Highly Chemoselective Palladium-Catalyzed Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds with Silicon Hydrides and Zinc Chloride Cocatalyst

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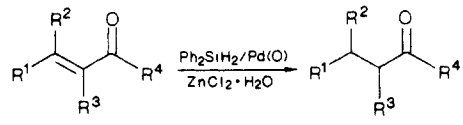
Abstract: A three-component system comprised of a soluble palladium catalyst, hydridosilane, and zinc chloride is capable of efficient conjugate reduction of α,β-unsaturated ketones and aldehydes. The optimal set of conditions includes diphenylsilane as the most effective hydride donor, any soluble palladium complex in either the 0 or II oxidation state, when it is stabilized by phosphine ligands, and $ZnCl_2$ as the best Lewis acid cocatalyst. The reaction is very general with respect to a broad range of unsaturated ketones and aldehydes, and it is highly selective for these Michael acceptors, as reduction of α,β-unsaturated carboxylic acid derivatives is very sluggish under these conditions. When dideuteriodiphenylsilane is used to reduce unsaturated ketones, deuterium is stereoselectively introduced at the less-hindered face of the substrate and regioselectively at the β-position. Conversely, when reductions are carried out in the presence of traces of D_2O, deuterium incorporation occurs at the α-position. On the basis of deuterium-incorporation experiments and ^1H NMR studies, a catalytic cycle is postulated in which the first step involves reversible coordination of the palladium complex to the electron-deficient olefin and oxidative addition of silicon hydride to form a hydridopalladium olefin complex. Migratory insertion of hydride into the coordinated olefin produces an intermediate palladium enolate which, via reductive elimination, collapses back to the Pd(0) complex and a silyl enol ether, which is then hydrolyzed to the saturated ketone. In addition to catalyzing that hydrolysis, $ZnCl_2$ facilitates the hydrosilation process.

Despite the bewildering variety of reducing agents available for synthetic chemistry, new and ever more selective reductants are in constant demand. Most popular of selective reducing agents are the various metal hydrides, mainly those of boron and aluminum,[1] an abundance of which have been designed over the past 4 decades and new derivatives of which are continuously being developed.[2] However, the hydridic nature of most of these group 13 and other metal hydrides can limit their usefulness, particularly when high chemoselectivity is required.

In recent years, we have been working on the design of an alternative family of reducing systems that can selectively transfer a hydride group to various electrophilic functionalities.[3-6] Our systems are comprised of at least two components, i.e., a relatively inactive source of hydride entities and a transfer agent that can deliver the hydride selectively from that donor to the target functionality. Group 14 metal hydrides, especially silicon and tin hydrides, represent a satisfactory choice of nonreactive hydride donors, as in the absence of a catalyst, they are known to be, in general, poor reducing agents.[7] Transition-metal complexes are attractive transfer agents because they readily insert into Si-H and Sn-H bonds[7,8] and also bind specifically to various functional groups. Thus, appropriate modification of a hydridosilane, judicious selection of a transition-metal transfer agent,[9,10] and, in some cases, use of cocatalysts provide an opportunity for creating a wide variety of reducing systems that exhibit improved chemoselectivity as well as regio- and stereocontrol.

We have recently demonstrated this approach with silicon hydrides and a soluble Pd(0) catalyst, a system that allows chemoselective allylic reductions to be carried out under very mild conditions and even in the presence of other easily reducible functionalities, such as Michael acceptors.[5] The chemistry of this system is fundamentally altered by the addition of catalytic amounts of zinc chloride.[6] This new three-component system exhibits novel reducing properties, enabling efficient conjugate reduction of α,β-unsaturated ketones and aldehydes (eq 1).



(1)

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In this paper we describe the scope and limitations of this three-component reducing mixture and set the stage for its employment as a general tool for conjugate reduction of unsaturated carbonyl compounds.

Results and Discussion

Reaction Conditions. The conjugate reduction of benzalacetone was chosen as a model for investigating the influence on the reaction of various parameters, such as the nature of the silane, the Lewis acid, the solvent, the type of palladium catalyst, etc. The results of this optimization study are described below.

Hydridosilane. Although the reaction takes place with various silanes, including mono-, di-, and trisubstituted varieties, diphenylsilane was found to be the most effective hydride donor. The order of reactivity of silanes in this reaction is similar to that which we found previously with respect to allylic reduction.[5]

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(8) Kaesz, H. D.; Saillant, R. B. *Chem. Rev.* **1972**, *72*, 231.

(9) Combinations of silicon hydrides with catalytic amounts of a ruthenium(II) complex in various organic solvents were found useful for conjugate reduction of α,β-unsaturated ketones, carboxylic acids, esters, amides, etc. Keinan, E.; Godinger, N.; Greenspoon, N., unpublished results.

(10) For reductions with silicon hydrides and Mo(0). Keinan, E.; Perez, D., unpublished results.

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Diphenylsilane is significantly more reactive than monohydridosilanes such as 1,1,3,3-tetramethyldisiloxane, dimethylethoxysilane, polymethylhydrosiloxane (PMHS), and triethylsilane. This observation agrees with the general trends of silane reactivities observed in hydrosilation reactions[11] where electron-deficient hydrides are more reactive than electron-rich varieties.[12] Accordingly, Et_3SiH, which is the most nucleophilic silane in this series (and which has proven useful for ionic hydrogenation[13] and for conjugate reductions in the presence of $TiCl_4$[14]) was nearly inert in our system. Phenylsilane, on the other hand, seems to be too reactive and is incompatible with the catalyst, decomposing it into metallic palladium.

The Lewis Acid. A number of Lewis acids were compared for their efficiency to cocatalyze the Pd-catalyzed reduction. Of the various acids checked, $ZnCl_2$ was found to be the most effective cocatalyst, leading to clean, rapid reactions. Yet, although at elevated temperatures (>100 °C) $ZnCl_2$ alone can catalyze the nonselective reduction of saturated as well as unsaturated carbonyl compounds,[15] it cannot catalyze the reduction at room temperature in the absence of Pd catalyst. Although $ZnCl_2$ is only slightly soluble in chloroform, addition of up to 2 equiv of this cocatalyst (with respect to the substrate) resulted in increasingly higher reaction rates. Even when using relatively high concentrations of zinc chloride (30–50%), the initially heterogeneous mixture turned homogeneous as the reaction proceeded.

Reduction was also clean with $MgBr_2$ and $AlCl_3$, but much more sluggish, with observed reaction rates about 35 and 70 times slower, respectively. Relatively fast and clean reductions were likewise observed in the presence of $FeCl_3$. However, the reaction stopped within 1 h, accompanied by evolution of hydrogen gas and decomposition of catalyst to metallic palladium; most of the starting material remained untouched. It appears that because Pd(II) complexes are efficiently reduced by diphenylsilane to Pd(0) (vide infra) and the latter is easily oxidized back to Pd(II) by ferric chloride, the predominant reaction is a Pd-catalyzed decomposition of the silane. Therefore, this Lewis acid, as well as other oxidants, represents a poor cocatalyst for our systems.

With the soluble, stronger acids $TiCl_4$ and $SnCl_4$, nonselective reduction occurred and the desired product, arising from 1,4-reduction, was accompanied by equal quantities of complex mixtures of unidentified side products, including the product of 1,2-reduction of the carbonyl. This nonselective reduction does not appear to be a palladium-catalyzed reaction,[14] as a very similar mixture of products was formed at a comparable rate when $TiCl_4$ was employed alone. With BF_3–OEt_2 or with titanium tetraisopropoxide, reduction proceeded very inefficiently with less than 20% conversion even after 24 h. Brønsted acids such as acetic acid and ammonium chloride were ineffective cocatalysts, and essentially no reduction was observed when they were employed.

The Solvent. Conjugate reductions of various enones were successfully carried out in $CHCl_3$, THF or benzene, with moderate differences in reaction rates. Nevertheless, chloroform was found to be the solvent of choice, as reduction of benzalacetone proceeded in this medium about 1.6 times faster than in THF and about 3.3 times faster than in benzene. Additionally, chloroform has some practical advantages, especially with respect to THF, as all inorganic and organometallic materials, including the palladium catalyst, are conveniently removed from this solvent by simple filtration through a short silica gel column.

Water Concentration. Traces of moisture have been reported to be necessary in some Lewis acid catalyzed Friedel–Crafts reactions, although the catalyst is destroyed by larger amounts of water.[16] A similar effect was recently observed in the zinc chloride catalyzed addition of chlorodiphenylmethane to olefin when carried out in dichloromethane.[17] Our reaction, however, when carried out in chloroform, is not as sensitive to water concentration. In fact, 1 equiv of H_2O is required to complete the reduction (vide infra). With carefully dried zinc chloride,[18] reduction rates were somewhat slower than those carried out in the presence of slightly wet, commercial $ZnCl_2$. Additional water (up to 2 equiv per $ZnCl_2$) does not significantly inhibit reaction, and 4 equiv of water reduces reduction rate to about one-half of its highest value. Therefore, no specific precautions are required with respect to the purity of the cocatalyst. High water concentrations (more than 20 equiv per $ZnCl_2$) led to phase separation, with concomitant retardation of the reaction, probably due to efficient extraction of $ZnCl_2$ from the organic phase.

The Catalyst. In our early work[6] we found, in general, that an inert atmosphere is not required for these reactions, and commercial solvents may be conveniently used without any pretreatment for removing moisture, oxygen, or other contaminants. The purity and quality of catalyst likewise has no appreciable effect on reaction rates. Indeed in many cases, when partially decomposed, dark-brown $Pd(PPh_3)_4$ was employed for reaction, it immediately turned bright yellow—the typical color of freshly prepared $Pd(PPh_3)_4$. This implies that Pd(II) complexes may also be used as catalysts, as they are reduced in situ to Pd(0).[19] In fact, any soluble palladium complex in either oxidation state, when it is stabilized by phosphine ligands, can be utilized with equal effect. Thus, catalytic activity of $PdCl_2(PhCN)_2$ + $4PPh_3$, or $Pd(OAc)_2$ + $4PPh_3$, and $PdCl_2$ + $4PPh_3$ were essentially identical with that of $Pd(PPh_3)_4$. The possibility of utilizing commercially available, highly stable palladium(II) complexes is an obvious practical advantage of this method. The role played by the phosphine ligands is twofold: (a) to inhibit undesirable $PdCl_2$-catalyzed decomposition of the silane[19,20] and (b) to stabilize and solubilize the catalyst and prevent its precipitation as metallic palladium. Yet, saturation of the catalyst with excess triphenylphosphine inhibits the reaction. Accordingly, slower reactions were observed with palladium complexed to a bidentate phosphine ligand, 1,2-bis(diphenylphosphino)ethane (dppe). For example, reduction of **8** in the presence of $Pd(dppe)_2$ proceeded at twice as slow a rate as with monodentate phosphine.

Synthetic Applications. On the basis of the above-described experiments, we suggest a general set of conditions for reduction of α,β-unsaturated ketones and aldehydes.[21] Reactions are typically carried out in an open flask at room temperature in chloroform using a slight excess of diphenylsilane, 1–2% palladium catalyst, and 10–50% $ZnCl_2$ (the lower quantities of $ZnCl_2$ being recommended for reduction of unsaturated aldehydes, which may be incompatible with large concentrations of this Lewis acid).

The generality of the method is apparent from the examples in Table I, which included unsaturated aldehydes and ketones possessing di-, tri-, and even tetrasubstituted double bonds, all of which are reduced with excellent yields. For example, citral (**9**) was transformed almost quantitatively to citronellal, the tetrasubstituted olefin in pulegone (**10**) was reduced in very high yield, 1,4-reduction of β-ionone (**4**) occurred selectively with no participation of either the 1,6- or 1,2-reduction modes,[22] aromatic bromide[23] **7** and cyclic acetal **11** are tolerated under the reaction conditions, and carvone (**5**) is reduced without isomerization or concurrent reduction of the isopropenyl group.

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(15) Frainnet, E. *Pure Appl. Chem.* **1969**, *19*, 489.

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(19) It has been observed that both $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ catalyze hydrosilation of terminal olefins at 100 °C: Tsuji, J.; Hara, M.; Ohno, K. *Tetrahedron* **1974**, *30*, 2143.

