the gel-like properties of these xanthan solutions may arise from lateral association of ordered chain sequences to form extended junction zones analogous to those in "true gels" but much weaker, so that the network structure is broken down under stress, allowing the solution to flow. It is interesting to speculate whether the cellulose backbone predisposes xanthan to single-helix formation in the process of primary conformational ordering and to rigid-rod-like behavior over a persistence length of more than 40 residues.[7,8] This would lead to an essentially one-dimensional structure even in a dimeric aggregate.

Conclusion

Scattering and rheological methods do not allow unambiguous determination of solution conformations of the ordered forms of aggregating polysaccharides used as food hydrocolloids. Kinetic studies of salt-induced transitions of these anionic biopolymers show that the primary process of conformational ordering can be readily separated from secondary aggregation and gelation. For the algal polysaccharides ι- and κ-carrageenan and agarose sulfate, ordering is a cooperative dimerization, with activation parameters for double-helix nucleation influenced by salt effects on the disordered form of the reactant. For the bacterial polysaccharide xanthan, both conformational equilibria and kinetics show that ordering is intramolecular and that single-helix and coil regions can be present at equilibrium within a single chain. Slow, secondary processes lead to sequential buildup of aggregates by lateral association of helices. Kinetic behavior may be correlated with primary structure, with the 1,3-glycosidic linkages in the algal polysaccharides predisposing the polymers to formation of hollow helices, and the β-1,4 link in xanthan to an extended ribbon structure.

Controlled Carbometalation as a New Tool for Carbon–Carbon Bond Formation and Its Application to Cyclization[†]

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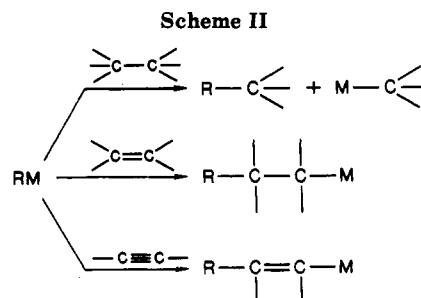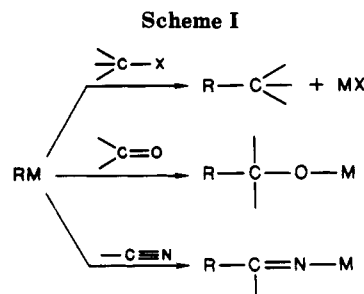
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Carbon–carbon bond formation by means of organometallics has most commonly been achieved by their reactions with polar carbon electrophiles, such as those shown in Scheme I.[1] In search for new types of selective organometallic carbon–carbon bond forming reactions, it is of interest to consider the corresponding reactions of carbon–carbon bonds (Scheme II). In this Account, we are concerned about the addition reactions of organometallics with alkenes and alkynes, for which the term *carbometalation* has been suggested[2] and widely adopted.[3]

In principle, carbometalation may involve carbon–metal double and triple bonds, i.e., metal–carbene and metal–carbyne complexes, as well as metallacycles, such as metallacyclopropanes and metallacyclopropenes. Their carbometalation reactions with alkenes and alkynes are expected to proceed as shown in Scheme III. The products in Scheme III may further undergo carbometalation to produce 6-, 7-, and even higher membered metallacycles.

In fact, most of the processes shown in Schemes II and III have been observed and/or proposed, and carbometalation is indeed ubiquitous in organotransition-metal chemistry.[4] The Ziegler–Natta polymerization

Scheme I

Scheme II

reaction[5] of alkenes catalyzed by an organoalane and titanium chloride, for example, is thought to be a car-

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[†] This Account is dedicated to Professor George Zweifel on the occasion of his 60th birthday.

