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New Rules of Selectivity: Allylic Alkylations Catalyzed by Palladium

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The formation of carbon–carbon bonds with high selectivity represents a continuing challenge in synthetic methodology. Chart I summarizes the types of selectivity that must be controlled. Whereas the carbonyl group represents the most important functional group for formation of C–C bonds, the π-isoelectronic olefinic linkage has proven much less useful, especially with respect to α alkylation (compare eq 1 and 2). The

α-carbonyl alkylation

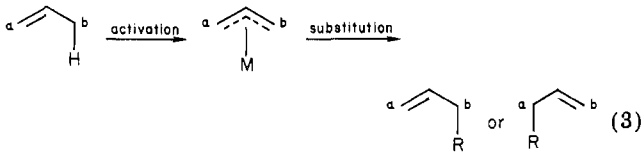
(1)

allylic alkylation

(2)

ready availability of olefins enhances the need for such processes. Of the more classical types of approaches, the most promising appears to be variations of the Alder ene reaction.[1]

A totally different concept envisions an allyl metal intermediate (eq 3), which is formed from the olefin in



(3)

an activation step. Such an approach has the benefit that added synthetic flexibility may be available during the substitution step in that the new carbon–carbon bond can be formed at either C(a) or C(b). Thus, variation of reaction conditions may permit allylic substitution with retention of the olefin at its original position or with allyl rearrangement. Lithiations have found utility, but such reactions lack chemoselectivity.[2] Transition metals offer greater hope for selectivity.

Barry M. Trost joined the faculty at the University of Wisconsin, where he is now the Evan P. and Marion Helfaer Professor of Chemistry, following receipt of the Ph.D. from Massachusetts Institute of Technology in 1965. He was born in Philadelphia and studied at the University of Pennsylvania for his undergraduate degree. Development of new reactions and reagents and the applications of these new methods to the total synthesis of natural products form a major part of his research program.

Chart I
Major Types of Selectivity

A. Chemoselectivity—functional group differentiation
B. Regioselectivity—selective addition of an unsymmetrical reagent to an unsymmetrical functional group
C. Stereocontrol
   1. Diastereoselectivity—control of relative stereochemistry
   2. Enantioselectivity—control of absolute stereochemistry

Allylic Activation with Palladium Salts

Palladium(2+) salts provide activation of the allylic position of an olefin and discriminate between a polarized and nonpolarized π unsaturation in favor of the latter,[3-6] as shown in eq 5.[6c] Steric factors also play a role as shown in eq 4[6c] and 5.[6d] The electrophilic nature of the palladating agent determines the facility of the

(1) For reviews see W. Oppolzer and V. Sineckus, *Angew. Chem., Int. Ed. Engl.*, **17**, 476 (1978); J. M. Conia and P. LePerchec, *Synthesis*, 1 (1975); H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969). For a few recent examples see B. B. Snider and D. M. Roush, *J. Am. Chem. Soc.*, **101**, 1906 (1979); G. B. Gill, *J. Chem. Soc., Chem. Commun.*, 380, 382 (1977); W. Oppolzer and K. K. Mahalanabis, *Tetrahedron Lett.*, 3411 (1975); W. Oppolzer, K. Bättig, and T. Hudlicky, *Helv. Chim. Acta*, **62**, 1493 (1979); C. H. Heathcock and F. Plavac, *Tetrahedron Lett.*, 2115 (1979).

(2) H. Yasuda, Y. Ohnuma, M. Yamauchi, H. Tani, and A. Nakamura, *Bull. Chem. Soc. Jpn.*, **52**, 2036 (1979); I. Clark and P. V. R. Schleyer, *J. Chem. Soc., Chem. Commun.*, 798 (1976); J. Hartmann, R. Muthukrishnan, and M. Schlosser, *Helv. Chim. Acta*, **57**, 2271 (1974); G. L. Hodgson, D. F. MacSweeney, and T. Money, *J. Chem. Soc., Perkin Trans. 1*, 2113 (1973); R. J. Crawford, W. F. Erman, and C. D. Broadhus, *J. Am. Chem. Soc.*, **94**, 4298 (1974); C. Agami, *Bull. Soc. Chim. Fr.*, 1619 (1970); R. Bates, S. Brenner, W. H. Deines, D. A. McCombs, and D. E. Potter, *J. Am. Chem. Soc.*, **92**, 6345 (1970).

(3) For reviews, see B. M. Trost, *Tetrahedron*, **33**, 2615 (1977); R. Huttel, *Synthesis*, 228 (1970).

(4) G. W. Parshall and G. Wilkinson, *Inorg. Chem.*, **1**, 896 (1962); D. Morelli, R. Ugo, F. Conti, and M. Donati, *Chem. Commun.*, 169 (1968); A. D. Ketley and J. Braatz, *ibid.*, 169 (1968); H. C. Volger, *Recl. Trav. Chim. Pays-Bas*, **88**, 225 (1969).

(5) R. Hüttel, J. Kratzer, and M. Bechter, *Chem. Ber.*, **94**, 766 (1961); R. Hüttel and H. Christ, *ibid.*, **96**, 3101 (1963); **97**, 1439 (1964); R. Hüttel, H. Dietl, and H. Christ, *ibid.*, **97**, 2037 (1964); R. Hüttel, H. Christ, and K. Herzig, *ibid.*, **97**, 2710 (1964); R. Hüttel and H. Dietl, *ibid.*, **98**, 1753 (1965).

(6) (a) B. M. Trost and T. J. Fullerton, *J. Am. Chem. Soc.*, **95**, 292 (1973); (b) B. M. Trost and P. E. Strege, *Tetrahedron Lett.*, 2603 (1974); (c) B. M. Trost, P. E. Strege, L. Weber, T. J. Fullerton, and T. J. Dietsche, *J. Am. Chem. Soc.*, **100**, 3407 (1978); (d) B. M. Trost and P. Metzner, *J. Am. Chem. Soc.*, **102**, 3572 (1980).

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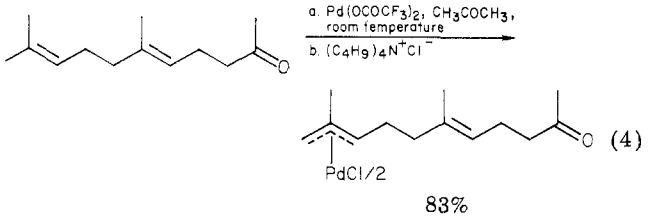
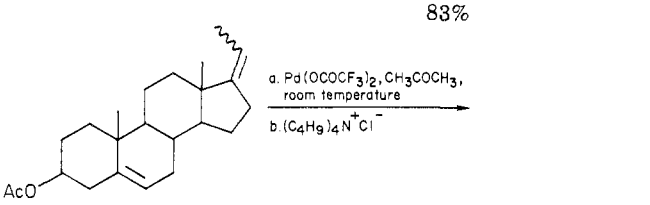
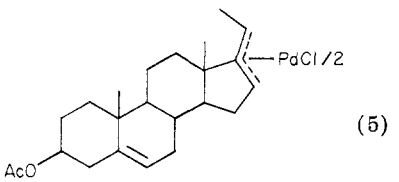


(4)

83%

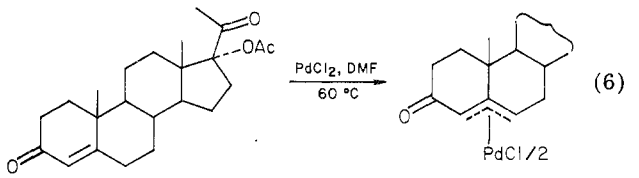




(5)

