ARTICLE

Zirconocene Complexes of Unsaturated Organic Molecules: New Vehicles for Organic Synthesis

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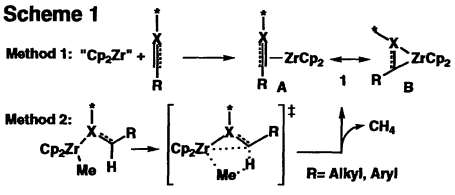
Transition metals are known to stabilize high-energy species and to activate otherwise unreactive ones. The zirconocene unit stabilizes highly strained alkynes and alkenes, allowing their use in selective carbon-carbon bond–forming reactions. This unit also increases the reactivity of unactivated molecules, enabling them to participate in nontraditional transformations. A general route has been developed that allows a wider variety of unsaturated fragments to participate in these reactions. The use of these zirconocene complexes in organic synthesis has led to the development of novel routes to a number of polyfunctionalized organic molecules.

Conventional methodology used in organic synthesis relies heavily on the use of polar functional groups that contain a carbon and a heteroatom; for example, carbonyl groups are often used. Reactions that form C-C bonds can then be effected either by the addition of a carbanionic nucleophile or by a deprotonation-alkylation sequence (*1*). The importance of such technology has been amply demonstrated in the total synthesis of a number of complex natural products. Techniques that make use of transition metals expand the nature of available C-C bond–forming procedures. In particular, organometallic reagents and catalysts are often able to use substrates that are conventionally thought of as being unactivated, including simple olefins and alkynes, which do not contain heteroatoms (*2*). This article deals with the use of zirconocene complexes of unsaturated organic molecules as a means to accomplish selective C-C bond formation.

Zirconocene Complexes: Synthesis, Structure, and Reactions

Synthesis. Two main routes for the synthesis of zirconocene complexes of unsaturated organic molecules, **1**, have been used (Scheme 1) (*3*, *4*). In the first, a synthetic equivalent of zirconocene, Cp_2Zr (where Cp is the cyclopentadienyl anion), is generated in the presence of an unsaturated organic molecule (*5*–*7*). In the second method, the zirconocene complex is generated by the loss of an alkane (such as CH_4) through a cyclometallation reaction (*3*, *4*). This process is an example of a C-H activation reaction (*2*). In contrast to method 1, in method 2 neither zirconocene nor the unsaturated molecule is free in solution at any time. The ramifications of this condition will become apparent below.

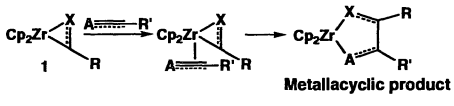
Scheme 1



Structure. The bonding schemes in transition-metal complexes of unsaturated molecules are readily described by the use of the Dewar-Chatt-Duncanson model (*2*, *8*). The two extreme resonance forms for a zirconocene complex of an unsaturated organic molecule **1** are shown in Scheme 1. In structure **A** the dashed line denotes that the C-X bond is either a double or a triple bond; in structure **B** it denotes either a C-X single or double bond (the notation X represents either a carbon or a heteroatom). In resonance structure **A**, the Zr is formally in a 2+ oxidation state and the π bond of the unsaturated organic species acts as a two-electron, σ donor ligand. In contrast, in resonance structure **B** the Zr is in a 4+ oxidation state, the C-X bond order is reduced by one, and the unsaturated organic group acts as a four-electron ligand because of back-bonding from the Zr center to the π^* orbital of the C-X group. The complexes discussed in this article are invariably better represented by structure **B** (*3*, *4*).

