Palladium-Mediated Cycloaddition Approach to Cyclopentanoids. Mechanistic Studies

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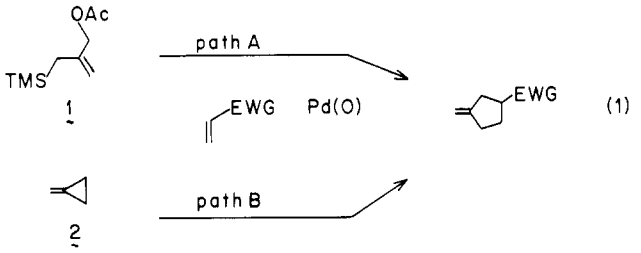
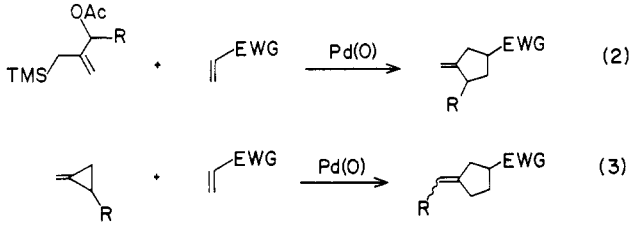
Abstract: The nature of the reactive intermediate in the palladium-catalyzed cycloaddition of (2-(acetoxymethyl)-3-allyl)-trimethylsilane with electron-deficient olefins is probed. The initial formation of an electrophilic π-allylpalladium cationic complex is verified by alkylation studies. Desilylation then provides the nucleophilic species responsible for (1) cycloaddition, (2) aldehyde addition, and (3) desilylative alkylation. Deuterium-labeling studies verify that an unsymmetrical species that can equilibrate all three methylene groups is responsible. The intervention of a (η^3-trimethylenemethane)palladium complex accommodates all the experimental observations. Some comments are offered to understand the differing results obtained herein compared to the cooligomerization of alkylidenecyclopropanes.

The ability to effect a cycloaddition of the type represented in eq 1 offers great promise for the synthesis of cyclopentanoid



(1)

natural products.[1-4] These seemingly related reactions, however, exhibit substantial differences. For example, reaction 1A requires an electron-deficient olefin and proceeds best with a palladium(0) catalyst that bears arylphosphine ligands, normally with a P:Pd ratio 4:1.[1,2] In fact, palladium-bearing alkylphosphines do not catalyze this reaction. On the other hand, reaction 1B proceeds with electron-rich olefins such as norbornene and ethylene and proceeds best with alkylphosphines in which the P:Pd ratio is 1:1.[3,4] Increasing this ratio can totally inhibit this reaction. With substituted complexes, quite different regiochemistry is observed (eq 2[5] and 3[4]). While the overall transformation seemingly implies related pathways, individual characteristics imply a divergence.



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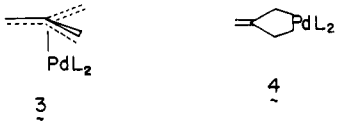
(3)

The mechanistic discussion relating to the cooligomerization of methylenecyclopropanes centers on the involvement of trimethylenemethane–palladium complexes **3** or possibly related



3 **4**

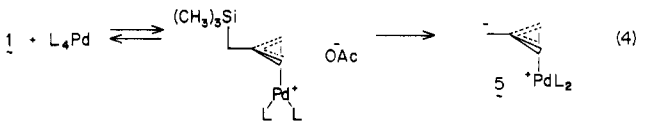
Table I. Pd-Catalyzed Alkylations of **1**[a]

	nucleophile anion[f]			yield of products[e]	
entry	X	Y	pK_a[d]	7	8
1	S	E	14	72	
2	E	E	13	73	
3[b]	S	S	12.2	54	18
4[c]	S	S	12.2		17
5	K	E	10.7		44
6	-(OC)$CH_2C(CH_3)_2CH_2$(CO)-		5.2		74

[a] All reactions were performed at room temperature in THF unless stated otherwise. [b] This reaction was carried out in refluxing THF. [c] This reaction was only partially completed. [d] See ref 12. [e] Isolated yields are based on **1**. [f] S = SO_2Ph; E = CO_2CH_3; K = $COCH_3$.

metallocycles such as **4**.[3,4,6] Such a suggestion is supported by the known ability of synthesizing TMM–metal complexes from the metal-induced disrotatory ring opening of alkylidenecyclopropanes in the case of iron[7] and molybdenum.[8] While such complexes have not been isolated from a Pd(0) reaction, a palladium chloride initiated disrotatory opening of methylenecyclopropanes leads to products that could derive from such complexes in which palladium is at a higher oxidation level.[9] On the other hand, TMM–Pd complexes appear to be logical intermediates in the reaction of **1**—a suggestion that conflicts with the above. In order to probe this apparent dichotomy, we initiated a study to define the nature of the reactive intermediate(s), if any, in the cycloaddition of **1**.

Silyl Acetate 1 as a Palladium(0) Substrate. Equation 4 summarizes the sequence that most likely would account for the formation of TMM–PdL_2 from **1**. In order to detect **5**, simple



5

(4)

allylic alkylations were performed.[10,11] Reaction of the sodium

(1) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.*, preceding paper in this issue.
(2) For preliminary reports of portions of this work, see: Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6432; **1980**, *102*, 6359.
(3) Binger, P.; Schuchardt, U. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 249; *Chem. Ber.* **1980**, *113*, 3334; **1981**, *114*, 3313.
(4) Binger, P.; Germer, A. *Chem. Ber.* **1981**, *114*, 3325. Germer, A. Ph.D. Dissertation, Ruhr-Universitat, Bochum, West Germany, 1978. We thank Professor P. Binger for a copy of this thesis. Binger, P.; Bentz, P. *J. Organomet. Chem.* **1981**, *221*, C33.
(5) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1981**, *103*, 5972. Nanninga, T., unpublished results in these laboratories.
(6) Binger, P.; Cetinkaya, M.; Doyle, M. J.; Germer, A.; Schuchardt, U. *Fundam. Res. Homogeneous Catal.* **1979**, *3*, 271.
(7) Noyori, R.; Nishimura, T.; Takaya, H. *J. Chem. Soc. D* **1969**, 80. Kagan, J.; Liu, W.-L. Cohen, S. M.; Schwartz, R. N. *J. Organomet. Chem.* **1974**, *90*, 67. Carpenter, B. K.; Pinhas, A. R. *J. Chem. Soc., Chem. Commun.* **1980**, 17. Samuelson, A. G.; Carpenter, B. K. *Ibid.* **1981**, 354.
(8) Barnes, S. G.; Green, M. *J. Chem. Soc., Chem. Commun.* **1980**, 267.
(9) Clemens, P. R.; Hughes, R. P.; Margerum, L. D. *J. Am. Chem. Soc.* **1981**, *103*, 2428.
(10) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1976**, *98*, 630; **1978**, *100*, 3435; **1980**, *102*, 4730; *J. Org. Chem.* **1976**, *41*, 3215.
(11) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385; *Pure Appl. Chem.* **1981**, *53*, 2357.

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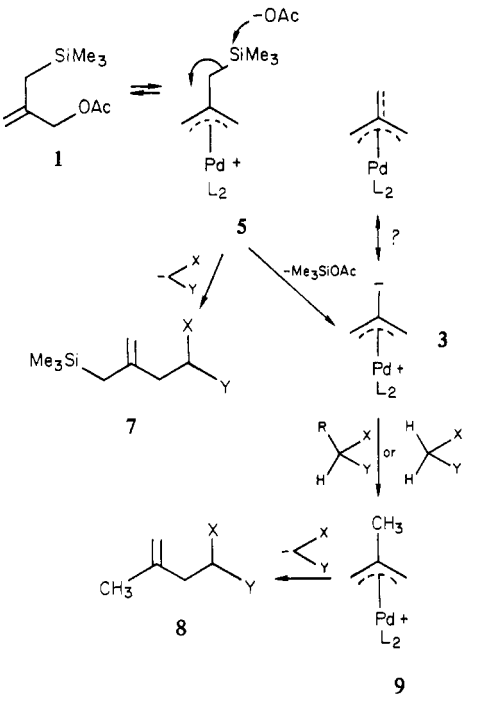
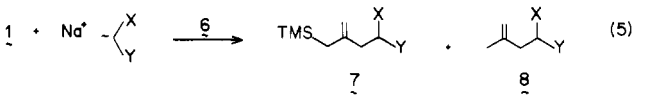
Scheme I. Formation of TMM-Pd Complex from 1



salt of carbon acids whose pK_a's range from 5 to 15 with **1** catalyzed by $(Ph_3P)_4Pd$ (**6**) proceeded at room temperature to reflux as summarized in Table I and eq 5. With the anions derived from

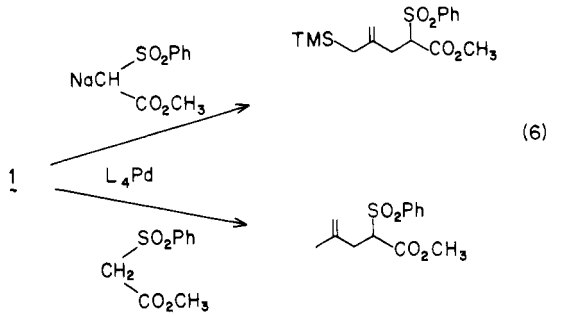


(5)

methyl (phenylsulfonyl)acetate and dimethyl malonate, only the expected product **7** was observed (entries 1 and 2). However, if more stabilized anions such as those derived from methyl acetoacetate and dimedone (entries 5 and 6) were employed, a desilylated alkylation product **8** was isolated instead. The anion derived from bis(phenylsulfonyl)methane (entries 3 and 4) appeared to be an unique case. Only **8** was obtained at room temperature, while both **7** and **8** (3:1) were observed at reflux. Further studies suggest that any nucleophile with a pK_a less than 12 will give desilylative alkylation product **8**. That **7** could not be a precursor of **8** was demonstrated by a control experiment. Compound **7** from entry 2 was recovered unchanged when it was resubjected to the same alkylation conditions. It is also known that allylsilanes react only with Pd(II) and not Pd(0).[13] Thus, some intermediate must be undergoing the desilylation that leads to the formation of **8**.

A working hypothesis for rationalizing these observations is presented in Scheme I. The initial formation of the π-allylpalladium complex **5** is confirmed by its trapping with a very nucleophilic anion (such as malonate) to give **7**. However, the lifetime of this intermediate is longer in the presence of less reactive nucleophiles (pK_a < 12). Under these conditions, **5** apparently suffers desilylation initiated by acetate anion to give the unique TMM-Pd complex **3**. The latter is protonated by the excess conjugate acid of the starting nucleophile or its alkylated product to give methallylpalladium complex **9**. The π complex then reacts with the anionic nucleophile to give the desilylated product **8**. This scheme would account for the simple alkylation with malonate, a competition between alkylation and desilylation with the sulfone system, and complete desilylation with dimedone.

