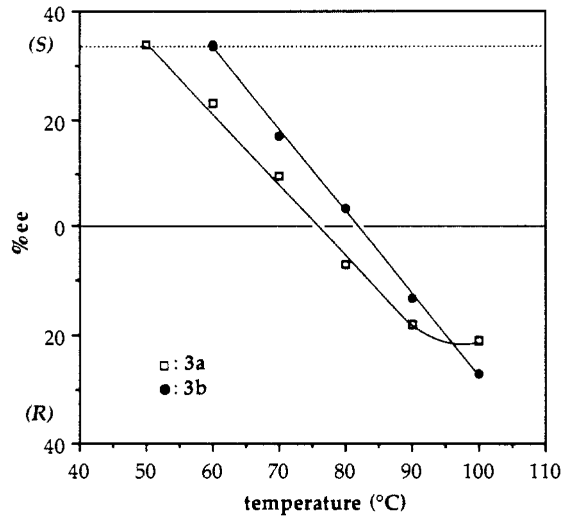

Figure 1. Temperature dependence of the stereochemistry of the cross-coupling products **3a** and **3b** derived from **1a** (34% ee).

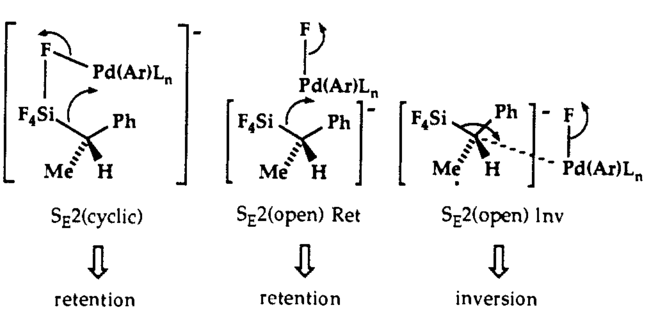

Figure 2. Proposed transition-state models for transmetalation.

When (*S*)-1-(4-methoxyphenyl)-1-(trifluorosilyl)ethane (**1b**) (18% ee) was allowed to react with phenyl triflate (**2c**) in THF at 60 °C, (*R*)-1-(4-methoxyphenyl)-1-phenylethane (**3c**) of 9% ee was obtained in 35% yield. Thus, the total stereochemistry was still retention, but an electron-donating group X of **1** was found to sharply diminish the % ee of the coupled product.

The palladium-catalyzed cross-coupling of an organosilane with a triflate is assumed to involve a pentacoordinate silicate which can be generated by the nucleophilic attack of fluoride ion to an organosilicon compound.[8] The transmetalation reaction between the silicate and an arylpalladium complex gives an intermediate (1-phenylethyl)(aryl)palladium species, whose reductive elimination affords a coupled product. Since the reductive elimination of a diorganopalladium complex takes place with retention of the configuration of the alkyl ligand,[9] the observed stereochemical outcome of the silicon-based coupling reaction should reflect that of the transmetalation step in a catalytic cycle. Although transmetalation is one of the important basic reactions of transition metal catalyzed transformations, its mechanistic aspect remained relatively unexplored. The stereochemistry reported for alkyl transfer from mercury to palladium[10] is retention of configuration, and that for the transmetalation in HMPA of a chiral benzyltin compound with an acylpalladium complex is inversion.[11] Our results clearly show for the first time that the stereochemistry of transmetalation is decisively influenced by the reaction temperature and the solvent used. To explain the above observations we consider three transition-state models for the transmetalation as illustrated in Figure 2. The retention of configuration in THF at low temperatures may be ascribed to a cyclic four-centered transition state (S$_E$2 (cyclic))[12] which should be promoted by a fluoride bridge. Hereby coordinative unsaturation of a pentacoordinate silicate[13] is essential for the smooth coupling reaction. Since a large excess of TBAF (6 equiv), which leads to coordinatively saturated hexacoordinate silicates,[14] completely suppressed the reaction of **1a** with **2b** at 60 °C, an alternative model (S$_E$2 (open) Ret)[15] seems unlikely, wherein the coordinative unsaturation of silicon species is dispensable. At higher temperatures or in HMPA-THF solvent, the fluoride bridge is cleaved to induce a back-side attack of the palladium complex, leading to the inversion of configuration (S$_E$2 (open) Inv).[16] The inversion observed for the reaction in HMPA-THF is fully consistent with the stereochemistry reported by Stille and Labadie for the reaction of the chiral benzyltin compound.[11]

In summary, we have found that the stereochemistry of the cross-coupling reaction using organosilicon compounds could be controlled from almost complete retention to inversion by tuning the reaction temperature and the solvent. The method described herein allows us to synthesize a wide range of optically active molecules. Studies on its synthetic application as well as mechanistic details are currently in progress in our laboratory.