Reactions to form metallacycles. The zirconocene complexes discussed in this article are 16-electron complexes (*9*), so they can bind a variety of unsaturated molecules. The binding of the π bond of an unsaturated compound, which acts as a two-electron donor ligand, produces an 18-electron intermediate (Scheme 2). The insertion of the unsaturated group into a C-Zr bond produces the metallacycle (a cyclic compound containing a metal in the ring). Many unsaturated molecules have been shown to be suitable coupling partners, including olefins, alkynes, ketones, aldehydes, nitriles, and imines. A number of studies relating to the regiochemistry of the insertion process have been carried out (*3*, *4*). From that work, three conclusions may be made: (i) the insertion reactions are usually reversible; (ii) in the cases in which one of the two ends of the unsaturated group contains a heteroatom, such as in the case of an imine, the regioisomer in which there is a Zr-heteroatom bond is the one that is formed exclusively; (iii) trialkylsilyl-substituted groups are preferentially bonded directly to the Zr center.

Scheme 2

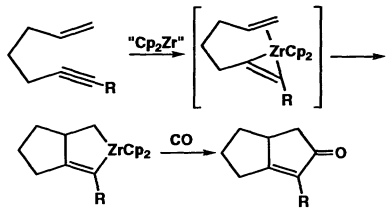


As will be explained below, in the ultimate step of a particular transformation, the metallacycle can be treated with any of a variety of reagents to form the desired organic product. These reactions liberate the organic portion from the metal, and the organic species can then be isolated and purified by conventional techniques of organic chemistry.

Comparison of Methods 1 and 2

Method 1 (Scheme 1) is most commonly used to prepare a transient version of **1**, which then participates in an intramolecular insertion reaction, an example of which is shown in Scheme 3. This methodology, pioneered by groups led by Nugent (*10*, *11*) and Negishi (*5*–*7*), has seen widespread use in organic synthesis. One important transformation couples an alkene, an alkyne, and CO to produce a cyclopentenone. This simple transformation represents an extremely efficient use of the functionality of the substrates. One C-O and two C-C π bonds are used to form three C-C σ bonds in a process that is analogous to the Pauson-Khand reaction (*12*). These procedures combine simple, readily available components to provide products of much greater complexity.

Scheme 3



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The development and use of synthetic techniques based on method 1, while of great current interest, have been the subjects of several recent reviews (*5*, *6*, *10*) and will not be discussed in detail in this article.

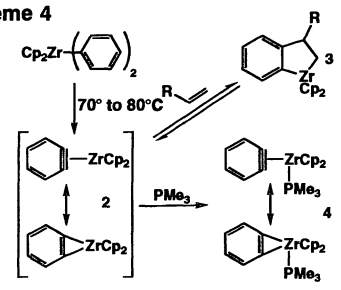
Method 1 suffers from several deficiencies: (i) the selective cross-coupling of two different unsaturated components is usually quite difficult; (ii) the use of strained or unstable molecules as one of the coupling partners is not easily achieved (*3*); and (iii) many desirable synthetic targets are not readily available. In addition, the requisite organic starting materials for method 2 are generally more simple and are often commercially available. Despite the utility of chemistry based on method 1, we feel that in many instances techniques based on method 2 are of significant utility.

Chemistry Based on Method 2

Chemistry based on method 2 alleviates the problems mentioned above and has thus proven to be complementary to chemistry based on method 1.

Early studies by Hagihara (*13*), Vol'pin (*14*), and their co-workers as well as others (*15*) set the stage for Erker's work in the late 1970s and early 1980s (*16*, *17*). Erker and his colleagues showed that thermolysis of diphenylzirconocene produced the zirconocene-benzyne complex **2** (Scheme 4). If **2** was generated in the presence of an olefin, then the metallacycle **3** was formed by a process involving the insertion of the olefin into the Zr-C bond. It was Erker who first noted the reversibility of this metallacyclization reaction. In addition, he demonstrated that **2** was formed by a concerted process involving cyclometallation rather than β hydrogen elimination. In 1986, Watson and colleagues confirmed in our laboratory the intermediacy of **2** in the thermolysis of

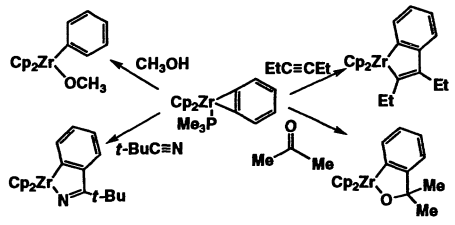
Scheme 4



diphenylzirconocene by carrying out this reaction in the presence of a large excess of trimethylphosphine (PMe_3, where Me represents methyl) (*18*). This small and extremely basic ligand trapped **2** and allowed its isolation and characterization by x-ray crystallography as the PMe_3 adduct **4**.