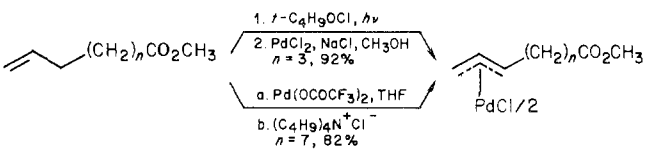
92%

reaction. Thus, by a switch from palladium chloride to palladium trifluoroacetate the reaction conditions may be tempered considerably.[6] Nevertheless, for cyclohexenes, the palladium chloride method is necessary since palladium trifluoroacetate effects disproportionation.[6] While nonconjugated olefins react faster, enones also form the desired complexes, as shown in eq 6.[7]

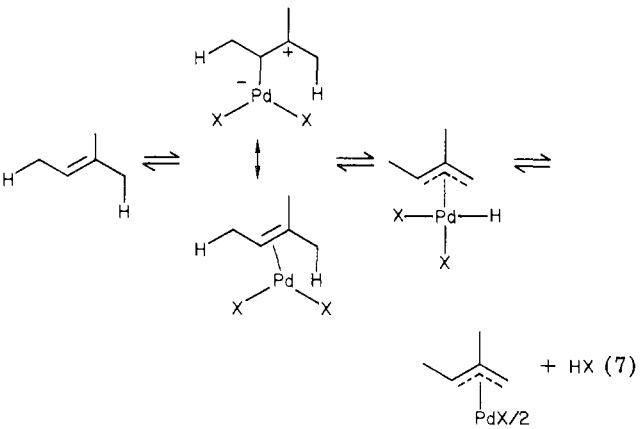


(6)

Monosubstituted olefins have been somewhat problematical. One solution involved initial allylic chlorination followed by the use of a more traditional reaction for forming the π-allylpalladium complex.[8] However, the use of palladium trifluoroacetate allows the direct one-step synthesis of the corresponding complex even in this case.[6d] Other methods such as the use of palladium acetate[9] and bis(benzonitrile)palladium chloride[10] may also proceed at room temperature but are not as general as the above methods.



The mechanism of this reaction appears to involve a palladium hydride species. Furthermore, the fact that the hydrogen lost is syn to the palladium[11] suggests the path outlined in eq 7.

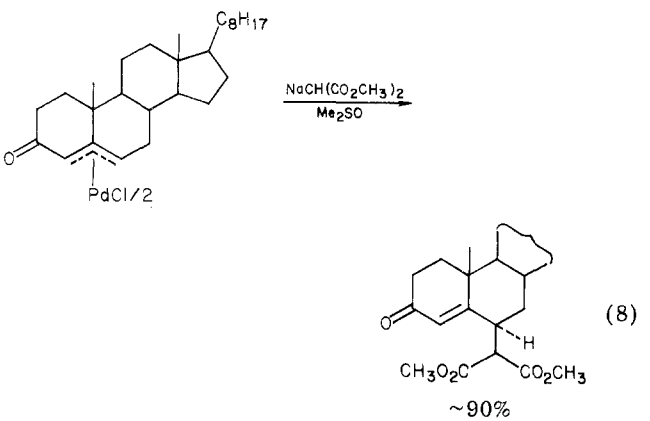


(7)

The regioselectivity is generally in accord with a Markovnikov-like process. Loss of hydrogen occurs preferentially at the position allylic to the more substituted end of the olefin. This selectivity can be rationalized in terms of the olefin–palladium complex in which greater positive character is built up at the more substituted olefinic carbon (see the resonance form in eq 7) and thus activation of the adjacent allylic hydrogen.

Alkylation of π-Allylpalladium Complexes

While organometallic reagents are normally thought of as nucleophiles, π-allylpalladium complexes are, in fact, electrophilic conjunctive reagents.[3] The most common nucleophile is a stabilized anion (conjugate acid with a $pK_A \sim 10\sim20$) such as dimethyl sodiomalonate. For π-allylpalladium chloride itself[12] or allyl complexes that bear electron-withdrawing groups,[13] nucleophilic attack occurs in a solvent such as dimethyl sulfoxide which itself is a ligand to palladium (see eq 8).

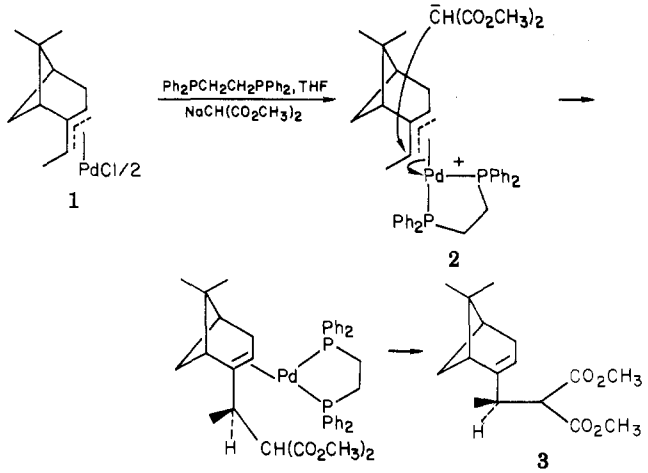


(8)

~90%

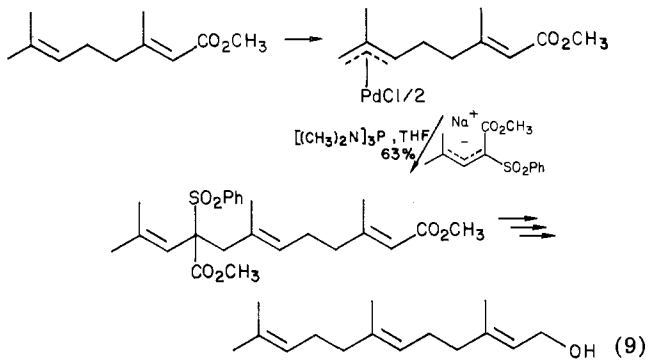
Alkyl-substituted complexes normally require activating ligands to increase the electrophilic nature of the π-allylpalladium complexes.[6a,14] Phosphines, phosphites, arsines, and stibines all suffice, but phosphines are the most common. Activation involves conversion of the chloride-bridged dimers to π-allylpalladium cationic complexes[15] (i.e., **1** to **2**). These cations are

(7) I. T. Harrison, E. Kimura, E. Bohme, and J. H. Fried, *Tetrahedron Lett.*, 1589 (1969).
(8) R. C. Larock and J. P. Burkhart, *Synth. Commun.*, 9, 659 (1979).
(9) J. E. Hallgren, private communication. For a novel reaction of palladium(II) *tert*-butyl peroxide trifluoroacetate see H. Mimoun, R. Charpentier, A. Mitschler, J. Fischer, and R. Weiss, *J. Am. Chem. Soc.*, **102**, 1047 (1980).
(10) B. W. Howsam and F. J. McQuillan, *Tetrahedron Lett.*, 3667 (1968); D. N. Jones and S. D. Knox, *J. Chem. Soc., Chem. Commun.*, 165 (1975); D. H. R. Barton and H. Patin, *ibid.*, 799 (1977); P. Boontanonda and R. Grigg, *ibid.*, 583 (1977).
(11) I. J. Harvie and F. J. McQuillin, *J. Chem. Soc., Chem. Commun.*, 747 (1978). Also see K. H. Henderson and F. J. McQuillin, *ibid.*, 15 (1978).
(12) J. Tsuji, H. Takahashi, and M. Morikawa, *Tetrahedron Lett.*, 4387 (1965); J. Tsuji, *Bull. Chem. Soc. Jpn.*, **46**, 1897 (1973).
(13) W. R. Jackson and J. V. G. Strauss, *Tetrahedron Lett.*, 2591 (1975); D. J. Collins, W. R. Jackson, and R. N. Timms, *ibid.*, 495 (1976).
(14) (a) B. M. Trost and L. Weber, *J. Am. Chem. Soc.*, **97**, 1611 (1975); (b) B. M. Trost and P. E. Strege, *ibid.*, **97**, 2534 (1975); (c) B. M. Trost, L. Weber, P. E. Strege, T. J. Fullerton, and T. J. Dietsche, *ibid.*, **100**, 3416 (1978); (d) *ibid.*, **100**, 3426 (1978).
(15) M. Oslinger and S. Powell, *Can. J. Chem.*, **96**, 274 (1973), and earlier references therein.



