, norbornadiene, 1,5-cyclooctadiene, etc.) that can serve as bidentate ligands to palladium serve better in such reactions since the initial intermediate is stabilized by internal coordination.[3] 2,6-Disubstituted bicyclo[3.3.0]octanes, of use as key intermediates in the synthesis of natural products and theoretically interesting systems, are easily available with varying substitution in the 2,6 positions.[150,151] It is interesting to note that cleavage of the C–Pd bond by lead tetraacetate proceeds with inversion of configuration. However, platinum derivatives appear to be the preferred catalysts for such reactions.[153]

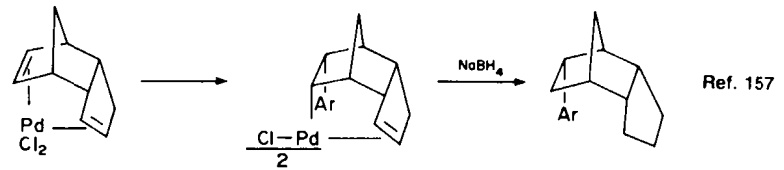
Formation of C–C bonds by nucleophilic addition to an olefin has been restricted to nonconjugated dienes that can serve as bidentate ligands to palladium.[154,155] In such cases, "soft" anions approach *trans* to the palladium in a reaction analogous to the π-allyl cases.

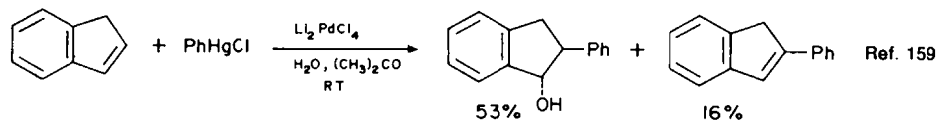
A much more general reaction involving C–C bond formation to an olefin catalyzed by palladium is known as the Heck reaction.[13,26,156] In this case, a σ-palladium species is formed which undergoes *cis* addition to an olefin. If a *cis* β-hydrogen with respect to the palladium can be realized, elimination of the elements of palladium hydride completes the sequence. Since the equivalent of a Pd(0) species is formed, addition of an oxidizing agent like cupric chloride allows the overall sequence to become catalytic in palladium. The restrictions with respect to the olefin do not appear to be severe. On the other hand, only R groups that do *not* bear β-hydrogens that can be easily eliminated (e.g. aryl, vinyl, carboalkoxy, phenylsulfonylmethyl, etc.) can be transferred.

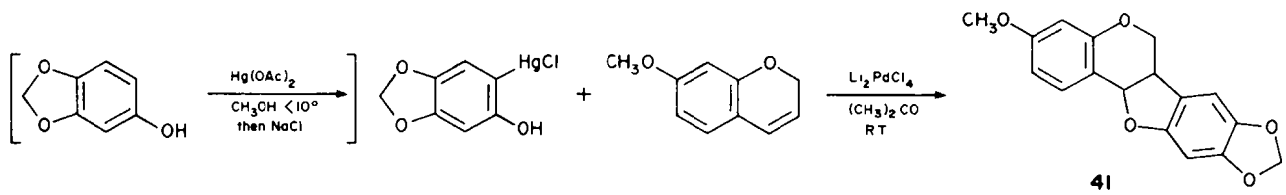
The most common source of the R group is the readily available organomercurials. Thus, treatment of dicyclopentadiene palladium dichloride with an aryl mercury leads to stereospecific and chemoselective introduction of the aryl group in the endo configuration onto the norbornene double bond.[157,158] Since a *cis* elimination of palladium hydride is precluded and the remaining double bond serves as a coordination site to palladium, the intermediate can be isolated and reacted as a typical organopalladium compound (e.g. carbonylation, etc.). Solvolysis of such σ-palladium intermediates has led to a net *trans* hydroxyarylation[159] and to an efficient synthesis of pterocarpin **41**.[160] This latter case illustrates an intramolecular trapping of the σ-palladium intermediate with the net result of a cyclization. The reaction of a cyclic enol acetate has produced a potentially very useful α-arylation of ketones and is exemplified by the isoflavone synthesis.[161]