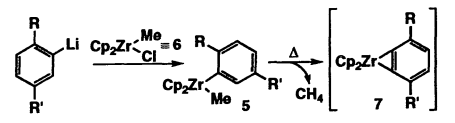
The C1-C2 bond length of 1.364(8) Å is similar to that of the other C-C bonds in the aromatic ring of **4**, indicating a high level of back-bonding and a high degree of zirconacyclopropene character. Compound **4** should therefore be thought of as having two Zr-C σ bonds; the reaction chemistry manifested by it is consistent with this view [Scheme 5 (Et, ethyl; Bu, butyl; *t*, tert)]. Thus, **4** reacts with nitriles, alkynes, and ketones to form the corresponding zirconacycles; treatment with methanol [1 equivalent (eq)] effects protonation of one of the Zr-C bonds (*3*).

Scheme 5



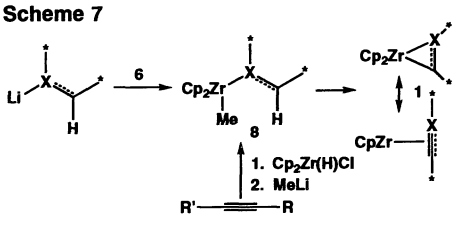
The isolation of **4** and its reaction chemistry provided the impetus for a large body of research in our laboratory. Although the chemistry of **2** and **4** was intriguing, we felt that significant improvements were required to increase its synthetic utility. A simple but practical breakthrough came when it was determined that aryl (Me) zirconocenes **5**, prepared by the addition of an aryllithium reagent to $Cp_2Zr(Me)Cl$, **6**, were excellent precursors to a variety of zirconocene complexes of

Scheme 6



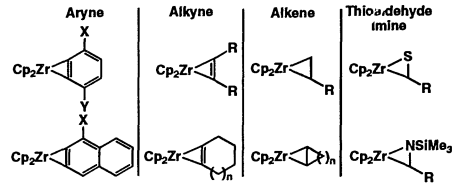
substituted benzynes (Scheme 6) (*3*). This development was significant for two reasons. First, because both of these reagents are readily available in multigram quantities, the chemistry may be performed on a reasonable scale. Second, if diaryl zirconocenes were used to generate the aryne complexes, one half of the aromatic precursor was thrown away in the elimination reaction; in the new procedure, this inefficiency was ameliorated. The use of **6** also allowed the generalization of this methodology to prepare zirconocene complexes of cyclic alkynes, cyclic alkenes,

Scheme 7



thioaldehydes, imines, and benzdiynes (*3*, *4*) (Scheme 7). The preparation of these complexes typifies the difference between methods 1 and 2: these strained high-energy species do not need to be generated independently and then trapped by "zirconocene," as would be required by method 1 (*19*). Additionally, related methods were developed to allow for the preparation of complexes of acyclic alkynes and alkenes (*3*, *4*, *7*) through routes that also proceeded by way of intermediate **8** or similar species. As can be seen in Scheme 7, discrete intermediate **8** is formed and converted, through a cyclometallation process, to **1**. This example of a C-H activation reaction is central to the preparation of **1** under extremely mild conditions. The transformation underscores a key difference between conventional organic and transition metal–mediated reactions, in which otherwise unreactive bonds are activated by a transition metal (in Scheme 7, a C-H bond is activated). The conversion of **8** to **1**, as either a 16-electron species or an 18-electron PMe_3 adduct, ensures that, in general, only a single reactive complex **1** is formed in solution. Upon the addition of an uncomplexed unsaturated organic substrate to **1**, selective cross-coupling (Scheme 2) takes place to form metallacyclic product free of homo-coupled (dimeric) side product. The types of complexes that we have prepared using this methodology are shown in Scheme 8. These complexes may generally be isolated as their PMe_3 adducts as air- and moisture-sensitive, thermally stable solids. Unless otherwise noted, complexes **1** were generated in situ and used directly for subsequent transformations.

