herence transfer[5,8] are shown in Figure 1. The signal to noise ratios (S/N) of the two spectra are comparable, but the directly detected ^{15}N spectrum was obtained with 10-fold greater volume of sample and 35-fold longer time. After correction for (a) different acquisition times, (b) relative sample volumes, (c) the INEPT enhancement factor,[10] and (d) the total intensity of the doublets in Figure 1B, the enhancement between the direct and indirect detection is found to be about 1230, compared to the theoretical 961.[11] The S/N of the ^{15}N projection of a two-dimensional data set gives a similar value for the sensitivity gain. The line width of the conventional amide proton spectrum of I is very broad (Figure 1D), because of ^{14}N quadrupolar relaxation. The sharpness of the ^{15}N satellites suggests additionally that much more precise NMR measurements of the proton spectra of amides are possible by this method.

Application of this method to nitrogen and proton NMR of amide resonances of larger peptides in water has considerable potential. Sensitivity is usually at a premium for such materials. The resulting two-dimensional spectra contain the $^1H/^{15}N$ connectivity information, have substantially improved separation of ^1H signals otherwise at equal shifts, and permit better determination of coupling constants because of the signal separation and because of the narrower lines of ^{15}N multiplets compared to the ^{14}N equivalents. These features are illustrated by the spectrum of thymosin α_1, a peptide implicated in the differentiation of T cells.[12] The conventional proton spectrum of the amide region, including the 28 peptidic amide proton signals, falls within 0.65 ppm, preventing the discrimination of any detail (Figure 2A). The two-dimensional $^1H/^{15}N$ spectrum (Figure 2B) shows a number of clearly resolved $^3J(H'-H^\alpha)$ couplings. The analysis of such couplings is important for determining the solution conformation of the peptide.

A further application of this experiment is the sensitive observation of labeled materials, with very high selectivity for the proton attached to the labeled nitrogen. Using this method we have been able to observe the resonance of a single amide proton in a highly overlapped region of more than 100 amide resonances from a protein/peptide complex of 22 000 daltons,[13] at 1.5 mM concentration in 5-min acqusition time. These techniques also present new opportunities for using stable isotope materials in studies of the metabolism of nitrogen, as has been suggested previously for ^{13}C studies.[14]

The demonstration of a 1000-fold sensitivity increase via heteronuclear multiquantum coherence transfer substantially reduces the restrictions on ^{15}N NMR arising from low sensitivity for compounds in which such coherence transfer can be obtained.[15] It may be expected that important enhancements, though less dramatic, can be observed for other nuclei (e.g., ^{13}C, ^{29}Si, and ^{113}Cd).

Note Added in Proof. Expected enhancements have been experimentally observed for several other nuclei.

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Registry No. 2-Pyrrolidinone, 616-45-5; thymosin α_1, 69521-94-4.

Mechanistic Duality in Cyclialkylation of Alkenylmetal Derivatives[1]

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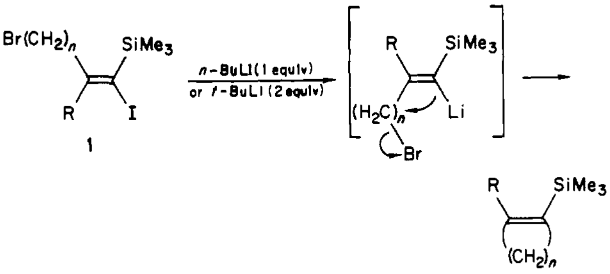
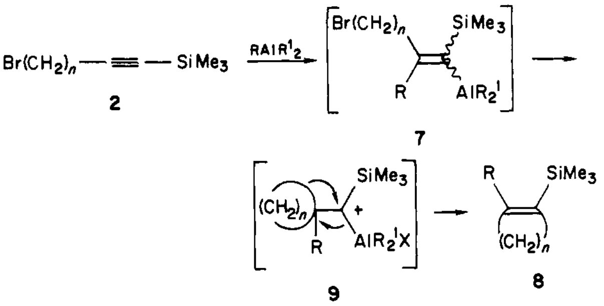
Received June 4, 1984