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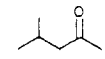
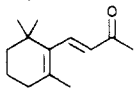
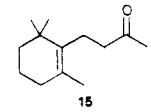
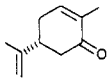
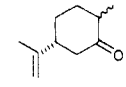
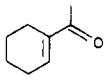
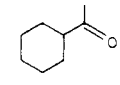
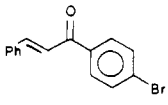
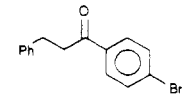
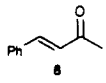
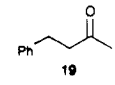
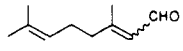
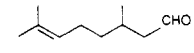
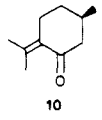
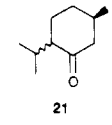
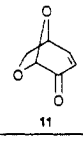
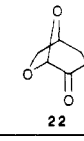
Table I. Conjugate Reduction of α,β-Unsaturated Ketones and Aldehydes

	starting material, mmol	Ph_2SiH_2, equiv	$ZnCl_2$, equiv	$Pd(PPh_3)_4$, equiv	time, h	product	yield, %
 1	1.26	1.0	0.36	0.018	1	 12	100[a]
 2	1.07	2.0	0.35	0.007	1	 13	95[a]
 3	1.48	1.2	0.16	0.005	0.5	 14	99[a]
 4	0.68	2.5	0.35	0.019	2	 15	96[b]
 5	1.01	1.7	0.52	0.013	2	 16	89[b,c]
 6	0.85	1.8	0.38	0.013	4	 17	85[b]
 7	0.58	2.4	0.77	0.014	3	 18	98[b]
 8	1.14	1.3	0.30	0.0009	2	 19	100[a]
 9	0.94	2.0	0.12	0.012	1.5	 20	96[a]
 10	0.85	1.55	0.40	0.018	3	 21	90[a,d]
 11	0.15	2.0	1.00	0.10	1	 22	95[b]

[a] All reactions were carried out according to the general procedure given in the Experimental Section. Yields were determined by GC. [b] Yields of isolated, distilled products. [c] Ratio of isomers trans:cis = 4:1. [d] Ratio of isomers trans:cis = 1:1.

Most of the above-described reactions were carried out with less than 1 mmol of substrate. The process, however, can be scaled up without difficulty. For example, reduction of **4** was performed with 10 g (52 mmol) of substrate under standard conditions, leading, after workup and distillation, to dihydro-β-ionone in 96% yield.[21]

Of special interest are the relative rates of reduction of the three cyclohexenyl enones: cyclohexenone (**1**), carvone (**5**), and acetylcyclohexene (**6**). While the enone system in **1** and **5** is frozen in its transoid form, **6** is flexible and may adopt either the transoid or cisoid conformation. The fact that all three substrates are reduced with comparable rates indicates that palladium interacts exclusively with the olefinic part of the enone, without significant participation of the carbonyl. This property is not necessarily shared by other transition metals. In conjugate reduction of enones with chromium[24] or molybdenum[10] catalysts, for example, the transoid and cisoid forms have markedly different reaction rates, the latter reacts faster.

Interestingly, this method was found to be highly selective for unsaturated ketones and aldehydes, as reduction of α,β-unsaturated esters, amides, and nitriles was very sluggish under these conditions.[25] Thus, benzalacetone was selectively and cleanly reduced in the presence of either methyl cinnamate (**25**), cinnamonitrile (**24**), or methyl cinnamamide (**23**) (Table II). Even under forcing conditions—increased amounts of palladium catalyst, triphenylphosphine (required to stabilize the catalyst), as well as zinc chloride and longer reaction times—these carboxylic acid derivatives could be reduced with only moderate yields. This lower reactivity may stem from a reduced tendency to form their palladium enolates (oxaallylpalladium complex, vide infra) as compared with palladium ketone enolates.[26] In the case of unsatrated nitriles, the situation is even worse due to the linearity of the CN group that prevents formation of a stable enolate analogue.

It appears that when compared to other transition-metal-assisted processes, our palladium-catalyzed reductions are less subject to steric effects, as steroidal enones **27–32** are effectively reduced under the above-described conditions (Scheme I and Table III). For example, conjugate reduction of the enone in testosterone with

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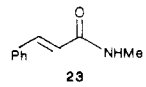
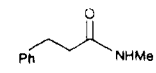
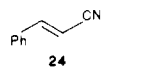
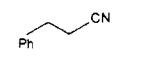
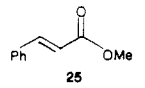
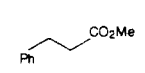
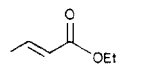
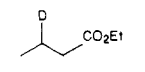
(25) For similar observations with Pt and Rh catalysts, see: (a) Stone, F. G. A.; Boag, N. M.; Barlow, A. P. *J. Organomet. Chem.* **1980**, *191*, 39. (b) Lappert, M. F.; Cornish, A. J. *J. Organomet. Chem.* **1979**, *172*, 153.

(26) The analogous inhibition of (π-allyl)palladium complex formation produced by an alkoxy substituent is well-known: Trost, B. M.; Gowland, F. W. *J. Org. Chem.* **1979**, *44*, 3448.

Table II. Conjugate Reduction of α,β-Unsaturated Carboxylic Acid Derivatives

starting material (mmol)	Ph_2SiH_2, mmol	$ZnCl_2$, mmol	$Ph(PPh_3)_4$	PPh_3	time, h	product (yield, %)
 **23** (0.25)	0.38	0.27	0.011	0.019	10	 (78[a])
 **24** (1.0)	1.25	0.66	0.013	0.05	72	 (49[a])
 **25** (1.15)	1.95	0.87	0.02	0.05	48	 (80[b])
 **26** (0.5)	0.61 (Ph_2SiD_2)	0.87	0.02	0.09	72	 (90[b])
8 (0.66) + **24** (0.62)	1.2	0.15	0.032		1	**19** (100[a,b]) + **24** (100[a,b])
8 (0.86) + **25** (0.89)	1.44	0.24	0.015		1	**19** (99[a,b]) + **25** (100[ab])
8 (0.10) + **23** (0.11)	0.12	0.045	0.01		1	**19** (100[a,b]) + **23** (96[a])

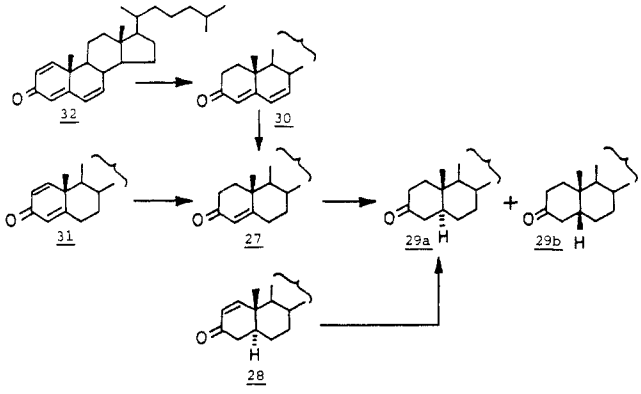
[a] Yields were determined by NMR. [b] Yields were determined by GC.

Table III. Conjugate Reduction of α,β-Unsaturated Steroidal Ketones[a]

entry	starting material (mmol)	Ph_2SiH_2, equiv	$ZnCl_2$, equiv	$Pd(PPh_3)_4$, equiv	time, h	products[b]	yield,[c] %
1	**27** (0.23)	3.5	4.0	0.095	7	**29a** + **29b** (60:40)	68
2	**28** (0.024)	13.3	1.2	0.071	1	**29a**	99
3	**30** (0.22)	1.1	0.59	0.027	4	**27** + **29a** + **29b** (68:18:14)	96
4	**32** (0.074)	1.6	0.90	0.067	1	**30**	71
5	**31** (0.034)	9.1	1.97	0.11	1	**27** + **29a** + **29b** (40:40:20)	77

[a] All reactions were carried out according to the general procedure in the Experimental Section. [b] Ratio of products was determined after chromatographic separation. [c] Yields of isolated products.

Scheme I



$NaHFe_2(CO)_8$[27] proceeds with less than 10% yield, while other substrates are efficiently reduced with the same reagent with yields usually greater than 90%. In contrast, both cholest-4-en-3-one (**27**) and cholest-1-en-3-one (**28**) was reduced by our method to cholestanone in high yields (Table III, entries 1 and 2). While reduction of the latter proceeded with high stereoselectivity (vide infra, reduction of **28** with dideuteriodiphenylsilane), the former was reduced with rather low selectivity, with both epimeric products **29a** and **29b** being formed in a 3:2 ratio. Those findings are reminiscent of the known distribution of products in the palladium-catalyzed hydrogenation or transfer hydrogenation of similar steroidal enones, where varying proportions of trans/cis isomers with respect to the A–B ring junction are produced.[28] Of particular interest was the finding that while dienones **30** and **31** and even trienone **32** are reduced all the way to cholestanone, partial reduction products can be isolated when the reaction is intercepted before completion. For example, halting the reduction of **32** after 1 h afforded dienone **30** in 71% yield.

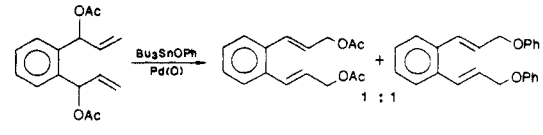
With substrates **30** and **31**, however, the first and second reduction steps proceed at comparable rates, leading to mixtures of partially and fully reduced products. For example, when reduction of **30** was stopped after 4 h, both **27** and **29** were isolated in a 68:32 ratio (entry 3, Table III). Similarly, when the reduction of **31** was quenched after 1 h, a 40:60 mixture of **27** and **29** was obtained (entry 5). The latter result, suggesting that both C-1 and C-4 olefins are reduced with similar rates, is quite intriguing in light of the experiments presented in entries 1 and 2, Table III. The relative reactivities of the simple enones **27** and **28** clearly indicate that reduction of the double bond at C-1 is at least 7 times faster than that of the C-4 double bond. This rate differential, which has already been observed in the catalytic hydrogenation of similar steroidal substrates over Pd/C or $RhCl(PPh_3)_3$,[28,29] was rechecked by a competition experiment using a 1:1 mixture of **27** and **28**. As expected, reduction of **28** was completed within 30 min, before any significant disappearance of **27** could be observed by ^1H NMR. Therefore, it seems that the different situation observed in the reduction of **31**, where both double bonds exhibit comparable reactivity (entry 5), arises from a certain interdependence between the two sequential reduction processes of this compound. If, for example, the palladium catalyst does not dissociate from the substrate following completion of the first reduction of the C-1 double bond, but is instead transferred intramolecularly to the second olefinic bond at C-4, the reduction of the latter to **29** could be accelerated substantially.[30]

(27) Collman, J. P.; Finke, R. G.; Matlock, P. L.; Wahren, R.; Komoto, R. G.; Brauman, J. I. *J. Am. Chem. Soc.* **1978**, *100*, 1119.

(28) (a) Loewenthal, H. J. E. *Tetrahedron* **1959**, *6*, 269. (b) Vitali, R.; Caccia, G.; Gardi, R. *J. Org. Chem.* **1972**, *37*, 3745.

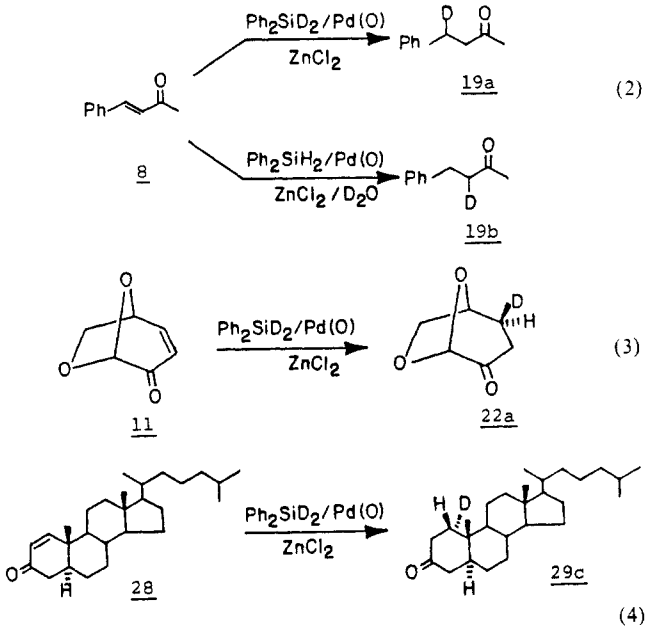
(29) (a) Djerassi, C.; Gutzwiller, J. *J. Am. Chem. Soc.* **1966**, *88*, 4537. (b) Rylander, P. *Catalytic Hydrogenation in Organic Syntheses*; Academic Press: New York, 1979, pp 51–58.