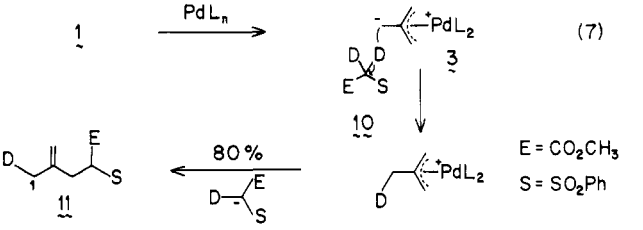
Using triethylamine or DBU as the base instead of NaH gave desilylated product **8** in every single alkylation, even with methyl (phenylsulfonyl)acetate and dimethyl malonate. Apparently, the anion concentration generated by the amines is so small that **5** has time to desilylate to **3**. Furthermore, if **1** is allowed to react with methyl (phenylsulfonyl)acetate under typical alkylation conditions but without the pregeneration of the anion by NaH, the desilylation alkylation product 8 was isolated in 70% yield (eq 6). This observation can best be explained by assuming proton



(6)

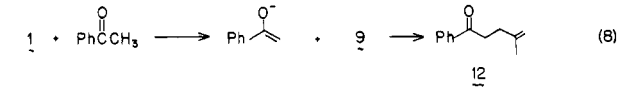
transfer from the active methylene compound to the TMM-Pd complex **3** to give **9**. The corresponding anion then attacks the methallyl complex **9** to give product **8** (similar to Scheme I); thus, the simple manipulation of the pH of the solution totally alters the reaction pathway.

To demonstrate the existence of such a proton-transfer step, we reacted **1** with deuterated sulfone ester **10** [95% dideuterated (by NMR) when prepared by exchange with $NaOCH_3/CH_3OD$]. After preparative TLC, which removed any exchangeable deuterons, the monodeuterated product **11** (91% deuterated by mass spectrometry) was isolated in 80% yield. The position of deuteration was determined by NMR spectroscopy. In the ^1H NMR spectrum, the allylic methyl signal at δ 1.66 integrated to ca. 2.2 H. Proton-decoupled ^{13}C NMR indicated that C(1) at δ 21.89 is a triplet with $J_{^{13}C-D}$ = 19.3 Hz, while all other carbons remain singlets. The product **11** is consistent with the mechanism proposed for the formation of desilylative alkylation product **8** (eq 7).



(7)

The above process is not limited to highly acidic nucleophiles (pK_a < 14). Reaction of **3** with acetophenone under similar conditions gave the product 1-phenyl-4-methyl-4-buten-1-one **12**, albeit in very moderate yields, [eq 8; 4–5 mol % $(Ph_3P)_4Pd$, 2–3



(8)

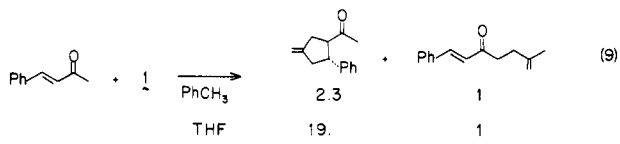
mol % dppe, 2–3 equiv of acetophenone, 22% in toluene, 15% in THF; reflux (dppe = bis(diphenylphosphino)ethane)]. While ketones do not react with allylic acetates in the absence of a base,[10,11] lithium enolates can be alkylated with allylic acetates in the presence of a Pd(0) catalyst.[14] The fact that desilylated alkylation product was obtained indicates that a base is formed in situ to generate the enolate of acetophenone and **9**.

With benzalacetone, competition between cycloaddition and desilylation alkylation occurs (eq 9). The dependence of this

(12) Extrapolated from the data of Bordwell. See: Bordwell, F. G.; Bares, J. E.; Bartmers, J. E.; Drucker, G. E.; McCollum, G. J.; Van der Puy, M.; Vanier, N. R.; Mathwes, W. S. *J. Org. Chem.* **1977**, *42*, 326. Bordwell, F. G.; Cornforth, F. J. *Ibid.* **1978**, *43*, 1763.

(13) Kliegman, J. M. *J. Organomet. Chem.* **1971**, *29*, 73.

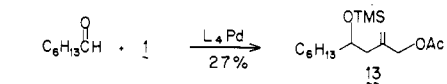
(14) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, 2591. Fiaud, J. D.; Malleron, J. L. *J. Chem. Soc., Chem. Commun.* **1981**, 1159.



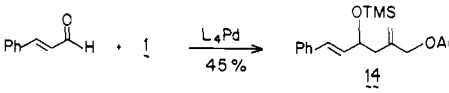
(9)

competition on solvent polarity suggests that the charge separation accompanying the conjugate addition is greater than that accompanying enolate formation. Fortunately, enolate formation could be suppressed relative to cycloaddition by such a simple manipulation. The formation of desilylated alkylated products, for which desilylation must occur along the reaction pathway, in competition with cycloaddition strongly implicates TMM–PdL_2 as an intermediate.

Reaction of 1 with Aldehydes. The desilylative alkylation suggested the presence of an anionic intermediate in these reactions that exhibited basic properties. In order to test its nucleophilicity, the reaction with heptanal was investigated. A carbonyl adduct identified as **13** indeed formed (eq 10). Such carbonyl addition

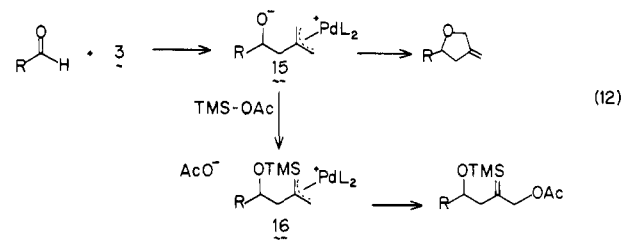


(10)



(11)

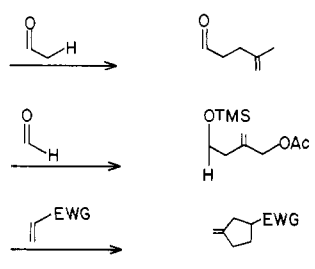
is more facile than cycloaddition as demonstrated by the exclusive formation of **14** in the reaction of cinnamaldehyde (eq 11). Such products could be envisioned to arise by the direct condensation of **1** with the electrophilic aldehyde.[15] However, such reactions are normally catalyzed by Lewis acids; it is difficult to conceive how Pd(0) catalysts facilitate such a nucleophilic addition especially since the reaction of **1** with Pd(0) has been shown to generate an electrophile! On the other hand, a nucleophilic TMM–PdL_2 species accounts nicely for these additions (eq 12). In this case,



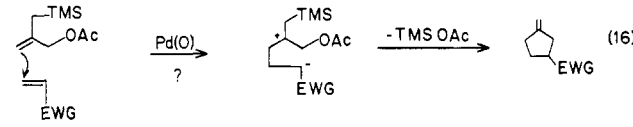
(12)

3 behaves as a nucleophile toward the reactive aldehyde carbonyl group to give **15**. The facts that alkoxides are relatively poor nucleophiles toward π-allylpalladium cationic complexes[16] and the steric strain created in such a 5-endo-trig[17] process conspires to slow the cyclization of **15** to the methylenetetrahydrofuran. On the other hand, the presence of TMS–OAc permits transsilylation to **16**, which collapses by charge neutralization to the observed product. Subsequent labeling studies support this interpretation.

Labeling Studies. So far the three reactions of **1** that have been disclosed (eq 13–15) have as a unifying feature the requirement



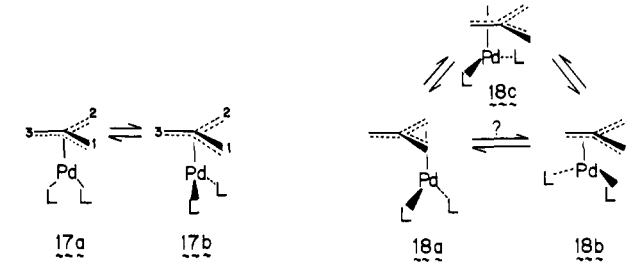
for an anionic center that serves as a base and/or a nucleophile. Can the allylsilane unit serve this role as illustrated in eq 16 for



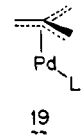
(16)

the cycloaddition reaction? Control experiments verify that all of these reactions require catalysis by Pd(0) complexes. It is difficult to envision how a Pd(0) species can enhance the nucleophilic/basic properties of an allylsilane. In fact, the alkylation studies clearly demonstrate that interaction of **1** with Pd(0) generates an electrophilic, *not* a nucleophilic, species! Failing **1** serving directly as such a nucleophilic/basic species, the question centers on what can play such a role. The fact that Pd(0) initiates reactions of **1** by ionization of acetate and that the alkylation requires loss of silicon prior to product formation leaves little choice but to suggest that the reactive intermediate has a formula of $C_4H_6PdL_n$. Could these reactions involve methylenecyclopropane as an intermediate? Our attempts to detect this species by reacting **1** with Pd(0) in the absence of any traps have failed.[18] More importantly, as already pointed out, substantial differences exist between the Pd(0)-catalyzed reactions of methylenecyclopropane and those of **1**. By elimination we are left with **3** or **4** as the most reasonable intermediates in these reactions.

Attempts to obtain direct evidence for this species have been frustrated by the failure to observe it by reaction of **1** with a stoichiometric amount of Pd(0). Only an ill-defined white solid (a polymer?) results. Failing direct observation, indirect structural data was sought. For a TMM–PdL_n species, both a η^4 (i.e., **17**) and η^3 (i.e., **18**) complex are possible. The TMM–metal complexes that have been characterized to date possess η^4 structures.[8,19] In **17a**, two types of methylene groups are present—C(1) and C(2) form one set and C(3) the other. Rotation of the TMM unit



relative to Pd converts **17a** into **17b**—a process that results in equivalency of all three methylene groups. Assuming such a process occurs fast relative to any intermolecular process,[20] structure **17** predicts that all three methylene groups of **1** would become equivalent in its reactions. The number of ligands on Pd has been assumed to be two in which palladium adopts an 18-electron configuration. A η^4 species **19** in which palladium has a 16-electron configuration is also possible. The arguments with respect to the symmetry of such a species are unchanged.



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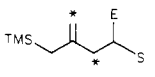
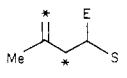
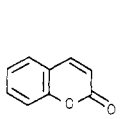
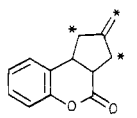
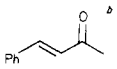
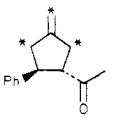
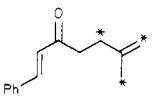
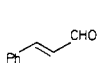
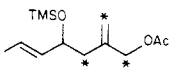
(15) Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, 3043. Sarkar, T. K.; Anderson, N. H. *Ibid.* **1978**, 3515.
(16) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615.
(17) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(18) Prof. P. Binger disclosed in a private communication that a very small amount of methylenecyclopropane could be detected.
(19) Emerson, G. F.; Ehrlich, K.; Giering, W. P.; Lauterbor, P. C. *J. Am. Chem. Soc.* **1966**, *88*, 3172. Almenningers, A.; Haaland, A.; Wahl, K. *Acta Chem. Scand.* **1969**, *23*, 1145. Churchill, M. R.; Gold, K. *Inorg. Chem.* **1969**, *8*, 401. Nesmeyanov, A. N.; Astakhova, I. S.; Zol'nikova, G. P.; Kritakaya, I. I.; Struchkov, Y. T. *J. Chem. Soc. B* **1970**, 85. Kerber, R. C.; Enholt, D. J. *J. Am. Chem. Soc.* **1973**, *92*, 525. Yasuda, N. Kai, Y.; Yusuoka, N.; Kassai, N.; Kakudo, M. *J. Am. Chem. Soc., Chem. Commun.* **1972**, 157.
(20) Albright, T. A. *J. Organomet. Chem.* **1980**, *198*, 159.