We have recently reported two cyclization reactions proceeding via [1-(trimethylsilyl)-1-alkenyl]metals containing a halogen leaving group.[3] On the basis of the available data, we suggested that the reaction of **1** with either *n*-BuLi or *t*-BuLi might be a σ-type cyclization process (eq 1), whereas that triggered by treatment of haloalkylsubstituted 1-(trimethylsilyl)-1-alkynes (**2**) with *i*-Bu_2AlH, $Me_3Al–Cl_2ZrCp_2$, or $Cl(H)ZrCp_2$ followed by $AlCl_3$ might be a π-type cyclization process, e.g., eq 2.



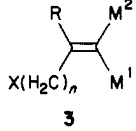
(1)



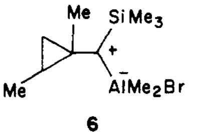
(2)

a, $n = 2$; b, $n = 3$; c, $n = 4$; R = H or C group; R^1 = C group

We now present data that not only support the above-mentioned mechanistic duality but reveal some striking differences between the two processes summarized in Table I. Perhaps more significantly, we find that the π-type process is of considerable generality with respect to the two metals of 1,1-dimetalloalkenes (**3**), providing a facile synthesis of cycloalkenylmetals containing metals readily replaceable with various electrophiles, such as halogens.



3



6

M^1 = Al, Zr, Zn, or Si;
M^2 = Si, Al, Zn, or Zr;
R = H or C group;
X = halogen

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[10] In theory, the advantage of INEPT should be 10-fold.[2] We achieve experimentally a factor of 8.5.

[11] The third-power dependence on (γ_H/γ_N) arises from the difference in spin polarization, magnetic moment, and detection frequency of the nuclei. We have neglected adjustments for instrumental effects such as differences in the Q factors of probes used (Abragam, A. "The Principles of Nuclear Magnetism"; Oxford University Press: Oxford, England, 1961; p 83) or for integrated intensities.

[12] White, A. In "Biochemical Actions of Hormones"; Academic Press: New York, 1980; Vol. VII, pp 1–46. Felix, A. M.; Heimer E. P.; Wang, C.-T.; Lambros, T. J.; Swistok, J.; Ahmad, M.; Roszkowski, M.; Confalone, D.; Meienhofer, J.; Trzeciak, A.; Gillessen, D. In "Peptides; Structure and Function", Proceedings 8th American Peptide Symposium; Hruby, V. J., Rich, D. H., Eds.; 1983; pp 889–898. Shift correlation maps for several smaller peptides have also been obtained.

[13] Live, D. H.; Breslow, E.; Davis, D. G.; Cowburn, D., unpublished results.

[14] Sillerud, L. O.; Alger, J. R.; Shulman, R. G. *J. Magn. Reson.* **1981**, *45*, 142–150.

[15] Bax, A.; Niu, C.-H.; Live, D. *J. Am. Chem. Soc.* **1984**, *106*, 1150–1151.

[1] Metal Promoted Cyclization. 5. Part 4: Miller, J. A.; Negishi, E. *Isr. J. Chem.* **1984**, *24*, 76.

[2] (a) A Proctor and Gamble Fellow. (b) On leave from Ube Industries, Ltd., Ube, Japan.

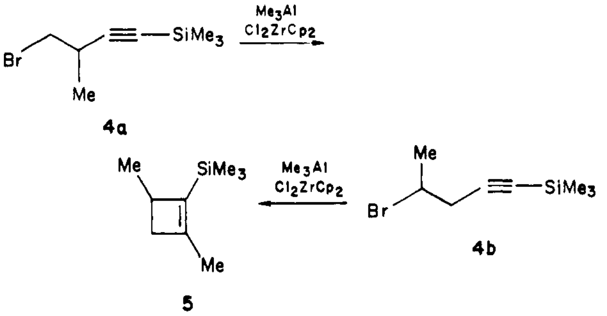
[3] Negishi, E.; Boardman, L. D.; Tour, J. M.; Sawada, H.; Rand, C. L. *J. Am. Chem. Soc.* **1983**, *105*, 6344.