(30) Two sequential reactions on a bifunctional substrate were also observed in the palladium-catalyzed nucleophilic substitution of two allylic acetates, as shown below. We found for a number of nucleophiles that the



second substitution is generally faster than the first one, probably due to intramolecular transfer of the catalyst from one site to another. Keinan, E.; Haviv, D.; Roth, Z., unpublished results.

Regio- and Stereochemistry. Information concerning the regio- and stereochemical course of reduction is highly valuable for gaining a better understanding of the reaction mechanism and for applying it in organic synthesis. A number of deuterium-incorporation experiments were carried out, from which one may easily conclude that the conjugate reduction is both regio- and stereoselective. Employment of dideuteriodiphenylsilane for the reduction of benzalacetone (**8**), levoglucosenone (**11**), and cholest-1-en-3-one (**28**) yielded, in all cases, saturated ketones (**19a**, **22a**, and **29c**) containing one deuterium atom at the β-position (eq 2–4). Conversely, reduction of benzalacetone in a medium

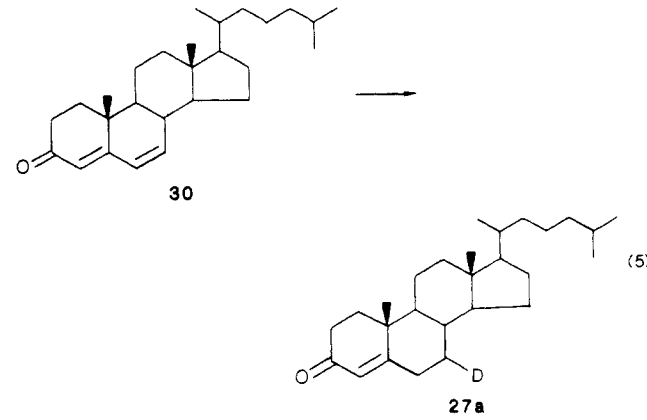


containing traces of D_2O resulted in benzylacetone monodeuterated at the α-position (**19b**) (eq 2). These observations indicate a net transfer of hydride from silane to the substrate β-carbon and proton transfer from water to the α-carbon.

Reductions of **11** and **28** (eq 3, 4) proceeded with high stereoselectivity, as indicated by the ^1H NMR spectra of the corresponding saturated, monodeuterated ketones **22a** and **29a**. The observed stereoselective incorporation of deuterium at the less-hindered exo face of **11** and the similar deuteride transfer to the less-hindered α-face of the steroid **28** are reminiscent of the stereoselectivity noticed in catalytic hydrogenation of steroidal enones[31] and supports a mechanism which involves intramolecular transfer of hydride from palladium to the coordinated olefin (vide infra). Reductions involving substrates in which both faces of the enone have similar abilities to form a palladium complex proceed, as expected, with poor stereoselectivity, a situation that has already been observed in catalytic hydrogenation of steroidal enones.[28] (See, for example, the above-described reduction of **27** to **29**.)

Although in this series of experiments, the stereochemistry of hydrogen substitution at the α-position could only be observed in two examples, namely, compounds **5** and **10** (Table I) in which both faces of the enone were nearly equally attacked, one would assume hydrogen substitution to be nonstereoselective even in cases where the two faces differ significantly. This is expected because formation of the final product occurs, at least partially, via nonselective protonolysis of the silicon enolate. Moreover, even if substitution would be stereoselective, the stereochemical integrity of the product is susceptible to acid-catalyzed equilbration at the α-position under the reaction conditions utilized.

The partial reduction of the linear dienone **30** to enone **27** represents an interesting case of a selective 1,6-reduction that is useful from the synthetic standpoint. Employment of Ph_2SiD_2 (eq 5) and interrupting the reaction after 4 h, followed by chromatographic separation, afforded pure 7-deuteriocholest-4-en-3-one (**27a**) in 65% yield. Regioselective incorporation of a single deuterium atom at C-7 of **27a** was evident from the mass spectrum.[32] However, on the basis of the discussion presented below of the reduction of cinnamylidene acetone (**34**) with dideuteriodiphenylsilane, one would expect to find deuterium atoms at both C-6 and C-7. The absence of deuterium atom at C-6 may be easily explained by its rapid exchange with water under the acidic conditions employed.



Perspective. A comparison of the Pd–silane–$ZnCl_2$ approach described here to various common methods for reducing olefinic bonds in α,β-unsaturated carbonyl compounds shows that our method is superior or complementary to these approaches. The traditional techniques, involving either dissolving metal reduction[33] or catalytic hydrogenation,[34] which were used extensively prior to the advent of hydride reducing agents, have certain technical advantages in particular systems but they generally lack chemoselectivity. The more recent developments in the area of conjugate reduction include mainly (a) employment of main-group metal hydrides, (b) stoichiometric use of transition-metal hydrides, and (c) various transfer-hydrogenation techniques. Aside from these general approaches, several other techniques utilizing miscellaneous reagents have been reported,[35] most of which are quite limited in terms of generality and chemoselectivity.

A number of recently described attractive procedures utilize main-group hydrides, including lithium or potassium Selectride (Aldrich), $NaBH_3CN$–$ZnCl_2$, H_2AlI, etc.[36] These reagents, however, tend to produce mixtures of products originating from both 1,4- and 1,2-reduction, and they are often too reactive to tolerate other functionalities. Similar difficulties are also en-

(31) Gurst, J. E.; Djerassi, C. *J. Am. Chem. Soc.* **1964**, *86*, 5542.

(32) Djerassi, C.; Brown, F. J. *J. Am. Chem. Soc.* **1980**, *102*, 807.

(33) (a) Smith, M. In *Reduction*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1968. (b) Birch, A. J.; Smith, H. *Quat. Rev. Chem. Soc.* **1958**, *12*, 17. (c) House, H. O. *Modern Synthetic Reactions*; W. A. Benjamin: Menlo Park, CA, 1972; pp 173–181. (d) Djerassi, C., Ed. *Steroid Reactions*; Holden-Day: San Francisco, CA, 1963; pp 267–288, 299–325. (e) Bowers, K. W.; Giese, R. W.; Grimsaw, J.; House, H. O.; Kolodny, N. H.; Kronberger, K.; Roe, D. K. *J. Am. Chem. Soc.* **1970**, *92*, 2783. (f) House, H. O.; Giese, R. W.; Kronberger, K.; Kaplan, J. P.; Simoene, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 2800. (g) Mueller, R. H.; Gillick, J. G. *J. Org. Chem.* **1978**, *43*, 4647. (h) Buchanan, J. G. St. C.; Woodgate, P. D. *Quat. Rev. Chem. Soc.* **1969**, *23*, 522.

(34) (a) Birch, A. J.; Walker, K. A. M. *J. Chem. Soc. C* **1966**, 1894. (b) Harmon, R. E.; Parsons, J. L.; Cooke, D. W.; Kupta, S. K.; Schoolenberg, J. *J. Org. Chem.* **1969**, *34*, 3684. (c) Biellman, J. F.; Jung, M. J. *J. Am. Chem. Soc.* **1968**, *90*, 1673. (d) Jardin, F. H.; Wilkinson, G. *J. Chem. Soc. C* **1967**, 270. (e) Candlin, J. P.; Oldham, A. R. *Discuss. Faraday Soc.* **1968**, *46*, 60, 92.

(35) (a) For reduction with benzylamine and potassium *tert*-butoxide, see: Malhorta, S. K.; Meakly, D. F.; Johnson, F. *J. Am. Chem. Soc.* **1967**, *89*, 2794. (b) For reduction with sodium dithionite, see: Gelbard, G.; Louis-Andre, O. *Tetrahedron Lett.* **1985**, *26*, 831. (c) For reduction with Et_3N–HCOOH, see: Nanjo K.; Suzuki, M.; Sekiya, M. *Chem. Pharm. Bull.* **1977**, 2396. (d) For reduction with 2-phenylbenzothiazoline, see: Chikashita, H.; Miyazaki, M.; Itoh, K. *Synthesis* **1984**, 308. (e) For reduction with NaHTe, see: Yamashita, M.; Kato, Y.; Suemitsu, R. *Chem. Lett.* **1980**, 847.

(36) For reduction with boron and aluminum hydrides, see ref 2c and: (a) Ashby, E. C.; Lin, J. .; Kovar, R. *J. Org. Chem.* **1976**, *41*, 1939. (b) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194. (c) Kadin, S. B. *J. Org. Chem.* **1966**, *31*, 620. (d) Pepin, Y.; Nazemi, H.; Payette, D. *Can. J. Chem.* **1978**, *56*, 41.

countered with transition-metal hydrides. In addition, their preparation often involves nontrivial procedures. The most useful reagents of this class are the hydrides of copper,[37] iron,[38] cobalt,[39] chromium,[40] and nickel.[41] For example, copper hydrides[37] lack chemoselectivity, with saturated ketones being reduced to alcohols under the reaction conditions, alkyl and aryl bromides being reduced to the corresponding hydrocarbons, and dimerization products appearing in some cases. Employment of iron hydrides according to Collman's procedure[27] is one of the most chemoselective and general methods for conjugate reduction of unsaturated aldehydes, ketones, esters, nitriles, and amides. It consumes, however, stoichiometric quantities of the air-sensitive binuclear hydridoiron cluster $NaHFe_2(CO)_8$.

Composite reducing systems, comprised of nonreactive hydride donors and a transfer agents, represent, conceptually, the most chemoselective approach. Various transfer-hydrogenation techniques may be included in this class, with alcohols and formate salts serving as common hydride donors and transition-metal complexes serving as transfer agents. Many of these reductions, however, require high temperatures.[42]

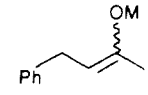
Ojima's Rh(I)-catalyzed hydrosilation approach, although employing an air-sensitive system (trialkylsilane and $RhCl(PPh_3)_3$),[22,43,44] is useful in a number of cases, as it produces high yields under relatively mild reaction conditions. In has, however, a number of shortcomings, particularly in comparison to our palladium-catalyzed reaction. The generality of that method is limited by the fact that the relative rates of 1,4- and 1,2-reduction modes are highly dependent on concentration, temperature, the nature of the silane and that of the substrate itself. For example, even under optimized conditions, varying proportions of the two reaction products are produced with common substrates such as **4**, **6**, **8**, and **10**.[22] Moreover, the method lacks chemoselectivity with respect to saturated ketones, aldehydes, imines, etc., which are rapidly hydrosilated in the presence of $RhCl(PPh_3)_3$ and various mono- and dihydridosilanes.[45]

In contrast, our palladium-catalyzed reaction showed no reduction of saturated ketones and aldehydes or 1,2-reduction of unsaturated ones. Moreover, the employment of relatively inexpensive palladium catalyst and a readily available hydridosilane, as well as the very simple and convenient experimental procedure involved, are clear advantages of this reduction. This method is superior to our previously reported tin hydride/Pd(0) approach,[4,46] because the palladium catalyst has limited lifetime in solutions containing tin hydride.

Proposed Catalytic Cycle. The above-described experiments are consistent with a catalytic cycle (Scheme II) that is reminiscent of the widely accepted mechanism of Pt-catalyzed hydrosilation of olefins.[11] Formation of complex I by coordination of the nucleophilic Pd(0)–phosphine complex to the electron-deficient olefin is a rapid, reversible process which is essentially complete within few seconds at room temperature. This fast equilibrium was clearly demonstrated by observation of spin saturation transfer in the NMR spectrum of a mixture of **8** and $Pd(PPh_3)_4$ even below room temperature (see Experimental Section).[47] Oxidative addition of silicon hydride to palladium in complex I would result in hydrido olefin palladium complex II. NMR experiments with boron trifluoride ethereate (vide infra) clearly indicated that formation of palladium hydride species via silane addition is a Lewis acid catalyzed processes. In principle, oxidative addition of silane may occur either before or after that coordination.