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(8) We have observed that [18-crown-6-K]$^+$,[Ph$_n$SiF$_{5-n}$]$^-$ (n = 1-3) (Damrauer, R.; Danahey, S. E. *Organometallics* **1986**, *5*, 1490) underwent the cross-coupling reaction and reactivity order was parallel to that of Ph$_n$SiF$_{4-n}$. This strongly suggests the participation of a pentacoordinate silicate as an active species in the silicon-based cross-coupling reaction: Hatanaka, Y.; Hiyama, T., to be published.

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The Equilibrium Constant for the Interconversion of Homocub-1(9)-ene and Homocuban-9-ylidene[1]

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Received March 12, 1990

Insertions of singlet carbenes into adjacent carbon-hydrogen and carbon-carbon bonds are normally irreversible.[3] Recently, highly strained alkenes have been found for which the reversion to the divalent state is energetically possible.[4] A spectacular example is the work of Eaton and Hoffmann in which 9-phenyl-1(9)-homocubene was shown to revert to the related carbene.[5] We have previously demonstrated that the parent carbene (**1**) and bridgehead alkene (**2**) interconvert using **3** and **4** as precursors.[6] In this communication we use a combination

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[†] The Ohio State University.

[‡] Princeton University.

(1) It gives us the greatest pleasure to dedicate this paper to Prof. Dr. Wolfgang Kirmse on the occasion of his 60th birthday. This work was supported both at Ohio State (Grant CHE-8814950) and Princeton (Grant CHE-8800448) by the National Science Foundation.

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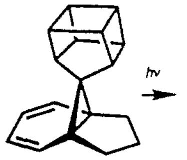

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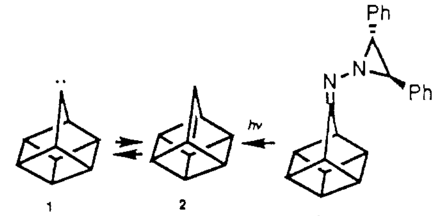

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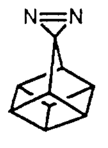
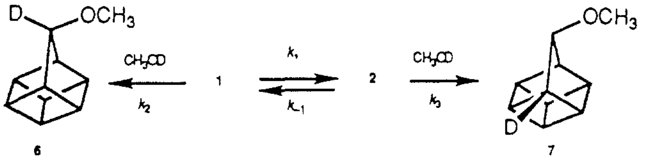


5

of chemical trapping and laser flash photolysis (LFP) techniques to estimate the equilibrium constant for the interconversion of **1** and **2**.

As neither **3** nor **4** was suitable for LFP work, the diazirine **5** was used instead.[7] Irradiation of **5** in benzene/CH_3OD led to **6** and **7**, the products of trapping of intermediates **1** and **2**.



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On photolysis of diazirine **5**, a plot of **7**/**6** vs $[CH_3OD]$ can be generated. It is linear, with a positive slope. If we assume that alkene **2** is formed first from this precursor, the conditions of the steady-state assumption lead to eq 1.

$$\frac{7}{6} = \frac{k_3k_1}{k_{-1}k_2} + \frac{k_3[\mathrm{CH_3OD}]}{k_{-1}} = 0.20 + 0.02[\mathrm{CH_3OD}] \qquad (R = 0.94)$$

$$k_1/k_2 = 8.1 \text{ and } k_{-1}/k_3 = 41 \qquad (1)$$

A similar treatment using published data on the photolysis of diene **3**[6b] yields consistent values. Here we assume that carbene **1** is formed first and that the steady-state assumption applies to generate eq 2.