Table I. Some Notable Features of σ- and π-Type Cyclization Processes[a]

feature	σ-process	π-process
M^1	Li	Al, Zr, Zn, or Si
M^2	not required	Si, Al, Zn, or Zr
alkene stereochemistry	*Z* geometry for the cyclizing groups required	unimportant
regiochemistry	regiospecific and retains regiochemistry	regioselective but nonregiospecific
ease of cyclization	facile in the cases where n = 2–5	facile if n = 1 or 2, moderate if n = 4, and slow if n = 3

[a] Based on the currently available data.

One of the most intriguing features of the cyclization of (ω-haloalkynyl)silanes shown in eq 2 is that it can proceed with rearrangement of the carbon skeleton, as represented by the conversion of **4a** to **5**.[4,5] If the reaction involves the intermediacy of a cyclopropylcarbinyl derivative and its 1,2-shift as we suggested,[3] both **4a** and its regioisomer **4b** should yield the same product, i.e., **5**. Carbometalation of **4b** with $Me_3Al–Cl_2ZrCp_2$ indeed yielded **5** as the sole cyclic monomeric product. Thus, the reactions shown in eq 3 are regioselective but nonregiospecific. The above regiochemical resultrs are not only in agreement with the intermediacy of **6**, but are difficult to accommodate by other mechanisms, such as those involving Si and/or Me migrations.



4a

5

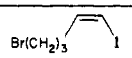
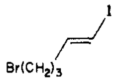
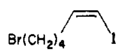
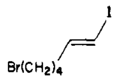
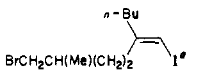
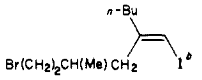
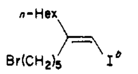
4b

(3)

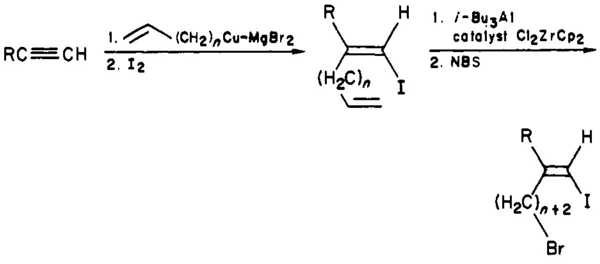
In sharp contrast with the reaction of **2a** with $Me_3Al–Cl_2ZrCp_2$, the corresponding reaction of **2b** gave only the carbometalation product **7b** (R = R^1 = Me) in ca. 60% yield. Even after 24 h at 25 °C, the extent of cyclization was at most ca. 10%, with most of **7b** remaining unchanged. We were therefore somewhat surprised to find that the reaction of **2c** with $Me_3Al–Cl_2ZrCp_2$ produced **8c**[4] (R = Me) via **7c** (R = R^1 = Me) in 53% yield (24 h, 25 °C). The observed relative ease of cyclization with respect to the ring size in these three cases, i.e., **4** >> **5** < **6**, is very abnormal. Nonetheless, it is in perfect agreement with the intermediacy of three-, four-, and five-membered ring species represented by **9**, respectively.

The results described above made it desirable to further delineate the scope and mechanism of the cyclization reaction induced by treatment of ω-haloalkenyl iodides with BuLi. That the reaction proceeds via the corresponding alkenyllithiums has been supported by the fact that the BuLi treatment at −78 °C followed by protonolysis or treatment with Me_3SiCl cleanly produces the expected protonolysis or silylated product, respectively. If the cyclization step indeed involves the proposed σ-process, it should require the cis relationship between Li and the cyclizing chain moiety at the time of cyclization. However, it should not require Si or any metal other than Li. Furthermore, such a σ-process should proceed with complete retention of regiochemistry. As the results summarized in Table II indicate, the reaction fulfills all of the above expectations. The required (*Z*)-ω-bromo-1-iodoalkenes except **10** and **11**[6] (Table II) were readily obtained via carbocupration[7] of terminal alkynes followed by hydroalumination[8]–brominolysis (eq 4). These results provide additional examples indicating that cis carbometalation of alkynes with functionalized organometals provides novel and convenient routes to cycloalkenes.[9]