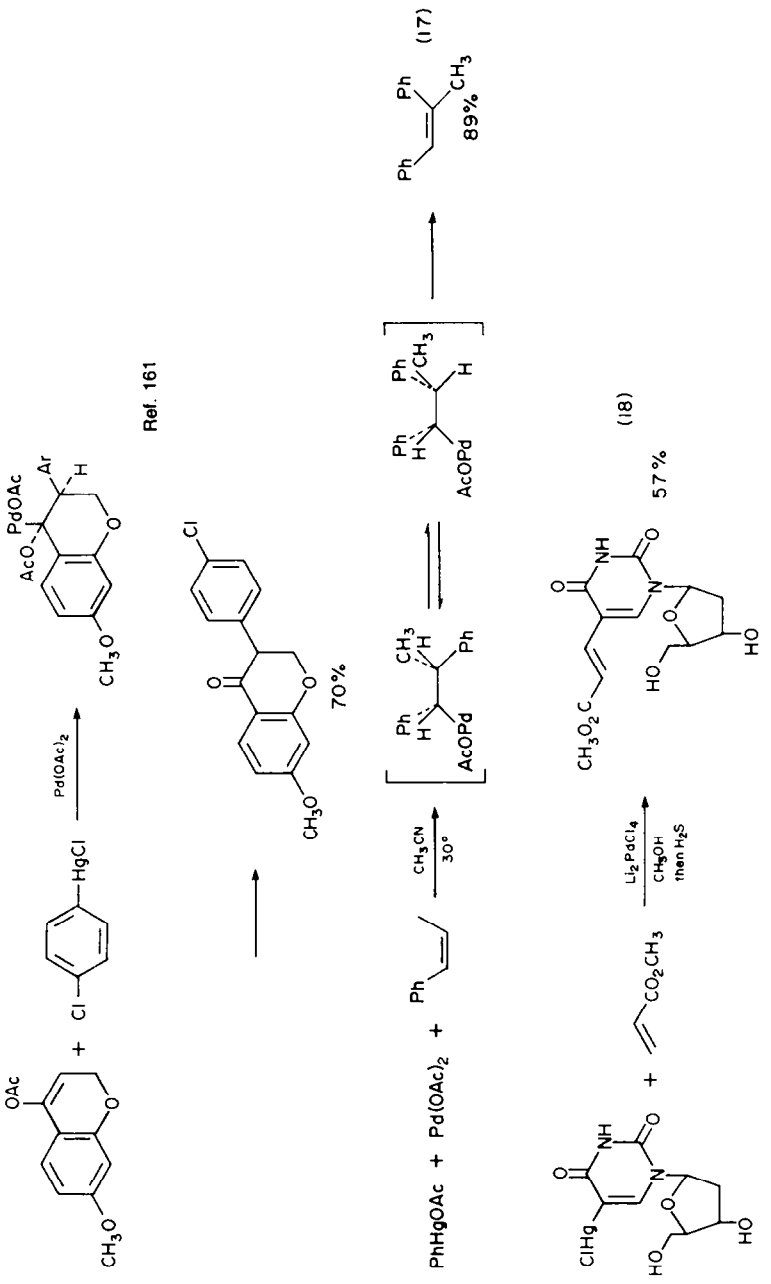
As illustrated in eqn (17), *cis* addition of Ph–Pd–X followed by *cis* elimination of H–Pd–X converts **Z**-1-phenylpropene to **Z**-1,2-diphenyl-1-propene (and correspondingly for the **E** isomer).[156a] The power of this method resides in the chemoselectivity as dramatically illustrated by the reaction with an unprotected nucleoside (eqn 18)[162] and further illustrated by the


R—Pd—
syn addition
Pd
R
syn elimination
+
R
Heck Reaction


Pd
Cl2
Ar
Cl—Pd
2
NaBH4
Ar
Ref. 157


+ PhHgCl
Li2PdCl4
H2O, (CH3)2CO
RT
Ph
OH
53%
+
Ph
16%
Ref. 159


O
O
OH
Hg(OAc)2
CH3OH < 10°
then NaCl
HgCl
O
O
OH
+
CH3O
O
Li2PdCl4
(CH3)2CO
RT
CH3O
O
O
O
O
41


Ref. 161
70%
PhHgOAc + Pd(OAc)2 +
CH3CN
30°
(17)
89%
(18)
57%
Li2PdCl4
CH3OH
then H2S

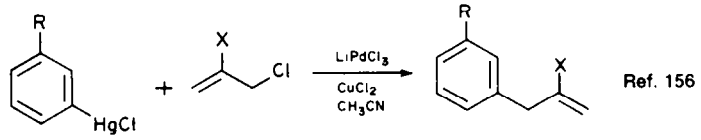
compatibility of an aldehyde and nitro group (eqn 10).[156,163] The presence of an allylic leaving group, e.g. chloride, leads to arylation with elimination of that group.[156] Aryl stannanes,[156g] stibines,[156g,164] arsines,[164] phosphines,[164,165] silanes,[166] boranes,[167] etc. can be used *in lieu* of the arylmercury derivatives although their less accessibility makes them synthetically less attractive. On the other hand, the ready thallation of aromatics to arylthallium (+3) salts[168e] makes these precursors quite attractive.[168b]

Aryl halides, bromides and especially iodides, also serve as sources of arylpalladium compounds by oxidative addition (probably to an *in situ* produced palladium (0) species).[169] Most interesting is their addition to allyl alcohols since elimination of the elements of palladium hydride lead to the enol form of the aldehyde or ketone. The product, the equivalent of a conjugate addition to an enal or enone, complements organocopper chemistry in that 1,2 versus 1,4 addition to enals is problematical and that this reaction employs the more stable and frequently more accessible allyl alcohol. The palladium product being a palladium (0) species initiates another sequence and thus the reaction is catalytic in palladium.

