$$\frac{dC^{\bullet}_{OUT}}{dt} = V_{max}[A - B] \quad \text{(i)}$$

$$A = \left[K^{\bullet}_{IN}\left(\frac{C^{0}_{IN}}{2} - C^{\bullet}_{OUT}\right)\right] \Big/ \left[K^{\bullet}_{IN}\left(\frac{C^{0}_{IN}}{2} - C^{\bullet}_{OUT}\right) + K^{-}_{IN}\left(\frac{C^{0}_{IN}}{2} - C^{-}_{OUT}\right) + C^{\bullet}_{OUT} + C^{-}_{OUT}\right]$$

$$B = [K^{\bullet}_{OUT}C^{\bullet}_{OUT}] / [K^{\bullet}_{OUT}C^{\bullet}_{OUT} + K^{-}_{OUT}C^{-}_{OUT} + C^{0}_{IN} - C^{\bullet}_{OUT} - C^{-}_{OUT}]$$

V_{max} is the maximum transport rate. A similar equation (ii) holds for dC^{-}_{OUT}/dt, where in eq i all (+) exponents are exchanged against (−) and conversely. The coupled rate equations i and ii are solved simultaneously on a UNIVAC 1108 computer using the combined Runge-Kutta and Hammings numerical iteration methods. The parameters K are iterated until the calculated curves are in satisfactory agreement with the experimental data. The set of values leading to agreement with experiment is not necessarily unique, but additional data (e.g., extraction coefficients) provide reference points for choosing a reasonable set.

(12) In extraction experiments[4] performed at different concentrations of sodium mandelate and sodium chloride the extraction selectivity (+)/(−) has been found to vary from 1.22 to 1.42; the extraction efficiency changes too. Although performed in different conditions, these extraction data foreshadow the transport results for the chloride case (D. J. Cram and M. Newcomb, private communication). The present analysis[11] of our data gives $K^{+}_{IN}/K^{-}_{IN} \sim 1.1$ and $K^{+}_{OUT}/K^{-}_{OUT} \sim 1.4$ and indicates that the extraction efficiency of mandelate increases when the concentration of antiport anion increases. A more detailed discussion of the experimental and theoretical results will be given in the final account of this work.

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(15) E.R.A. No. 265 du C.N.R.S.

J. M. Lehn,* A. Moradpour, J. P. Behr
Institut de Chimie, Université Louis Pasteur
67008 Strasbourg, France[15]
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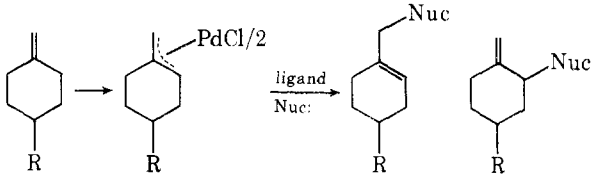
On the Regio- and Stereoselectivity of Allylic Alkylation

Sir:

The utility of allylic alkylation via π-allylpalladium complexes stems from its control of the course of the carbon-carbon bond forming reaction.[1,2] We have established that the nucleophile bonds to the face of the π-allyl unit opposite to palladium.[3] In extending our studies to cyclic compounds, we discovered a remarkable regioselectivity and stereoselectivity in methylenecyclohexane derivatives.[4]



(1)

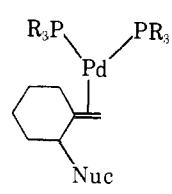
1

Treatment of **1** (R = H) with the anions derived from methyl methylsulfonylacetate, methyl phenylsulfonylacetate, methyl phenylthioacetate, and methyl malonate in the presence of hexamethylphosphorus triamide (**2**) leads to substitution at the primary rather than the secondary carbon atom (see eq 1 and Table I). On the other hand, utilizing a bulky activating ligand, such as tri-*o*-tolylphosphine (**3**) leads to predominate reaction at the secondary carbon atom.[5] At present, the reaction is best considered as a nucleophilic attack on η^3-allylpalladium cationic complexes.[2a,6] Thus, this selectivity may be attributed to the stability of the presumed initial product of alkylation—the olefin-palladium π complexes **4** and **5**[7]—compared to the steric hindrance to the approach of the nucleophile. Normally, the

Table I. Regioselectivity of Allylic Alkylation[a]

π-Allyl	Phosphine[b]	Alkylating agent[c]	Yield[d]	Attack at[i] Primary (%)	Attack at[i] Secondary (%)
1 R = H	HMP	$CH_3SO_2CH_2CO_2CH_3$	58	100	...
1 R = H	HMP	$CH_3SO_2CH_2CO_2CH_3$	90[e]	100	...
1 R = H	TOT	$CH_3SO_2CH_2CO_2CH_3$	90	15	85
1 R = H	HMP	$PhSO_2CH_2CO_2CH_3$	34	71	29
1 R = H	TOT	$PhSO_2CH_2CO_2CH_3$	83	26	74
1 R = H	HMP	$PhSCH_2CO_2CH_3$	..[f]	57	47
1 R = H	TOT	$PhSCH_2CO_2CH_3$	18	<1	>99
1 R = H	HMP	$CH_2(CO_2CH_3)_2$	34	79	21
1 R = H	TOT	$CH_2(CO_2CH_3)_2$	57	26	74
1 R = t-C_4H_9	HMP	$CH_3SO_2CH_2CO_2CH_3$	31	95	5
1 R = t-C_4H_9	TOT	$CH_3SO_2CH_2CO_2CH_3$	52[g]	45	55
1 R = t-C_4H_9	HMP	$CH_2(CO_2CH_3)_2$	95	63	37
1 R = t-C_4H_9	TOT	$CH_2(CO_2CH_3)_2$	83[h]	21	79