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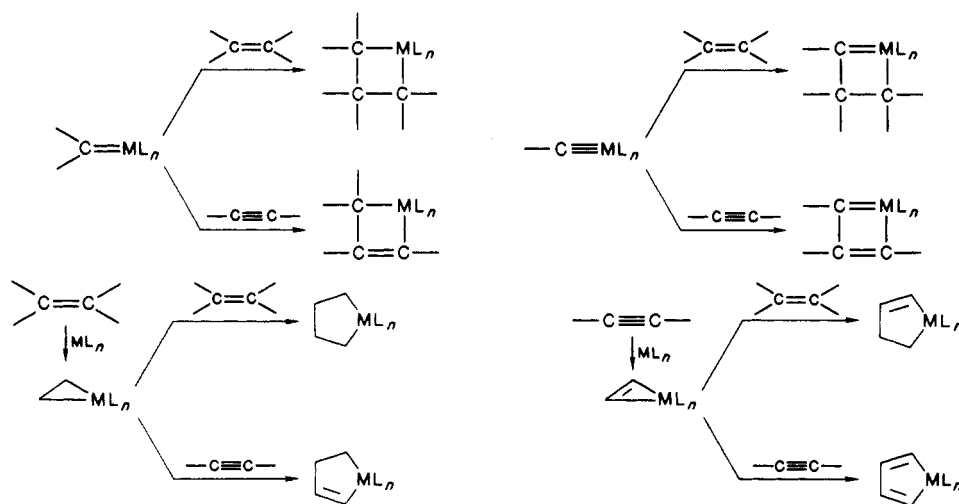
(2) (a) Van Horn, D. E.; Negihsi, E. *J. Am. Chem. Soc.* 1978, *100*, 2252. (b) Negishi, E. *Pure Appl. Chem.* 1981, *53*, 2333.

(3) See, for example: Normant, J. F.; Alexakis, A. *Synthesis* 1981, 841.

(4) See, for example: Collman, J. P.; Hegedus, L. S. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valey, CA, 1980.

Scheme III

bometalation reaction of the C–Ti bond with alkenes, the degree of polymerization of which is uncontrolled and represented by a distribution. Some uncontrolled polymerization reactions of alkynes are also known.[6] In these reactions, carbometalation of alkenes and alkynes with organometals produces new organometals possessing similar reactivity, which makes it generally difficult to control the degree of polymerization. In some cases, however, the degree of polymerization (or oligomerization) can be controlled to give uniform products. A Rh-catalyzed acyclic dimerization of ethylene to give 2-butene,[7] a linear dimerization of phenylacetylene to give a 50% yield of 1,4-diphenyl-1,3-butenyne,[8] and some linear dimerization reactions of butadiene and isoprene to give octatriene derivatives catalyzed by Zr–Al[9a] and Pd[9b] complexes are representative examples of controlled acyclic oligomerization. Far more widely observed are controlled cyclic oligomerization reactions of alkenes, alkynes, and dienes. Although conversion of alkenes into cyclobutanes catalyzed by Fe[10a] and Ir[10b] complexes still is of very limited scope, controlled cyclooligomerization reactions of alkynes[11] and dienes[12] to give cyclic dimers, trimers, and tetramers have been widely known and reviewed. Controlled acyclic and cyclic oligomerization reactions involving alkenes alkyne, alkene–diene, and alkyne–diene mixtures are also known.[4,13] However, the products of the above-mentioned controlled oligomerization reactions are mostly simple and symmetrical,

and until recently, relatively little efforts had been made to apply these reactions to the synthesis of complex natural and unnatural compounds, one of the notable exceptions being the synthesis of steroids and other polyfused systems via cyclotrimerization of alkynes.[11b,c] Over the past 10–15 years, however, considerable efforts have been made to develop various types of controlled acyclic and cyclic carbometalation reactions of alkenes and alkynes suitable for the synthesis of complex organic compounds. The main purpose of this Account is to present the current scope and the future outlook of such carbometalation reactions with emphasis on those that have been developed in our laboratories and are applicable to the synthesis of cyclic structures.

Controlled Monocarbometalation of Alkenes and Alkynes

Stereo- and regioselective single-state addition, i.e., monocarbometalation, of organometals to alkenes and alkynes producing new organometallic species (Scheme II) can be a valuable synthetic tool. At present, such reactions of organotransition metals producing alkyl-transition metals as discrete products are very rare except for some conjugate addition of organocoppers to α,β-unsaturated carbonyl compounds[14] and that of various organometals to alkenes and dienes producing π-allylmetal derivatives.[15] In the Heck reaction, aryl-or alkenylpalladium species add to alkenes to produce alkylpalladium intermediates which undergo dehydropalladation to give aryl- or alkenyl-substituted alkenes.[16] The reaction is applicable to the synthesis of unsymmetrical complex molecules, although it is often not stereo- and/or regioselective.