Migratory insertion of hydride into the electrophilic β-carbon of the coordinated olefin can result in an intermediate palladium enolate, III. This process is expected to be both regioselective and reversible, as was generally observed in a number of analogous cases involving other transition metals. These include conjugate reductions carried out with a ruthenium catalyst,[9] enone reductions with hydridoiron complexes,[27] and hydride migration to coordinated α,β-unsaturated carbonyl compounds from either hydridocobalt pentacyanide ($HCo(CN)_5^{3-}$)[48] or the dihydridotriosmium carbonyl cluster $H_2Os_3(CO)_{10}$.[49] With regard to Collman's reduction,[27] this reversibility was proven by employment of the deuterioiron complex leading to deuterium incorporation into the recovered, unreacted starting material and an inverse deuterium isotope effect. In our case, however, such reversibility was not evident. When employing dideuteriodiphenylsilane for the reduction of benzalacetone (**8**) or mesityl oxide **2**, we observed small, regular deuterium isotope effects (k_H/k_D = 1.5 and 1.1, respectively). Likewise, deuterium was not incorporated into recovered **8** and **2** during these reactions. There are a number of reported cases where migratory insertion of hydride into an olefin—e.g. catalytic hydrogenation, isomerization, hydroformylation, etc.—is a relatively slow process and may even be a rate-determining step.[50] This could be true in our reaction as well.

Coupling of the silicon moiety to the enolate ligand by reductive elimination from intermediate III could complete the catalytic hydrosilation cycle, resulting in silyl enol ether IV. In principle, this is also a reversible process, although the reverse transformation—going from the silyl enol ether and Pd(0) complex back to palladium enolate—is not observed. We found that in a solution containing stoichiometric quantitites of $Pd(PPh_3)_4$ in benzene, silyl enol ether **33a** derived from benzalacetone[51] is stable



33a, M=SiEt3
b, M=SiHPh2

for several days at room temperature. With Pd(II) complexes,

(37) For reduction with copper hydride, see: (a) Boeckman, R. K., Jr.; Michalak, R. *J. Am. Chem. Soc.* **1974**, *96*, 1623. (b) Masamune, S.; Bates, G. S.; Georghiou, P. E. *J. Am. Chem. Soc.* **1974**, *96*, 3686. (c) Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. *J. Org. Chem.* **1977**, *42*, 3180. (d) Ashby, E. C.; Lin, J. J.; Goel, A. B. *J. Org. Chem.* **1978**, *43*, 183. (e) Saegusa, T.; Kawasaki, K.; Fujii, T.; Tsuda, T. *J. Chem. Soc., Chem. Commun.* **1980**, 1013.

(38) For reduction with iron hydrides, see ref 27 and: (a) Noyori, R.; Umeda, I.; Ishigami, T. *J. Org. Chem.* **1972**, *37*, 1542. (b) Boldrini, G. P.; Umani-Ronchi, A. *J. Organomet. Chem.* **1979**, *171*, 85.

(39) (a) For reduction with $HCo(CO)_4$, see: Goetz, R. W.; Orchin, M. *J. Am. Chem. Soc.* **1963**, *85*, 2782. For reduction with $HCo(CN)_5^{3-}$, see ref 48 and: (b) Reger, D. L.; Habib, M. M.; Fauth, D. J. *J. Org. Chem.* **1980**, *45*, 3860.

(40) (g) For reduction with chromium hydrides, see: (a) Zurqiyah, A.; Castro, C. E. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 993. (b) Boldrini, G. P.; Umani-Ronchi, A. *Synthesis* **1976**, 596.

(41) (a) For reduction with nickel hydrides, see: Imamoto, T.; Mita, T.; Yokomoto, M. *J. Chem. Soc., Chem. Commun.* **1984**, 163. (b) Burnet, J. J.; Mordenti, L.; Caubere, P. *J. Org. Chem.* **1979**, *44*, 2203.

(42) (a) Sasson, Y.; Blum, Y. *J. Org. Chem.* **1975**, *40*, 1887. (b) Azran, J.; Bouchman, O.; Ibrahim, A.; Blum, J. *J. Mol. Catal.* **1986**, *34*, 229. (c) Speier, G.; Marko, L. *J. Organomet. Chem.* **1981**, *210*, 253. (d) Johnstone, A. W.; Wilby, A. H.; Entwistle, I. D. *Chem. Rev.* **1985**, *85*, 129. (e) Beaupere, D.; Bauer, P.; Uzan, R. *Can. J. Chem.* **1979**, *57*, 218. (f) Cortese, N. A.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 3985. (g) For reduction with $Rh_6(CO)_{16}$, CO, H_2O, and $Rh_4(CO)_{12}$, see: Kitamura, T.; Sakamoto, N.; Joh, T. *Chem. Lett.* **1973**, 379. Kitamura, T.; Joh, T.; Hagihara, N. *Chem. Lett.* **1975**, 203. (h) For reduction with R_3Al–Ni, see: Caporusso, A. M.; Giacomelli, G.; Lardicci, L. *J. Org. Chem.* **1982**, *47*, 4640.

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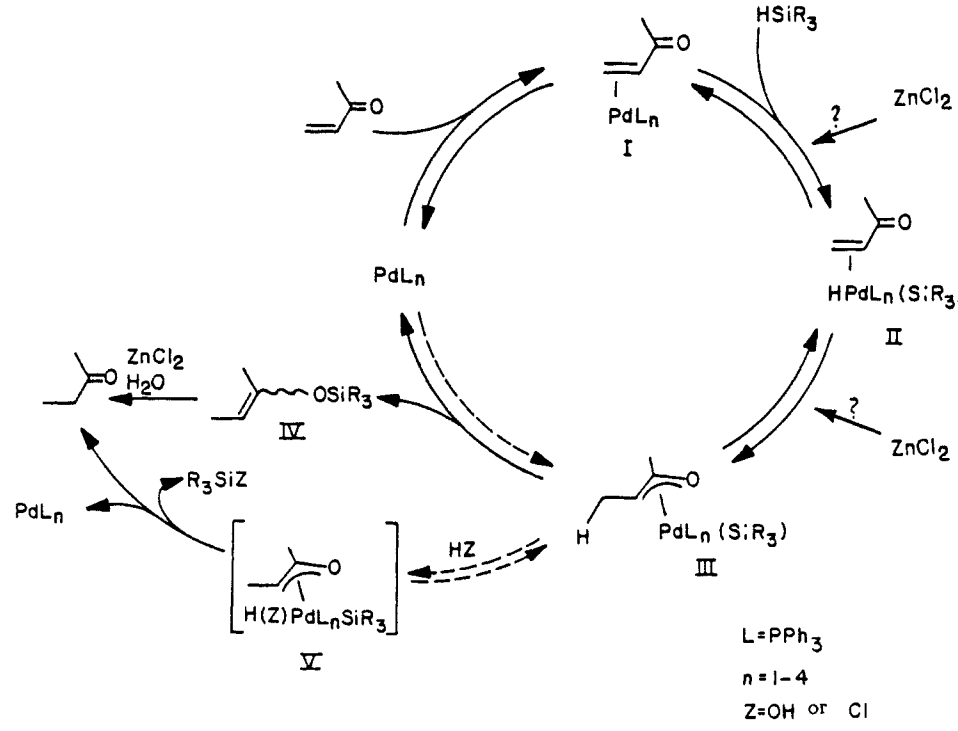
(51) Silyl enol ether **33** (mixture of *E* and *Z* isomers at a 1:1 ratio) was prepared via Rh(I)-catalyzed hydrosilation of benzalacetone, see ref 22.

Scheme II



however, the transformation of IV to III, has been reported and even utilized as a synthetic tool for the preparation of α,β-unsaturated carbonyl compounds.[52]

Silyl enol ethers are prone to acid-catalyzed hydrolysis, yielding the saturated ketone. Indeed, addition of $ZnCl_2$ (0.3 equiv) to a chloroform solution of **33a** resulted in its rapid cleavage to the parent saturated ketone. In fact, when following the reduction of benzalacetone by proton NMR, we initially observed accumulation of small quantities (<10%) of the two isomeric silyl enol ethers **33b** (*Z* and *E* in a 3:1 ratio) that disappeared toward the end of the reaction.

A possible alternative pathway for the transformation of III to a saturated ketone, one that circumvents the formation of a silyl enol ether IV, involves the protonolysis of the palladium enolate III via oxidative addition of a proton donor ZH (Z = OH or Cl), yielding a Pd(IV) intermediate which collapses to the saturated carbonyl and R_3SiZ, along with regenerated Pd(0) catalyst. The relative importance of these two alternatives is yet unknown (Scheme II).

One might envisage an alternative mechanism for the palladium-catalyzed hydrosilation of unsaturated ketones that is analogous to that currently accepted for the rhodium-catalyzed reaction, namely initial coordination of the transition metal to the carbonyl, followed by migratory insertion of silicon to oxygen, generating an α-siloxyalkylmetal hydride intermediate. This scheme was first proposed by Kumada[53] and subsequently proved by Kagan[54] and Ojima[22] (see, for example, the upper part of Scheme III). This possibility, however, seems remote in our case because, in contrast to the rhodium situation, our palladium reaction conditions did not yield alcoholic side products resulting from direct 1,2-carbonyl reduction. In fact, no 1,2-carbonyl reduction was observed in any of the substrates we reduced, including saturated and α,β-unsaturated ketones and aldehydes.

Moreover, careful inspection of the products obtained from conjugate reduction of the dienone system in cinnamylideneacetone (**34**) provided convincing evidence against a "silicon first" mechanism. Three products were obtained with Ph_2SiH_2/Pd(0)/$ZnCl_2$: 6-phenylhexan-2-one (**35**), 6-phenylhex-5-en-2-one (**36**), and 6-phenylhex-4-en-2-one (**37**) in a ratio of 3:5:1, respectively. This product distribution indicates almost equal preference (5:4) for the 1,4- and 1,6-reduction modes (see Scheme III), a situation that is expected due to similar acceptor properties of the two olefinic bonds. This similar affinity for Pd(0) was nicely confirmed by ^1H NMR spectrum of a mixture of **34** and Pd(PPh$_3$)$_4$ in toluene-d_6, in which two $^2\eta$-olefin palladium complexes (with the α–β and with the γ–δ double bonds) were formed in about 2:1 ratio, respectively (as shown by the integrated spectra).

In contrast, hydrosilation of **34** with triethylsilane and rhodium(I) catalyst, followed by methanolysis (Ojima's conditions), afforded a significantly different product distribution: compounds **36** and **35** were obtained in a 9:1 ratio and no traces of **37** were observed. This result is expected from a "silicon first" mechanism (Scheme III), which reduces the probability of 1,6-reduction.

Further support of our "hydride first" proposal was provided by reduction of 34 with dideuteriodiphenylsilane. In the case of the "silicon first" mechanism, formation of the doubly reduced product, 35, would involve 1,6 hydrosilation followed by hydrolysis of the resulting silyldienol ether to give the α,β unsaturated ketone which undergoes 1,4-hydrosilation and hydrolysis (Scheme III). This sequence would result in incorporation of two deuterium atoms into the product. In the "hydride first" mechanism (see the lower part of Scheme III), however, 1,6-hydride addition would generate (π-allyl)palladium intermediate **38**, which is prone to reduction with 1 equiv of silane. Therefore, in this latter case one expects incorporation of three deuterium atoms into **35**. Indeed, when dideuteriodiphenylsilane was employed for the reduction of **34**, product **35** was found to contain three deuterium atoms, at positions β, γ, and δ to the carbonyl. This regioselectivity of deuterium incorporation was confirmed by comparing the mass spectrum of **35** thus obtained to an authentic sample of trideuterio-**35**, obtained from catalytic deuteration of **34** with D_2/Pd/C, followed by treatment with K_2CO_3 in methanol (see Experimental Section).