Table II. Reaction of **20** with Acceptors[a]

entry	trap	product[e,f]	(yield)[d]
		A. Alkylation[b]	
1		 **21**	(74)
2		 **22**	(90) (92)[c]
		B. Cycloaddition	
3		 **23**	(52)
		C. Cycloaddition/Alkylation	
4		 **24**	(30)
	 **25**		(15)
		D. Carbonyl Addition	
5		 **26**	(58)

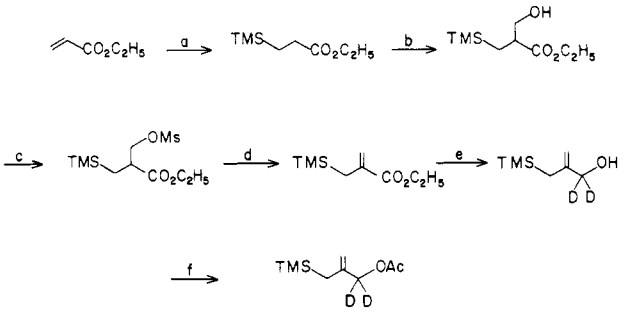
[a] Reactions are carried out with 1 equiv of **20**, 1.7-2.6 equiv of the trap, 5-9 mol % $(Ph_3P)_4Pd$, 1.7-2.8 mol % dppe in refluxing THF. [b] This reaction was performed in toluene at 110 °C. [c] This reaction was carried out at room temperature. [d] Isolated yields are based on amounts of **20** used. [e] *—carbon atom containing deuterium label. [f] Deuterium content of products was determined by mass spectroscopy. [g] E = CO_2CH_3, S = SO_2Ph.

Alternatively, the η^3 structure **18** also has two types of methylene groups—a set of two and a set of one. Symmetrization is achieved only if the Pd migrates among the various η^3 complexes **18a** → **18c**. In fact, only one migration effects full equivalency of all methylene groups. In this case, it is not possible to, a priori, predict the rate of this interconversion. Thus, a species such as **18** may exhibit reactions in which one methylene group remains distinct or in which all three become equivalent. The full equivalency of the three methylene groups would then provide strong support for the presence of TMM-PdL_n.

An additional possibility envisions a palladocycle as in **4**.[6] Such a structure can be regarded as a σ form related to the η^3 complex. Of the two structures, one tends to favor the π form because of its resemblance to the known geometry of a number of π-allylpalladium complexes.[21] The symmetry arguments for the σ form exactly parallel those presented for the π form **18**. Thus, for simplicity in the further discussion, only the latter is considered.

Specific labeling of one of the three carbons of **1** would permit determination of the symmetry of the intermediate. For this purpose, we chose the dideuterated derivative **20** whose synthesis is outlined in Scheme II. This synthesis can also serve as an alternative to **1**. While somewhat lengthy with only a modest overall yield, only inexpensive reagents are needed and the reactions proceed readily on very large scale.[22] NMR analysis of **10** revealed the virtual absence of the absorption of δ 4.4; mass spectroscopy indicated it contained 91.4% d_2 and 3.3% d_1.

Scheme II. Synthesis of Dideuterated Substrate **20**

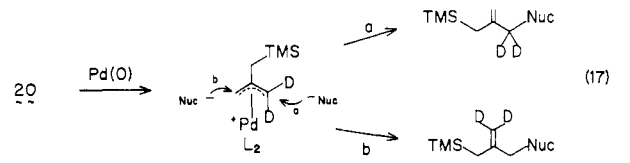


[a] Me_3SiCl, Li, THF; then dilute HCl, 44%. [b] LDA, THF, −78 °C, then $(HCHO)_n$, 44%. [c] CH_3SO_2Cl, Et_3N, ether, 0 °C, ether, 92%. [d] DBU, ether, room temperature, 80%. [e] LAD, ether, −25 °C, 70%. [f] AcCl, pyridine, CH_2Cl_2, 0 °C, 60%.

With the labeled substrate in hand, the three basic reactions of alkylation, cycloaddition, and carbonyl addition (eq 13–15) were explored. Table II presents the results.

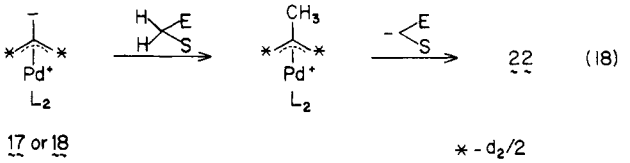
The products were identified by comparison with the undeuterated materials. The distribution and relative amounts of deuterium labels were determined by ^1H (270 and 100 MHz) as well as ^2H (C_6F_6, 15.3 MHz) NMR spectroscopy. The adducts were found to retain 91–98% of the original deuterium content by mass spectroscopy.

The first system (entry 1) established the deuterium distribution for the simple alkylation of the π-allylpalladium species related to **20**. Alkylation of **20** with methyl(phenylsulfonyl)acetate sodium salt under the usual conditions gave the product **21** with deuterium atoms located in two methylene groups (see Experimental Section). This distribution of label is expected because the two termini of the π-allyl system are equally susceptible to the attack by the nucleophilic anion (eq 17).



(17)

In the deprotonation/alkylation of **20** with methyl (phenylsulfonyl)acetate (entry 2), only two of the three carbons in **23** were found to be labeled. Since we have established that some $C_4H_6PdL_2$ species is involved in this process, such a species must be capable of retaining differentiation of the carbon that originally bore silicon. Such an observation would be consistent with either **17** or **18** provided that the depicted equilibrations were slow relative to deprotonation as depicted in eq 18.



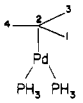
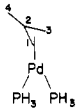
(18)

On the other hand, cycloaddition of **20** to coumarin (entry 3) produced the methylenecyclopentane **23**, which showed an even distribution of the deuterium label to all three methylene carbons. In addition to verifying the loss of silicon prior to cycloaddition,

(21) Mason, R.; Russell, D. R. *Chem. Commun.* **1967**, 26. Smith, A. E. *Acta Crystallogr.* **1965**, *18*, 331.

(22) Cf.: Somers, L. H.; Marans, N. S. *J. Am. Chem. Soc.* **1950**, *72*, 1935. Hosomi, A.; Hashimoto, H.; Sakurai, H. *Tetrahedron Lett.* **1980**, 951. Picard, J. P.; Ekouya, A.; Dunogues, J.; Duffant, N.; Calas, R. *J. Organomet. Chem.* **1974**, *66* C39; **1975**, *93*, 51.

Table III. Charge Distribution in TMM-Pd$(PH_3)_2$

atom	 17-PH_3	 18-PH_3
Pd	+1.158	+1.140
C(1)	−0.364	−0.340
C(2)	+0.202	+0.226
C(3)	−0.364	−0.340
C(4)	−0.589	−0.696
P	+0.448	+0.441

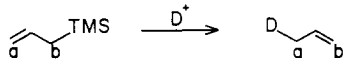
this result also demands that the $C_4H_6PdL_2$ intermediate be capable of equilibrating all three methylene groups—again in accord with **17** or **18**.[23]

Further experimental evidence in support of an unsymmetrical species that is capable of scrambling was obtained when the alkylation/cycloaddition reactions with benzalacetone in toluene were examined. As expected, cycloadduct **24** showed complete scrambling within experimental error. In the concurrent alkylation reaction, the product **25** also showed virtually complete scrambling. Thus, with a less acidic trap (pK_a of benzalacetone ~21 and that of (phenylsulfonyl)acetate ~14), the rate of protonation of the initial TMM complex is slower than the equilibration of **17** or **18**. Finally, the intermediacy of a TMM–Pd complex in carbonyl addition is established by the reaction of **20** with cinnamaldehyde (entry 5). The adduct **26** again has the deuterium distributed among the three methylene groups.

Theoretical Considerations. Calculations by both Albright[20] and ourselves[24] have considered structures **17** and **18** for the TMM–PdL_2 system. Table III demonstrates that either geometry predicts that all three methylene carbons are negative with one substantially more so than the others. Thus, the complex is a zwitterion with the organic fragment at the anionic portion and the metal and its attendant ligands the cationic portion. Considering the orbital interaction diagram, Albright concluded that the barrier to rotation in **17** would be negligible[20,25]—i.e., interconversion of **17a** and **17b** would be fast. In essence, the argument derives from the degeneracy of the HOMO and LUMO of TMM and the ability of the highest filled metal orbital to interact to exactly the same extent with each. These calculations also suggest that **18** is more stable than **17**. Both theoretical studies favor an unsymmetrical geometry and zwitterionic formulation for a d^{10} TMM–Pd complex.

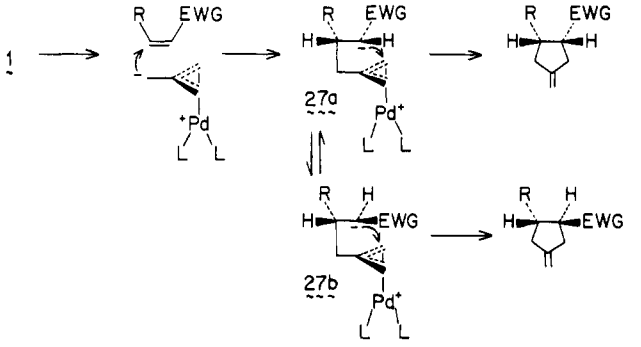
Discussion

The sequence as defined in Scheme I is strongly supported by the labeling studies reported herein. The initial generation of **5** is directly demonstrated by the simple alkylation studies. On the other hand, the question of whether **5** can also serve as the nucleophile responsible for reactions 13, 14, and 15 rather than a desilylated $C_4H_6PdL_2$ species is more subtle. The deprotonation/alkylation suggests that such a desilylation must precede proton transfer. A saturated carbon–silicon bond is not normally susceptible to protonation except under extreme acid conditions.[26] Allylsilanes undergo protodesilylation with allyl inversion (eq 19).[26] Application of such a sequence to the case

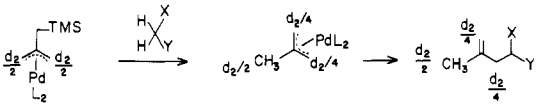


(19)

Scheme III. Distal Approach Mechanism of Cycloaddition



of deprotonation/alkylation would predict a deuterium distribution to all three methylene groups of the TMM unit as in eq 20—a prediction not in accord with observation. On the other hand,

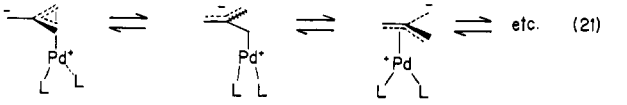


(20)

this observation fully conforms to the path outlined in eq 18. The further fact that **5** shows normal electrophilic properties of a π-allylpalladium species reinforces the above argument that **5** is not the nucleophilic species responsible for the subsequent steps.