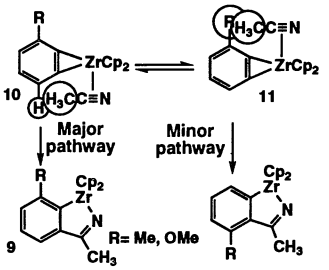
Scheme 8



Zirconocene Complexes of Substituted Arynes

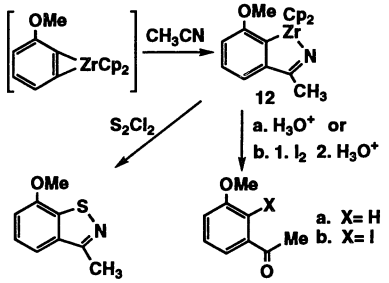
Benzynes. The ability to generate readily zirconocene complexes of substituted benzynes **7** was a significant advance in our chemistry. To examine further the reaction chemistry of these species, we studied the regiochemistry of the reactions of **7**. When **7** (Scheme 6, in which R represents Me or MeO) was generated in the presence of acetonitrile, a reaction to form the corresponding azametallacycle **9** took place with high levels of regiocontrol (*3*, *4*). As is shown in Scheme 9, steric factors control the regiochemical outcome of this transformation. Structures **10** and **11** represent the two intermediates just before insertion that lead, respectively, to the major and minor regioisomers. In both **10** and **11**, the nitrile is bound to the

Scheme 9



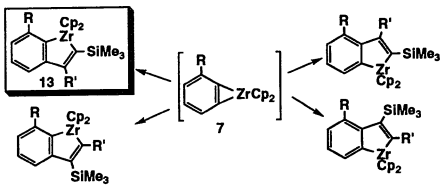
lowest unoccupied molecular orbital, a Zr-centered a_1 orbital (*20*), which lies in the plane of the aromatic ring. In **11**, the Me-*R* interaction is more severe than the Me-H interaction in **10**. This result turns out to be quite general and allows the prediction of the regiochemical outcome of such coupling reactions with high levels of certainty. Shown in Scheme 10 are some of the transformations of **7** that illustrate the synthetic utility of this chemistry. For example, metallacycle **12** (R represents OMe) can be transformed to the anti–Friedel Crafts ketone by hydrolysis. The selective cleavage of the Zr-C bond in **12** by I_2, followed by hydrolysis, provides a novel route to 1,2,3-trisubstituted aromatic compounds. If **12** is treated with S_2Cl_2, the corresponding isothiazoles are produced. The reaction of **7** with nitriles proceeds with high levels of regiocontrol. In addition to the steric arguments presented above, the regiochemical outcome observed is also due to the directing effect of the N atom (see above).

Scheme 10



The reactions of **7** with unsymmetrical alkynes to form the corresponding zirconacyclopentenes **13** provide an increased challenge to the attainment of regiocontrol (*4*). In principle, four regioisomeric metallacycles are possible. At the outset, we felt that steric factors similar to those seen for nitriles would apply to this reaction; thus, the formation of only two regioisomers seemed likely. Earlier work from these laboratories on the reactions of zirconocene complexes of acyclic alkynes (*21*) had shown a distinct regiochemical preference in the reaction of trialkysilylacetylenes for the formation of the regioisomeric metallacycle in which the trialkylsilyl group ends up on the C α to the Zr. As is shown in Scheme 11, when **7** is generated in the presence of a trimethylsilylacetylene, the single regioisomer highlighted is produced with ≥20:1 selectivity.