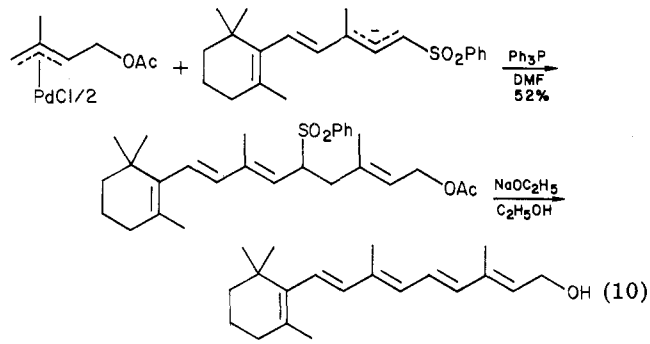
highly reactive toward nucleophiles which approach the π-allyl moiety on the face opposite to that of palladium (i.e., **2** to **3**). In conventional terms, the alkylation occurs by a normal inversion of configuration at carbon, with palladium(0) becoming the leaving group.

Applications of this methodology in the synthesis of natural products have already shown promise. For example, terpenes are composed of five carbon units related to isoprene. Direct introduction of such a C(5) unit using an anion of a sulfonyl ester allowed construction of a sesquiterpene from a monoterpene (eq 9)



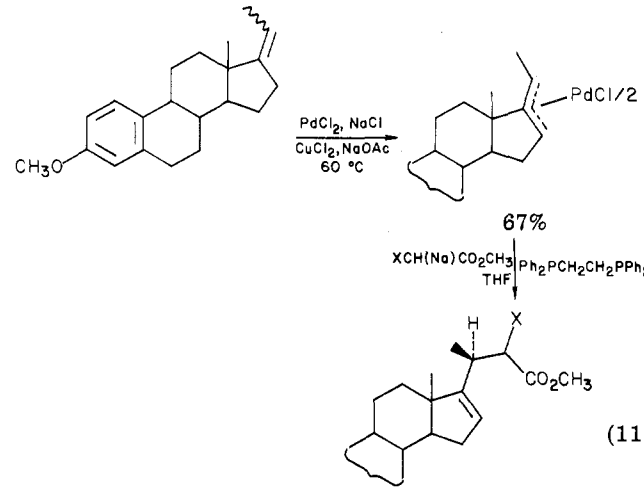
(9)

and a diterpene (geranylgeraniol) from a sesquiterpene (methyl farnesoate).[14d,16,17] This prenylation sequence should have general applicability in terpene synthesis. Use of the anion of an allyl sulfone served as the key carbon–carbon bond-forming step in a synthesis of vitamin A alcohol (eq 10).[18] Recently, steroids possessing



(10)

an abnormal stereochemistry at C(20) have been isolated from marine organisms.[19] This palladium-based allylic alkylation creates this stereochemistry with complete control as illustrated in eq 11, regardless of

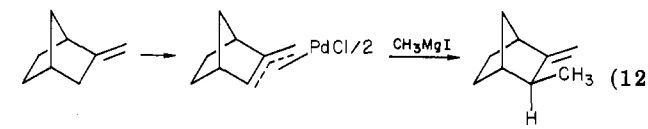


(11)

X = CO_2CH_3, 81%
X = $PhSO_2$, 82%

the initial olefin geometry.[20] The fact that the starting olefins are synthesized from 17-keto steroids via the Wittig olefination makes this a very attractive stereocontrolled synthesis of these substances.

The use of less stabilized carbanions has previously been discouraging. However, subsequent work with a corresponding catalytic allylic alkylation suggests the need for reexamination of this area. Most recently, a coupling with methylmagnesium iodide of a π-allylpalladium complex that cannot eliminate to form a diene has been reported (eq 12).[21] However, this reaction appears to involve formation of the new C–C bond on the same face of the allyl unit as the palladium (i.e., a retention mechanism)—a fact that suggests a totally different type of reaction. A related acylation process is also known.[22]



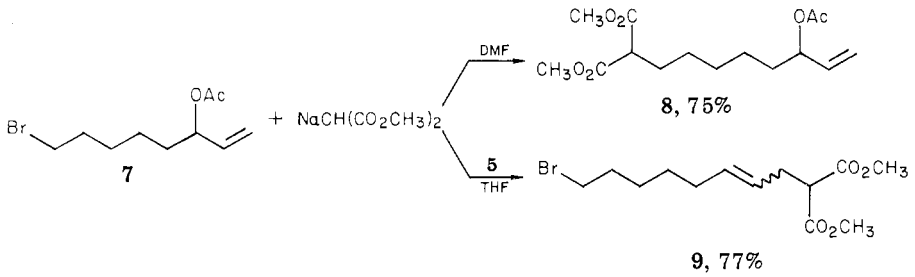
(12)

90%

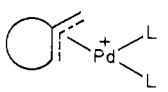
Among heteroatom nucleophiles, only those based upon oxygen[23] and nitrogen[24] have been examined in stoichiometric reactions. In the case of nitrogen, an inversion of configuration analogous to the normal carbon case has been observed. More extensive examination of heteroatom nucleophiles represents one of the current frontiers.

From these examples, several generalizations emerge. The stereochemistry of the alkylation product reflects the stereochemistry of the π-allyl complexes in which

(16) B. M. Trost, P. W. Conway, P. E. Strege, and T. J. Dietsche, *J. Am. Chem. Soc.*, **96**, 7165 (1974).
(17) B. M. Trost and L. Weber, *J. Org. Chem.*, **40**, 3617 (1975).
(18) P. S. Manchand, H. S. Wong, and J. F. Blount, *J. Org. Chem.*, **43**, 4769 (1978).
(19) D. J. Vanderah and C. Djerassi, *J. Org. Chem.*, **43**, 1442 (1978).
(20) B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **98**, 630 (1976); **100**, 3435 (1978).
(21) Y. Castanet and F. Petit, *Tetrahedron Lett.*, 3221 (1979).
(22) S. Numata, H. Kurosawa, and R. Okawara, *J. Organomet. Chem.*, **102**, 259 (1975).
(23) R. F. Heck, *J. Am. Chem. Soc.*, **90**, 5542 (1968); Y. Takahashi, K. Tsukiyama, S. Sakai, and Y. Ishii, *Tetrahedron Lett.*, 1913 (1970); S. Wolfe and P. G. C. Campbell, *J. Am. Chem. Soc.*, **93**, 1499 (1971); D. N. Jones and S. D. Knox, *J. Chem. Soc., Chem. Commun.*, 166 (1975); R. Santi and M. Marchi, *J. Organomet. Chem.*, **182**, 117 (1979).
(24) B. Akermark, J. E. Bäckvall, A. Lowenborg, and K. Zetterberg, *J. Organomet. Chem.*, **166**, C33 (1979); B. Akermark and K. Zetterberg, *Tetrahedron Lett.*, 3733 (1975).



the syn complexes are preferred to the anti complexes. Since either the *E* or *Z* olefin forms the same π-allyl complex (i.e., thermodynamic control), this method constitutes a stereocontrolled synthesis of *E* olefins. High regioselectivity is observed in which the nucleophile bonds to the less substituted carbon. For complexes of type **4** attack of the nucleophile is also gen-