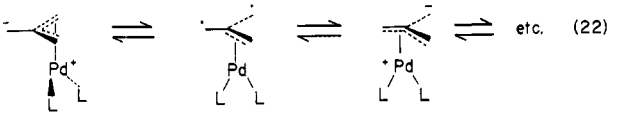
With a compelling argument for the intermediacy of a $C_4H_6PdL_n$ species in these reactions, we are led to **4**, **17**, and **18** as possibilities. The labeling results demand that the species be unsymmetrical but capable of symmetrizing at a rate competitive with intermolecular processes. The η^4 structure **17** meets that requirement provided that rotation of the palladium fragment relative to the TMM unit is slow. Bonding considerations indicate the opposite, i.e., that this rotation should be fast.[20] Thus, between **17** and **18**, **18** appears as the more likely candidate for the structure of the reactive intermediate. There is no experimental or theoretical basis to distinguish between **4** and **18** except the general bias of π rather than σ structures for palladium complexes. Thus, in the remainder of the discussion, we will utilize **18** as the structure but with the realization that **4** cannot be dismissed.

Two mechanisms account for the equilibration among **18**, **a**, **b**, and **c**. By analogy to the syn–anti interconversion of π-allylpalladium complexes, a $\pi \rightarrow \sigma \rightarrow \pi$ interconversion as illustrated in eq 21 provides a scrambling mechanism.[27,28] An alternative



(21)

suggestion invokes a π-olefin diyl species as in eq 22. While



(22)

theoretical calculations indicate that such a η^2 diyl species lies only about 4 kcal higher in energy than the η^3 form **18**,[20] simple π complexation to an isolated olefin with palladium is generally less favorable than σ-bond formation.[29] Considering the better

(23) The possibility that silicon migration in **5** accounts for the equilibration can be excluded. In substituted systems, recovery of starting material in partial reactions fails to reveal any silicon migration. As expected, acetate migration does occur.

(24) Gordon, D. J.; Fenske, R. F.; Nanninga, T. N.; Trost, B. M. *J. Am. Chem. Soc.* **1981**, *103*, 5974; also see ref 2.

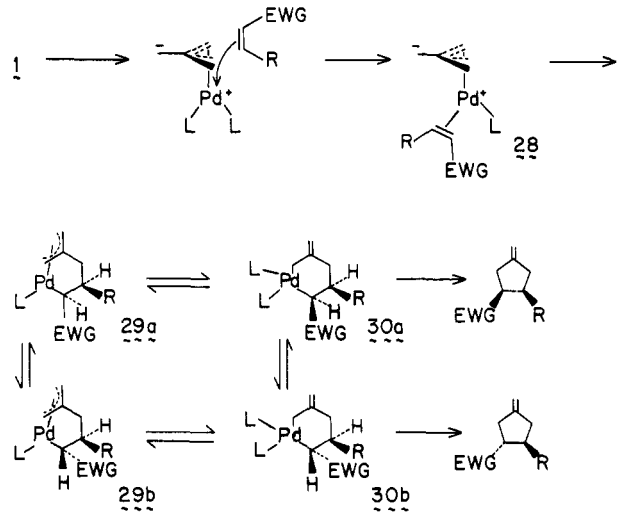
(25) Also see: Albright, T. A. *Acc. Chem. Res.* **1982**, *15*, 149.

(26) Fleming, I. *Chem. Soc. Rev.* **1981**, *10*, 83.

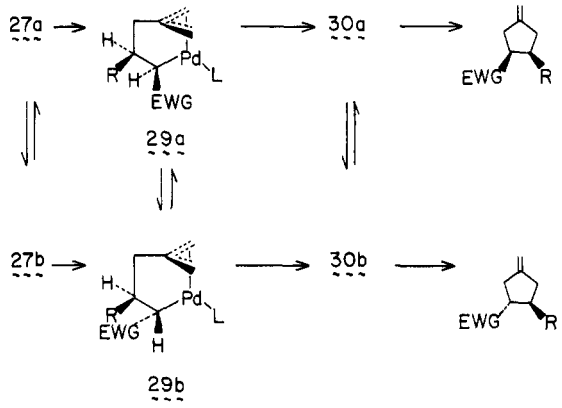
(27) Cotton, F. A.; Fuller, J. W.; Musco, A. *Inorg. Chem.* **1967**, *6*, 179. Corradinia, P.; Maglio, G.; Musco, A.; Maiaro, G. *Chem. Commun.* **1966**, 618. Chien, J. C. W.; Dehm, H. C. *Chem. Ind. (London)* **1961**, 745. Parker, G.; Werner, H. *Helv. Chim. Acta* **1973**, *56*, 2819. Lefters, J. A.; Aleksanyan, V. T.; Bukalov, S. S.; Rubezhov, A. Z. *J. Chem. Soc. D* **1971**, 265.

(28) Faller, J. W.; Incorvia, M. J.; Thomson, M. E. *J. Am. Chem. Soc.* **1969**, *91*, 518. Faller, J. W.; Thomson, M. E.; Mattina, M. J. *Ibid.* **1971**, *93*, 2542. Faller, J. W.; Mattina, M. J. *Inorg. Chem.* **1972**, *11*, 1296.

Scheme IV. Proximal Approach Mechanism of Cycloaddition



Scheme V. Modified Distal Approach Mechanism of Cycloaddition

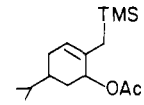


precedence for the type of intermediate postulated in eq 21, we favor that pathway.

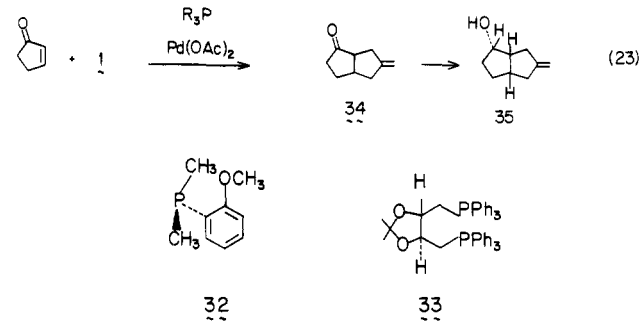
With **18** as the reactive intermediate, the mechanism of the cycloaddition is best described in terms of a two-stage process to accommodate the partial loss of stereochemistry of the acceptor during the course of the reaction. Schemes III and IV both take this observation into account. These two schemes differ fundamentally in the way the acceptor approaches the TMM unit. In Scheme III, the electrophile approaches the TMM unit on the face opposite the metal. The initial adduct **27a** can cyclize directly, in which case olefin geometry is fully retained, or it can undergo a rotation to form **27b** prior to cyclization, in which case olefin geometry is partially or totally lost. The geometry for the cyclization step derives by analogy to nucleophilic attack of stabilized anions on π-allyl complexes.[10,30] Geometrical constraints for such a 5-endo-trig cyclization would suggest it is necessarily strained. In a modified version of the distal approach mechanism, complexation to palladium prior to C–C bond formation can obviate this argument as shown in Scheme V.

Scheme IV directly invokes C–C bond formation via reductive elimination via **29** and/or **30**. This proposal mainly suffers from the suggestion that an electrophilic acceptor initially attacks the electrophilic end of the TMM–PdL_2 complex as required in forming **28**. The possibility that one of the ligands on the Pd(0) catalyst is already an acceptor so that **28** is the initial complex cannot be dismissed. On the other hand, phosphine or phosphite ligands are required for the cycloaddition, which suggests that such phosphine(phosphite)palladium complexes are the required catalysts.

Initial attempts to probe the possibility of proceeding via **29** or **30** by examination of the stereochemistry utilizing **31** have been

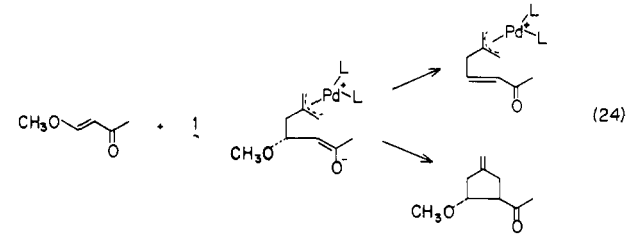


thwarted by the unreactivity of **31** toward Pd(0). An alternative approach considered the effect that optically active ligands might have on a process as depicted in Scheme III as opposed to one in Scheme IV or V. In the latter cases, the proximity of a chiral ligand to the site of C–C bond formation should induce some optical activity in the product[31] whereas such considerations would predict much lower optical activity in the product for a route of the type represented in Scheme IV.[32] Performing the cycloaddition of **1** with cyclopentenone in the presence of (R)-CAMP (**32**)[33] or (+)-DIOP (**33**)[34] led to the cycloadduct **34** with $[\alpha]^{25}_D$ +7.05° (*c* 4.4, $CDCl_3$) and $[\alpha]^{25}_D$ 0° (*c* 3.3, ether), respectively.



Determination of the optical purity of **34** from the reaction utilizing (R)-CAMP by using $Eu(hfbc)_3$-induced shifts of the related alcohol **35** revealed a 7 ± 2% ee. Such a low degree of asymmetric induction is better in accord with Scheme III.

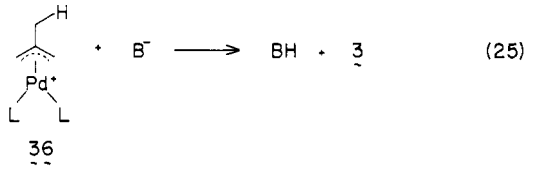
Such a mechanism not only rationalizes many of our observations but it also leads to some interesting conclusions. For example, the fact that 1-methoxybuten-3-one gives cycloadduct at all means that cyclization is faster than β-elimination (eq 24).



There exists a preference for such a two-step process over a concerted cycloaddition even though there is no orbital-symmetry reason precluding a concerted process.

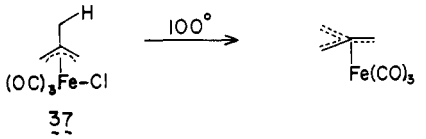
The facility of the desilylation of **5** to give **3** suggests that the methallyl complex **36** should be relatively acidic (eq 25). The fact that **3** can enolize a ketone but not an ester suggests that **36** has a kinetic acidity of between 21 and 25. The possibility that species such as **36** can be precursors of TMM–metal complexes

(29) Maitlis, P. M. "The Organic Chemistry of Palladium"; Academic Press: New York, 1971; Vol. I.
(30) Trost, B. M.; Weber, L. *J. Am. Chem. Soc.* **1975**, *97*, 1611. Trost, B. M.; Weber, L.; Strege, P. E.; Fullerton, T. J.; Dietsche, T. J. *Ibid.* **1978**, *100*, 3416.
(31) For asymmetric induction in C–C bond-coupling reactions via the metal, see: Hayashi, T. *ACS Symp. Ser. 185*, 1982, 177–186.
(32) Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1649. Trost, B. M.; Dietsche, T. J. *Ibid.* **1973**, *95*, 8200.
(33) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *Adv. Chem. Ser.* **1974**, *132*, 274. Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 6429.
(34) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.
(35) Nordberg, R., unpublished results in these laboratories.