Addition of organotransition metals to alkynes can produce discrete organometallic products, i.e., alkenylmetals, more readily than the corresponding reactions involving alkenes. Although various monocarbometalation reactions of alkynes[17] are known, Normant's

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(13) For a review, see: Heck, R. F. *Organotransition Metal Chemistry*; Academic: New York, 1974; Chapter 8.
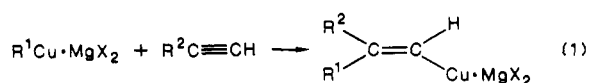
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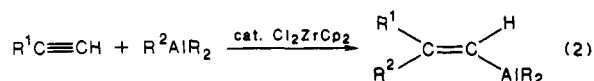
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carbocupration[3,18] is probably the first such reaction of high selectivity, reasonable generality, and considerable synthetic utility. The reaction has been extensively reviewed.[3,18]

$$R^1Cu \cdot MgX_2 + R^2C \equiv CH \longrightarrow \begin{matrix} R^2 \\ R^1 \end{matrix} C = C \begin{matrix} H \\ Cu \cdot MgX_2 \end{matrix} \quad (1)$$

Despite a number of satisfactory features, the difficulty in accommodating the uniquely important methylcopper reagents, the thermal instability of organocoppers, and the capricious effects of proximal heteroatoms in alkynes have limited the usefulness of carbocupration. This and other considerations led us to develop the Zr-catalyzed carboalumination of alkyne[2] (eq 2). Since this reaction has also been extensively

$$R^1C \equiv CH + R^2AlR_2 \xrightarrow{\text{cat. } Cl_2ZrCp_2} \begin{matrix} R^1 \\ R^2 \end{matrix} C = C \begin{matrix} H \\ AlR_2 \end{matrix} \quad (2)$$

reviewed,[2b,19] its discussion here is brief. Although the mechanism of the reaction remains to be clarified, the available data indicate that, in typical cases, the reaction may involve Zr-assisted direct carboalumination.[20] With alkylalanes containing β-hydrogens, hydroalumination via hydrozirconation can be a serious side reaction. It can, however, be suppressed by the use of $R_2Al-R(Cl)ZrCp_2$ or $R_2AlCl-Cl_2ZrCp_2$ reagent systems.[20] It may, on the other hand, be promoted to achieve clean Zr-promoted hydrometalation reactions, such as Zr-catalyzed hydroalumination[21] and hydrozirconation with t-BuMgCl-Cl_2ZrCp_2.[22] The use of $R_2Zn-I_2ZrCp_2$ achieves a related carbozincation.[23] Controlled carbometalation of alkynes can also be achieved with Al–Ti reagents.[24] However, these reactions are still of very limited scope.

The Al moiety of the products in eq 2 can be readily replaced with H,[2a] D,[2a] I,[25] Hg,[26] B,[27] Zr,[27] various one-carbon groups,[28] such as hydroxymethyl, methoxymethyl, carboxyl, and carbethoxy, two- and multicarbon groups, such as hydroxyethyl[29] and γ-oxoalkyl,[27] alkyl,[30] homoallyl,[30] homobenzyl,[30] homopropargyl,[30] allyl,[31] benzyl,[32] aryl,[33] alkenyl,[33] alkynyl,[33] heteroaryl,[34]

and acyl[35] groups. The reaction has been applied to the synthesis of various natural products including mokupalide,[29b] brassinosteroids,[36] milbemycin,[37] and verrucarins.[38]

Carbometalation of Functionalized Alkynes and Carbometalation with Functionalized Organometals as a Tool for Cyclization

Since carbometalation achieves formation of a carbon–carbon bond with simultaneous generation of a new metal–carbon bond, the use of either functionalized alkynes or functionalized organometals can lead to the formation of cyclic compounds:
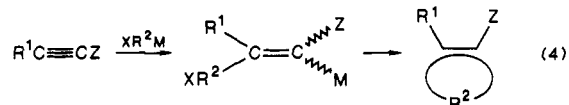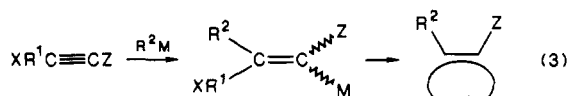
Formation of cycloalkenes as shown in eq 3 requires (i) relatively rare anti addition of MR^2 followed by cyclization with retention, (ii) syn addition of MR^2 followed by cyclization with inversion, or (iii) some alkenylmetal cyclization reactions uninhibited by either geometry of the alkenylmetal intermediates.