Table II. Cyclialkylation Reaction of ω-Bromo-1-iodo-1-alkenes with *n*- or *tert*-Butyllithium

ω-bromo-1-iodo-1-alkene	product	isolated yield, %
 **10**	cyclopentene	85
	polymer only	
 **11**	cyclohexene	76
	polymer only	
	1-*n*-butyl-4-methyl-1-cyclohexene	56
	1-*n*-butyl-5-methyl-1-cyclohexene	75
	1-*n*-hexylcycloheptene[c]	67

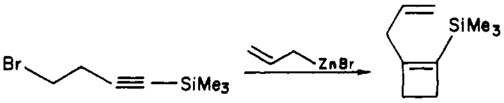
[a] Prepared by hydroboration–oxidation–bromination of (*Z*)-2-*n*-butyl-5-methyl-1-iodo-1,5-hexadiene. [b] Prepared by the procedure shown in eq 4. [c] Riemschneider, R.; Hoyer, G.-A. *Monatsh. Chem.* **1968**, *99*, 642.



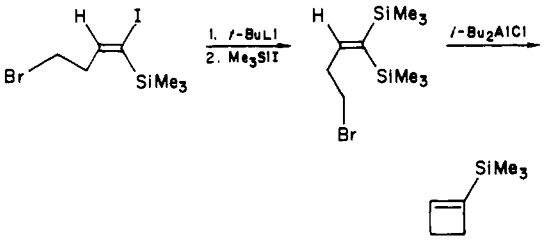
(4)

R = alkyl; n = 2 or 3

Irrespective of the precise course of reaction, cyclization of (ω-halo-1-silyl-1-alkenyl)metals (**3**, M^2 = Si), appears to be reasonably general with respect to M^1. Thus, in addition to Li, Al, and Zr(Al) mentioned above, Zn and even Si, when assisted by Al, induce the cyclization reaction, as exemplified by eq 5 and 6.



(84%) (5)



(61%) (6)

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(4) All isolated compounds have yielded spectral data consistent with the assigned structures.

(5) The regioselectivity of the reactions shown in eq 3 is opposite to that observed in the corresponding reactions of **4** with i-Bu_2AlH.[3] This contrasting behavior itself supports the intermediacy of **6** and must, at least in part, stem from varying steric requirements at the migration origin and terminus.

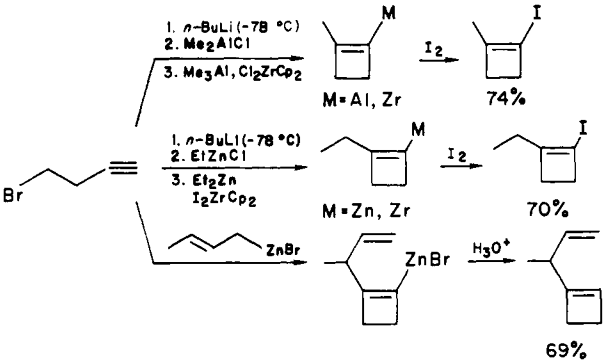
(6) These compounds were prepared by hydroboration of respective ω-bromo-1-iodo-1-pentynes followed by treatment with HOAc (Zweifel, G.; Arzoumanian, H. *J. Am. Chem. Soc.* **1967**, *89*, 5086).

(7) For a review, see: Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.

(8) Negishi, E.; Yoshida, T. *Tetrahedron Lett.* **1980**, *21*, 1501.

(9) Negishi, E. Miller, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 6561.