[a] All reactions were carried out at room temperature in DMSO as solvent unless otherwise specified. [b] HMP = hexamethylphosphorus triamide. TOT = tri-*o*-tolylphosphine. [c] The anions were generated by treatment of the active methylene compound with sodium hydride in the solvent of the reaction. [d] Yields are for isolated purified compounds. [e] THF was employed as solvent in this run. [f] Not determined. [g] Ligand and complex were heated at 70° for 1.5 hr. [h] Ligand and complex were heated at 60° for 1.5 hr. [i] Ratio determined by NMR spectroscopy of the crude product as well as the purified product utilizing the ratio of the absorptions for the vinyl protons at δ 5.4–5.6 for the product of primary attack and δ 4.5–5.0 for the product of secondary attack.



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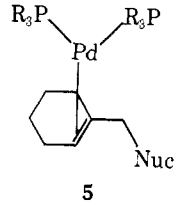
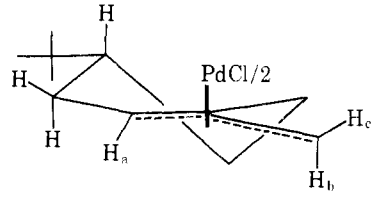


5

nucleophile prefers to approach at the less-hindered end of the π-allyl system to generate **5**.[2] However, if the palladium bears very bulky phosphines, the steric congestion that develops in the transition state for the formation of **5** increases the energy of this transition state such that the nucleophile is "directed" toward the more substituted carbon to generate the less congested olefin-palladium π complex **4**.[8]

Complex **1** (R = t-C_4H_9) shows similar behavior. Furthermore, it allows determination of the stereochemistry of alkylation at a ring carbon. NMR data[9] indicate this complex to be approximately a 3:2 mixture of **6** and **7** (**6**, H_a (δ 4.26, bs), H_b (2.67, bs), H_c (3.60, bs); **7**, H_a (δ 4.18, d, J = 7 Hz), H_b (2.57, bs), H_c (3.60, bs). The splitting of H_a in these complexes is in accord with the major isomer having a dihedral angle between this proton and the adjacent methy-



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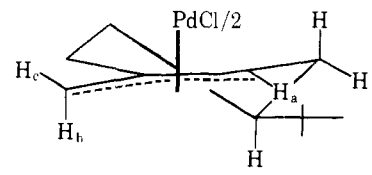
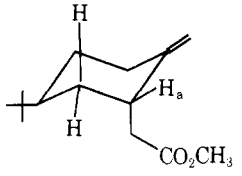


7

lene hydrogens of about 60° and the minor isomer having a dihedral angle of this proton and one of the protons of the adjacent methylene group of about 20° [10] In the unsubstituted complex (**1**, R = H), this proton appears as a doublet (J = 3 Hz) at δ 4.20 which would be in agreement with a rapid interconversion of the two half-chair forms. The alkylation product of **1** (R = t-C_4H_9) with malonate utilizing **3** as the activating ligand was decarbomethoxylated (LiI, NaCN, DMF, 110°) to give an 18:1 mixture (by VPC)[11] of two isomers resulting from attack at the secondary carbon. The major isomer, isolated pure by preparative VPC, showed an allylic methine H_a at δ 2.94 with only small coupling constants to the adjacent ring methylene protons indicative of an equatorial, not an axial proton, in the proton NMR spectrum.[9] Thus, structure **8** was assigned. Indepen-



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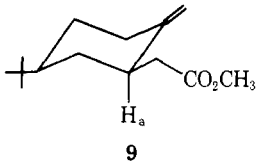
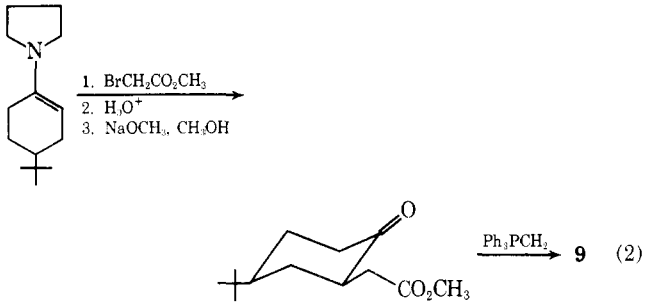


9

dent synthesis of the alternative isomer **9** from 4-*tert*-butylcyclohexanone (eq 2) confirms this conclusion.[12] The com-