The role played by Lewis acid cocatalyst in this reaction is, undoubtedly, the most intriguing mechanistic question. Certainly, protonolysis of the silyl enol ether IV could be significantly accelerated under acid catalysis. Our earlier observations[4] that the conjugate reduction of α,β-unsaturated ketones and aldehydes with Bu_3SnH/Pd(0) is substantially promoted by the presence of wet NH_4Cl may also be interpreted on this basis. Similar results were reported also by Guibe[46] who used either acetic acid or $ZnCl_2$ for

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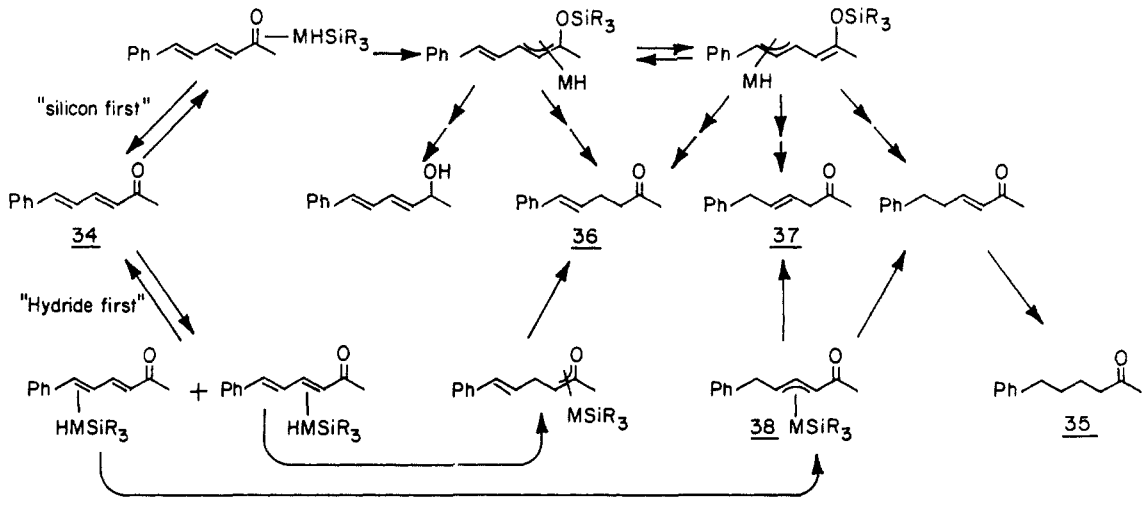
Scheme III



conjugate reductions with tin hydride and palladium catalysts.

Nevertheless, as mentioned above, all three components (silane, Pd catalyst, and $ZnCl_2$) are essential for the reaction, as neither reduction nor formation of silyl enol ether takes place at room temperature[15] in the absence of any one of them. Moreover, the lack of correlation between reaction rates, the strength of the various acids checked (vide supra), and particularly the fact that $ZnCl_2$ is not the strongest acid[55] but is the most effective in this reaction indicate that $ZnCl_2$ may have some other advantages in this system. Since, for example, at least 1 equiv of water is essential to complete the reduction, it is possible that the compatibility of $ZnCl_2$ with water makes it superior to the stronger Lewis acids, such as $TiCl_4$ and BF_3–OEt_2 which react rapidly and irreversibly with water.

Considering the catalytic cycle suggested in Scheme II, one may envision a number of points where intervention of Lewis acid may promote the reaction. For example, the cocatalysts may be responsible for some modification of the hydride donor, one possibility being a significant enhancement of hydride nucleophilicity via formation of a penta- or hexacoordinated silane.[56] However, it is not known whether such a change will indeed accelerate the oxidative addition of Si–H to Pd, as the more nucleophilic silanes, such as Et_3SiH, are substantially less reactive in our case (vide supra). Alternatively, one may speculate that activation of the hydridosilane is mediated via partial or total transfer of hydride from silicon to zinc (or to Mg and Al when these metal chlorides are used)—i.e., formation of "Zn–H" or "Zn–H–Si" species.[57] Such an hypothesis may be supported by the fact that in the absence of a Pd catalyst Ph_2SiH_2 dissolved in wet Me_2SO reacts with $ZnCl_2$ with vigorous evolution of hydrogen gas. Lewis acids are known to catalyze disproportionation reactions of diphenylsilane at high temperatures.[58]

That oxidative addition of hydridosilane to palladium is promoted by Lewis acids is clearly evident from ^1H NMR experiments. Addition of $Pd(PPh_3)_4$ to a $CDCl_3$ solution of diphenylsilane and BF_3–OEt_2 (that was chosen for its solubility) gave rise to rapid appearance of two upfield signals at an integration ratio of 10:1, respectively: δ −6.97 (dt, J = 175.5, 13.5 Hz), which may represent $PdH(PPh_3)_3^+$ cation,[59] and a singlet at δ −13.22, which may be assigned to a neutral *trans*-$PdHX(PPh_3)_2$ (X = $SiHPh_2$, halide, etc.).[8] Addition of **8** to the mixture resulted in immediate disappearance of these upfield signals with quantitative formation of **19**. In contrast, when that experiment was carried out in the absence of the Lewis acid a singlet of very low intensity at δ −8.64 slowly appeared. Although this signal may be attributed to a certain Pd–H species, addition of **8** to the mixture caused neither disappearance of this singlet nor formation of any detectable amounts of **19**.

Additionally, polarization of the substrate carbonyl by coordination to a Lewis acid could decrease electron density on the olefin and thus facilitate coordination to palladium. More importantly, such polarization could catalyze the migratory insertion of hydride into the olefin, much like the well-documented ability of Lewis acids to accelerate migratory insertion of alkyl groups into unsaturated, electrophilic ligands.[60] The lower reactivity of α,β-unsaturated carboxylic acid derivatives[25] observed in our reactions can be explained by the sensitivity of reaction rates to acceptor properties of the substrate. A similar trend in the relative reactivities of Michael acceptors has been generally observed with respect to conjugate addition of organometallics, such as organocopper reagents, to these substrates.[61]

Conclusion

This study describes the use of a three-component system comprised of Pd(0), diphenylsilane, and zinc chloride for conjugate reduction of α,β-unsaturated carbonyl compounds. The suggested catalytic cycle, proposed on the basis of deuterium incorporation experiments and NMR studies, involves a 1,4-hydrosilation process that is catalyzed by Pd(0) and cocatalyzed by the Lewis acid. The primary product, silyl enol ether, is hydrolyzed to the saturated carbonyl under the reaction conditions. Even before a full understanding of the reaction mechanism is achieved, the system described may be effectively utilized for highly controlled organic synthesis.

Experimental Section

General Methods. Melting points (uncorrected) were determined on a Buchi apparatus. Infrared spectra were measured on the neat compounds with an FT Infrared Nicolet Mx-1 spectrometer and are given in reciprocal centimeters. ^1H NMR spectra were measured in deuteriochloroform (unless otherwise cited) on a Varian FT-80A or Bruker WH-270 NMR spectrometers. All chemical shifts are reported in δ units downfield from Me_4Si, and the J values are given in hertz. Splitting

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patterns are designated as follows: s, singlet; d, doublet; t, triplet, q, quartet; m, multiplet; br, broad. ^{13}C NMR were measured in deuteriochloroform on a Bruker WH-90 NMR spectrometer. GC–MS analyses were carried out on a Finnigan 4500 spectrometer. High-resolution mass spectra were determined on a Varian Mat-731 spectrometer. Thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60, F254, Art 5549). Column chromatography separations were performed on silica gel (Merck, Kieselgel 60, 230-400 mesh, Art 9385) under pressure of 0.4 atm (flash chromatography). Preparative TLC was performed on glass plates precoated with silica gel (Merck, Kieselgel 60 F-254, Art 5717). GC analyses were performed on a Spectra Physics 7100 (FI detector) gas chromatograph equipped with a 0.125 in. × 2 ft column packed with 10% SE-30 on Chromosorb W. Preparative GC separations were carried out with a Varian Aerograph 90P (TC detector) equipped with either a $^1/_2$ in. × 20 ft column packed with 10% carbowax 20M on Chromosorb W or a $^3/_8$ in. × 20 ft column packed with 10% SE-30 on Chromosorb W. Distillations were usually performed with a Buchi kugelrohr apparatus and the temperatures given are pot temperatures.

Materials. Tetrahydrofuran was distilled over sodium benzophenone ketyl. $CHCl_3$ and $CDCl_3$ were filtered through neutral alumina prior to use. Tetrakis(triphenylphosphine)palladium, $Pd(dppe)_2$,[62] $PdCl_2(PhCN)_2$,[63] and $Pd(OAc)_2$[64] were prepared as reported. All silanes were purchased from Petrarch, except for PMHS (Aldrich). Dideuteriodiphenylsilane was prepared by reduction of dichlorodiphenylsilane with $LiAlD_4$ in ether. $TiCl_4$, $SnCl_4$, and $FeCl_3$ were purchased from BDH, $MgBr_2$ from Fluka, and $AlCl_3$ from Merck. Commercial $ZnCl_2$ (Merck 8816) was used without any treatment. Starting materials **1** and **3** were purchased from Aldrich; compounds **2**, **4**, **5**, **9**, and **27** from Fluka; **8** from Merck; and **10** from Eastman-Kodak. Compounds **6**,[65] **7**,[66] and **11**[67] and steroidal substrates **28** and **30–32**[68] were prepared as reported.

Reductions of Benzalacetone with Various Silanes. $Pd(PPh_3)_4$ (11.5 mg, 0.01 mmol, 5 mol %) was added to a 5-mm NMR tube containing benzalacetone (**8**) (29.2 mg, 0.2 mmol), the appropriate silane (0.35) mmol), and $ZnCl_2$ (7.5 mg, 0.05 mmol, 25 mol %) in $CDCl_3$ (0.7 mL). The tubes were placed in the WH-270 NMR probe at 23 °C, and reactions were followed by ^1H NMR. The mixtures were vigorously shaken during the time they were kept outside the NMR probe. Seven representative silanes were checked, and the following was observed: (a) with diphenylsilane, the reaction was completed in less than 40 min; (b) with phenylsilane the desired reduction reached 75% conversion in 40 min. This reaction, however, was accompanied with black precipitation of metallic palladium; (c) with 1,1,3,3-tetramethyldisiloxane, 20% conversion was attained within 40 min; (d) with dimethylethoxysilane or triethylsilane <10% conversion was observed after 40 min (about 20–25% conversion was observed within 2 h, before decomposition of the catalyst to metallic palladium); and (e) with either polymethylhydrosiloxane or diethoxymethylsilane, no product was observed within 2 h.

Reduction of Benzalacetone with Various Lewis Acid Cocatalysts. $Pd(PPh_3)_4$ (11.5 mg, 0.01 mmol, 5 mol %) was added to a 5-mm NMR tube containing benzalacetone (**8**) (29.2 mg, 0.2 mmol), diphenylsilane (64.2 mg, 0.35 mmol), and a Lewis acid (generally 0.05 mmol, 25 mol %) in $CDCl_3$ (0.7 mL). The tube was placed in the WH-270 NMR probe at 23 °C and the reactions were monitored by ^1H NMR. For some of the reactions, due to their heterogeneous nature, the mixtures were removed from the NMR probe between measurements and vigorously shaken.

A. $ZnCl_2$. Six experiments were carried out with the following quantities of zinc chloride: (a) 1.5 mg (5 mol %), (b) 2.5 mg (10 mol %), (c) 7.5 mg (28 mol %), (d) 33 mg (125 mol %), (e) 65 mg (240 mol %), (f) same as (e) but in the absence of Pd catalyst. The following observations were made with respect to each of these experiments: (a) The reaction reached about 50% conversion after 90 min and stopped with the sudden precipitation of metallic palladium. (b) The reaction reached 50% conversion within 50 min. (c) The reaction reached 50% conversion within 35 min. (d) The reaction reached 50% conversion within 8 min. (e) The reaction was complete within 5 min. (f) No reaction could be detected within 45 min. However, when Pd(0) catalyst was then added, 100% conversion took place within 8 min.

B. $TiCl_4$. Unclean, nonselective reduction of **8** was observed. After 1 h a complex mixture was obtained containing 20% starting material, 40% benzylacetone, and 40% of other side products, including 1-phenylprop-1-en-3-ol and some unidentified components. Longer reaction times led to an even more complex mixture. A second experiment was carried out with quantities and conditions similar to those used previously, but without the Pd catalyst. A complex mixture, very similar to that formed in the first experiment was also produced here on a comparable time scale.