Although unclear, the role of Si in the π-type process might be mainly to increase the nucleophilicity of the alkene group through σ donation. If so, it should, in principle, be possible to replace Si with other metals. The results shown in eq 7–9 demonstrate that Si may indeed be replaced with Zn as well as with Al and/or Zr. All of these reactions appear to require two metals and involve the π-process. Unlike cycloalkenylsilanes, cycloalkenylmetals containing Al, Zn, or Zr are readily convertible into the corresponding halides and other demetalated derivatives by known methods, thereby significantly augmenting the synthetic utility of the alkenylmetal cyclization methodology.



(7)

(8)

(9)

Acknowledgments are made to the National Science Foundation, the National Institutes of Health, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support. Trimethylalane was kindly supplied by Ethyl Corp. We thank Marisol Vera-Colon of our Department for performing NOE experiments.

Supplementary Material Available: IR, MS, and ^{1}H and ^{13}C NMR of compounds mentioned (3 pages). Ordering information is given on any current masthead page.

Intramolecular Electron Transfer at Metal Surfaces. 4. Dependence of Tunneling Probability upon Donor-Acceptor Separation Distance

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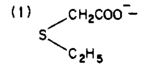
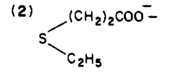
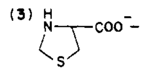
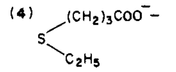
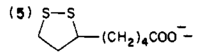
Received May 18, 1984

There is currently much interest in elucidating the manner in which electron transfer occurs for large separations between the donor and acceptor sites.[1-5] Activity in this area has been heightened recently with the examination of a number of binuclear transition metal and related systems in which the redox centers are separated by a variety of saturated, relatively rigid organic linkages.[1-3] These data indicate that reasonably facile electron transfer can occur over substantial distances (10–20 Å), probably via highly nonadiabatic pathways.

Table I. Rate Data for Reduction of $Co^{III}(NH_3)_5X$ with Surface-Attaching Ligands X

X	surface	k_{et}^{-300},[a] s^{-1}	α_{et}[b]	k_{Ru},[c] M^{-1} s^{-1}
(1) 	Au	9.5×10^3	0.57	0.022
	Hg	4.5×10^3	0.56	
(2) 	Au	3.0×10^3	0.61	0.025
	Hg	4.0×10^3	0.60	
(3) 	Au	1.0×10^3	0.60	0.023
	Hg	5.5×10^3	0.80	
(4) 	Au	1.4×10^2	0.60	0.024
	Hg	3.0×10^3	0.60	
(5) 	Au	2.0	0.60	0.016
	Hg	5.5×10^3	0.62	

[a] Unimolecular rate constant for reduction of surface-attached complex in 0.1 M $NaClO_4$ + 5 mM $HClO_4$ at -300 mV vs. SCE, determined by using rapid linear sweep voltammetry as described in ref 6c. [b] Transfer coefficient of electron-transfer step, from $\alpha_{et} = -(RT/F)(d \ln k_{et}/dE)$. [c] Second-order rate constant for homogeneous reduction of Co(III) complex by $Ru(NH_3)_6^{2+}$ in 0.05 M sodium trifluoracetate-trifluoroacetic acid evaluated as described in ref 6c.

A key question concerns the dependence of the electron-tunneling probability on the donor–acceptor separation distance. We have recently been examining the kinetics of a number of "surface intramolecular" processes, i.e., where one of the redox centers is replaced by a metal surface.[6] Included are surface attachment groups consisting of extended organic bridges.[6c] Here we report measurements on a series of such systems containing saturated surface anchoring groups. The results provide the first direct information on electron-tunneling–distance relationships for heterogeneous systems.