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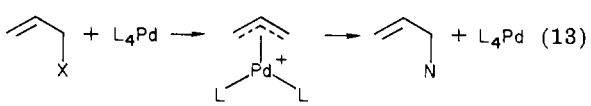
erally preferred at the carbon exocyclic to the ring. However, for six-membered ring systems, variation of ligands to the palladium has led to variation in attack at the exocyclic vs. endocyclic carbon in which the latter can even predominate (e.g., L = tri-*o*-tolylphosphine).[14] π-Allylpalladium complexes are available from many precursors besides simple olefins.[3] When combined with the types of substitution reactions outlined above, these become novel ways to create the carbon framework of organic molecules. Among the more synthetically useful is the elaboration of a diene via the intermediacy of such complexes.[3]

A Catalytic Reaction

The uniqueness of the allylic alkylation and the ease of recovering and recycling palladium give the stoichiometric reaction applicability to problems in fine organic synthesis. Nevertheless, the ultimate development of a catalytic procedure is clearly desirable from an economic point of view. A potentially promising method involving nucleophilic attack on an olefin–palladium(2+) complex appears limited to the simplest olefins and has a very low turnover for palladium.[25]

An alternative catalytic reaction is outlined in eq 13.[20,26-28] In this process, the allylic position is



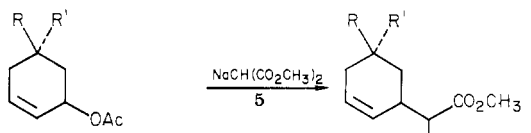
(13)

"activated" by a potential leaving group. Palladium(0) complexes initiate ionization to form the same intermediate as in the stoichiometric process. Nucleophilic attack yields the allylic alkylation product and regenerates the palladium. Turnover numbers can be very high. Typical catalysts include tetrakis(triphenylphosphine)palladium (**5**) and bis[1,2-bis(diphenylphosphino)ethane]palladium (**6**). In situ reduction of palladium salts (e.g., palladium acetate) in the presence of phosphine ligands also generates catalytically active species, but the reactions frequently give lower yields.[26,27] For ease of recovery and enhanced selectivity, the palladium(0) has been immobilized on an inert phosphinylated polystyrene or silica gel support.[29] Use of a palladium template to effect allylic alkylation enhances and complements selectivity achieved under more conventional conditions. This reaction can also reverse the type of selectivity normally obtained and, in that sense, open a new dimension of control for the synthetic chemist.

General Characteristics

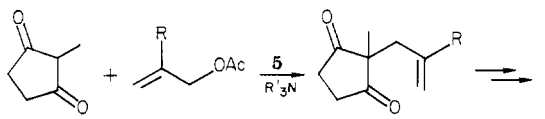
The chemoselectivity can be totally altered. For example, the bifunctional alkylating agent **7** exhibits the normal higher reactivity of the alkyl bromide to give the expected alkylated product **8** in DMF. However, the intrinsic reactivity of the bromide and allylic acetate groups reverses upon use of the palladium catalyst in THF to give **9** as the major product.[28b] No product arising by displacement of the bromide is seen.

In displacement reactions, stereochemical inversion of configuration is normally expected. The palladium-assisted alkylation proceeds with net retention of configuration as illustrated by reacting the stereochemical pair **10** and **11**.[28] C- vs. O-alkylations frequently are

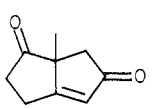


10, R = CO_2CH_3, R' = H
11, R = H, R' = CO_2CH_3

a problem with 1,3-dicarbonyl compounds. For example, 2-methylcyclopentane-1,3-dione underwent C-allylation to give **12** (R = H) in only 30% yield with allyl



12



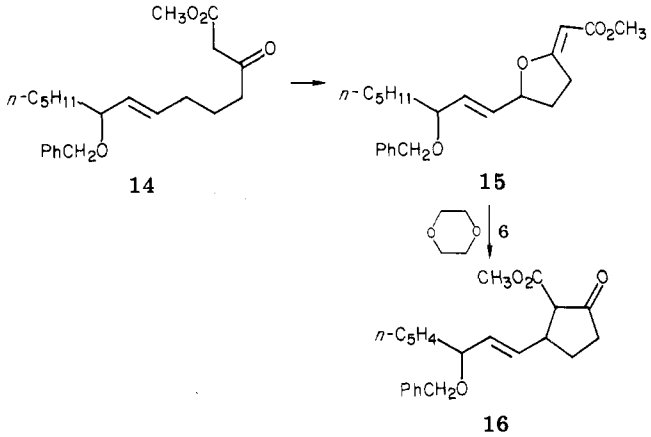
13

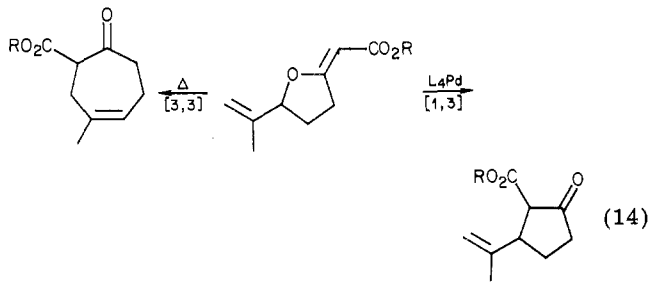
bromide under optimized conditions,[30] but gave a 94% yield of **12** (R = H) with allyl acetate in the presence

(25) L. S. Hegedus, T. Hayashi, and W. H. Darlington, *J. Am. Chem. Soc.*, **100**, 7747 (1978).
(26) K. Takahashi, A. Miyaki, and G. Hata, *Bull. Chem. Soc. Jpn.*, **45**, 230 (1972).
(27) K. E. Atkins, W. E. Walker, and R. M. Manyik, *Tetrahedron Lett.*, 3821 (1970).
(28) (a) B. M. Trost and T. R. Verhoeven, *J. Org. Chem.*, **41**, 3215 (1976); (b) *J. Am. Chem. Soc.*, **102**, 0000 (1980).
(29) B. M. Trost and E. Keinan, *J. Am. Chem. Soc.*, **101**, 7779 (1978). Also see C. U. Pittman, Jr., and Q. Ng, *J. Organomet. Chem.*, **153**, 85 (1978).
(30) M. S. Newman and J. H. Manhart, *J. Org. Chem.*, **26**, 2113 (1961).

of palladium.[31] Use of 2-ethoxyallyl acetate gave **12** (R = OC_5H_5) in 76% yield (DBU, $PhCH_3$, reflux). This served as a critical reaction in a new cyclopentenone annulation by which the novel building block **13** becomes readily available.[31]

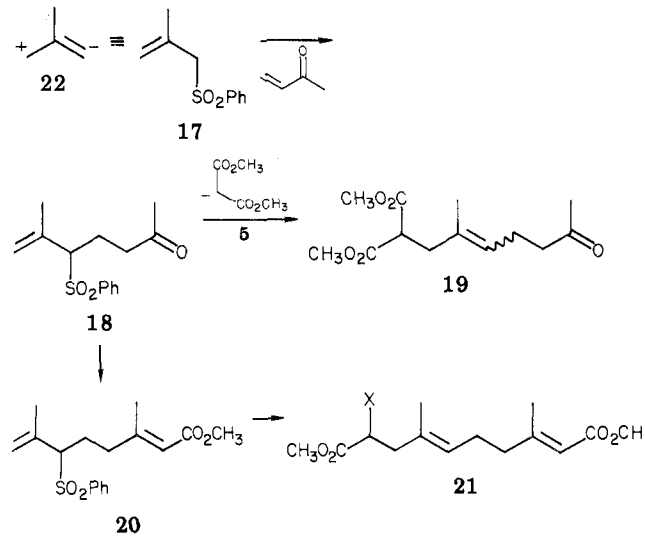
In an intramolecular case to generate a five-membered ring, even the palladium reaction leads to O-alkylation (**14** → **15**).[32] However, the O-alkylated product **15** smoothly rearranges to the desired cyclopentanone **16** in 69% yield upon treatment with 3–5 mol % of **6**.[33] This isomerization demonstrates the complementarity of the transition-metal reaction to standard thermal methods (eq 14).[34,35]