(a) Cyclialkylation of Alkenylmetals. Quite serendipitously, we have discovered two novel cyclialkylation reactions of alkenylmetals that fall into the last category listed above. To explore the chemoselectivity of the Zr-catalyzed carboalumination reaction of alkynes, we reacted various propargyl and homoprogargyl derivatives containing OH, $OSiMe_2Bu$-t, SPh, or halogens (Cl, Br, and I). In cases where the alkynes are terminal, the carbometalation reaction proceeded normally.[39] On the other hand, 1-trimethylsilyl-4-halo-1-butynes did not give the expected carbometalation products. Instead, they gave 2-methyl-1-trimethylsilyl-1-cyclobutene in excellent yields.[40] Subsequent studies have clearly established that the alkene moiety extensively participates in this reaction (π-*process*), as shown in eq 5.[40,41] In accord with this mechanism, the reaction is nonregiospecific, although it can be highly regioselective. The stereochemistry of the alkenylmetal intermediates is unimportant. Although three- and six-membered rings can also be prepared analogously,

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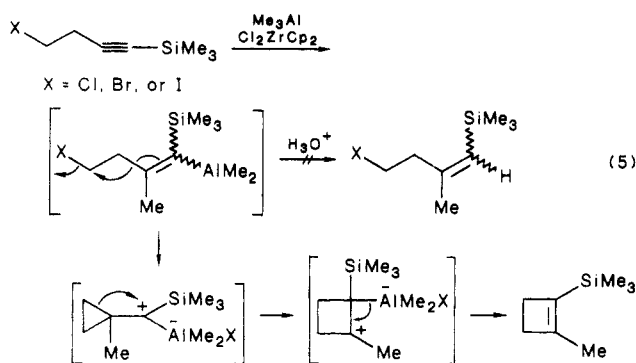
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five-membered rings are not readily formed.[40,41]

In search for a more general and regiospecific procedure, we have found that ω-halo-1-silyl-1-alkenyllithiums cyclize readily and regiospecifically to give three- through eight-membered cycloalkenes regardless of the alkene geometry.[40-42] In this case, however, the syn relationship between the C–Li bond and the ω-haloalkyl group is required and attained through Si-promoted isomerization.[43] The available data indicate that, if the alkenyl–metal bond is sufficiently polar and nucleophilic, e.g., C–Li bond, it can directly participate in cyclialkylation[44] (σ-process). Such cyclization reactions are regiospecific but require the syn relationship between the C–M bond and the ω-haloalkyl group. Some related cyclialkylation,[45] cycliacylation,[46] and cyclic carbonyl and conjugate addition reactions[46a,47] of organolithiums have also been developed by us and others over the past few years. On the other hand, relatively covalent and nonnucleophilic alkenyl–metal bonds, e.g., C–Al bond, appear to require the second carbon–metal bond, e.g., C–Si bond, as a "nucleophilicity booster" and make use of the alkene π-bond as a nucleophilic site. The reaction is nonregiospecific.

(b) Allylmetalation and Higher Alkenylmetalation. As shown in eq 4, carbometalation of alkynes with functionally substituted organometals (XRM) would provide attractive routes to cycloalkenes. In reality, however, such carbometalation reactions are rather rare, presumably because the functional group in an organometallic species tends to interfere with the desired carbometalation. We have therefore focused our attention on allylmetalation and related reactions with homologous alkenylmetals. The scope of allylmetalation as of several years ago has been reviewed.[3] Although the possibility for six-centered transition states might suggest that allylmetalation can occur widely, the scope of controlled allylmetalation of alkynes producing 1,4-dienylmetals as discrete products[48]

was surprisingly limited to a few reactions, such as allylboration of alkoxy- or aminoalkynes,[49] allylzincation of alkynylzincs generated in situ,[3,50] and anti allylmagnesiation of propargyl alcohols and related derivatives.[51,52] As such, allylboration and allylzincation are of limited synthetic utility. However, the Cu-catalyzed anti allylmagnesiation[52] (eq 6) appears to be a carbometalation reaction of considerable synthetic use, as discussed later.
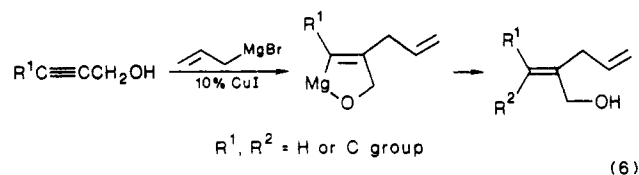
We have found that alkynylsilanes react regioselectively with allylzinc halides to produce 1,4-pentadienylzinc halides in high yields, although the reaction is only about 85% stereoselective[53] (eq 7). The corre-

sponding reaction of terminal alkynes is generally complicated by competitive zincation of alkynes and double allylzincation,[50] while internal alkynes fail to react with allylzinc halides. Fortunately, both terminal and internal alkynes undergo Zr-catalyzed allylalumination[54] (eq 8). The reaction is >98% stereoselective but only
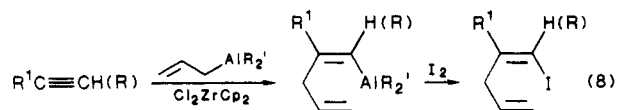
ca. 75% regioselective. The use of a deficient amount of an electrophile, e.g., I₂, can produce isomerically pure alkene derivatives. Internal alkynes also undergo a similar Zr-promoted allylzincation with diallylzinc reagents in the presence of I₂ZrCp₂.[53a]