Table I contains rate data for the reduction of pentaamminecobalt(III) anchored to gold or mercury surfaces by means of a series of thioalkylcarboxylate ligands. Each ligand contains one or two strongly adsorbing sulfur atoms, being separated from the coordinated carboxylate group by means of a variable-length alkyl chain. The synthesis of these complexes followed the general procedures described in ref 6c. Each reactant is sufficiently strongly adsorbed at gold so to yield a close-packed monolayer (surface concentration, Γ, ca. $(1.5–2) \times 10^{-10}$ mol cm^{-2}) even for very low (10–50 μM) bulk concentrations. Both rate and adsorption data were obtained by using rapid linear sweep voltammetry as described in ref 6c. The rate constants, k_{et}^{-300} (s^{-1}), refer to the reduction of surface-attached Co(III) at -300 mV vs. saturated calomel electrode (SCE). [Other choices of the common potential yielded essentially the same relative values of k_{et} since the transfer coefficients, α_{et} $(=-(RT/E)(d \ln k_{et}/dE))$, are approximately invariant, 0.58 ± 0.02 (Table I).]

Inspection of Table I reveals that the values of k_{et}^{-300} at gold decrease substantially (ca. 10^4-fold) as the number, n, of alkyl carbons increase from one to five. Lengthening the pendant thiol

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(1) (a) Winkler, J. R.; Nocera, D. G.; Yocum, K. M.; Bordignon, E.; Gray, H. B. *J. Am. Chem. Soc.* **1982**, *104*, 5798. (b) Yocum, K. M.; Winkler, J. R.; Nocera, D. G.; Bordignon, E.; Gray, H. B. *Chem. Scr.* **1983**, *21*, 29. (c) Kostic, N. M.; Margalit, R.; Che, C.-M.; Gray, H. B. *J. Am. Chem. Soc.* **1983**, *105*, 7765.

(2) (a) Isied, S. S.; Worosila, G.; Atherton, S. J. *J. Am. Chem. Soc.* **1982**, *104*, 7659. (b) Isied, S. S.; Kuehn, C.; Worosila, G. *J. Am. Chem. Soc.* **1984**, *106*, 1722. (c) Isied, S. S.; Vassihan, A. *J. Am. Chem. Soc.* **1984**, *106*, 1726, 1732.

(3) (a) Stein, C. A.; Lewis, N. A.; Seitz, G. *J. Am. Chem. Soc.* **1982**, *104*, 2596. (b) Richardson, D. W.; Taube, H. *J. Am. Chem. Soc.* **1983**, *105*, 40.

(4) (a) Calcaterra, L. T.; Closs, G. L.; Miller, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 670. (b) Huddleston, R. K.; Miller, J. R. *J. Chem. Phys.* **1983**, *79*, 5337. (c) Miller, J. R.; Calcaterra, L. T.; Closs, G. L. *J. Am. Chem. Soc.* **1984**, *106*, 3047.

(5) (a) Larsson, S. *J. Am. Chem. Soc.* **1981**, *103*, 4034. (b) Larsson, S. *J. Chem. Soc., Faraday Trans. 2* **1983**, *79*, 1375. (c) Beretan, D. N.; Hopfield, J. J. *J. Am. Chem. Soc.* **1984**, *106*, 1585. (d) Logan, J.; Newton, M. D. *J. Chem. Phys.* **1983**, *78*(2), 4086.

(6) (a) Part 1: Barr, S. W.; Weaver, M. J. *Inorg. Chem.* **1984**, *23*, 1657. (b) Part 2: Guyer, K. L.; Weaver, M. J. *Inorg. Chem.* **1984**, *23*, 1664. (c) Part 3: Li, T. T.-T.; Liu, H. Y.; Weaver, M. J. *J. Am. Chem. Soc.* **1984**, *106*, 1233. (d) Barr, S. W.; Guyer, K. L.; Li, T. T.-T.; Liu, H. Y.; Weaver, M. J. *J. Electrochem. Soc.* **1984**, *131*, 1626.

(7) Bond distances: C–C, 1.54; C–O, 1.36; O–Co(III), 2.3; C–S, 1.8; S–Au, ca. 2.3 Å. Values taken from: Gordon, A. J., Ford, R. A., Eds. "The Chemist's Companion"; Wiley: New York, 1972; p 108.

0002-7863/84/1506-6107$01.50/0