$$\frac{6}{7} = \frac{k_2k_{-1}}{k_1k_3} + \frac{k_2[\mathrm{CH_3OD}]}{k_1} = 4.3 + 0.15[\mathrm{CH_3OD}] \qquad (R = 0.99)$$

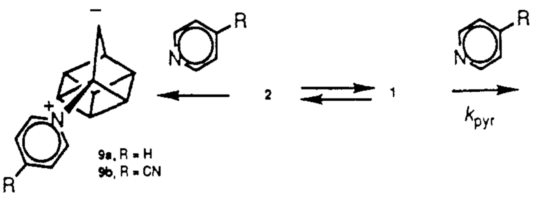
$$k_1/k_2 = 6.7 \text{ and } k_{-1}/k_3 = 29 \qquad (2)$$

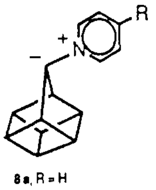
Although convenient for the steady-state analysis, the assumptions used in developing eqs 1 and 2 are not necessary for the derivation of K. The data demonstrate that precursors **3** and **5** decompose to different nonequilibrium mixtures of **1** and **2**, but do not require that each precursor exclusively form either carbene **1** or alkene **2** initially. However, at the lowest $[CH_3OD]$ used (ca. 1 M, oligomeric alcohol) the product ratios obtained with **3** or **5** as precursor converge to a common value (**7**/**6** = 0.20–0.23). Thus, when $[CH_3OD] < 1$ M, equilibration between **1** and **2** must be complete. The ratio of **7**/**6** formed at equilibrium is given in eq 3.

$$7/6 = K(k_3/k_2) = 0.20\text{–}0.23 \qquad (3)$$

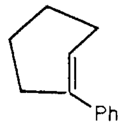
Except for the extremely stable dimethoxy- and difluorocarbene, all carbenes react with oligomeric methanol with rate constants within a factor of 3 of diffusion control ($k_{\mathrm{dif}} = (1\text{–}2) \times 10^{10}$ M^{-1} s^{-1}).[8] As carbene **1** shows no obvious stabilization, and as kinetic isotope effects in singlet carbene insertion reactions are typically quite small,[8,9] it is reasonable to assume that k_2 is close to k_{dif}. This means that $k_3/k_2 \leq 1$, and the equilibrium constant K must be $\geq$0.20–0.23.

LFP of **5** in the presence of pyridine or *p*-cyanopyridine produces transient spectra [$\lambda_{\max}(\mathrm{pyr})$ = 410 nm; $\lambda_{\max}(\mathrm{CNpyr})$ = 425 nm], attributable to the ylides **8a** and **8b**.[10] The spectra are very similar to those observed from reactions of other dialkyl- and alkylchlorocarbenes with pyridine.





8a, R = H
8b, R = CN



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Attribution of the transient produced by LFP to **9a**/**9b** (from capture of alkene **2**) is problematic, as this 1,3-dipole is not expected to have a chromophore different from isolated carbanions and pyridinium salts. Furthermore, in our hands *trans*-1-phenylcyclohexene (**10**; produced by LFP of the cis isomer)[11] which is easily monitored at 380 nm, does not react with 1 M pyridine at a measurable rate, nor does it produce a new detectable transient species in the presence of pyridine.

The yield of ylide produced in a LFP experiment is proportional to the change in optical density of the sample at 410 nm following the laser pulse, and is denoted by ϕ. Of course $\phi = 0$ when [pyridine] = 0, but ϕ increases steadily as [pyridine] increases, achieving a constant value when [pyridine] reaches 0.04–2.0 M. When [pyridine] > 0.04 M, the equilibrating pair of intermediates is completely diverted to ylide. The yield of ylide (ϕ) is reduced upon LFP of **5** in the presence of constant [pyridine] (0.04 M) and variable concentrations of quenchers of **1** and **2**. Under these conditions Stern–Volmer plots are linear, as predicted by eqs 4 and 5,[12] in which k_{alk} is the absolute rate constant of the reaction of carbene **1** with an alkene.[13]

$$\left(\frac{\phi^\circ}{\phi}\right)_{\mathrm{MeOD}} = 1 + \frac{k_2 + k_3K}{k_{\mathrm{pyr}}[\mathrm{pyridine}]}[\mathrm{CH_3OD}] \qquad (4)$$

$$\left(\frac{\phi^\circ}{\phi}\right)_{\mathrm{alk}} = 1 + \frac{k_{\mathrm{alk}}}{k_{\mathrm{pyr}}[\mathrm{pyridine}]}[\mathrm{alkene}] \qquad (5)$$

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[7] CAUTION! Compound **5** is explosive and must be used with the greatest care. N.C. would like to thank Prof. J. E. Jackson for helpful discussions of the properties of **5**.