The products of allylmetalation have indeed proved to be useful in preparing cyclic compounds via cyclialkylation and cycliacylation[53a] (eq 9) as well as via carbonylation discussed later.
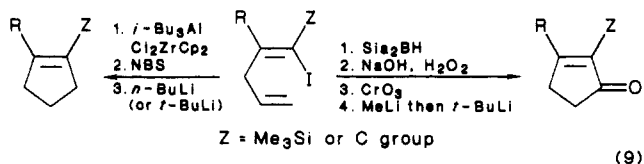
For incorporation of the homoallyl and higher alkenyl groups, carbocupration of alkynes appears to be general

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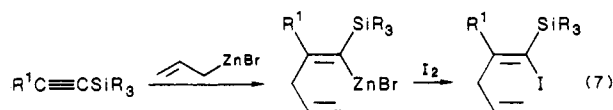
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and regio- and stereoselective. Iodinolysis of the carbocupration products provides dienyl iodides in which the iodine atom is cis to the ω-alkenyl group. The Zr-catalyzed hydroalumination–brominolysis–cyclialkylation of the dienyl iodides, as described for the synthesis of cyclopentenes (eq 9), readily provides cyclohexenes and higher cycloalkenes[41] (eq 10).

$$RC\equiv CH \xrightarrow[\text{2. I}_2]{\text{1. } \diagup(CH_2)_nCu\cdot MgBr_2}$$

$$\text{(}n = 2, 3, \text{etc.)} \quad (10)$$

The products of the Cu-catalyzed allylmagnesiation reaction of propargyl alcohols can be protonated or iodinated to give trisubstituted or tetrasubstituted alkenes, respectively, that are di-, tri-, or even tetra-functional and regio- and stereochemically pure.[52] These compounds can, in turn, serve as intermediates for stereodefined exocyclic alkenes,[54] as shown in eq 11 and 12. Importantly, all products shown in eq 11 and 12 were formed as isomerically >97–98% pure compounds. Although the number and range of exocyclic alkenes prepared by the method are still limited, its selectivity and potential versatility are noteworthy.

$$(11)$$

$$(12)$$

3a: R^1 = Me, R^2 = Bu-n (43%)   **3b:** R^1 = Bu-n, R^2 = Me (48%)
4a: R^1 = Me, R^2 = Bu-n (38%)   **4b:** R^1 = Bu-n R^2 = Me (45%)

(c) Cyclic Carbometalation of Alkynes. Cyclic carbometalation of alkynes may be represented by eq 13. It possesses some features of both carbometalation of functionalized alkynes and carbometalation with functionalized organometals. If the process were regio- and stereoselective, it could provide another attractive route to exocyclic alkenes.

Unfortunately, the previously known cyclic carbometalation reactions of alkynes involving, Li,[55] Mg,[56]

$$(13)$$

and Cu[57] generally suffer from the lack of stereoselectivity and various side reactions attributable, at least in part, to the intermediacy of radical species. We therefore felt that, if the formation of radical intermediates could be avoided, some stereoselective processes would be developed. We treated 6-trimethylsilyl-1-hexen-5-yne and 7-trimethylsilyl-1-hepten-6-yne with 1.1 equiv of i-Bu$_3$Al and 10 mol% of Cl$_2$ZrCp$_2$ and obtained **5a** and **5b** in 85% and 72% yields, respectively[58] (eq 14).

5a: n = 2
5b: n = 3

$$(14)$$

Unfortunately, we were very disappointed to find that the formation of **6** under the same conditions was not stereoselective (eq 15). Evidently, α-silylalkenylalanes are configurationally unstable.[43b] We can, however, take advantage of this feature to achieve a highly stereoselective, chelation-controlled cyclic carbometalation[58] (eq 16).

$$(15)$$

$$(82\%, 97\% \text{ }(E))$$

$$(16)$$

Somewhat unexpectedly, treatment of 6-bromo-1-silyl-1-hexyne derivatives with Mg has recently been shown to induce cyclic carbomagnesiation which is ca. 90% stereoselective.[59]

(d) Cyclic Acylmetalation. In addition to cyclialkylation and cycliacylation shown in eq 15, the products of allylmetalation of alkynes appeared attractive as precursors to α-methylenecyclopentenones, which represent a number of natural products of medicinal interest. Specifically, we hoped to prepare α-methylenecyclopenenenones via carbonylation of 1,4-pentadienyl iodides. We have indeed found that treatment of various 1,4-dienyl iodides with CO (1.1 atm) in the presence