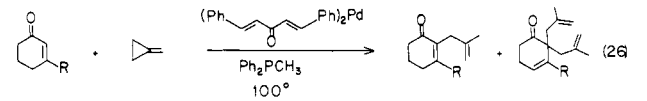
36

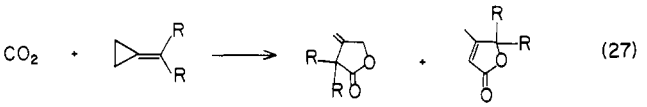
is an intriguing phenomenon. The thermal extrusion of the elements of HCl from **37** lends credence to this suggestion.[36]



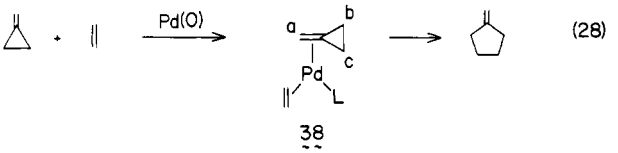
37

If the reactions of **1** involve TMM–PdL_2 complexes, what accounts for the differences with the Pd-catalyzed cycloadditions of alkylidenecyclopropanes. Two important features of the latter reaction that differ from the reactions of **1** are (1) trialkylphosphines are the preferred ligands for the alkylidenecyclopropane process whereas the cycloadditions of **1** totally fail with such ligands and (2) a ligand to Pd ratio of 1 is highly preferred for the cooligomerization process but ratios >4:1 of P:Pd are the rule for the cycloaddition of **1**. In addition to the cooligomerization of methylenecyclopropane, Pd(0) complexes also initiate a deprotonation/alkylation (eq 26)[37] and a carboxylation (eq 27)[38] with methylenecyclopropanes. These two processes have the characteristics reminiscent of a zwitterion intermediate of the type related to **3**.





A possible explanation is that in one case the η^3 intermediate **3** is involved whereas in the other case the σ complex **4** intervenes. However, it is difficult to imagine that a high barrier exists for the interconversion of **3** and **4** as would be necessitated by the observed differences. Alternatively, two pathways may account for the reactions of the alkylidenecyclopropanes. A direct cross coupling of the highly reactive alkylidenecyclopropane with an olefin as illustrated in eq 28 rationalizes the successful reactions

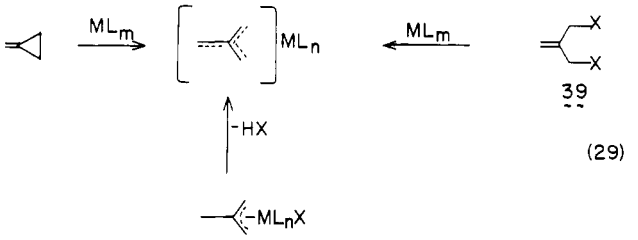


38

with simple olefins like ethylene and strained olefins like norbornene. In particular, the dependence on the nature and number of the phosphine ligands supports an intermediate such as **38**.

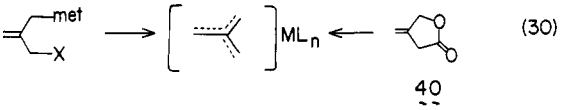
Discussion of the details involved in the conversion of **38** to product would be inappropriate at this time. Suffice it to say that bonding can be initiated between the olefin acceptor and C(a), C(b), or C(c) of the methylenecyclopropane to account for the substitution pattern observed. If the reorganization of **38** is slow, a competing ring opening of **38** to the TMM–PdL_2 complex can occur. This transformation then places the reaction in the same manifold as the reactions of **1**. Thus, some of the cycloadditions with electron-poor olefins and the reactions outlined in eq 26 and 27 may proceed via the same pathway as **1**. Such a duality of mechanism available to the reactions of methylenecyclopropanes but not of **1** provides an integrated picture of this $C_4H_6PdL_2$ surface.

While only the reaction of palladium has been examined, **1** holds promise as being a new entry into TMM–metal complexes. Up to the present, the methods include (1) the ring opening of alkylidenecyclopropanes,[3,4,7,8] (2) the reduction of α,α'-disubstituted precursors such as **39**,[39] and (3) the single example of a thermal extrusion of the elements of HX from a methallyl complex (see eq 29).[36] These methods frequency suffer from inaccessibility



(29)

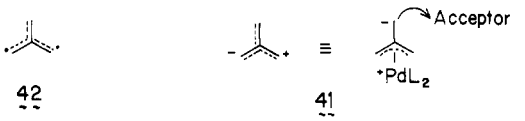
of starting materials and/or low yields. The method developed herein represents an example of an approach utilizing a push–pull precursor (possesses both a nucleophilic and electrophilic center), which generates the TMM–metal species under very mild conditions (see eq 30). The lactone **40** has recently been reported to generate such complexes and, as such, also represents a push–pull precursor.[38]



40

(30)

The advantage of the palladium complex is its high reactivity. As such it has all the properties of a zwitterion as reproduced in **41** in which the subsequent reactions are initiated by the electrofugal end. In addition to imposing a polar character to trimethylenemethane **42**,[40] the metal dramatically improves the intermolecular reactions of this basic and utilitarian building block.



42 41

Experimental Section

General Methods. All anhydrous reactions were performed in flame-dried glassware under a positive pressure of dry nitrogen unless otherwise noted. Anhydrous solvents were transferred by flame-dried syringe. Solvents were distilled before use: hexamethylphosphoric triamide (HMPA), dimethyl sulfoxide (Me_2SO), dimethylformamide (DMF), acetonitrile (CH_3CN), dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), carbon tetrachloride (CCl_4), pyridine (C_5H_5N), hexane (C_6H_{14}), tetramethylethylenediamine (TMEDA), and pentane (C_5H_{12}) from calcium hydride; diethyl ether (Et_2O), tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), 1,4-dioxane, toluene ($PhCH_3$), and benzene (C_6H_6) from sodium benzophenone ketyl; methanol from magnesium; chlorotrimethylsilane from tributylamine. All palladium(0) catalysts were transferred under a nitrogen atmosphere in a glovebag. The term in vacuo refers to the removal of solvent on a Büchi–Brinkman Rotoevaporator at water-aspirator pressure; this is followed by evacuation of the flask (~0.1 mmHg) for 15–30 min [except for volatile compounds (bp <200 °C)]. Silica gel (Merck 60-PF 254) was used for analytical and all preparative (1.5 mm thick) thin-layer chromatography (TLC). The preparative TLC plates were activated at 120 °C for 2 h before use. Plastic-support precoated (Merck Silica gel 60 F_{254}, 0.2 mm) plates were also employed. Typical loadings on preparative plates were up to 80 mg on 20 × 10 cm, 80–200 mg on 20 × 20 cm, and 200–450 mg on 20 ×

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Table IV. Experimental Details for Pd-Catalyzed Alkylation of **1**[a]

XCH_2Y, entry; compound; equiv	NaH, equiv	**1**, weight, mg; mmol	$(Ph_3)_4Pd$, weight, mg; mol %[b]	THF, volume, mL; time, h	product, compound(s); weight, mg; yield,[b] %
1; methyl (phenylsulfonyl)acetate; 1.5	1.4	500; 2.6	250; 8.5	18; 41	7; 630; 72
2; same as 1; 2.3	none	1.2	76; 6.5	5.5; 1.5	8; 220; 70
3; bis(phenylsulfonyl)methane; 1.2, 1.5		270; 1.4	290; 17	10; 20[c]	7, 312, 53; 8, 90, 19
4; same as 3; 1.0, 1.2		292; 1.5	173; 10	10; 48	7; 95; 17[d]
5; methyl acetoacetate; 1.4	1.1	287; 1.5	165; 9.0	7; 23	8; 100, 44[e]
6; dimedone; 1.5, 1.3		280; 1.5	160; 9.3	13; 63	8; 200; 74
7; methyl (phenylsulfonyl)dideuterioacetate;[f] 2,2	none	211; 1.1	81; 6.2	5.5; 24	11; 245; 80
8; acetophenone; 2.6	none	254; 1.4	70; 4.5	4.5; 72[c]	12; 43; 15[h]
9; acetophenone; 2.3	none	464; 2.4	114; 4.2	7; 84[g]	12; 87; 22[h]

[a] All reactions were conducted at room temperature unless stated otherwise. [b] Relative to **1**. [c] This reaction was performed in refluxing THF. [d] Reaction was only partly completed. [e] A small amount of bis(alkylated) product was also observed. [f] The dideuterated starting material was prepared by stirring the methyl (phenylsulfonyl)acetate with catalytic NaOMe and MeOD for 5 days at 55 °C. The workup was performed in D_2O and without any chromatographic purification. The product was 95% dideuterated by ^1H NMR spectroscopy. [g] This reaction was performed in refluxing toluene. [h] Other volatile products were also observed.

40 cm. Column chromatography was accomplished with Grace (grade 62, 60–200 mesh) silica gel. Removal of the material from silica gel was performed by extraction/washing with ethyl acetate or ether (for volatile products). High-pressure liquid chromatography (HPLC) was performed analytically on a Waters M6000 instrument with a porasil silica gel column (10 μm, Waters p/n 27477) unless stated otherwise. Preparative HPLC was performed on a Waters Prep 500 instrument with a self-packed, semiprep (2.5 × 30 cm, μPorasil, 37–75 μm, 50–400 mg) silica gel column or a Prepak-500 silica gel column (75 μ, 1–20 g). R_v refers to retention volume (CV = column volume). Flash chromatography was performed according to the method reported by Still.[41] Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Gas chromatography was performed on a Varian Aerograph Model 90P (R_t = retention time). Column A refers to a 8 ft × $^3/_8$ in. column packed with 10% DC 710 on Chromosorb W. Column B refers to a 12 ft × 0.25 in. column packed with 15% Carbowax 20 M on Chromosorb W.

Proton NMR spectra were determined in chloroform-*d* (unless stated otherwise) on a Jeolco MH-100 (100 MHz) instrument or a Bruker WH-270 (270 MHz) spectrometer. Chemical shifts are reported in δ units, parts per million (ppm) downfield from tetramethylsilane Me_4Si. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; br, broad. Coupling constants are reported in hertz (Hz). Infrared spectra (IR) were determined in the indicated solvent in 1-mm thick solution cells on a Perkin-Elmer 267 or a Beckman Acculab 7 instrument and are reported in cm^{-1}. Carbon (^{13}C) NMR spectra were determined on a Jeolco FX-60 (15.4 MHz) or a Jeolco FX-200 (50.1 MHz) spectrometer. Chemical shifts are reported in δ units and splitting patterns are designated as with ^1H NMR. Deuterium (^2H) NMR spectra were determined on a Varian XL-100 (15.36 MHz) spectrometer. Chemical shifts are reported in δ units. Mass spectra were obtained on an AEI-902 instrument at an ionizing current of 98 mA and an ionizing voltage of 70 eV unless stated otherwise. Microanalyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI.