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[12] A derivation of this equation is available as supplementary material. This equation assumes only that **1** and **2** are completely at equilibrium when $[CH_3OD] < 1$ M. This is the conclusion from product studies using **3** and **5** as precursors. Equation 6 does not assume which intermediate or mixture of intermediates (**1** and **2**) is formed first upon decomposition of **5**.

[13] Equation 5 assumes that only carbene **1** reacts with alkenes. Equations 4–6 assume that only carbene **1** reacts with pyridine. These assumptions seem reasonable as the optical yield of ylide **8a** is comparable to that observed for other carbenes.

J. Am. Chem. Soc. 1990, 112, 7796-7797

Table I. Relative Reactivities of Homocuban-9-ylidene (**1**) Compared to That of PhCCl[8]

reactant	**1** (25 °C)	PhCCl (25 °C) (k, $M^{-1}\ s^{-1}$)
methanol	3.3	3.8 (1.3×10^9)
tetramethylethylene	1.9	0.2–0.4 ($(0.7–1.2) \times 10^8$)
pyridine	1.0	1.0 (3.4×10^8)

Stern–Volmer analysis gives the relative reactivities of **1** toward various quenchers (Table I). The selectivity of **1** is comparable to that of chlorophenylcarbene[8] and is rather insensitive to temperature.

The relative reactivity of carbene **1** toward CH_3OD and tetramethylethylene determined by LFP and product analysis is in good agreement; $k_2/k_{tme} = 2.2$ (chemical analysis) and 1.7 (LFP). The relative rate data obtained by LFP used pyridine and CH_3OD concentrations (>0.2 M) sufficient to ensure complete oligomerization of the alcohol and were therefore consistent with the conditions used in the product analysis.

At [pyridine] = 0.05 M, the observed absolute rate constant for formation of ylide **8a**, k_{obs}, is given by eq 6.[12]

$$\frac{k_{pyr}[\text{pyridine}]}{K + 1} = k_{obs} \text{ or } K = \frac{k_{pyr}[\text{pyridine}]}{k_{obs}} - 1 \qquad (6)$$

The maximum value of K is defined by the maximum possible value of k_{pyr} ($\leq 5 \times 10^9\ M^{-1}\ s^{-1}$)[13] and the minimum value of k_{obs} ($\geq 5 \times 10^7\ s^{-1}$) determined by LFP. Thus, at +25 °C, K is bracketed as in eq 7.[15]

$$0.23 \leq K \leq 4 \qquad (7)$$

Supplementary Material Available: Derivations for eqs 4–6, preparation of **5**, plots of the dependence of the products formed from **1** and **2** on [CH_3OD] for the decomposition of both **3** and **5**, transient spectra of **8a**,**b**, the absolute rate of formation of **8a**, and Stern–Volmer plots (14 pages). Ordering information is given on any current masthead page.

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(14) Values of k_{pyr} for several carbenes are known[10] and never exceed $5 \times 10^9\ M^{-1}\ s^{-1}$.

(15) Any reaction of **2** with pyridine to produce an invisible dipole (**9**, for example) will raise this value. This is not considered likely as the yield of **9a**/**9b** is comparable to that realized with other carbenes.