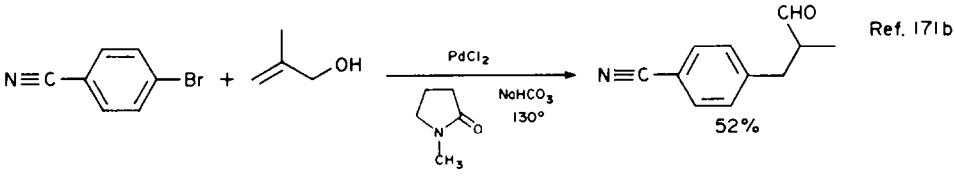
The direct palladation of aromatics has also served in these arylations.[12] The reaction proceeds best with more electron rich aromatics, (including heteroaromatics) but even in such cases the yields are moderate.[172-176] The palladation follows the normal regioselectivity observed for electrophilic aromatic substitution with a preference for para in the case of ortho-para directing groups. The intramolecular version of the reaction has served as a key step in a short synthesis of the iboga system (see Scheme 7).[110,115] These reactions that are stoichiometric in palladium can be made catalytic by employing cupric or silver acetate and oxygen.[176]

The presence of coordinating ligands on the aromatic ring (azo group, amine, thioether, phosphate, phosphine, etc.) can greatly facilitate the palladation and direct it ortho.[177-188] An interesting regiochemistry for the palladation was observed with polysubstituted aromatic rings (eqns 20 and 21) which illustrates the potential that these reactions may have in the syntheses of complex organic systems.

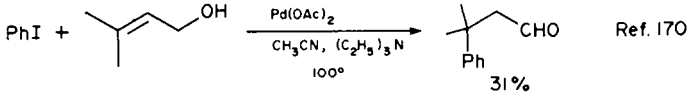
The transfer of groups other than aryl depends upon the stability of the palladium intermediates. Addition of the closely related vinylpalladium salts to olefins proceed



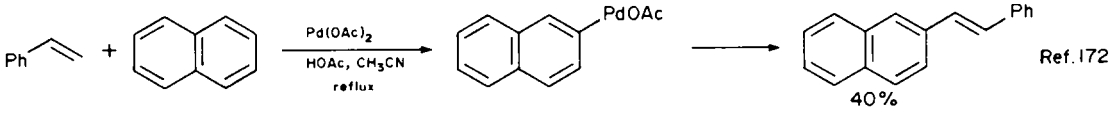
Ref. 156



Ref. 171b



Ref. 170



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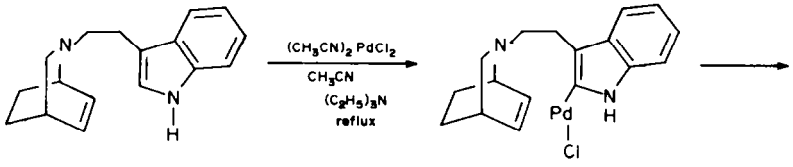
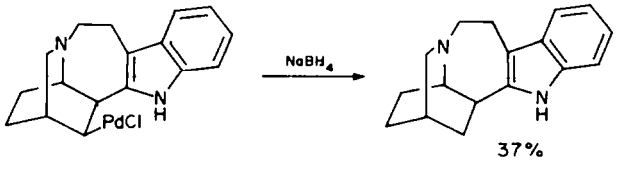
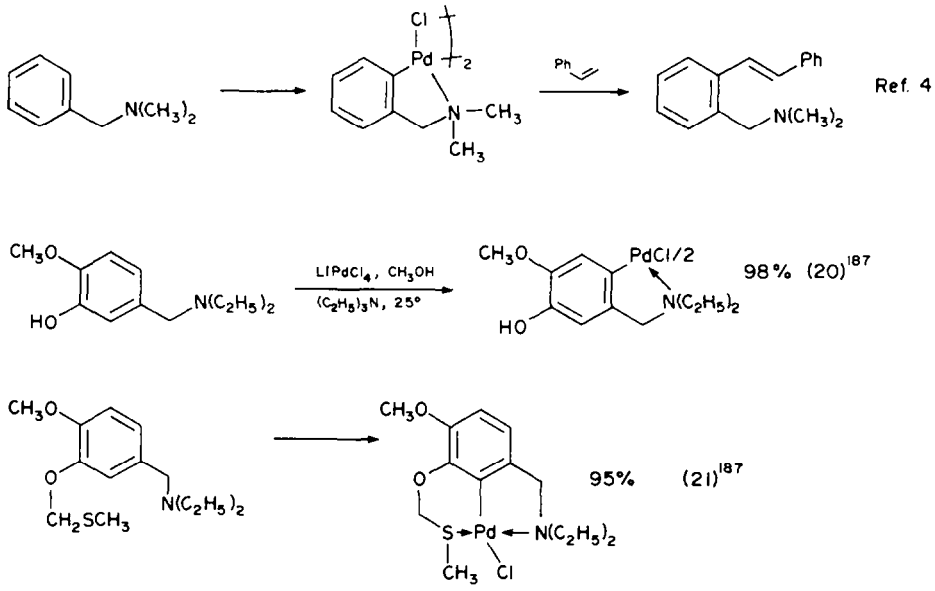
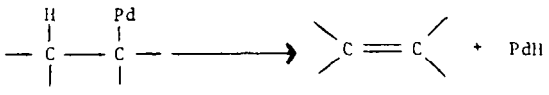