General Procedure for Pd-Catalyzed Alkylation of 1. Synthesis of Methyl 2-(Methoxycarbonyl)-4-methylene-5-(trimethylsilyl)-1-pentanoate (7, X = Y = CO_2CH_3) (Table IV). To a suspension of sodium hydride [50% oil dispersion, washed with hexane (3 × 2 mL), 78 mg, 1.6 mmol] in 7 mL of THF was added dimethyl malonate (271 mg, 2.0 mmol). After the initial hydrogen evolution, the reaction was stirred for 20 min. (2-(Acetoxymethyl)-3-allyl)trimethylsilane (**1**) (280 mg, 1.5 mmol) and tetrakis(triphenylphosphine)palladium (150 mg, 0.13 mmol) were added. The orange solution was stirred at room temperature for 25 h. The cloudy mixture was filtered through a short plug of silica gel and eluted with ether (100 mL). The eluent was concentrated in vacuo, and the residue was purified by preparative TLC to yield 280 mg (73% based on **1**) of the title compound: R_f 0.55 (1:2 ether/pentane); ^1H NMR (270 MHz) δ 4.49 (br s, 1 H), 4.47 (br s, 1 H), 3.62 (s, 6 H), 3.53 (t, J = 8.1 Hz, 1 H), 2.47 (d, J = 8.1 Hz, 2 H), 1.42 (br s, 2 H), 0.01 (s, 9 H); ^{13}C NMR (15 MHz) δ 168.8, 143.2, 108.2, 51.8, 50.0, 36.4, 26.5, −1.9; IR (neat) 2955, 1755, 1740, 1640, 1438, 1249, 1150, 1030, 855 cm^{-1}; mass spectrum, m/e (%) M^+ 258 (14), 126 (11), 123 (14), 122 (54), 95 (43), 94 (40), 89 (38), 75 (16), 74 (11), 73 (100), 59 (35), 45 (26), 44 (14). Calcd for $C_{12}H_{22}O_4Si$: 258.1281. Found: 258.1288.

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Methyl 2-(Phenylsulfonyl)-4-methylene-5-(trimethylsilyl)-1-pentanoate (7, X = SO_2PH; Y = CO_2CH_3): TLC R_f 0.7 (3:3:1 ether/pentane/chloroform); ^1H NMR (270 MHz) δ 7.84 (m, 2 H), 7.66 (m, 1 H), 7.54 (m, 2 H), 4.52 (br s, 1 H), 4.49 (br s, 1 H), 4.12 (X of ABX, J = 8.4, 6.6 Hz, 1 H), 3.59 (s, 3 H), 2.57 (AB of ABX, m, 2 H), 1.47 (d of AB, J = 13.2 Hz, 1 H), 1.37 (d of AB, J = 13.2 Hz, 1 H), −0.07 (s, 9 H); IR ($CHCl_3$) 3015, 2960, 1743, 1639, 1450, 1439, 1326, 1250, 1203, 1148, 1083, 850 cm^{-1}; mass spectrum, m/e (%) 127 (100), 126 (11), 125 (10), 95 (62), 77 (31), 67 (34), 55 (22), 43 (12), 41 (18). Calcd for $C_{16}H_{24}O_4SSi$: 340.1158. Found: 340.1156.

1,1-Bis(phenylsulfonyl)-3-methylene-4-(trimethylsilyl)butane (7, X = Y = SO_2Ph): TLC R_f 0.35–0.50 (1:2 ethyl acetate/hexane); ^1H NMR (270 MHz) δ 7.93 (m, 2 H), 7.68 (m, 1 H), 7.55 (m, 2 H), 4.62 (t, J = 5.1 Hz, 1 H), 4.56 (br s, 1 H), 4.55 (br s, 1 H), 2.80 (d, J = 5.1 Hz, 2 H), 1.37 (br s, 2 H), −0.03 (s, 9 H); IR ($CHCl_3$) 3003, 2948, 1640, 1448, 1330, 1249, 1150, 1076, 848 cm^{-1}; mass spectrum, m/e (%) 281 (14), 209 (78), 135 (25), 125 (30), 86 (22), 85 (57), 84 (41), 83 (100), 78 (11), 77 (37), 73 (56), 67 (15), 47 (21), 36 (11). Calcd for $C_{20}H_{26}O_4S_2Si$: 422.1035. Found: 422.1042.

1,1-Bis(phenylsulfonyl)-3-methylenebutane (8, X = Y = SO_2Ph): TLC R_f 0.23–0.35 (1:2 ethyl acetate/hexane); mp 98–100 °C; ^1H NMR (270 MHz) δ 7.96 (m, 4 H), 7.69 (m, 2 H), 7.56 (m, 4 H), 4.04 (br s, 1 H), 3.91 (br s, 1 H), 3.89 (t, J = 5.1 Hz, 1 H), 2.78 (d, J = 5.1 Hz, 2 H), 1.61 (br s, 3 H); IR ($CHCl_3$) 3005, 1655, 1447, 1329, 1150, 1129, 1072, 902 cm^{-1}; mass spectrum, m/e (%) 210 (8), 209 (100), 125 (8), 78 (5), 77 (14), 67 (7), 44 (7). Calcd for $C_{17}H_{18}O_4S_2$: 350.0642. Found: 350.0645.

Methyl 2-Acetyl-4-methyl-5-pentenoate (8, X = $COCH_3$; Y = CO_2CH_3): TLC R_f 0.4–0.5 (1:2 ether/pentane). This compound was characterized by ^1H NMR only (100 MHz): δ 4.72 (br s, 1 H), 4.64 (br s, 1 H), 3.68 (s, 3 H), 3.64 (t, J = 7 Hz, 1 H), 2.50 (d, J = 7 Hz, 2 H), 2.18 (s, 3 H), 1.77 (br s, 3 H).

5,5-Dimethyl-2-isopropenyl-1,3-cyclohexanedione (8, X = Y = $-COCH_2C(CH_3)_2CH_2CO-$): TLC R_f 0.2 (2:1 ether/pentane); mp 125–130 °C; ^1H NMR (270 MHz) δ 6.56 (br s, 1 H), 4.95 (br s, 1 H), 4.91 (br s, 1 H), 3.17 (br s, 2 H), 2.34 (br s, 2 H), 2.27 (br s, 2 H), 1.71 (br s, 3 H), 1.08 (s, 6 H); IR ($CHCl_3$) 3600–3100, 2960, 1733, 1705, 1618, 1374, 1203, 1152, 1052, 898 cm^{-1}; mass spectrum, m/e (%) M^+ 194 (20), 179 (17), 126 (20), 119 (29), 111 (39), 83 (36), 57 (27), 56 (28), 55 (37), 45 (19), 44 (18), 43 (100), 42 (17), 41 (51), 39 (23). Calcd for $C_{12}H_{18}O_2$: 194.1302. Found: 194.1307.

Methyl 2-(Phenylsulfonyl)-4-methylenepentanoate (8, X = SO_2Ph; Y = CO_2CH_3). A solution of (2-(acetoxymethyl)-3-allyl)trimethylsilane (**1**) (220 mg, 1.18 mmol), tetrakis(triphenylphosphine)palladium (88 mg, 0.08 mmol), methyl (phenylsulfonyl)acetate (580 mg, 2.71 mmol), bis(diphenylphosphino)ethane (11 mg, 0.03 mmol) in 5.5 mL of THF was stirred at room temperature for 24 h. The solution was concentrated under nitrogen and purified by preparative TLC to give 220 mg (70%) of the title compound: R_f 0.51 (2:2:1 ether/pentane/chloroform); ^1H NMR (270 MHz) δ 7.84 (m, 2 H), 7.66 (m, 1 H), 7.54 (m, 2 H), 4.80 (br s, 1 H), 4.68 (br s, 1 H), 4.17 (X of ABX, J = 9.0, 6.2 Hz, 1 H), 3.62 (s, 3 H), 2.70 (AB of ABX, m, 2 H), 1.70 (br s, 3 H); IR (neat) 3085, 2960, 1748, 1660, 1450, 1327, 1148, 1086, 906, 725, 690 cm^{-1}; mass spectrum, m/e (%) 128 (21), 127 (100), 126 (41), 125 (30), 111 (24), 96 (18), 95 (85), 85 (17), 78, (24), 77 (47), 68 (11), 67 (66), 59 (27), 55 (49), 41 (30). Calcd for $C_{13}H_{16}O_4S$: 268.0765. Found: 268.0761.

Table V. Reaction of **20** with TMM-Traps—Experimental Details

entry; trap; equiv	**20**, weight, mg; mmol	$(Ph_3P)_4Pd$, weight, mg; mol %	dppe, weight, mg; mol %	solvent,[c] volume, mL; time, h	product(s), weight, mg; yield, %
1;[a] methyl (phenylsulfonyl)sodioacetate; 1.7	195; 1.0	92; 7.4	10; 2.4	THF; 7; 5	**21**; 259; 74
2;[a] methyl (phenylsulfonyl)acetate; 1.7	278; 1.5	87; 5.1	10; 1.7	THF; 7; 21[d]	**22**; 360; 90
3;[b] coumarin; 1.9	300; 1.6	170; 9.2	10; 1.6	THF; 7; 9	**23**, 166, 52%
4;[b] benzalacetone; 2.6	357; 1.9	125; 5.8	15; 2.0	toluene; 7; 20	**24**, **25**, (1:2);[e] 172; 45
5;[b] cinnamyl aldehyde; 2.6	213; 1.1	120; 9.2	10; 2.7	THF; 6; 6	**26**; 208; 8

[a] See general procedure for alkylation of **1** for reaction conditions of this run. [b] See general procedure for cycloadditions for reaction conditions of these experiments in ref 35. [c] All reactions were performed at refluxing temperature of the solvent unless stated otherwise. [d] This run was performed at room temperature. [e] Products were separated by VPC, see ref 1.

Methyl 2-(Phenylsulfonyl)-5-deuterio-4-methylenepentanoate (11): same procedure as above (see Table IV, entry 7 for detail); ^1H NMR (100 MHz) δ 7.80–8.00 (m, 2 H), 7.50–7.80 (m, 3 H), 4.78 (br s, 1 H), 4.66 (br s, 1 H), 4.14 (t, J = 7 Hz, 1 H), 3.56 (s, 3 H), 3.68 (d, J = 7 Hz, 2 H), 1.66 (br s, 2.2 H); ^{13}C NMR (15 MHz) δ 165.9, 139.6, 137.2, 134.3, 129.2, 129.1, 113.5, 69.50, 52.75, 34.41, 21.89 (t, J = 19.3 Hz); mass spectrum, m/e (%) 129 (17), 128 (76), 127 (30), 97 (11), 96 (39), 95 (16), 78 (16), 77 (64), 69 (33), 68 (23), 67 (12), 59 (11), 56 (40), 55 (29), 51 (35), 44 (100), 43 (26). Calcd for $C_{13}H_{15}DO_4S$: 269.0826. Found: 269.0836, 91% d_1.