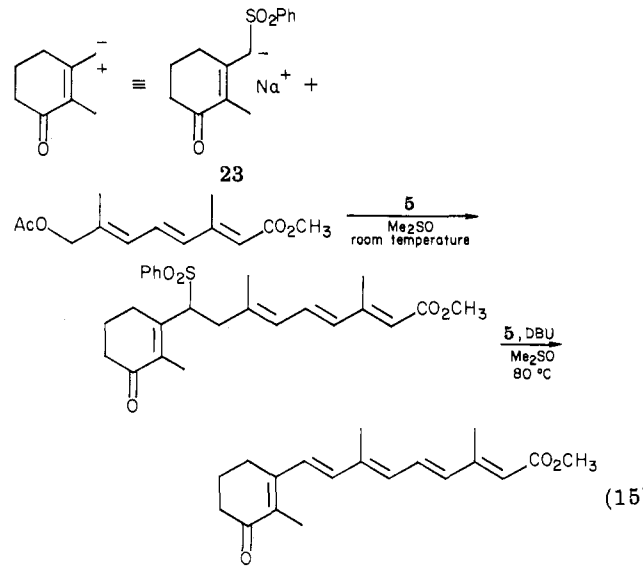




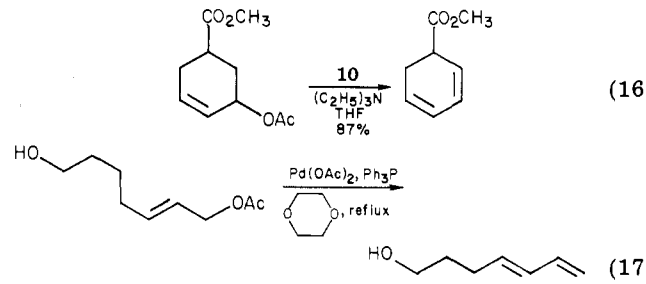
The nature of the leaving group (X in eq 13) has not been fully defined. The most common has been acyloxy such as acetoxy. While acyl ethers and even hydroxyl groups have served as leaving groups,[26,27] they are generally less satisfactory than acyloxy.

Sulfur leaving groups represent specially versatile types.[36] For example, the allyl sulfone **18** undergoes alkylation with dimethyl sodiomalonate in the presence of **5** to give **19** without protecting the carbonyl group.[37] Alternatively, the allylic sulfone in **18** is stable to typical carbonyl reagents such as olefination reagents (the anion of trimethyl phosphonoacetate) to give **20**. Subsequent activation of the sulfone by palladium(0) catalysts allows chemoselective alkylation to give **21** (X = CO_2CH_3) which is a precursor of the dimethyl ester of the sex pheromone of the Monarch butterfly, **21** (X = H). Since **18** arises from the allyl sulfone **17** by reaction of the corresponding allyl anion with methyl vinyl ketone, allyl sulfones such as **17** serve as synthetic equivalents of 1,3-dipoles of type **22**. A one-pot allylic alkylative elimination takes special advantage of this dual role of sulfones, as shown in eq 15. Use of the





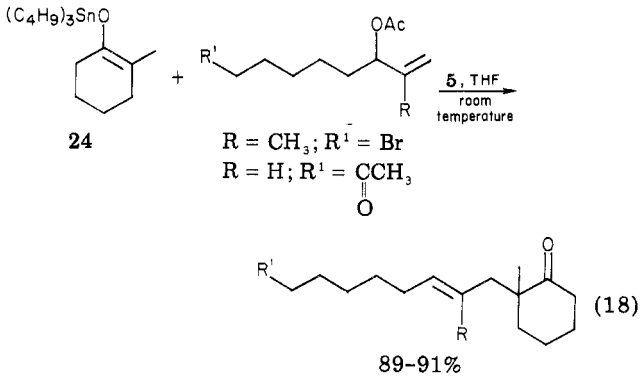
sulfone-stabilized anion leads to selective γ-alkylation of **23** at room temperature. Addition of DBU and raising the temperature to approximately 80 °C effect sulfone activation for elimination to the vitamin A ester analogue.[38] Note that in this sequence the allyl sulfone **23** serves as an equivalent of a 1,1-dipole. Analogous elimination of allylic acetates (eq 16 and 17) also represent useful synthetic entries into 1,3-dienes.[39,40] At



(31) B. M. Trost and D. Curran, unpublished observations.
(32) B. M. Trost, T. A. Runge, and L. N. Jungheim, *J. Am. Chem. Soc.*, **102**, 2840 (1980).
(33) For a related reaction in platinum chemistry, see G. Balavoine and F. Guibe, *Tetrahedron Lett.*, 3949 (1979).
(34) S. J. Rhoads and J. M. Watson, *J. Am. Chem. Soc.*, **93**, 5813 (1971).
(35) E. Demole and P. Enggish, *Chem. Commun.*, 264 (1969).
(36) For a palladium-catalyzed arylation of allyl sulfides see H. Okamura and H. Takei, *Tetrahedron Lett.*, 3425 (1979).
(37) B. M. Trost and N. Schmuff, unpublished observations.
(38) B. M. Trost and M. Miller, unpublished observations.
(39) B. M. Trost, T. R. Verhoeven, and J. Fortunak, *Tetrahedron Lett.*, 2301 (1979).
(40) J. Tsuji, T. Yamakawa, M. Kaito, and T. Mandai, *Tetrahedron Lett.*, 2075 (1978).

present, the range of leaving groups remains to be established.

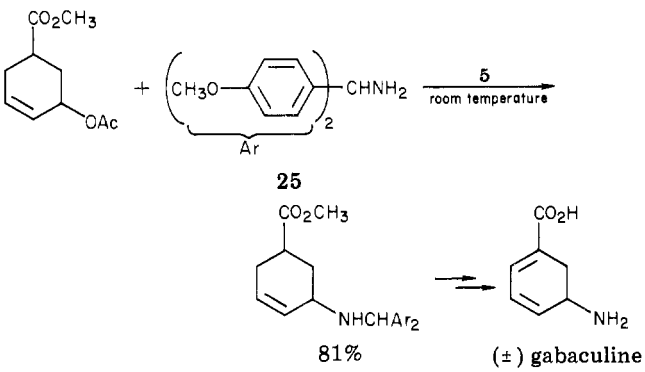
The range of the nucleophiles remains undefined. Originally, only stabilized anions (from conjugate acid of pK ~ 10–20) were employed. The vinylogues of some of these nucleophiles as represented by **23** also are excellent partners. Less stabilized nucleophiles such as simple enolates appear to successfully react,[41,42] but in a noncontrolled fashion. Enol stannanes such as **24** react rapidly and in high yield to give the desired C-alkylated product in a highly chemo- and regioselective fashion, as shown in eq 18.[17] Use of enamines as the



(18)

nucleophiles has also led to introduction of an allyl group alpha to a carbonyl group.[43] The carbon analogue of the enol stannanes, i.e., allylstannanes, has led to an allyl–allyl coupling[44] of very restricted scope and therefore limited synthetic interest at present.