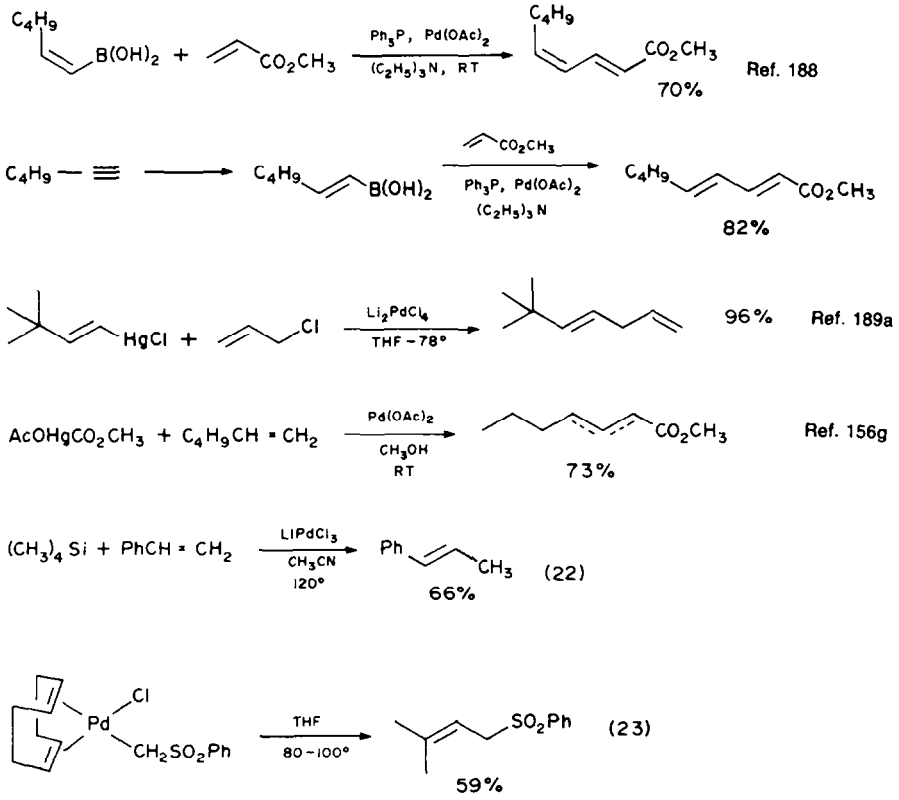


quite well. While vinyl iodides normally serve as the progenitors of the vinylpalladium intermediate, vinylboronic acids gave higher stereospecificity.[188] Vinylmercury[189a] and vinylsilyl[189b] derivatives also serve this function. The ready availability of vinylboron derivatives from acetylenes[190] makes this approach quite attractive for the stereocontrolled synthesis of olefins.

Carboalkoxy transfer has been observed utilizing the readily available carbomethoxymercuric acetate, generated by carboxylation of mercuric acetate in methanol.[156g] Extension to alkyl groups is going to be limited to those that do not have the possibility to eliminate palladium hydride in a *cis syn* fashion. Methyl (eqn 22)[166] and heteroatom substituted methyl (eqn 23)[191]



transfer has been observed. These reactions require considerably more stringent conditions than aryl transfer, but have been much less exploited. The main

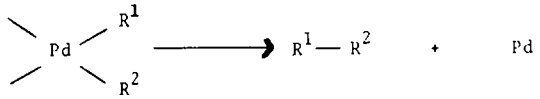


restriction of this very exciting approach to carbon–carbon bond formation is the nature of the olefinic partner. To date, relatively simple terminal olefins have been utilized. Whether this reaction can be extended to a broader spectrum remains obscure.