Preparation of (*E*)-2-(Acetoxymethyl)-6-phenyl-4-(trimethylsiloxy)-1,5-hexadiene (14). A solution of 304 mg (1.6 mmol) of **1**, 290 mg (2.2 mmol) of cinnamaldehyde, 147 mg (7.8 mol %) of $(Ph_3P)_4Pd$, and 21 mg (3.2 mol %) of dppe in 6 mL of THF was refluxed for 3 h. After TLC indicated complete consumption of **1**, the reaction was concentrated under a stream of air. Preparative TLC of the residue gave 225 mg (45%) of the title product: TLC R_f 0.32 (1:10 ether/pentane); ^1H NMR (270 MHz) δ 7.36–7.15 (m, 5 H), 6.51 (d, J = 16 Hz, 1 H), 6.18 (d of d, J = 16, 6.5 Hz, 1 H), 5.12 (m, 1 H), 5.02 (m, 1 H), 4.61 (d of AB, J = 13 Hz, 1 H), 4.55 (d of AB, J = 13 Hz, 1 H), 4.40 (g of d, J = 6.5, 1 Hz, 1 H), 2.35 (m, 2 H), 2.08 (s, 3 H), 0.13 (s, 9 H); IR ($CHCl_3$) 3030, 2960, 1735, 1655, 1378, 1053, 972, 850 cm^{-1}; mass spectrum, m/e (%) 205.5 (100), 186 (11), 155 (14), 131 (20), 129 (23), 128 (12), 117 (27), 115 (18), 91 (32), 82 (13), 77 (13), 75 (38), 74 (15), 73 (72), 55 (17), 54 (16). Calcd for $C_{18}H_{26}O_3Si$: 318.1655. Found: 318.1643.

Preparation of 1-Acetoxy-2-methylene-4-(trimethylsiloxy)decane (13). A solution of 308 mg (2.7 mmol) of *n*-heptanal, 207 mg (1.1 mmol) of **1**, 103 mg (8 mol %) of $(Ph_3P)_4Pd$, and 14 mg (3.0 mol %) of dppe in 4.5 mL of THF was refluxed for 2.5 h. After workup as above, there was obtained 90 mg (27%) of the titled product: TLC R_f 0.4 (1:10 ether/pentane); ^1H NMR (270 MHz) δ 5.09 (m, 1 H), 4.97 (m, 1 H), 4.54 (s, 2 H), 3.76 (quintet, J = 6.4 Hz, 1 H), 2.21 (d, J = 6.4 Hz, 2 H), 2.09 (s, 3 H), 1.28 (m, 10 H), 0.88 (br t, J = 7 Hz, 3 H), 0.10 (s, 9 H); IR ($CHCl_3$) 2920, 2850, 1730, 1645, 1375, 1050, 840 cm^{-1}; mass spectrum, m/e (%) 189 (11), 187 (100), 155 (16), 129 (10), 117 (38), 103 (40), 97 (22), 95 (16), 83 (30), 81 (20), 75 (30), 74 (20), 73 (76), 72 (33), 71 (10), 70 (14), 69 (18), 57 (19), 55 (54), 54 (15). Calcd for $C_{16}H_{32}O_3Si$: 300.2112. Found: 300.2112.

Preparation of Ethyl 3-(Trimethylsilyl)propionate.[22] A flame-dried 2-L three-necked flask equipped with a 250-mL addition funnel, nitrogen inlet, thermometer, and mechanical stirrer was charged with lithium (ca. 8.0 g, 1153 mmol, in the form of small pieces of ribbon). THF (550 mL) was added, and the reaction was rigorously stirred for 1 h under argon. Chlorotrimethylsilane (140 mL, 1109 mmol) was then added dropwise at ice-bath temperature. The mixture was stirred for 45 min (the lithium ribbons took on a shiny appearance). A solution of ethyl acrylate (42 g, 420 mmol) in 50 mL of THF was then added over 5 h, with the temperature of the reaction maintained between 4 and 8 °C. The cloudy mixture was warmed to room temperature and stirred for an additional 40 h. The reaction was allowed to settle, and the supernatant liquid was cannulated into a 1-L flask. The solid residue (lithium chloride and unreacted lithium) was rinsed with ether. The combined organic solution was concentrated in vacuo. Dilute hydrochloric acid (~3%, 300 mL) was added and the mixture stirred vigorously for 45 min. Ether (200 mL) was then added, and the aqueous layer was extracted with ether (100 mL). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo and the residue (ca. 90 g) distilled via a Vigreux column to give 45 g of a light yellow liquid (bp 90–100 °C (20 mmHg)). Redistillation gave 36.5 g (50%) of the title compound (bp 90–95 °C (16 mmHg)). The NMR spectrum was identical with that of an authentic sample.

Preparation of Ethyl 2-(Hydroxymethyl)-3-(trimethylsilyl)propionate. To a solution of *n*-BuLi (1.5 M in hexane, 130 mL, 195 mmol) in 600 mL of THF at −78 °C was added diisopropylamine (30 mL, 214 mmol). Ethyl 2-(trimethylsilyl)propionate (30 g, 172 mmol) in 150 mL of THF was added dropwise over 45 min, and the solution was stirred for an additional 45 min. Solid paraformaldehyde (43.5 g, 1.45 mmol) was then added all at once, and the mixture was allowed to warm to room temperature with mechanical stirring. After 14 h, the mixture was cooled to 0 °C and 300 mL of saturated disodium monohydrogen phosphate was added. The mixture was again stirred for 15 min after which 200 mL of ether was introduced. The aqueous layer was extracted with ether (300 mL), and the combined organic layers were dried over magnesium sulfate. The solution was concentrated in vacuo and the residue distilled under reduced pressure to give 20 g of a yellow oil (bp 85–100 °C (0.6–1.5 mmHg)). Redistillation gave 15.6 g (44%) of the title compound (bp 85–90 °C (0.6–0.7 mmHg)). An analytical sample was obtained by preparative VPC: R_t 8.5 min (column A, T = 140 °C, flow rate = 60 mL/min); ^1H NMR (270 MHz) δ 4.16 (q, J = 7.1 Hz, 1 H), 4.15 (q, J = 7.1 Hz, 1 H), 3.71 (A of ABX, J = 10.8, 8.5 Hz, 1 H), 3.65 (B of ABX, J = 10.8, 4.2 Hz, 1 H), 2.65 (X of ABS, m, 1 H), 2.57–2.44 (br s, 1 H), 1.29. (t, J = 7.1 Hz, 3 H), 0.90 (d of d, J = 14.7, 8.5 Hz, 1 H), 0.65 (d of d, J = 14.7, 6.3 Hz, 1 H), 0.03 (s, 9 H); IR (neat) 3460, 2960, 1738, 1253, 1185, 847 cm^{-1}; mass spectrum, m/e (%) (30 eV) 173 (3), 143 (2), 103 (3.5), 85 (2), 77 (3.5), 76 (2.9), 75 (67), 73 (100), 69 (8), 68 (4), 66 (2), 59 (6), 58 (4), 57 (3), 56 (3), 55 (8), 53 (3), 47 (3). Anal. Calcd for $C_9H_{20}O_3Si$: C, 52.88; H, 9.87. Found: C, 59.90; H, 9.68.

Preparation of Ethyl 2-(((Methylsulfonyl)oxy)methyl)-3-(trimethylsilyl)propionate. To a solution of ethyl 1-(hydroxymethyl)-2-(trimethylsilyl)propionate (14.4 g, 70 mmol) and triethylamine (17 mL, 120 mmol) in 100 mL of ether at 0 °C was added methanesulfonyl chloride (6 mL, 78 mmol) dropwise over 5 min. The cloudy mixture was stirred for 1 h and diluted with 400 mL of ether. The organic layer was washed with saturated copper sulfate (200 mL) and water (50 mL) and dried over magnesium sulfate. The solution was concentrated in vacuo to yield 18.2 g (92%) of the desired mesylate. It was carried on to the next step without further purification: ^1H NMR (270 MHz) δ 4.42–4.07 (m, 2 H), 3.00 (s, 3 H), 2.84 (m, 2 H), 1.29 (t, J = 7.3 Hz, 3 H), 0.90 (d of d, J = 14.8, 9.5 Hz, 1 H), 0.68 (d of d, J = 14.8, 5.5 Hz, 1 H), 0.05 (s, 9 H); IR (neat) 2950, 1738, 1358, 1257, 1175, 835 cm^{-1}; mass spectrum, m/e (%) 267 (12), 209 (7), 187 (21), 173 (18), 171 (8), 155 (5), 154 (5), 153 (78), 143 (40), 129 (14), 114 (7), 103 (5), 101 (5), 99 (11), 86 (13), 75 (31), 74 (6), 73 (100), 69 (51), 59 (6), 55 (24), 41 (41), 40 (43). Calcd for $C_{10}H_{22}O_2SSi$: 282.0951. Found: 282.0953.

Preparation of Ethyl 2-Methylene-3-(trimethylsilyl)propionate. 1,8-Diazabicyclo[5.4.0]undec-6-ene (13 mL, 86 mmol) was added to a solution of the above mesylate (18.2 g, 64 mmol) in 160 mL of ether at 16 °C over a period of 1 min. The white cloudy reaction was stirred for 12 h at room temperature, diluted with ether (500 mL), washed with saturated copper sulfate (3 × 100 mL) and water (100 mL), and dried over magnesium sulfate. The solvent was removed in vacuo and the residue distilled to give 10.0 g (80%) of the title compound as a light yellow liquid: bp 56–60 °C (3.5–4.0 mmHg); ^1H NMR (270 MHz) δ 5.92 (m, 1 H), 5.23 (m, 1 H), 4.12 (q, J = 7.1 Hz, 2 H), 1.77 (m, 2 H), 1.23 (t, J = 7.1 Hz, 3 H), 0.00 (s, 9 H); IR (neat) 2945, 1720, 1623, 1323, 1302, 1253, 1187, 1108, 852 cm^{-1}; mass spectrum, m/e (%) M^+ 186 (2), 171 (5), 143 (10), 131 (4), 119 (3), 117 (3), 85 (4), 77 (12), 75 (31), 74 (5), 73 (100), 69 (29), 68 (20), 59 (5), 55 (4), 47 (3), 45 (16), 44 (62), 43 (13), 41 (7). Calcd for $C_9H_{18}O_2Si$: 186.1071. Found: 186.1061.