C. $SnCl_4$. A mixture very similar to that observed in case A was produced here but at a slower rate. After 2 h, the solution still contained 80% unreacted starting material along with about 10% benzylacetone and an equal amount of unidentified side products.

D. $AlCl_3$. Very slow but selective reduction was observed. After 12 h, the reaction mixture contained 75% starting material **8** and 25% benzylacetone.

E. $FeCl_3$. Because paramagnetic Fe ions interfere with NMR measurements, these experiments were monitored by GC. Reaction mixtures contained benzalacetone (1 mmol), diphenylsilane (1.05 mmol), $Pd(PPh_3)_4$ (0.05 mmol), 5 mL of $CHCl_3$, and the following quantities of ferric chloride: (a) 42 mg (0.25 mmol) and (b) 8 mg (0.05 mmol). Evolution of hydrogen gas was observed in both experiments. With the higher concentration (a), about 50% conversion to benzylacetone was observed within 1 h; the reaction, however, stopped at that stage and the catalyst suddenly decomposed to metallic palladium. With the lower concentration of $FeCl_3$ (b), although metallic Pd did not form, the reaction still halted at 50% conversion after 1 h due, this time, to decomposition of diphenylsilane.

F. $MgBr_2$. Selective reduction was observed, and after 12 h the mixture contained 52% starting material and 48% benzylacetone.

G. BF_3–OEt_2. Very slow reduction was observed, with 20% conversion within 7 h and no further reaction even after 24 h. When the same reaction was carried out in the absence of $Pd(PPh_3)_4$, no reaction was observed within 24 h.

H. Ti(O-*i*-Pr)$_4$. A very slow reduction was observed, with less than 10% conversion after 20 h.

I. AcOH. No reaction was observed even after 12 h.

J. NH_4Cl. Less than 5% conversion was detected after 12 h.

Reduction of Benzalacetone in the Presence of Water. $Pd(PPh_3)_4$ (15 mg, 1.3 mol %) was added to a mixture of benzalacetone (146 mg, 1 mmol), diphenylsilane (190 mg, 1.1 equiv), zinc chloride (40 mg, 0.3 equiv), and various amounts of water. In all experiments, freshly dried chloroform was used (5 mL, filtered through active basic alumina), and reactions were carried out in flame-dried flasks. The mixtures were stirred at room temperature and reactions were monitored by GC using an internal standard. Seven experiments were performed in which (a) dry $ZnCl_2$, prepared from zinc and HCl,[18] was used; (b) commercial $ZnCl_2$ (Merck 8816), dried under vacuum (0.1 mmHg) at 100 °C for 24 h, was used; (c) commercial $ZnCl_2$ was used without treatment, with no special precautions being taken to eliminate moisture; (d) water (6 mg, 0.33 mmol) was added to the reaction mixture after addition of commercial zinc chloride and before addition of palladium catalyst; (e) same as in (d) but with 11 mg (0.61 mmol) water; (f) same as in (d) but with 22 mg (1.22 mmol) water; and (g) same procedure as in (d) was used, but with 100 mg (5.56 mmol) water. The following conversions were observed after 10 min: (a) 54%; (b) 63%; (c) 72%; (d) 63%; (e) 61%; (f) 34%; (g) 22%. In (f) and (g) the reaction was totally inhibited after 10 min, when separation of the reaction mixture into two phases was observed.

Reduction of Benzalacetone in Various Solvents. Three mixtures were prepared, each comprised of benzalacetone (73 mg, 0.5 mmol), diphenylsilane (190 mg, 1.05 mmol), $ZnCl_2$ (39 mg, 57 mol %), and 5 mL of (a) chloroform, (b) tetrahydrofuran, or (c) benzene. $Pd(PPh_3)_4$ (25 mg, 4.3 mol %) was added under magnetic stirring to each of these mixtures, and the reductions were followed by GC. The various reactions reached 75% conversion within the following times: (a) 15, (b) 25, and (c) 50 min.

Reduction of Benzalacetone with Various Pd Catalysts. A solution of the appropriate palladium complex in 0.1 mL of $CDCl_3$ was added to a 5-mm NMR tube containing benzalacetone (**8**) (29.2 mg, 0.2 mmol), diphenylsilane (0.35 mmol), $ZnCl_2$ (7.5 mg, 0.05 mmol, 25 mol %) in $CDCl_3$ (0.7 mL) at 23 °C, and the reaction was followed by ^1H NMR (270 MHz). Using various catalysts, the following results were obtained: (a) with both $PdCl_2(C_6H_5CN)_2$ (4 mg, 0.01 mmol) and PPh_3 (13 mg, 0.05 mmol), reduction was completed within 40 min; (b) with both $Pd(OAc)_2$ (3 mg, 0.013 mmol) and PPh_3 (5 mg, 0.02 mmol), conversion reached 90% within 30 min but the reaction stopped at that stage due to decomposition of the catalyst to metallic palladium; (c) with both

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$Pd(OAc)_2$ (3 mg, 0.013 mmol) and PPh_3 (10.5 mg, 0.04 mmol), reaction was completed within 35 min; (d) with $Pd(PPh_3)_4$ (11.5 mg, 0.01 mmol) alone, complete conversion was attained within 40 min; (e) with $Pd(dppe)_2$ (9 mg, 0.01 mmol), the reaction reached 50% conversion within 40 min and was completed in 2 h; (f) with $PdCl_2$ (2 mg, 0.011 mmol) and PPh_3 (11 mg, 0.04 mmol), no reaction was observed within 2 h (probably due to catalyst insolubility under these conditions); (g) with $PdCl_2$ (2 mg, 0.011 mmol) and PPh_3 (11 mg, 0.04 mmol) (which were stirred in 1 mL of $CDCl_3$ for 16 h after which the reactants were added), complete reduction was attained within 40 min.

General Procedure for Conjugate Reduction of α,β-Unsaturated Ketones and Aldehydes. The α,β-unsaturated carbonyl (0.5–1.5 mmol) was dissolved in chloroform (3–5 mL) along with diphenylsilane (1.0–2.5 equiv) and zinc chloride (0.1–0.5 equiv). $Pd(PPh_3)_4$ (1–2 mol %) was added and the mixture was stirred at room temperature (inert atmosphere was not required); the reaction was monitored by either TLC or GC. Upon completion, the solution was filtered through a short silica gel column, and the products were purified by either Kugelrohr distillation or flash chromatography with an appropriate mixture of ethyl acetate and hexane. In cases where yields determined by GC, an external standard method was used. Further experimental details and yields are given in Tables I and II. Products **12i–14**, **17**, **19**, **20**, and 21 were identified by comparison (NMR, GC, MS) to commercial materials (Fluka). Compound **27** was compared (NMR, TLC, MS) to a commercial sample (Fluka). Others, including **15**,[69] **16**,[70] **18**,[71] **22**,[72] **29a**, **29b**,[73] and **30**,[68] were compared to literature data. More physical properties of **15**, **16**, and **18** are given below.

15: NMR δ 2.51 (t, J = 8.5, 2 H), 2.26 (t, J = 8.5, 2 H), 2.15 (s, 3 H), 1.91 (t, J = 6.3, 2 H), 1.56 (m, 5 H), 1.41 (m, 2 H), 0.96 (s, 6 H).

16 (the two isomers were separated by preparative GC): NMR (trans isomer) δ 4.78 (s, 1 H), 4.76 (s, 1 H), 2.50–2.22 (m, 4 H), 2.16–2.07 (m, 1 H), 1.99–1.88 (m, 1 H), 1.74 (s, 3 H), 1.65 (m, 1 H), 1.45–1.33 (m, 1 H), 1.03 (d, J = 6, 3 H)[(cis isomer) 4.84 (s, 1 H), 4.71 (s, 1 H), 2.62–2.5 (m, 2 H), 2.46–2.35 (m, 2 H) 1.92–1.80 (m, 2 H), 1.75 (s, 3 H), 1.67–1.52 (m, 1 H), 1.34–1.20 (m, 1 H), 1.10 (d, J = 7, 3 H).

18: NMR δ 7.78 (d, J = 8.6, 2 H), 7.56 (d, J = 8.6, 2 H), 7.23 (m, 5 H), 3.23 (t, J = 7.2, 2 H), 3.03 (t, J = 7.2, 2 H); MS (relative intensity), m/z 290 (70), 288 (70), 209 (23), 185 (100), 183 (100), 181 (41), 169 (50), 157 (25), 155 (25), 131 (55), 119 (61), 105 (50), 91 (40), 77 (21); Mp 101 °C (lit. 101 °C[71]).

Competition Experiments. A. Reduction of 8 in the Presence of Carboxylic Acid Derivatives 23–25. $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) was added to a mixture of benzalacetone (**8**) (156 mg, 0.11 mmol), *N*-methylcinnamamide (**23**) (16 mg, 0.1 mmol), zinc chloride (6 mg, 0.045 mmol), and diphenylsilane (22 mg, 0.12 mmol) in 0.5 mL of deuteriochloroform. The mixture was stirred at room temperature; the progress of the reaction was monitored by NMR. Reduction of benzalactone was complete within 60 min, with concomitant reduction (<4%) of methylcinnamamide to dihydrocinnamamide.

A similar experiment was carried out with **8** (29 mg, 0.2 mmol), methyl cinnamate (**25**) (35 mg, 0.22 mmol), zinc chloride (8 mg, 0.06 mmol), $Pd(PPh_3)_4$ (8 mg, 0.007 mmol), and diphenylsilane (49 mg, 0.26 mmol) in 0.5 mL of deuteriochloroform. Conversion of **8** to **19** was complete within 30 min, with no observable change in the methyl cinnamate concentration.

A similar experiment was carried out with **8** (96 mg, 0.66 mmol), cinnamonitrile (**24**) (80 mg, 0.62 mmol), zinc chloride (21 mg, 0.15 mmol), $Pd(PPh_3)_4$ (37 mg, 0.032 mmol) and diphenylsilane (220 mg, 1.2 mmol) in 5 mL of chloroform. Progress of the reaction was monitored by GC. Conversion of **8** to **19** was complete within 3 h and no change was observed in the cinnamonitrile concentration.

B. Reduction of 28 in the Presence of 27. $Pd(PPh_3)_4$ (3 mg, 0.0026 mmol, 10 mol %) was added to a 5-mm NMR tube containing a 0.5-mL $CDCl_3$ solution of **27** (10 mg, 0.026 mmol), **28** (10 mg, 0.026 mmol), diphenylsilane (13 mg, 0.07 mmol), zinc chloride (0.5 mg, 0.004 mmol) and the internal standard bibenzyl (10 mg, 0.05 mmol). The tube was placed in the WH-270 NMR probe at 23 °C, and ^1H spectra were measured every 2 min. Complete reduction of **28** was observed within the first 30 min, whereas most of **27** (96%) remained intact.

Deuterium Incorporation Experiments. A. Reduction of Cholest-1-en-3-one with Ph_2SiD_2. $Pd(PPh_3)_4$ (13 mg, 7.2 mol %) was added to a chloroform solution 4 mL) of cholest-1-en-3-one (**28**) (38 mg, 0.1 mmol), dideuteriodiphenylsilane (75 mg, 4 equiv), and zinc chloride (56 mg, 4 equiv). The mixture was stirred at room temperature for 1 h until complete reduction was observed by TLC. Flash chromatography (with 1:30 ethyl acetate:hexane) afforded 35 mg of 1α-deuteriocholestan-3-one (**29c**) (92%) in the form of colorless crystals. The stereochemistry at C_1 was determined by 360-MHz ^1H NMR. The triplet of doublets assigned to proton 2β in the nondeuterated compound,[74] 2.38 (td, J = 13, 6, 1 H), was transformed into a doublet of doublets in 1α-D-cholestanone: 2.38 (dd, J = 13, 6, 1H), ($J_{2\beta,2\alpha} = J_{2\beta,1\alpha}$ = 13, $J_{2\beta,1\beta}$ = 6).