A "classic" addition to olefins catalyzed by palladium is hydrocarboxylation.[192] This reaction too proceeds best with terminal olefins. The main difficulty is the ratio of unbranched to branched carboxylic acid or ester. Mixed palladium–tin catalysts give the optimum results.[193] The reaction is initiated by the formation and addition of a palladium hydride species and the intermediacy of σ palladium complexes means that carbonylation of internal olefins is frequently accompanied by migration of the substitution along the chain. The increased regioselectivity observed in the presence of a Lewis acid may result from both steric and electronic considerations. Use of chiral phosphines has led to optically active product.[195] A most interesting reaction is the extension to homopropargylic alcohols.[195-197] A key to this reaction is the presence of thiourea which may serve as a mild reducing agent to generate the requisite hydridopalladium intermediate. The neighboring group effect of the hydroxyl substituent directs the regiochemistry of the addition as well as serves as an internal trap for the acylpalladium species. The ready availability of the homopropargylic alcohols from epoxide opening especially with alkyne aluminum species[196,198] makes this a very attractive approach to α-methylenelactones, of importance as key structural units in many antitumor agents.

Under oxidizing conditions, with controlled amounts of cupric chloride, and in the presence of acetate buffer, a biscarbonylation generates a novel succinic ester synthesis.[146] The *cis* addition of *in situ* produced carbomethoxypalladium chloride followed by insertion of CO with retention of configuration rationalizes this reaction. The intermediacy of simple σ-palladium intermediates restricts the reaction to those cases where *cis syn* elimination of palladium hydride is inhibited (as in bicyclics or by internal chelation) or to terminal olefins.

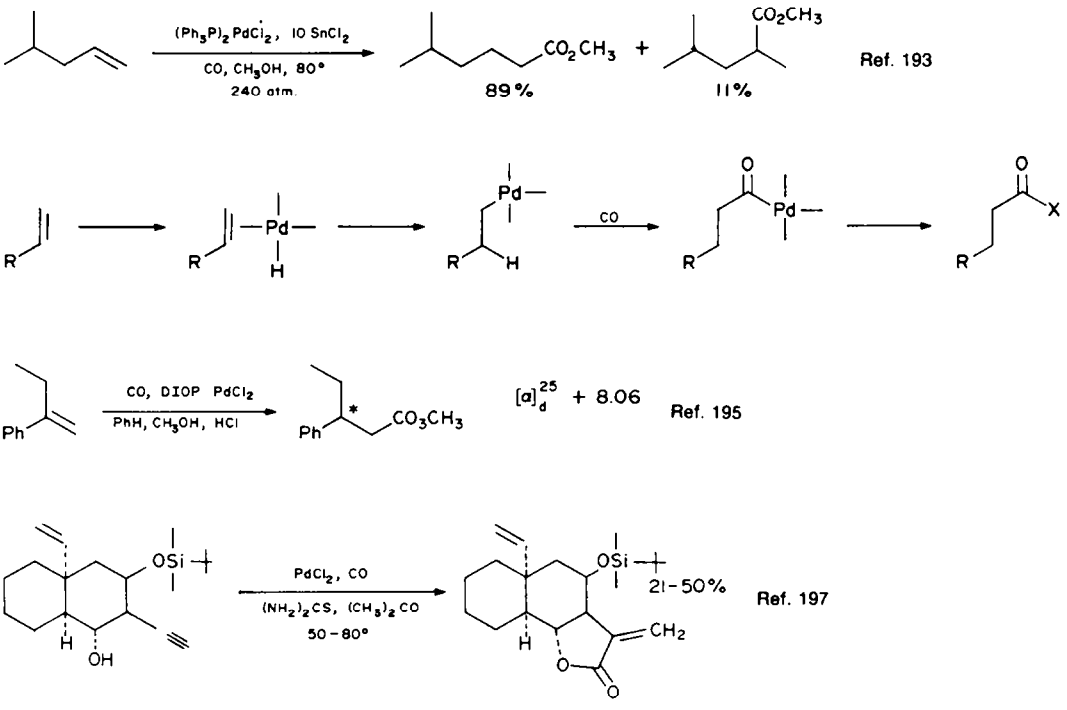
Coupling reactions. The oxidative coupling of aromatic hydrocarbons represents a prototype of an ever increasing number of carbon–carbon bond forming reactions. The formation of a disubstituted palladium

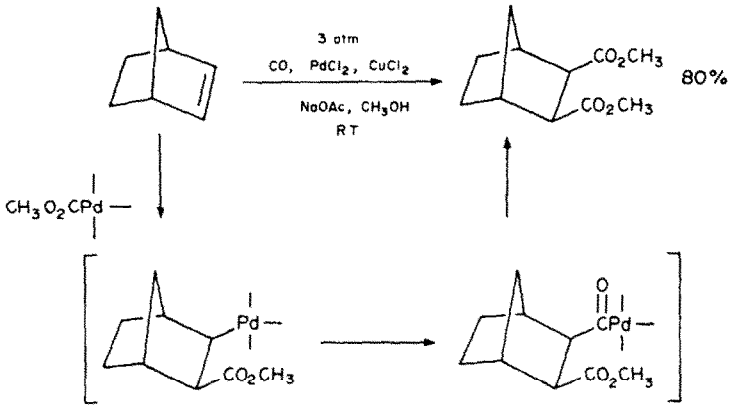


species followed by reductive elimination to give coupling product can be envisioned to be the prime pathway for most of these reactions.