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Scheme IV

a = CO(600 psi), Cl$_2$Pd(PPh$_3$)$_2$ (5 mol %), NEt$_3$ (1.5 equiv),
MeOH (4 equiv), CH$_3$CN-C$_6$H$_6$, 100 °C, 18-24 h

of 1-1.1 equiv each of Pd(PPh$_3$)$_4$ and NEt$_3$ in THF at
60 °C produces **7** including an antibiotic, methyleno-
mycin B (**7b**),[53a] in 50-75% yields. The results can be
explained by a mechanism shown in eq 17.

(17)

7a: R = n-Hex,   **7b**: R = Z = Me (51%)   **7c**: R and Z =
Z = SiMe$_3$ (54%)   -(CH$_2$)$_3$- (75%)
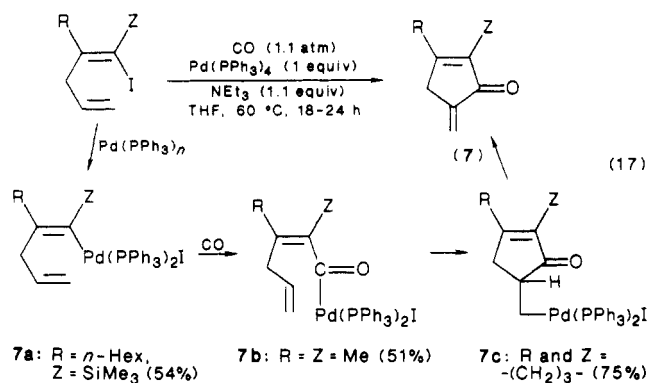
The mechanism shown above suggests that, in the
presence of NEt$_3$, the reaction should be catalytic in Pd.
Although we have so far been unable to make the
transformation shown in eq 17 catalytic, we have de-
veloped a related catalytic reaction shown in Scheme
IV.[60]

We believe that both the stoichiometric reaction
shown in eq 17 and the catalytic reaction shown in
Scheme IV proceed via oxidative addition, migratory
insertion of CO, and cyclic acylpalladation, as shown
in eq 17. In the latter reaction, however, the second CO
insertion and methanolysis occur instead of dehydro-
palladation. In the absence of methanol, only polym-
erization products are obtained. The intermediacy of
the alkenyl- and acylpalladium intermediates has been
supported by trapping experiments.[60] Although there
have been some acyclic acylmetalation reactions of en-
ones,[61] both single-state[62] and polymeric[63] acyclic
acylmetalation reactions, and quinone-producing in-
termolecular acylmetalation reactions,[64] cyclic acyl-

metalation reactions have been extremely rare.[65] A
related carbonylation reaction proceeding in an "endo"
mode suitable for the synthesis of polycyclic quinones[66]
has also been developed.[67]

Controlled Carbometalation with Metallacyclopropanes and Metallacyclopropenes

The metal-carbon bonds of metal-carbene and
metal-carbyne complexes as well as of metallacyclo-
propanes and metallacyclopropenes have been shown
to be highly reactive toward alkenes and alkynes
(Scheme III). Although pioneering works mainly by
Schrock[68] on the chemistry of metal-carbyne complexes
show some synthetic potentials, the use of metal-car-
byne complexes in organic synthesis is still in its in-
fancy. On the other hand, metal-carbene complexes
have been widely used in organic synthesis.[69] Their
reactions that are thought to proceed via carbo-
metalation include olefin metathesis, cyclopropanation
of alkenes, and alkene and alkyne polymerization.
Some of the more recent efforts have been directed
toward controlled and selective cyclization reactions of
metal-carbene complexes with alkenes and alkynes,
such as the Cr-promoted synthesis of quinones and
hydroquinones by Dötz,[70] Semmelhack,[71] Wulff,[72] and
Yamashita,[73] the W-catalyzed enyne cyclization reaction
of Katz,[74] and the reaction of titanium-carbene com-
plexes with alkynes and alkenes by Tebbe[75] and
Grubbs.[76]

Our own attention has been directed to those carbo-
metalation reactions that are thought to involve me-
tallacyclopropanes and metallacyclopropenes. One
particularly attractive feature of these three-membered
metallacycles is that they can be in situ generated by
the reaction of alkenes and alkynes with transition-
metal complexes via oxidative coupling (Scheme III).
Since Reppe's synthesis[77] of benzene and cyclo-
octatetraene from acetylene catalyzed by Ni and other
transition-metal complexes is thought to involve me-
tallacyclopropenes, the history of this branch of chem-