B. Reduction of Levoglucosenone with Ph_2SiD_2. $Pd(PPh_3)_4$ (12 mg, 6 mol %) was added to a chloroform (5 mL) solution containing levoglucosenone (**11**) (21 mg, 0.17 mmol), dideuteriodiphenylsilane (67 mg, 0.36 mmol), and zinc chloride (30 mg, 0.22 mmol). The solution was stirred for 1 h at room temperature, after which no substrate could be detected by TLC. The usual workup followed by flash chromatography with 1:2 ethylacetate/hexane afforded 20 mg (94%) of (1*R*,5*S*,4*S*)-4-deuterio-7,8-dioxabicyclo[3.2.1]octanone (**22a**).

Spectra of **22** and **22a** were taken while irradiating at 4.69 ppm (in order to eliminate the couplings related to H_5 and thereby simplify the spectrum). PANIC calculations were performed with Bruker Aspect 2000 PANIC (version 820601) based on the following chemical shifts (ppm) and coupling constants (Hz): 1.94 (H_{4eq}), 2.21 (H_{4ax}), 2.31 (H_{3eq}), 2.62 (H_{3ax}), $J_{3ax,3eq}$ = 17.4; $J_{3ax,4ax}$ = 13.0; $J_{3ax,4eq}$ = 9.1; $J_{3eq,4eq}$ = 0; $J_{3eq,4ax}$ = 7.6; $J_{4eq,4ax}$ = 13.5 (see the paragraph at the end of the paper about Supplementary Material).

C. Reduction of Benzalacetone with Ph_2SiD_2. Reduction of benzalacetone (**8**) (50 mg, 0.34 mmol) was carried out in $CDCl_3$ (1 mL) according to the general procedure with $Pd(PPh_3)_4$ (10 mg, 2.3 mol %), dideuteriodiphenylsilane (100 mg, 0.54 mmol), and zinc chloride (20 mg, 0.15 mmol). The solution was stirred for 2 h at room temperature, after which complete conversion of **8** into 4-deuterio-4-phenylbutan-2-one (**19a**) was observed by NMR (the reaction mixture was filtered through a cotton plug in order to improve NMR spectrum quality). NMR 7.4 (br s, 5 H), 2.83 (tt, J = 7.2, 2.1; 1 H), 2.65 (d, J = 7.2, 2 H), 2.02 (s, 3 H); MS, m/z 149 (67), 134 (14), 116 (3), 107 (22), 106 (100), 92 (89), 91 (13), 80 (18), 79 (19), 78 (29), 77 (23), 66 (18), 65 (12)8 52 (14), 51 (39).

D. Reduction of Benzalacetone with Ph_2SiH_2/D_2O. An experiment similar to C was carried out with **8** (50 mg, 0.34 mmol) in $CDCl_3$ (1 mL, dried over active alumina and then saturated with D_2O), $Pd(PPh_3)_4$ (10 mg, 2.3 mol %), diphenylsilane (100 mg, 0.54 mmol), and zinc chloride (freshly dried, 20 mg, 0.15 mmol). The mixture was stirred for 2 h at room temperature, after which complete conversion of **8** into 3-deuterio-4-phenylbutan-2-one (**19b**) was observed by NMR (the reaction mixture was filtered through a cotton plug in order to improve NMR spectrum quality). NMR δ 7.4 (br, s, 5H), 2.83 (d, J = 7.2, 2 H), 2.65 (br, t, J = 7.2, 1 H), 2.02 (s, 3 H); MS, m/z 149 (55), 148 (44), 134 (10), 115 (3), 106 (72), 105 (68), 104 (15), 91 (100), 77 (31), 65 (22).

E. Reduction of 30 with Ph_2SiD_2. Reaction was carried out according to the general procedure with cholesta-4,6-dien-3-one (**30**) (40 mg, 0.1 mmol), dideuteriodiphenylsilane) (76 mg, 0.4 mmol), zinc chloride (49 mg, 0.33 mmol), $Pd(PPh_3)_4$ (20 mg, 17 mol %), and chloroform (3 mL). The mixture was worked up after 1 h at room temperature. Flash chromatography (ethyl acetate/hexane 1:15) afforded 7-deuteriocholest-1-en-3-one (**27a**) (25 mg, 65%), in the form of colorless crystals. The position of the deuterium atom in the product was proven by mass spectrometry:[32] MS (**27a**, partial list), m/z 385 (57, M^+), 370 (8, $M^+ - CH_3$), 343 (16, $M^+ - C_2H_2O$), 262 (25), 230 (27), 124 (100); (**27**) 384 (57), 369 (11), 342 (25), 261 (27), 229 (37), 124 (100).

NMR Studies. A. Spin Saturation Transfer between Free and Complexed Benzalacetone. Benzalacetone (**8**) (9 mg, 0.06 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.03 mmol) were dissolved in 1 mL of C_6D_6 in a 5-mm NMR tube, and ^1H spectra were taken at 6.5 °C. Two sets of olefinic signals were observed in approximately equal integration: (a) the original absorptions of **8**, 7.26 (d, J = 16, 1 H), 6.53 (d, J = 16, 1 H); and (b) two broad multiplets at 5.30 and 4.97 ppm, assigned as the olefinic protons of the Pd(0)–olefin complex. Four double-irradiation experiments were carried out: (a) Upon irradiation at 7.26 ppm, the doublet at 6.53 turned to a singlet and the signal at 5.30 ppm disappeared from the spectrum. (b) Upon irradiation at 6.53 ppm, the doublet at 7.26 turned to a singlet and the signal at 4.97 ppm disappeared from the spectrum. (c) Upon irradiation at 5.30 ppm, the signal at 4.97 turned

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to a narrow multiplet and the signal at 7.26 ppm disappeared from the spectrum. (d) Upon irradiation at 4.97 ppm, the signal at 5.30 ppm turned to a narrow multiplet and the signal at 6.53 ppm disappeared from the spectrum.

B. Addition of 8 to a Mixture of Diphenylsilane and $Pd(PPh_3)_4$. Diphenylsilane (7 mg, 0.038 mmol) was dissolved in $CDCl_3$ (0.5 mL) and mixed with $Pd(PPh_3)_4$ (32 mg, 0.028 mmol). A singlet of very low intensity at δ −8.64 was slowly developed within 1 h. Addition of benzalacetone (**8**) (5 mg, 0.034 mmol) to that solution and stirring it at room temperature for 2 h had no effect on that upfield signal. No traces of **19** could be detected in the NMR spectrum of the mixture.

C. Addition of 8 to a Mixture of Diphenylsilane, BF_3–OEt_2, and $Pd(PPh_3)_4$. Diphenylsilane (7 mg, 0.038 mmol) was dissolved in $CDCl_3$ (0.5 mL) and mixed with BF_3–OEt_2 (6 mg, 0.043 mmol). No changes in the NMR spectrum of the mixture could be observed within 1 h. Addition of $Pd(PPh_3)_4$ (32 mg, 0.028 mmol) resulted in immediate appearance of two upfield signals: −13.32 (s) and −6.97 (dt, J = 175.5, 13.5) in an integration ratio of 1:10, respectively. Addition of **8** (5 mg, 0.034 mmol) resulted in immediate disappearance of these high-field signals and concomitant formation of **19**.

D. Formation and Hydrolysis of 33a. $RhCl(PPh_3)_3$ (5 mg, 0.017 mmol) was added to a mixture of **8** (99 mg, 0.68 mmol) and triethylsilane (147 mg, 1.25 mmol) and the resultant solution was stirred under argon atmosphere for 30 min[22] followed by addition of $CDCl_3$ (1 mL). ^1H NMR showed that the mixture contained silyl enol ether **33a** (a 1:1 mixture of E and Z isomers) and 1-phenyl-3[(triethylsilyl)oxy]butene at a 2:1 ratio, respectively. Zinc chloride (7.5 mg, 0.056 mmo6) was then added and the mixture was stirred at room temperature. After 60 min the mixture contained **33a** and **19** in a 15:85 ratio and after 90 min compound **33a** could not be detected.

E. Detection of Silyl Enol Ether 33b. When following the reduction of benzalacetone (with 1.7 equiv of diphenylsilane, 25% zinc chloride, and 5 mol % Pd(0) in a $CDCl_3$) by proton NMR, we initially observed accumulation of small quantitites (<10%) of the silyl enol ether **33b**, as was evident from the two sets of signals corresponding to the Z and E isomers at a 3:1 ratio, which disappeared toward the end of the reaction. E isomer: 5.02 (t, J = 7, H), 3.25 (d, J = 7, 2 H). Z isomer: 4.66 (t, J = 7, 1 H), 3.41 (d, J = 7, 2 H).[75]

Determination of Kinetic Isotope Effect. A. Reduction of Mesityl Oxide. Two pairs of experiments were performed according to the above-described general procedure and with the following quantities: mesityl oxide (65 mg, 0.65 mmol), $ZnCl_2$ (63 mg, 0.47 mmol), $Pd(PPh_3)_4$ (27 mg, 0.023 mmol), chloroform (5 mL), and 120 mg (0.65 mmol) of either dihydridodiphenylsilane or dideuteriodiphenylsilane at 23 °C. Progress of both reactions was monitored by GC and relative rates were determined on the basis of conversions measured at 40 min of reaction: k_H/k_D = 1.1 ± 0.07.

B. Reduction of Benzalacetone. Experiments were performed according to the general procedure with the following: benzalacetone (25 mg, 0.17 mmol), chloroform (3 mL), $ZnCl_2$ (20 mg, 0.15 mmol), $Pd(PPh_3)_4$, dihydridodiphenylsilane (95 mg, 0.51 mmol), and dideuteriodiphenylsilane (96 mg, 0.51 mmol). The reaction mixture was stirred at 23 °C for 30 min and then subjected to GC–MS. The ratio between the two products benzylacetone (**19**) and β-deuteriobenzylacetone (**19a**) was assumed to reflect their relative rate of formation. This ratio (**19**/**19a** = 1.5 ± 0.1) was derived from the relative intensities of the following m/e peaks: 148/149 (M^+), 133/134 ($M^+ - CH_3$), 105/106 ($M^+ - COCH_3$), 91/92 (tropylium ion).

C. Reduction Of Benzalacetone. An experiment similar to that described in A was carried out with the following: benzalacetone (139 mg, 0.95 mmol), zinc chloride (74 mg, 0.55 mmol), $Pd(PPh_3)_4$ (28 mg, 0.024 mmol), chloroform (5 mL), and 258 mg (1.4 mmol) of either dihydridodiphenylsilane or dideuteriodiphenylsilane, at 23 °C. The progress of both reactions was monitored by GC, and relative rates were determined on the basis of conversions measured at 10 min of reaction: k_H/k_D = 1.6 ± 0.2.

Reduction of Cinnamylideneacetone (34). A. With Diphenylsilane/Pd(0)/$ZnCl_2$. Reduction of **34** (26 mg, 0.15 mmol) was carried out according to the general procedure with diphenylsilane (44 mg, 0.24 mmol), zinc chloride (2 mg, 0.015 mmol), and $Pd(PPh_3)_4$ (4 mg, 0.003 mmol) in 3 mL of chloroform at room temperature. Upon completion of the reaction (4 h, monitored by TLC), the mixture was worked up as usual, yielding a mixture of three products, 6-phenylhexan-2-one (**35**), 6-phenylhex-5-en-2-one (**36**), and 6-phenyhex-4-en-2-one (**37**), together in 75% yield. Product ratio (3:5:1, respectively) was determined by NMR (using diphenylmethane as an internal standard) and confirmed by GC–MS.

MS of 35: m/z 176 (32), 158 (6), 129 (17), 118 (51), 117 (41), 105 (8), 104 (7), 103 (6), 92 (15), 91 (100), 85 (20), 79 (5), 78 (9), 77 (15), 71 (42), 65 (30), 59 (5), 58 (28), 51 (15). **NMR of 36**: δ 6.40 (d, J = 15.8, 1 H), 6.18 (dt, J = 15.8, 6.61, 1 H), 2.59 (t, J = 6.89, 2 H), 2.46 (dd, J = 6.61, 6.89, 2 H), 2.14 (s, 3 H). **NMR of 37**: δ 5.64 (m, 2 H), 3.37 (d, J = 11.32, 2 H), 3.14 (d, J = 11.92, 2 H), 2.14 (s, 3 H). **MS of 36 and 37 (Mixture)**: m/z 174 (64), 131 (52), 129 (17), 128 (11), 117 (55), 116 (24), 115 (53), 104 (30), 91 (100), 77 (13), 65 (20), 63 (11), 53 (10), 51 (27).