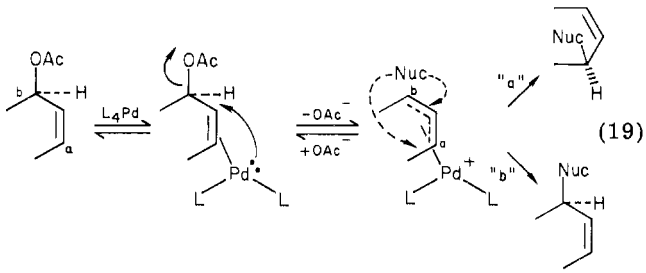
In addition to carbon nucleophiles, heteroatom nucleophiles also react[26,46a]—especially those of nitrogen.[26,27] Primary and secondary amines serve as excellent nucleophiles, and monoalkylation products can be obtained in good yield.[26] However, ammonia does not serve as a nucleophile. Use of 4,4′-dimethoxybenzhydrylamine (**25**) in the alkylation step followed



by treatment with aqueous formic acid to cleave the benzhydryl group serves as an equivalent of monoalkylation with ammonia.[45] When this approach is used, the naturally occurring amino acid gabaculine, an important inhibitor of γ-aminobutyrate aminotransferase, becomes readily available. Unlike the case of carbon nucleophiles, stereochemistry of starting materials is scrambled with the amine nucleophiles.

(41) The alkylation of phenylacetone was reported in unstated yield. See ref 27.
(42) B. M. Trost and E. Keinan, *Tetrahedron Lett.*, 0000 (1980).
(43) H. Onone, I. Moritani, and S. Murahashi, *Tetrahedron Lett.*, 121 (1973).
(44) B. M. Trost and E. Keinan, *Tetrahedron Lett.*, 0000 (1980); J. Godschalx and J. K. Stille, *ibid.*, 0000 (1980).
(45) (a) B. M. Trost and J. P. Genet, *J. Am. Chem. Soc.*, **98**, 8516 (1976); (b) B. M. Trost and E. Keinan, *J. Org. Chem.*, **44**, 3451 (1979).

Equation 19 summarizes a likely mechanistic path.

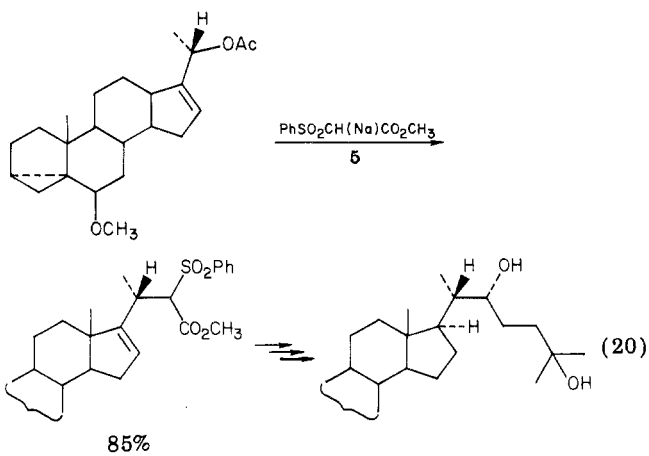


(19)

When coordination of palladium occurs on the face of the olefin distal to the acetate, palladium displaces the acetate with inversion to give the π-allyl complex. Note that the regiochemistry of the starting allyl acetate is lost in this step—a fact that provides enhanced synthetic flexibility. The regioisomeric nature of the product is independent of the regioisomeric nature of the starting material. Whichever regioisomeric allyl derivative is more readily available can become the starting material. The regioselectivity in the product is determined by a combination of factors: (1) the nature of the nucleophile; (2) the nature of the substituent on the π-allyl unit; and (3) the nature of the ligands on palladium. The nucleophile attacks the π-allyl cationic complex on the face opposite to that occupied by palladium at either site "a" or site "b". The double inversion (inversion in the palladium-assisted ionization and in the nucleophilic addition) creates a net retention for this alkylation process. The ability for amines to lead to stereochemical scrambling apparently relates to their coordinating ability to palladium which enhances syn–anti interconversions and coupling by both retention and inversion mechanisms.[45]

Application of Catalytic Reaction

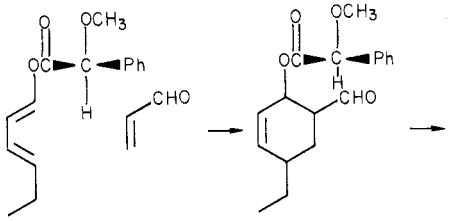
The selectivity intrinsic in these reactions make them ideal in applying to a wide variety of natural products. A stereocontrolled synthesis of the side chains of cholesterol[20] and ecdysone, the insect molting hormone (eq 20), took advantage of the stereochemical retention of



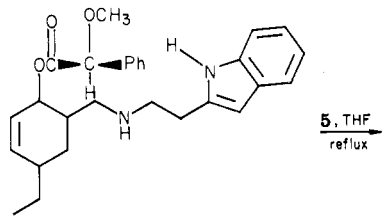
(20)

configuration for this C–C bond-forming reaction.[46b] The stereochemical features of the reaction become particularly advantageous when combined with the endo selectivity of the Diels–Alder reaction.[45a] Thus, the adduct **26**, produced optically active as a result of

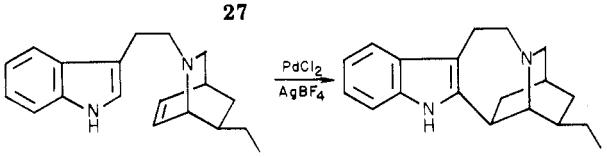
(46) (a) J. Tsuji and T. Mandei, *Chem. Lett.*, 975 (1977); also see L. E. Overman and F. M. Knoll, *Tetrahedron Lett.*, 321 (1979); (b) B. M. Trost and Y. Matsumura, *J. Org. Chem.*, **42**, 2036 (1977).



26



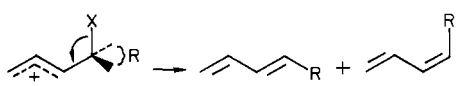
27



45% ibogamine

asymmetric induction by the *S*-mandelate group, possesses the formyl group and acyloxy group cis to each other. Use of the formyl group to construct an internal nucleophile (i.e., by reductive amination to give **27**) requires the subsequent amine alkylation to proceed with retention of configuration but with allyl inversion. Indeed, **27** cyclizes under the influence of the palladium(0) catalysts to give the isoquinuclidine which is cyclized to optically active ibogamine by a different palladium-promoted reaction.[47] This same approach was used to synthesize cantharanthine, a key component of the clinically important antitumor compounds vinblastine and vincristine.[48]

New applications of these reactions takes advantage of the fact that these π-allylpalladium cationic complexes can be considered to be allyl cations which have been stabilized by coordination to the metal. By attenuation of the reactivity of carbonium ions, reactions which were precluded may become possible or reaction courses may be grossly altered. For example, a fragmentation of the type shown in eq 21 may be precluded



(21)

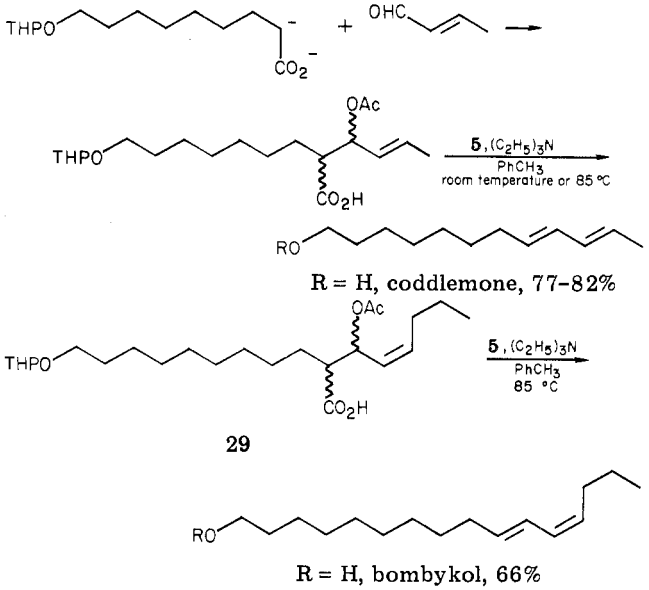
because of the reactivity of the cation or may generate stereochemical mixtures unless the stereochemistry of the starting material is defined. For example, methods to effect decarboxylative elimination of **28** require **28** to be stereohomogeneous in order to generate stereochemically pure dienes.[49] Unfortunately, the most facile entry into such substrates, the addition of the enolates of carboxylic acids or their derivatives, to carbonyl partners, produces diastereomeric mixtures.