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istry is by no means new. As mentioned earlier, however, the development of procedures suitable for the synthesis of unsymmetrically substituted cyclic or acyclic products is of recent origin, a systematic investigation of Co-catalyzed alkyne cyclotrimerization by Vollhardt[11b,c] being a prototypical example.
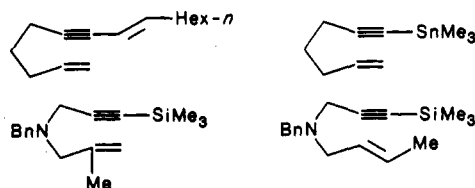
Transition-Metal-Promoted Bicyclization of Dienes, Enynes, and Diynes. Transition-metal complexes that can act as "14-electron" species, e.g., "ZrCp$_2$", can react readily with alkenes and alkynes to form metallacyclopropanes and metallacyclopropenes, respectively. Some such compounds containing both early, e.g., $(Me_5C_5)_2Ti(CH_2CH_2)$,[78] and late, e.g., $(Ph_3P)_2Pt(PhCCPh)$,[79] transition metals are known. In many cases, these metallacylces are capable of reacting further with alkenes and alkynes to form five-membered metallacycles, as shown in Scheme III. Formation of metallacyclopentanes and metallacyclopentadienes have been observed with various metals including Ti,[80] Zr,[81] Ta,[82] Fe,[83] Co,[84] Rh,[85] Ir,[86] Ni,[87] and Pd.[88] Some of these metallacycles have been carbonylated to give the corresponding five-membered ketones. Although rare, some metallacyclopentenes[89] and metallaindans[90] have also been prepared.

From the viewpoint of organic synthesis, it is essential to attain high regioselectivity and cross–homo selectivity. For example, a metal-promoted cyclization reaction of an unsymmetrical alkene with an unsymmetrical alkyne can produce up to ten metallacyclopentanes, -pentenes, and -pentadienes. On the other hand, the corresponding reaction of an enyne of proper chain length may give a single product. We have indeed found that the reaction of ω-vinyl-1-silyl-1-alkynes with "ZrCp$_2$" produces in excellent yields zirconabicycles (8), which can be protonated, iodinated, or carbonylated to give 9, 10, and 11, respectively[91] (eq 18). Various alkyl-substituted 7-silylhept-1-en-6-ynes can be conveniently prepared by the conjugated allylation of methyl alkenyl ketones followed by conversion of methyl ketones into silylalkynes.[91]

Although the reaction of Cl_2ZrCp_2 with Mg (10 equiv) and HgCl$_2$[81c] was initially used to generate "ZrCp$_2$", we

(18)
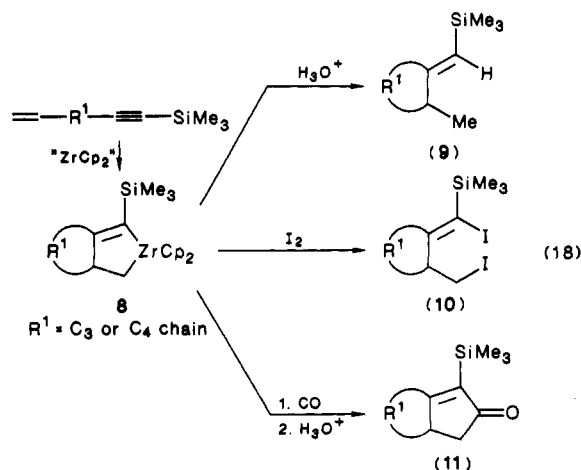
have since found that treatment of Cl_2ZrCp_2 with 2 equiv of n-BuLi in THF is a convenient alternative.[92] Some of the enynes that have been converted into zirconabicyclic derivatives in >80% yields by this procedure are shown below,[93] and the scope of the reaction appears to be reasonably general. Comparison of its scope with that of the Co-promoted bicyclization–carbonylation reaction of enynes based on Pauson's discovery[84] and developed mainly by Schore,[94] Billington,[95] and Magnus[96] is still premature. However, the extremely mild reaction conditions ($\leq$25 °C) and the clean and discrete formation of metallacyclopentenes that can be readily protonated and iodinated make the Zr-based methodology unique.