B. With Dideuteriodiphenylsilane/Pd(0)/$ZnCl_2$. Reduction was carried out as described above, except that Ph_2SiD_2 was employed instead of Ph_2SiH_2.

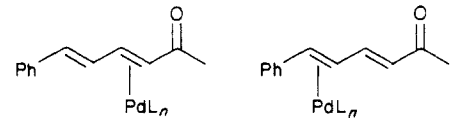
MS of Trideuterio-35: m/z 180 (3), 179 (11), 178 (9), 132 (5), 131 (7), 130 (8), 121 (19), 120 (43), 119 (53), 118 (6), 117 (5), 107 (5), 106 (8), 105 (9), 104 (6), 94 (4), 93 (22), 92 (100), 91 (63), 88 (6), 87 (16), 86 (9), 80 (6), 79 (10), 78 (16), 77 (14), 73 (22), 72 (58), 66 (24), 65 (30), 63 (8), 60 (7), 59 (25), 58 (32), 53 (4), 52 (10), 51 (27).

C. With D_2/Pd/C. Catalytic deuteration of **34** (20 mg, 0.12 mmol) was performed at atmospheric pressure using 5% Pd on activated charcoal (15 mg) in ethanol (5 mL) for 6 h. The mixture was filtered through Celite, mixed with potassium carbonate (50 mg), and stirred overnight at room temperature, filtered again, and analyzed by GC–MS.

MS of Trideuterio-35: m/z 180 (5), 179 (8), 131 (6), 130 (5), 122 (8), 121 (24), 120 (35), 119 (27), 118 (8), 107 (6), 106 (7), 105 (7), 94 (8), 93 (45), 92 (100), 91 (7), 88 (9), 87 (17), 86 (8), 80 (6), 79 (10), 78 (13), 77 (10), 74 (8), 73 (33), 72 (50), 67 (8), 66 (27), 65 (25), 63 (7), 60 (9), 59 (31), 58 (35), 53 (5), 52 (10), 51 (24).

D. With $RhCl(PPh_3)_3$/Et_3SiH. $RhCl(PPh_3)_3$ (5 mg, 0.005 mmol) was added to a mixture of **34** (30 mg, 0.176 mmol) and triethylsilane (50 mg, 0.43 mmol) in 2 mL of benzene. The mixture was stirred at 50 °C and the progress of the reaction was monitored by TLC. After 24 h the reaction mixture was cooled to room temperature, mixed with methanol (3 mL) and K_2CO_3, stirred for 1 h, and then filtered over a short silica gel column. Product ratio was determined by GC–MS and NMR. While products **36** and **35** were present at a 9:1 ratio, respectively, no traces of **37** could be detected.

NMR Studies of Complexation between $Pd(PPh_3)_3$ and 34. Cinnamylideneacetone (**34**) (5.4 mg, 0.31 mmol) and $Pd(PPh_3)_4$ (19 mg, 0.016 mmol) were dissolved in perdeuterated toluene (0.5 mL) in a 5-mm NMR tube, and ^1H NMR spectra were taken at 0 °C. In addition to certain broadening of the original olefinic absorptions of **34** (δ 7.05 (H_β covered by the signals of the aromatic protons), 6.47 (m H_γ and H_δ), 6.02 (d, J = 15.7, H_α)) two new signals appeared, at δ 5.19 (m) and 4.67 (d, J = 9.9), in a 2:1 integration ratio. Three double-irradiation experiments were carried out: (a) Upon irradiation at 7.05 (H_2), the doublet at 6.02 collapsed into a singlet and the integration ratio between the signals at 5.19 and 4.67 became 1:1 (instead of 2:1). (b) Upon irradiation at 6.47, the ratio between the signals at 5.19 and 4.67 became 1:1. (c) Upon irradiation at 6.02, the signal at 4.67 disappeared from the spectrum. On the basis of these observations, we assign the above absorptions to complexes I and II. Complex I: H_α, 4.67; H_β, 5.19; H_γ, H_δ, 6.47 ppm.



I II

Complex II: H_α, 6.02, H_β, 7.05, H_γ, H_δ, 5.19 ppm. The observed spin saturation transfer phenomena indicate that both complexes exist in rapid equilibria with the free ligand **34** even at 0 °C. At room temperature the spectrum becomes less interpretable, as the system approaches the coalescence temperature.

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Registry No. 1, 930-68-7; **2**, 141-79-7; **3**, 930-30-3; **4**, 14901-07-6; **5**, 99-49-0; **6**, 932-66-1; **7**, 2403-27-2; **8**, 122-57-6; **9**, 5392-40-5; **10**, 15932-80-6; **11**, 37112-31-5; **12**, 108-94-1; **13**, 563-80-4; **14**, 120-92-3; **15**, 17283-81-7; (*cis*)-**16**, 3792-53-8; (*trans*)-**16**, 5948-04-9; **17**, 823-76-7; **18**, 1669-51-8; **19**, 2550-26-7; **19a**, 61898-90-6; **19b**, 97039-60-6; **20**, 106-23-0; (*cis*)-**21**, 491-07-6; (*trans*)-**21**, 89-80-5; **22**, 104371-26-8; **22a**, 104292-56-0; **23**, 2757-10-0; **24**, 4360-47-8; **25**, 103-26-4; **26**, 10544-63-5; **27**, 601-57-0; **27a**, 104292-57-1; **28**, 50557-39-6; **29a**, 566-88-1; **29b**, 601-53-6; **29c**, 5618-10-0; **30**, 566-93-8; **31**, 566-91-6; **32**, 3464-60-6; (*E*)-**33a**, 82798-31-0; (*Z*)-**33a**, 82798-46-7; (*E*)-**33b**, 104292-58-2; (*Z*)-**33b**, 104322-40-9; **34**, 4173-44-8; **35**, 14171-89-2; **35** (trideuterio), 104292-60-6; **36**, 69371-59-1; **37**, 104292-59-3; I, 104267-52-9; II, 104267-53-0; $TiCl_4$, 7550-45-0; $MgBr_2$, 7789-48-2; $Pd(PPh_3)_4$, 14221-01-3; Ph_2SiD_2, 17950-94-6; $RhCl(PPh_3)_3$, 14694-95-2; *o*-$C_6H_4[CH(OAc)CH{=}CH_2]_2$, 97337-70-7; *o*-$C_6H_4(CH{=}CHCH_2OAc)_2$, 102821-

24-9; o-C_6H_4(CH=$CHCH_2OPh)_2$, 104292-61-7; Bu_3SnOPh, 3587-18-6; PPh_3, 603-35-0; $PhCH_2CH_2CONHMe$, 940-43-2; $PhCH_2CH_2CN$, 645-59-0; $PhCH_2CH_2CO_2Me$, 103-25-3; $H_3CCHDCH_2CO_2Et$, 104292-55-9; diphenylsilane, 775-12-2; zinc chloride, 7646-85-7; triethylsilane, 617-86-7; 1-phenyl-3-[(triethylsilyl)oxy]butene, 82798-48-9; phenylsilane, 694-53-1.

Supplementary Material Available: Figure of observed and simulated NMR spectra of **22** and **22a** (1 page). Ordering information is given on any current masthead page.

Systematic pH Study on the Acid- and Base-Catalyzed Racemization of Free Amino Acids To Determine the Six Constants, One for Each of the Three Ionic Species

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Abstract: Computer analysis of pH profiles for racemization of four amino acids at 142 °C led to the determination of the six absolute rate constants, one for each ionic species of amino acid in aqueous solution catalyzed by hydronium and hydroxide ions. A comparison is made to show the effect of using all six constants to express the observed rate constants, as opposed to using only four in previous studies.[2] The analyses also allowed the calculation of amino acid pK_a values at elevated temperatures.

Amino acids are ubiquitous, and the L enantiomers of the amino acids have become associated with the presence of life. L-Amino acids racemize or epimerize in natue to their D isomer. When D/L measurements are carefully determined on fossils or samples of geological interest accompanied with suitable calibration, racemization and epimerization can be used as a method of dating. Samples of only a few years old and others as old as many hundreds of thousands of years have been studied. Racemization and epimerization of amino acids, peptides, and proteins occur at measurable rates in the laboratory at elevated temperatures (>100 °C) (see ref 2 and 3).

To accurately determine racemization or epimerization rates on amino acids found in shells, bones, or other geological material is difficult because many factors influence the rates of these reactions, e.g., temperature, hydrolysis, ionic strength, position of the amino acid in the peptide chain, moisture, pH, metal ions, and other environmental and structural factors. To more accurately apply racemization (or epimerization) studies to geological samples, a better understanding is needed of the fundamental chemistry of these reactions under laboratory-controlled conditions.

Absolute rate constants are pH independent. However, the observed rate of racemization (or epimerization) of an amino acid is pH dependent. The amino acid exists in three species (+, 0; +, −; and 0, −). Racemization (or epimerization) of these three species can be both acid and base catalyzed. As a consequence, there are six absolute racemization (or epimerization) rate constants involved in these reactions (k_1–k_6). As mentioned, the relative concentration of the three species is pH dependent. The observed rate constant can be expressed as a function of these rate constants, the concentration of each species, and the concentration of the hydronium and hydroxide ions, eq 1.

$$k_{obsd} = k_1\alpha_{+0}[H^+] + k_2\alpha_{+0}[OH^-] + k_3\alpha_{+-}[H^+] + k_4\alpha_{+-}[OH^-] + k_5\alpha_{0-}[H^+] + k_6\alpha_{0-}[OH^-] \quad (1)$$

Bada and Shou[2] reported calculated absolute rate constants for some amino acids at 142 °C. Their calculations involved only four absolute rate constants (eq 2).

$$k_{obsd} = k_1\alpha_{+0}[H^+] + k_2\alpha_{+0}[OH^-] + k_4\alpha_{+-}[OH^-] + k_6\alpha_{0-}[OH^-] \quad (2)$$

This prompted us to study the importance of considering all six constants when calculating values for the absolute racemization rate constants and pK_a's and predicting overall observed racemization rate constants.

Results and Discussion

The study of Bada and Shou[2] only involved analysis of isolated areas of the pH curve for racemization. They assumed that the ionic species of major concentration were the only species necessary to consider. As a result they could only calculate values for pK_2, not pK_1.

Our study allows the analysis of the entire system with all species of amino acids and catalysts being considered at every point on the pH profile. It also allows calculation of both pK's of the amino acids (see Experimental Section).

We have studied the applicability of this method by calculating the log k vs. pH curves to match the experimental curves for the racemization of Ala and Phe.[3] These figures are not reproduced here. However, the six absolute rate constants are included in Table I in order that their values can be readily compared with Bada and Shou's values and the reevaluated values we obtained by applying this method to their data. A comparison of the pK_a values is given in Table II. The two methods (Bada and this study) give similar but significantly different results for rate constants and pK values. Another method of calculating pK's of amino acids was applied at 142 °C by assuming that the classical empirical equation of Robinson and Stokes[4] would give accurate results for aqueous systems above the boiling point of water. The Robinson and Stokes equations gave reasonably similar results

(1) To be presented at the 192nd National Meeting of the American Chemical Society, Anaheim, CA, Sept. 7–12 1986. Baum, R. M.S. Thesis, Utah State University, 1985.

(2) (a) Bada, J. L.; Shou, M. Y. In *Biogeochemistry of Amino Acids*; Hare, H. E., Hoering, T. C., King, K., Jr., Eds.; Wiley: New York, 1980; p 235. (b) Shou, P. M.-Y.; Bada, J. L. *Naturwissenschaften* **1980**, *67*, S37. (c) Shou, P. M.-Y. Ph.D. Thesis, University of California, CA, Scripps Institution of Oceanography, 1979.

(3) Smith, G. G.; Sivakua, T. *J. Org. Chem.* **1983**, *48*, 627.

(4) Robinson, R. A.; Stokes, R. H. *Electrolyte Solutions*, 2nd ed.; Butterworths: London, 1965.

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