(47) B. M. Trost, S. A. Godleski, and J. P. Genet, *J. Am. Chem. Soc.*, 100, 3930 (1978).

(48) B. M. Trost, S. A. Godleski, and J. Belletire, *J. Org. Chem.*, 44, 2052 (1979).

(49) For some methods, see W. Adam, J. Baeza, and J.-C. Liu, *J. Am. Chem. Soc.*, 94, 2000 (1972); A. P. Krapcho and E. G. E. Jahngen, Jr., *J. Org. Chem.*, 39, 1322, 1650 (1974); S. Hara, H. Taguchi, H. Yamamoto, and H. Nozaki, *Tetrahedron Lett.*, 1545 (1975); A. Eschenmoser, A. Rüttiman, and A. Wick, *Helv. Chim. Acta*, 58, 1451 (1975); J. Mülzer, G. Brüntrup, and A. Chucholowski, *Angew. Chem., Int. Ed. Engl.*, 18, 622 (1979).

Carboxylic acids **28** and **29**, obtained as diastereomeric



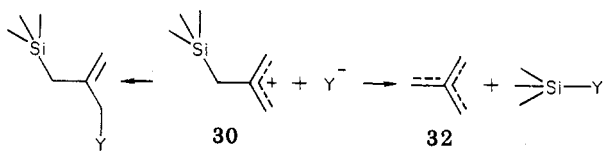
R = H, coddlemone, 77–82%

29

R = H, bombykol, 66%

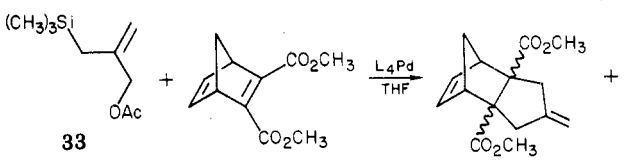
mixtures in just such a fashion, when subjected to normal decarboxylative eliminations would produce a mixture of dienes. However, palladium(0) catalysts initiate a stereoconvergent decarboxylative elimination to give predominantly the dienes with the *E* configuration at the newly formed double bond[50]—the insect sex pheromones coddlemone and bombykol.

An approach to transition-metal-complexed trimethylenemethane takes advantage of this principle. In the intermediate **30**, most facile attack is expected

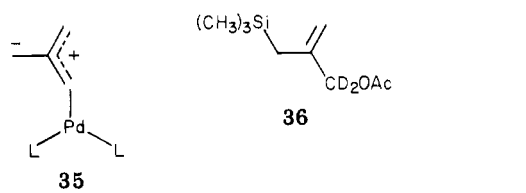


31 30 32

at carbon to give **31** rather than at silicon to give **32**. By complexing the allyl cation to palladium, this competition should become more favorable to generate **32**. Indeed, treatment of **33** with a palladium(0) catalyst,



33 34



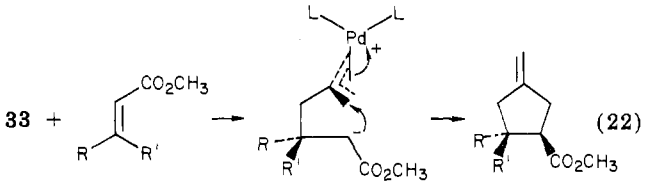
35 36

either preformed or generated in situ, in the presence of the olefin **34** as a trap led to smooth methylenecyclopentane annulation at the electron-deficient double bond.[51] The intermediacy of the trimethylenemethane

(50) B. M. Trost and J. M. Fortunak, *J. Am. Chem. Soc.*, 102, 2841 (1980).

(51) (a) B. M. Trost and D. M. T. Chan, *J. Am. Chem. Soc.*, 101, 6429 (1979); (b) unpublished observations.

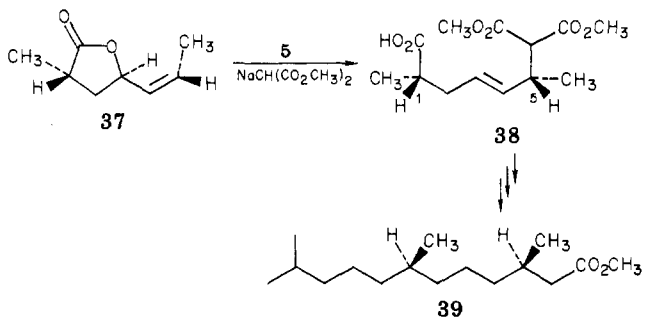
(TMM) complex **35** was in part demonstrated by the total scrambling observed when labeled precursor **36** was employed.[51b,52] The palladium complex of TMM behaves as a zwitterion as represented in **35**. The cycloaddition is rationalized as involving a conjugate addition followed by collapse to form the observed product as represented in eq 22. This scheme is also consistent



with the virtually complete retention of stereochemistry when *E* olefins are traps but only partial stereochemical retention with *Z* olefins as traps.[51]

Treatment of methylenecyclopropanes in the presence of olefins with palladium(0) catalysts also led to methylenecyclopentanes.[53] A palladium complexed TMM has been invoked to explain these results; however, direct codimerization catalyzed by palladium cannot be ruled out. Whereas cycloaddition to norbornene is observed in this case, such a reaction fails when **33** is the precursor. This clear discrepancy needs yet to be resolved.

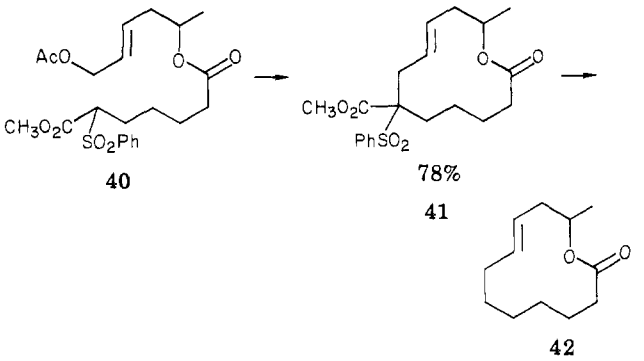
Palladium templates have promise as conformational control reagents in conformationally nonrigid systems. For example, synthesis of acyclic compounds such as **38** with chiral centers in a 1,5 relationship are difficult to obtain in a stereodefined fashion. Transfer of chirality of a vinyl lactone such as **37** in reaction with a nucleophile catalyzed by palladium represents a solution to this problem.[54] This remarkable selectivity requires that (1) ionization of **37** occurs preferentially from one conformation, (2) alkylation of the π-allylpalladium intermediate is faster than mechanisms for loss of stereochemical information, and (3) regioselective alkylation occurs at the allyl carbon distal to the carboxylate, giving the product of allyl rearrangement and retention of configuration. This example illustrates the application toward the side chain of vitamin E, **39**.