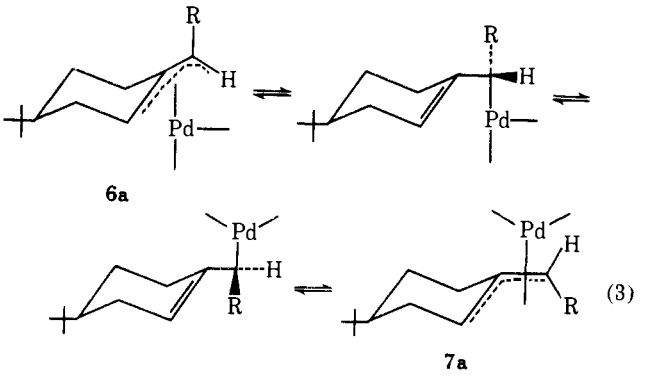


(2)

pound obtained by this latter route, which is different spectrally and chromatographically from **8**, should be the thermodynamically more stable cis isomer **9**. Comparison of **9** with the minor product from the allylic alkylation indicates their identity.

These results demonstrate that allylic alkylation shows a ratio for axial vs. equatorial bond formation of 18:1. Comparison to enolate alkylations, which show a similar tendency for axial bond formation, is striking.[12,13] Attributing both results to stereoelectronic control in which axial bond formation leads to a chair cyclohexane ring whereas equatorial bond formation leads to an initial boat conformation appears reasonable.

At first glance the stereochemistry of bond formation at the ring carbon may appear at odds with the stereospecificity of bond formation at an acyclic carbon. This apparent discrepancy can be understood if it is realized that interconversion of the allylic palladium cationic complexes through the σ complex (eq 3)[14,15] may be fast relative to alkylation. In such a case, the stereochemistry of the alkylation at the ring carbon is independent of the stereochemistry of the π allyl complex and is determined by the relative rates of reaction of the two complexes **6a** and **7a**. Since the nucleophile approaches trans to palladium, **7a** must react more rapidly. It should be noted that such a process does not affect the stereochemistry at the acyclic carbon relative to palladium. Reaction of **6a** or **7a** at the acyclic end of the π-allyl unit trans to the palladium leads to the same stereoisomer. Synthetically, the preferential formation of the less stable axial isomer enhances the utility of these intermediates for alkylations.



6a

7a

(3)

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References and Notes

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(6) Subjection of the independently generated cationic complex from 1 (R = H) and diphos to reaction with the anion of methyl methylsulfonylacetate gave the identical product distribution as the normal alkylation procedure. For cationic complexes see M. Oslinger and J. Powell, *Can. J. Chem.*, **51**, 274 (1973); D. L. Tibbetts and T. L. Brown, *J. Am. Chem. Soc.*, **92**, 3031 (1970); K. Vrieze, P. Cossee, A. P. Praat, and C. W. Hilbers, *J. Organomet. Chem.*, 11, 353 (1968); K. Vrieze, A. P. Praat, and P. Cossee, *Ibid.*, **12**, 533 (1968); J. M. Jenkins, M. S. Lupin, B. L. Shaw, and A. C. Smithers, *Proc. Int. Conf. Coord. Chem.*, **9**, 184 (1966).

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(8) Alternatively, a related kinetic argument may be considered. The η^3-allylpalladium complex probably possesses the palladium unsymmetrically disposed with respect to the two ends of the π-allyl system with it lying closer to the less substituted end (K. Oda, N. Yasuoka, T. Ueki, N. Kasai, and M. Kakudo, *Bull. Chem. Soc. Jpn.*, **43**, 362 (1970)). Consequently, alkylation at the more substituted end minimizes loss of bonding energy. While the major controlling factor with normal ligands will be steric hindrance to approach of the nucleophile (and therefore preference for reaction at the less substituted end of the π allyl system), if the asymmetry of the complex increases, the cost in loss of bonding energy between palladium and carbon can become predominant. Increasing the steric bulk of the phosphine ligands will increase this asymmetry. No evidence exists to invoke σ complexes. In any event, rationalization involving them as intermediates can be considered as extremes of the above two cases.

(9) Obtained at 270 MHz.

(10) For the nonplanarity of the substituents of the π allyl system see R. Mason and A. G. Wheeler, *J. Chem. Soc. A*, 2543 (1968).

(11) On a ¼ in. × 8 ft 10% DC-710 on Chromsorb W, injector 215°, detector 215°, column 175°, flow rate 150 cm³/min. Retention times: compound **8**, 4.6 min; **9**, 5.35 min; product of primary attack 7.95 min.

(12) Cf. H. O. House, B. A. Tefertiller, and H. D. Olmstead, *J. Org. Chem.*, **33**, 935 (1968); H. E. Baumgarten, P. L. Creger, and C. E. Villars, *J. Am. Chem. Soc.*, **80**, 6609 (1958).

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(16) Camille and Henry Dreyfus Teacher-Scholar 1970–1975.

Barry M. Trost,*[16] Paul E. Strege

Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

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