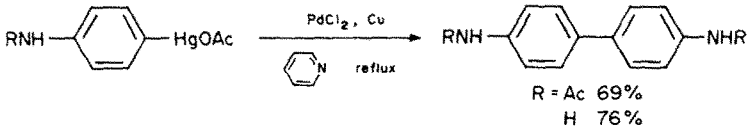
Synthetically, the aryl coupling reaction, which appears to be quite compatible with many functional groups, is best achieved from the preformed mercury derivative.[199] Polycondensed and heteroaromatic systems serve as suitable substrates. The reaction appears to tolerate many functional groups except hydroxyl or carboxylic acid. A somewhat less satisfactory procedure utilizes the aryl iodides to generate the requisite palladium intermediates. A most interesting variant employs the direct palladation of an aromatic ring to generate the arylpalladium intermediate in a cyclization.[201] This reaction tolerated nitro, carboxylate, halogen, and methoxy substituents.

A most useful variation allows unsymmetrical aryl–aryl coupling at low temperatures. In this version, addition of an organomagnesium bromide or an organolithium to a phosphine complexed arylpalladium halide, formed by oxidative addition of a palladium (0) complex to an aryl halide (iodide > bromide > chloride) generates the diarylpalladium which collapses to the biaryl and regenerates the palladium (0) catalyst.[209] As little as 0.01 mol % of catalyst has been employed. Tetrakistriphenylphosphinepalladium also serves as a catalyst for this reaction.