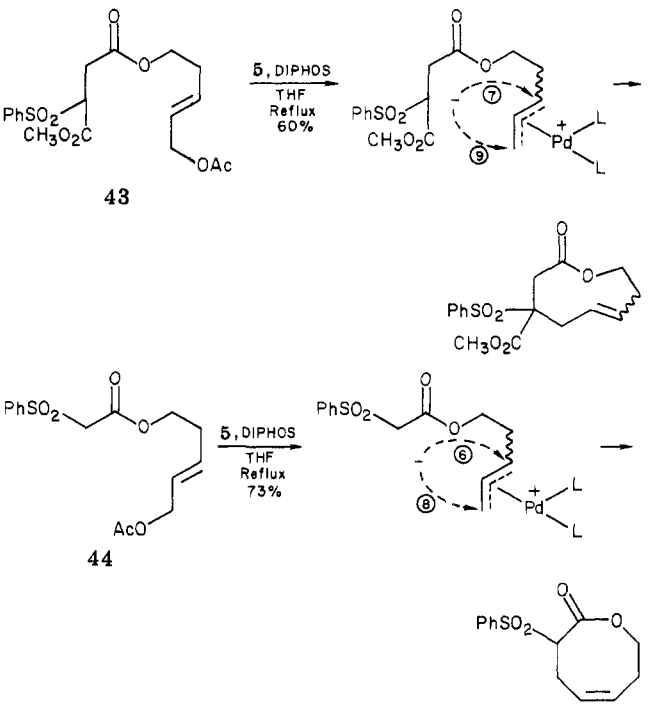
This approach to acyclic systems has much flexibility since the distance between the chiral centers can be varied by either altering the location of the substituent on the lactone or changing the size of the lactone ring.

The palladium-based reaction complements the reaction of these vinyl lactones with organocopper reagents which give products of allyl rearrangement and inversion of configuration and with lower stereochemical control.[55] Use of chiral phosphines as ligands to palladium has resulted in asymmetric induction in these allylic alkylations.[56]

This unusually high conformational control translates to intramolecular alkylations to form large rings.[57] For example, palladium-assisted intramolecular alkylation to form a 14- and a 16-membered ring occurred facilely, the latter leading to a synthesis of exaltolide, a constituent of perfumes. Exclusive formation of the 12-membered ring **41** in the palladium-initiated cyclization



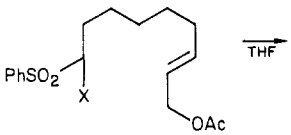
of **40** evolved into an efficient synthesis of the naturally occurring macrolide (±)-recifeiolide (**42**).[57c,58] Phoracantholides I and J, naturally occurring ten-membered-ring lactones, were available via analogous macrocyclizations via C–C bond formation. Most remarkable was the selectivity for formation of nine- and eight-membered rings in the cyclizations of **43** and **44**,



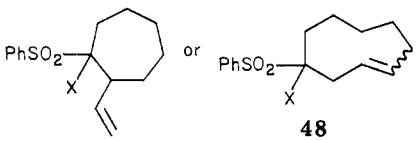
respectively, even though the usually heavily favored seven- and six-membered rings were possible.[57b,c] The

(52) B. M. Trost and D. M. T. Chan, *J. Am. Chem. Soc.*, **101**, 6432 (1979).
(53) P. Binger and U. Schuchardt, *Angew. Chem., Int. Ed. Engl.*, **16**, 249 (1977); P. Binger, M. Cetinkaya, M. J. Doyle, A. Germer, and U. Schuchardt, *Fundam. Res. Homog. Cat.*, **3**, 271 (1979). Also see G. Balavoine, C. Eskenazi, and M. Gillemot, *Chem. Commun.*, 1109 (1979); Y. Inone, T. Hibi, M. Sataki, and H. Hashimoto, *J. Chem. Soc., Chem. Commun.*, 977 (1979).
(54) B. M. Trost and T. P. Klun, *J. Am. Chem. Soc.*, **101**, 6756 (1979).
(55) B. M. Trost and T. P. Klun, unpublished observations.
(56) B. M. Trost and P. E. Strege, *J. Am. Chem. Soc.*, **99**, 1649 (1977).
(57) (a) B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **99**, 3867 (1977); (b) *ibid.*, **101**, 1595 (1979); (c) *ibid.*, **102**, 0000 (1980).
(58) B. M. Trost and T. R. Verhoeven, *Tetrahedron Lett.*, 2275 (1978).

sensitivity of the regioselectivity to substrate is highlighted by subjecting the all-carbon analogue of **43**, i.e., **45**, to the same cyclization conditions. In this case, a



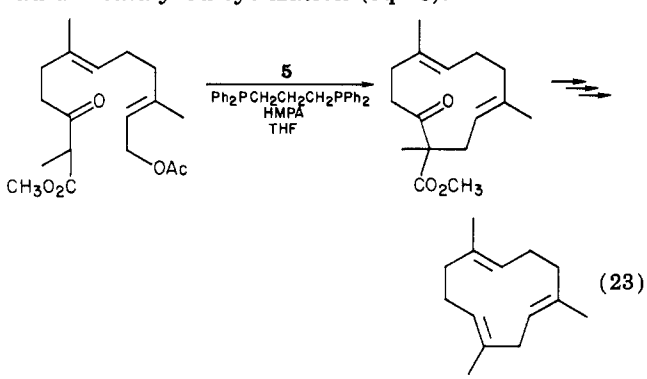
45, X = CO_2CH_3
46, X = $PhSO_2$



47 **48**

turnaround in regioselectivity was seen; the seven-membered-ring product **47** (X = CO_2CH_3) was obtained.[59] On the other hand, increasing the steric bulk of the attacking nucleophile by going from **45** to **46** enhanced formation of the nine-membered ring product. Substrate **46** produced a 3:2 ratio of seven- to nine-membered ring with **5** as the catalyst but only the nine-membered ring product **48** (X = $PhSO_2$) with the diphos catalyst **6**. Unlike virtually any other method for cyclization, this method does not show an intrinsic preference for formation of any particular ring size. On the contrary, the interplay of a number of factors—(1) palladium ligands, (2) type of nucleophile, and (3) chain substitution—controls the ring size and offers a flexibility in synthetic design not available with more classical methods.

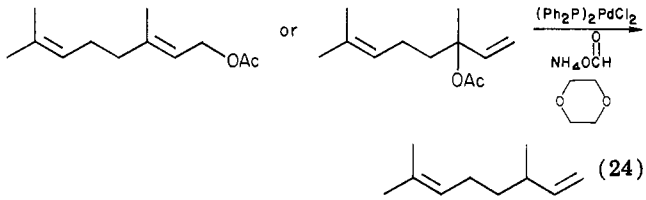
Relying on C–C bond formation as the key bond-making step in this macrolide synthesis allows this methodology to extend to carbocyclic compounds (cf. **45** and **46**). This potential has been further realized in an ingenious synthesis of the macrocyclic terpene humulene in which the key ring-forming step was a palladium-catalyzed cyclization (eq 23).[60]



(23)

(59) B. M. Trost and D. Martina, unpublished observations.

While attention has focused on attack of carbon and heteroatom nucleophiles, the nature of these intermediates offers other synthetically useful reactions. For example, hydrogenolysis of allylic acetates or phenyl ethers (eq 24) involves hydride transfer to the π-allyl-



(24)

palladium cationic intermediate.[61] An equilibration of allylic isomers in which the leaving group returns at the allylically related carbon has also been noted.[39,46,62] *O*-Allyl phosphorothionates equilibrate with *S*-allyl phosphorothiolates in the presence of **5**—a type of reaction that may be useful for heteroatom interconversion.[63] Isomerization of vinyl epoxides to dienols and β,γ-unsaturated ketones are envisioned to involve these intermediates.[64]

Conclusions

Many opportunities to alter the normal reactivity of organic molecules by transition-metal catalysis are on the horizon. Such a level of control of reactivity has immense implications in terms of the degree and kind of selectivity that can be achieved. This account summarizes just one aspect—allylic alkylations catalyzed by palladium templates—but already the ability to manipulate reactivity is evident. Applications to complex molecules appear especially promising since increased selectivity should translate to increased efficiency.

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