The above procedure is also applicable to the cyclization of diynes and dienes[92] (eq 19). Although a sim-

R = alkyl or SiMe$_3$ n = 2–4 (75–100%) n = 5 (ca. 60%)

(19)
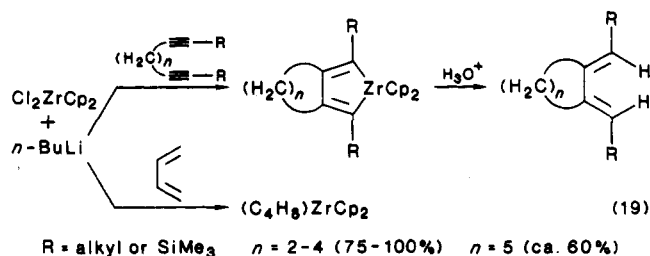
ilar Ti-promoted bicyclization reaction of diynes is known,[97] the Zr-promoted reaction appears to be generally cleaner and more satisfactory. Also noteworthy are the Pd- and Rh-promoted cyclization reactions of dienes[98] and enynes.[99] The enyne cyclization reaction

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has been applied to the synthesis of (±)-sterepolide (12).[99b] In these reactions, metallabicyclic intermediates presumably undergo dehydrometalation–reductive elimination to give monocyclic products. It now appears that most or essentially all d-block transition metals can participate in bicyclization of enynes, dienes, and diynes, and they will collectively provide a powerful new tool for the synthesis of mono-, bi-, and polycyclic structures.

The product of the reaction of butadiene with "ZrCp$_2$" was originally prepared by Nakamura[100a] by the reaction of Cl$_2$ZrCp$_2$ with 2-buten-1,4-diylmagnesium and by Erker by photolysis of Cp$_2$ZrPh$_2$ in the presence of butadiene.[101a] Interestingly, the product obtained by the former is (s-cis-η^4-butadiene)zirconocene (13), whereas the latter product contains its s-trans isomer (14). These compounds not only react readily with


12   13   14
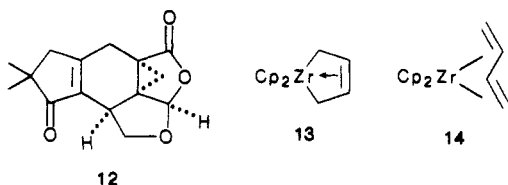
ketones and nitriles but also undergo carbometalation with alkenes and alkynes.[100,101] Significantly, the carbometalation reactions of (s-cis-isoprene)zirconocene are often highly regioselective and form carbon–carbon bonds away from the methyl group of isoprene[100c] (eq 20).

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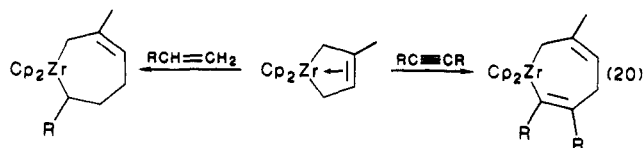
Concluding Remarks

Until recently, carbometalation reactions had been used nearly exclusively to synthesize polymers and symmetrically structured oligomers of alkenes and alkynes. It now appears that controlled carbometalation provides a new powerful tool for construction of unsymmetrical and complex organic structures as well. The crucially important aspects of controlled carbometalation include (i) controlling the degree of polymerization or oligomerization, (ii) attaining a high regio-, stereo-, and/or chemoselectivity, and (iii) attaining a high cross–homo selectivity. The fact that carbometalation leads to the simultaneous formation of a carbon–carbon bond and a new carbon–metal bond can be exploited in the preparation of various ring structures. The cyclization methods discussed here include (i) cyclialkylation, (ii) cycliacylation, (iii) Zr-catalyzed cyclic carboalumination, (iv) acylpalladation, (v) Zr-promoted bicyclization of enynes, dienes, and diynes. Collectively, these reactions promise to provide attractive routes to cyclic structures. Many additional cyclization procedures involving carbometalation are expected to be developed in the near future. Highly needed in this connection are further explorations of carbometalation reactions involving functionalized alkynes and alkenes as well as functionalized organometals.

Asymmetric Synthesis of Carbon–Carbon Bonds Using Sulfinyl Cycloalkenones, Alkenolides, and Pyrones

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Prior to 1975, asymmetric syntheses proceeding with >90% enantiomeric excess (ee, percent of one enantiomer minus percent of its antipode) were the rare

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exception. In recent years, however, many research groups have reported ee's of >90%, and the research activity generated by this scientific revolution is leading to a publication explosion in this area. This scientific revolution has stimulated development not only of new synthetic methods but also of new chromatographic methods for analytical and preparative scale separation of enantiomers, development of new NMR techniques for evaluating enantiomeric purity easily and accurately, and development of new and practical industrial processes for asymmetric synthesis of valuable organic in-