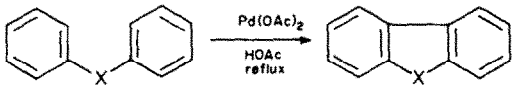


Ref. 146



R = Ac 69%
H 76%

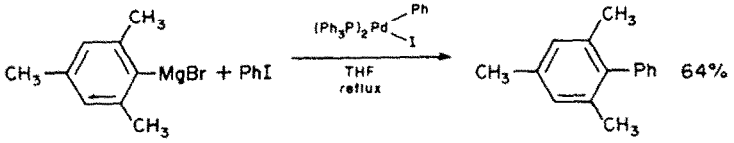
Ref. 199

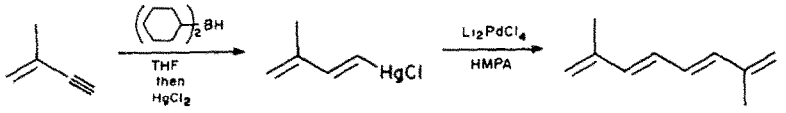


X = O 90%
NH 70%
CO 65%

Ref. 201

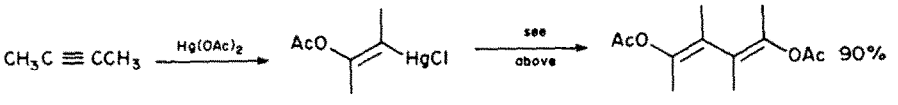
Ref. 209

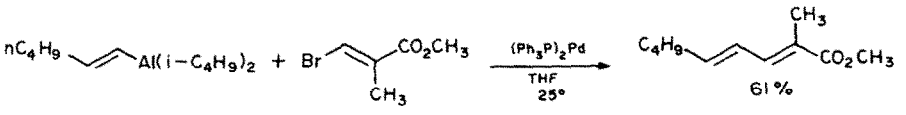




95%

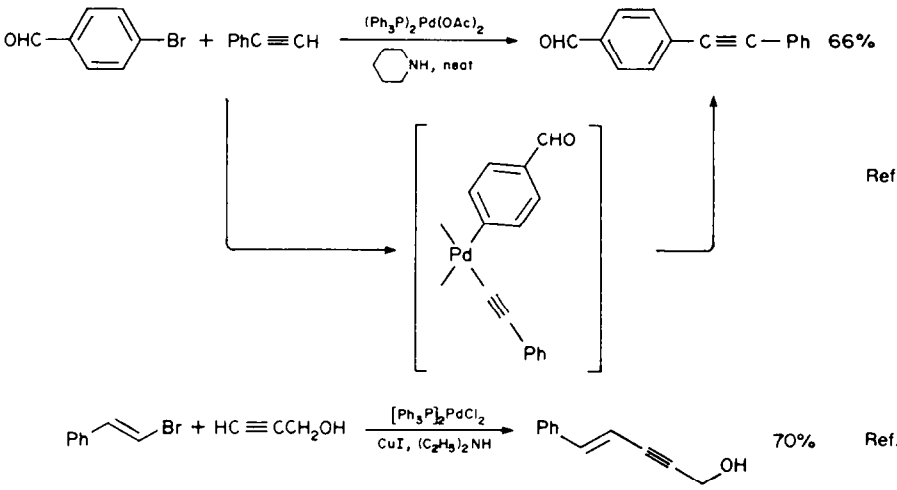
Ref. 202





61%

Ref. 203

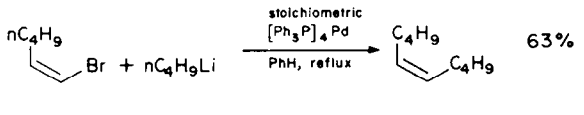


The corresponding vinyl derivatives behave completely analogously. The ready availability of the vinylmercuric halides makes this a very attractive diene synthesis from acetylenes.[202] This vinyl–vinyl coupling procedure proceeds with complete retention of configuration suggesting that transfer from mercury to palladium and the reductive elimination proceed with retention of configuration at carbon. In a cross coupling reaction, the catalyst was generated *in situ* by reduction of *bis*-triphenylphosphinepalladium chloride with 2 equivalents of diisobutylaluminum hydride.[203] A vinyl alane, itself available from acetylenes by hydroalumination, added to the vinylpalladium halide intermediate.

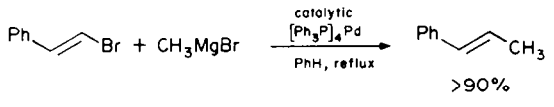
Terminal acetylenes undergo a facile cross-coupling with aryl and vinyl halides with retention of stereochemistry in the latter cases in the presence of amine bases.[204–206] *In situ* formation of a reactive palladium (0) species[205–6] or use of tetrakis - triphenylphosphinepalladium[206] initiates the process. The preliminary examples illustrate a high chemoselectivity.

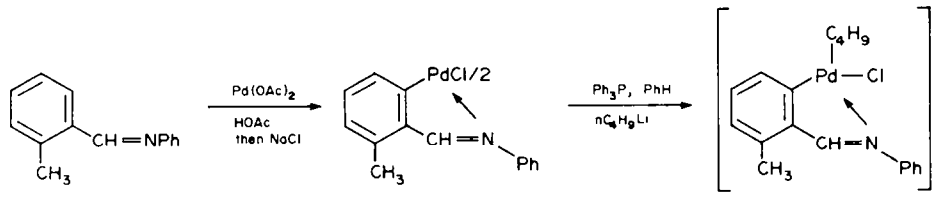
Alkyl groups even couple to aryl and vinyl halides (bromides or iodides) under these conditions.[207–209] While use of organolithium reagents require a stoichiometric amount of palladium complex, use of the Grignard reagents allow the reactions to proceed catalytically.[208] An ortho substitution reaction has been achieved utilizing this concept in which the organopalladium intermediate was formed by directed palladation.[183] The nature of the coupling step remains elusive. The key role of phosphine ligands has been especially noted in this last case.[183] In a complementary process, coupling of a vinylpalladium species with an alkyl acetate occurs with retention at the vinyl carbon and inversion at the acetoxy bearing carbon.[202c,210]

Not surprisingly, these vinyl and arylpalladium intermediates generated from aryl or vinyl halides, mercury salts, etc. undergo carbonylation and trapping to generate aldehydes,[211] esters,[212] or amides.[213] The reaction appears to be compatible with many functional