Preparation of 2-Methylene-3-(trimethylsilyl)-1,1-dideuteriopropan-1-ol. A solution of ethyl 2-methylene-3-(trimethylsilyl)propionate (5.8 g, 32 mmol) in 30 mL of ether was added dropwise over 45 min to a stirring suspension of lithium aluminum deuteride (99% deuteriation, 1.0 g, 22 mmol) in 30 mL of ether at −10 °C. After 45 min of stirring, the reaction was quenched by sequential addition of water (1 mL), 15% sodium hydroxide (1 mL), and water (1 mL). The cloudy mixture was diluted with 140 mL of ether and dried over magnesium sulfate. The

solution was concentrated in vacuo carefully, and the residue was purified by preparative HPLC (1:2 ether/pentane) to give 3.55 g (70%) of the title compound as a colorless oil: ^{1}H NMR (270 MHz) δ 4.90 (m, 1 H), 4.66 (m, 1 H), 2.17 (br s, 1 H), 1.53 (m, 2 H), 0.03 (s, 9 H); IR (neat) 3340, 2955, 1640, 1250, 1164, 1086, 857 cm^{-1}; mass spectrum, *m/e* (%) M$^+$ 146 (2.3), 131 (16), 76 (85), 75 (100), 74 (8), 73 (92), 61 (5), 59 (6), 56 (57), 55 (15), 47 (6), 45 (34), 44 (9), 43 (27), 42 (6), 41 (13), 40 (17), 39 (14). Calcd for $C_7H_{14}D_2OSi$: 146.1092. Found: 146.1091.

Preparation of 1-Acetoxy-1,1-dideuterio-2-((trimethylsilyl)methyl)-2-propene (20) (Table V). Acetyl chloride (5 mL, 70 mmol) was added dropwise to a solution of the dideuterated alcohol (3.2 g, 22 mmol) in pyridine (9.5 mL, 118 mmol) and 30 mL of dichloromethane at 0 °C. The white cloudy mixture was stirred for 30 min and diluted with ether, washed with saturated sodium bicarbonate, saturated $CuSO_4$, and water, and dried over anhydrous potassium carbonate. The solvent was removed in vacuo to give 3.8 g of residue. It was purified by preparative HPLC (pentane), and the desired product was further purified by Kugelrohr distillation. The title compound (2.4 g, 60%) was obtained as a colorless oil: bp 80 °C (4–5 mmHg); ^{1}H NMR (270 MHz) δ 4.89 (m, 1 H), 4.73 (br s, 1 H), 2.09 (s, 3 H), 1.55 (br s, 2 H), 0.04 (s, 9 H); IR (neat) 2955, 1745, 1643, 1370, 1252, 1164, 858 cm^{-1}; mass spectrum, *m/e* (%) M$^+$ 188 (9), 173 (6), 146 (18), 145 (34), 131 (30), 129 (6), 118 (12), 117 (63), 113 (8), 91 (7), 83 (5), 77 (13), 76 (32), 75 (90), 74 (53), 73 (98), 72 (16), 71 (6), 70 (8), 69 (9), 62 (6), 61 (26), 60 (17), 59 (33), 58 (22), 57 (37), 56 (84), 55 (46), 54 (20), 53 (10), 47 (23), 46 (15), 45 (97). Calcd for $C_9H_{16}D_2O_2Si$: 188.1197. Found: 188.1198; 91.4% d_2, 3.3% d_1.

21: ^{1}H NMR (C_6F_6, 100 MHz) δ 7.16 (m, 5 H), 4.64 (s, 0.51 H), 4.56 (s, 0.51 H), 3.96 (m, 1 H), 3.70 (s, 3 H), 2.36 (m, 0.88 H), 1.58 (br s, 2 H), 0.06 (s, 9 H); ^{2}H NMR (C_6F_6, 15.36 MHz) δ 4.52 (br s, 1.00 D), 2.46 (br s, 1.13 D); mass spectrum, *m/e* (%) (30 eV) M$^+$ 343 (1.2), 156 (98), 145 (12), 126 (11), 125 (100), 110 (11), 97 (13), 78 (17), 77 (86), 75 (18), 73 (58), 72 (22), 69 (23), 59 (52), 57 (17), 51 (24). Calcd for $C_{16}H_{22}D_2O_4SSi$: 342.1284. Found: 342.1276; 97.4 d_2, 13.8% d_1.

22: ^{1}H NMR (C_6F_6, 100 MHz) δ 7.96–7.60 (m, 5 H), 4.83 (s, 0.05 H), 4.70 (s, 0.50 H), 4.02 (m, 1 H), 3.66 (s, 3 H), 2.60 (m, 0.85 H), 1.76 (s, 3 H); ^{2}H NMR (C_6F_6, 15.36 MHz) δ 4.56 (br s, 1.00 D), 2.45 (br s, 1.17 D); mass spectrum, *m/e* (%) (30 eV) M$^+$ 156 (19), 129 (100), 125 (21), 97 (26), 77 (22). Calcd for $C_{13}H_{14}D_2O_4S$: 270.0891. Found: 270.0882; 82.1% d_2, 9.1% d_1.

23: ^{1}H NMR (270 MHz) δ 7.27–7.02 (m, 4 H), 4.95 (m, 1.30 H), 3.43 (d of t, J = 9.5, 7.3 Hz, 1 H), 3.14 (t of d, J = 7.3, 4.0 Hz, 1 H), 3.03 (d of quintet, J = 17.5, 0.7 Hz, 0.67 H), 2.85–2.65 (m, 1.33 H), 2.39 (br d of d, J = 16.0, 9.5 Hz, 0.65 H); ^{2}H NMR (C_6F_6, 15.36 MHz) δ 4.01 (br s, 1.00 D), 2.91–2.27 (m, 2.01 D); mass spectrum, *m/e* (%) M$^+$ 202 (100), 201 (9), 174 (16), 173 (10), 159 (6), 146 (8), 131 (7). Calcd for $C_{13}H_{10}D_2O_2$: 202.0960. Found: 202.0963; 89.8% d_2, 5.9% d_1.

24: ^{1}H NMR (C_6F_6, 100 MHz) δ 7.07 (m, 5 H), 4.80 (m, 1.3 H), 3.20–2.25 (m, 4.5 H), 1.90 (s, 3 H); ^{2}H NMR (C_6F_6, 15.36 MHz) δ 4.88 (br s, 1.00 D), 2.40–2.70 (m, 2.31 D); mass spectrum, *m/e* (%) (30 eV) 200 (48), 157 (100), 156 (58), 129 (28), 127 (53), 109 (22), 95 (26), 43 (48). Calcd for $C_{14}H_{14}D_2O$: 202.1323. Found: 202.1288.

25: ^{1}H NMR (C_6F_6, 100 MHz) δ 7.40 (m, 5 H), 6.64 (d, J = 16 Hz, 1 H), 4.63 (br s, 1.41 H), 2.76 (m, 2.31 H), 2.28 (m, 1.45 H), 1.78 (br s, 2.57 H); ^{2}H NMR (C_6F_6, 15.36 MHz) δ 4.62 (br s, 1.00 D), 2.23 (br s, 1.01 D), 1.74 (br s, 1.11 D); mass spectrum, *m/e* (%) (30 eV) 132 (20), 131 (100), 104 (14), 103 (86), 77 (41), 43 (13). Calcd for $C_{14}H_{14}D_2O$: 202.1323. Found: 202.1328; 89.2% d_2, 6.2% d_1.

26: ^{1}H NMR (C_6F_6, 100 MHz) δ 7.0 (br s, 5 H), 6.5–6.0 (m, 2 H), 4.90 (m, 1.4 H), 4.40 (br s, 1.5 H), 2.24 (d, J = 7 Hz, 1.5 H), 1.92 (s, 3 H), 0.04 (s, 9 H); ^{2}H NMR (C_6F_6, 15.36 MHz) δ 5.2–4.0 (m, 2.4 D), 2.3 (br s, 1.0 D).

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Registry No. 1, 72047-94-0; **6**, 14221-01-3; **7** (X = Y = Co_2CH_3), 84681-27-6; **7** (X = SO_2Ph; Y = CO_2CH_3), 74976-76-4; **7** (X = Y = SO_2Ph), 84681-28-7; **8** (X = Y = SO_2Ph), 84681-29-8; **87** (X = $COCH_3$; Y = CO_2CH_3), 20962-71-4; **8** (X = Y = $-COCH_2C(CH_3)_2CH_2CO-$), 72085-94-0; **8** (X = SO_2Ph; Y = CO_2CH_3), 74976-77-5; **11**, 74976-79-7; **13**, 84681-30-1; **14**, 84681-31-2; **17**-PH_3, 84681-32-3; **20**, 74976-80-0; **21**, 84681-33-4; **22**, 84681-34-5; **23**, 84681-35-6; **24**, 84681-36-7; **25**, 84681-37-8; **26**, 84681-38-9; (*E*)-cinnamaldehyde, 14371-10-9; *n*-heptanol, 111-71-7; ethyl 3-(trimethylsilyl)propionate, 17728-88-0; chlorotrimethylsilane, 75-77-4; ethyl acrylate, 140-88-5; ethyl 2-(hydroxymethyl)-3-(trimethylsilyl)propionate, 84681-39-0; ethyl 2-(trimethylsilyl)propionate, 13950-55-5; paraformaldehyde, 30525-89-4; ethyl 2-(((methylsulfonyl)oxy)methyl)-3-(trimethylsilyl)propionate, 84681-40-3; ethyl 2-methyl-3-(trimethylsilyl)propionate, 74976-84-4; 2-methylene-3-(trimethylsilyl)-1,1-dideuteriopropan-1-ol, 84681-41-4; coumarin, 91-64-5; acetophenone, 98-86-2; benzalacetone, 122-57-6; methyl (phenylsulfonyl)acetate anion, sodium, 60729-65-9; dimethyl malonate anion, sodium, 18424-76-5; bis(phenylsulfonyl)methane anion, sodium, 34782-39-3; methyl 3-oxobutanoate anion, sodium, 34284-28-1; dimedone anion, sodium, 17372-26-8.

Kinetics and Thermodynamics of the Structural Transformations of Thiamine in Neutral and Basic Aqueous Media. The UV Spectrum of the Tetrahedral Pseudobase Intermediate

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Abstract: pH-jump techniques in chemical relaxation have been used to establish the general mechanism of the structural transformations of thiamine in neutral and mildly basic (pH <11) aqueous media. All the rate and equilibrium constants involved in this mechanism are measured and reported here for the first time. The formation of a tetrahedral pseudobase from thiamine occurs in neutral and acidic media by hydration with a second-order rate constant $k_{H^+} = 1.15 \times 10^6$ M^{-1} s^{-1} and an equilibrium constant $K_{H_2O} = 1.95 \times 10^{-10}$ M and in basic media by rate-limiting hydroxyl addition with a second-order rate constant $k_{OH} = 19.6$ M^{-1} s^{-1}. The ring opening of the pseudobase is very fast and is always base promoted with a second-order rate constant $k_T = 6.75 \times 10^4$ M^{-1} s^{-1} at 5 °C and an equilibrium constant $K_T = 1.15 \times 10^{-9}$ M at 25 °C. The pseudobase ring opens probably through basic deprotonation. The pseudobase, which had not been previously detected in the case of thiamine, is isolated kinetically and its UV spectrum is measured point by point. It exists in aqueous solutions between pH 9.2 and 9.4, to the extent of 16% of the overall thiamine concentration.

Ever since Williams' discovery of the structure of thiamine, the antiberiberi vitamin B_1, its structural transformations in aqueous media[1-4] and its vitally important action in the decarboxylation of pyruvates[5-8] have been extensively studied. In neutral and

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