Biocompatible Catalysis. Enzymic Reduction of Metalloporphyrin Catalysts in Phospholipid Bilayers

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Received January 8, 1990
Revised Manuscript Received July 2, 1990

Models of the active-site chemistry of heme-containing monooxygenases such as cytochrome P-450 have attracted sustained attention for over a decade. Comparisons of the enzyme and synthetic metalloporphyrins have established that the catalytic cycle involves substrate binding at the active site, reduction of the unusual iron(III) thiolate to iron(II), and binding and reductive cleavage of molecular oxygen to generate a high-valent iron–oxo species responsible for substrate oxidation.[1] The two electrons required for oxygen activation are provided by NADPH through a coupled electron transfer flavoprotein, cytochrome P-450 reductase, and/or cytochrome b_5.[2a]

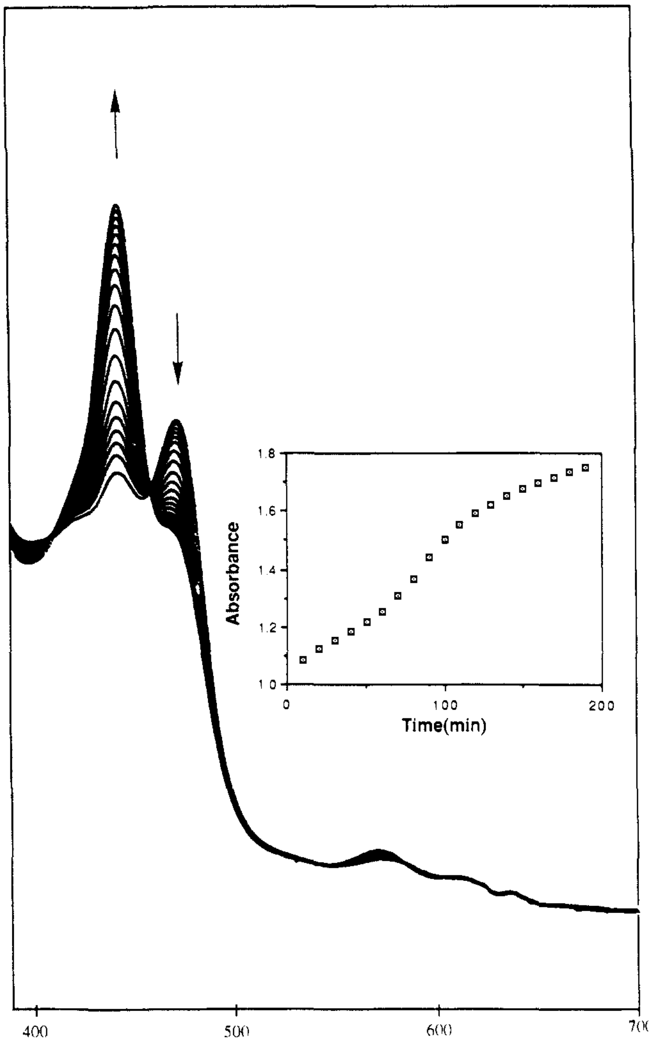

Figure 1. Visible spectral changes observed in a 0.5-cm cuvette during the anaerobic reduction of Mn^{III}(ChPCl) (I) (2.4×10^{-5} M) by a pyruvate (4.2×10^{-2} M)/pyruvate oxidase (4.8×10^{-7} M) system in the presence of amphiphilic flavin (II) (4.8×10^{-5} M) in DPPC (2.4×10^{-3} M) vesicles at pH 6 (1.6 mL of 0.05 M potassium phosphate buffer containing 0.01 M $MgCl_2$ and 0.1 M KCl). Measurements were taken every 10 min after the addition of sodium pyruvate. Inset: time course of the reaction monitored by the increase in absorbance at 440 nm.

Cytochrome P-450 and the reductases are integral membrane proteins.[2b] While numerous catalytic systems mimicking the oxygen-transfer step of cytochrome P-450 have been described, model systems designed to understand the electron-transfer steps and the role of the membrane environment in the overall enzymatic process are few in number.[3,4] We have recently reported the design and characterization of a membrane-spanning porphyrin that associates with phospholipid bilayers and catalyzes the oxygenation of sterols and polyunsaturated fatty acids with remarkable regioselectivity.[4] We describe here a multicomponent catalytic vesicular assembly in which electrons derived from the enzymic decarboxylation of pyruvic acid serve to reduce a synthetic, membrane-spanning manganese(III) cholesteryl porphyrin and to mediate subsequent oxygen activation and transfer.

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