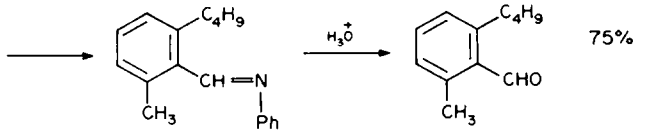


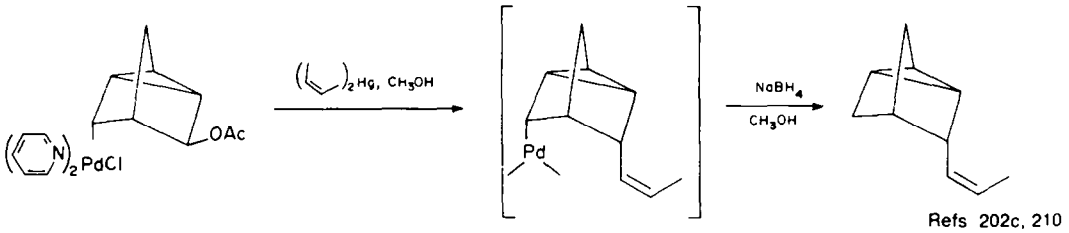
Ref 208



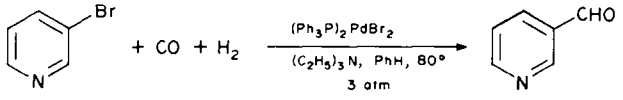


Ref. 183

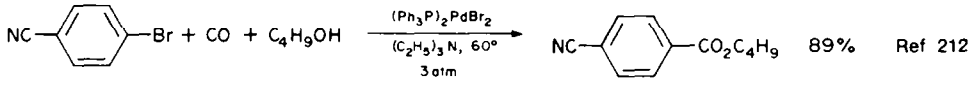




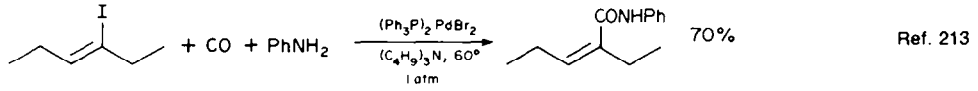
Refs 202c, 210



80% Ref 211



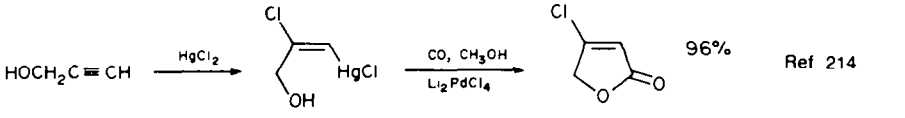
89% Ref 212



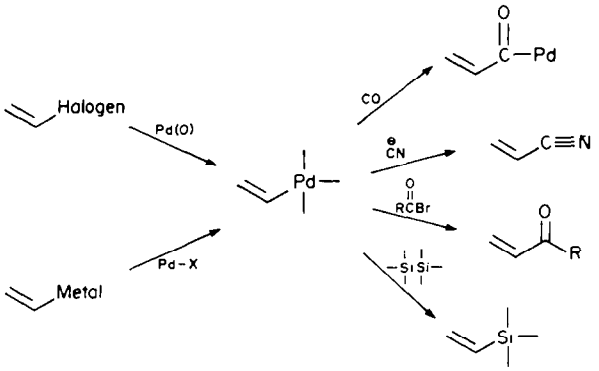
70% Ref. 213

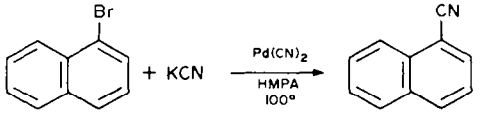
groups including nitrile, ester, ketone, nitro, alcohol, etc. Electron withdrawing groups on the aromatic ring facilitate and electron donating groups retard the reaction. The stereospecificity with vinyl halides is dependent upon the phosphine concentration (the higher the concentration, the higher the specificity) and acyl trapping reagent (highest in amide formation). Intramolecular acyl trapping allows cyclization as in the case of butenolide formation.[214]

In addition to trapping intermediate aryl or vinylpalladium intermediates with carbon monoxide, the related cyanide ion allows an analogous reaction to form nitriles.[216,217] While the reaction succeeds by *in situ* formation of the palladium (0) catalyst in dipolar aprotic

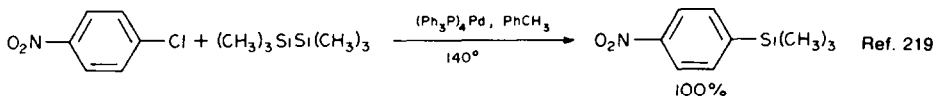


96% Ref 214



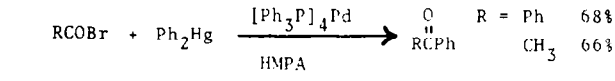


95% Ref. 217



100% Ref. 219

solvents (best in HMPA), an improved version utilizes tetrakis-(triphenylphosphine)palladium or *bis*(triphenylphosphine)phenylpalladium iodide. A ketone synthesis from organomercurials derives from acylation with acyl halides catalyzed by palladium (0) complexes.[218] The growing importance of organosilanes in synthesis makes



the observation that aryl silanes (and presumably vinyl silanes) are available from the halides via similar coupling methods quite significant.[219] While bromides and iodides are preferred, activation by electron withdrawing groups allows chlorides to be also used.

There are a horde of additional reactions that have been uncovered but not included. Most notably is the oligomerization of acetylenes and the catalytic reduction of olefins, acetylenes, etc. These are covered in many reviews and fall outside the intent of this review.

CONCLUSIONS

Industrial syntheses of small molecules based upon palladium intermediates has been well accepted and adopted. As understanding of these complex processes has emerged, new horizons appear to open for application to complex synthesis. The foregoing has only summarized those which seem the most promising at the present and many more are lurking in the chance observations of some investigators and in mechanistic papers. Even so, the more understood reactions have only been meagerly exploited although that aspect is rapidly changing. The tremendous benefit that derives from organopalladium chemistry is selectivity—in a chemical and stereochemical sense. The compatibility of these reactions with many functional groups avoids the necessity for blocking or activating groups. Surely one of the great challenges to the synthetic chemist is to target his reaction to a specific site in a polyfunctional molecule with minimum expenditure of energy. Palladium chemistry begins to provide a few avenues for the investigator. Success will require a greater understanding of the subtleties than in many standard synthetic organic reactions. The immense effect of small changes in the nature of the ligands is the most difficult to fully appreciate. The immensity of the reward, however, makes the challenge well worth facing.

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