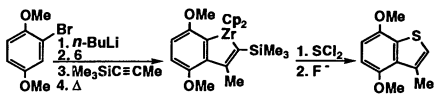
Scheme 11



The relation of the zirconacyclopentenes to a variety of important compounds can be seen by the comparison of their structure to those of indoles, benzo[b]thiophenes, and benzofurans. Therefore, we sought the means to convert **7** to these important species.

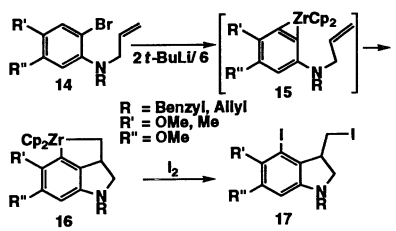
The preparation of benzo[b]thiophenes with the chemistry described above was reasonably straightforward (*22*). We were able to convert simple bromoaromatic precursors to benzo[b]thiophenes by generating **7** in the presence of either a symmetrical alkyne or a trialkylsilylacetylene to produce metallacycles in regiochemically pure form. The treatment of the crude metallacycle with freshly distilled SCl_2 produced the benzo[b]thiophenes, as exemplified in Scheme 12.

Scheme 12



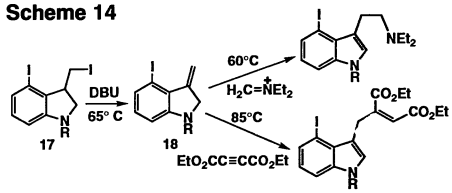
The highly desirable extension of this chemistry to the preparation of indoles proved problematic. In particular, a number of synthetic equivalents of RN^{2+} produced a low yield of the corresponding indoles or failed to produce them at all (*23*). As an alternative, we investigated the reaction sequence in which a zirconocene complex of a benzyne possessing a 3-*N*-allyl substituent, such as **15**, could be generated. In **15**, the olefinic moiety would be suitably disposed to undergo an intramolecular insertion reaction to form the tricyclic metallacycle **16** (Scheme 13). In practice, the treatment of **14**

Scheme 13



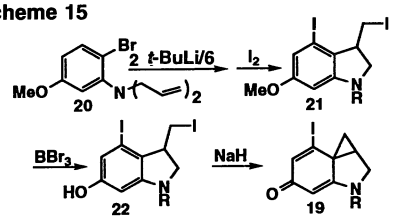
admixed with **6**, in tetrahydrofuran (THF) at −78°C, with 2 eq of *tert*-butyllithium (*t*-BuLi), followed by warming of the reaction mixture to room temperature, produced the indoline metallacycle **16** (*24*–*26*). Treatment of **16**, without isolation, with an excess of I_2 produced the diiodoindoline **17** in ~65% overall yield based on **14**. The sequence **14** → **17** accomplishes three things: a five-membered ring is constructed, a functionalized 3′-methyl group is generated, and a 4-substituted indoline is produced. We have used this methodology to prepare 3,4,5- and 3,4,6-substituted indoline derivatives along with 3,4- and 3,4,5-substituted indoles (*26*). Our first application of this methodology involved the diiodoindoline **17**. The heating of **17** to 65°C in toluene in the presence of the base diazabicycloundecane (DBU) produced the exocyclic methylene indoline **18** in virtually quantitative yield, as judged by proton nuclear magnetic resonance spectroscopy. After removal of the precipitated DBU·HI by filtration, activated enophiles were added to the solution of **18** and the reaction mixture was heated to between 45° and 85°C to effect an ene-type reaction. This sequence provides access to a number of functionalized 4-iodoindole derivatives (*24*) (Scheme 14). Although transition metal–based methods for the construction of 4-substituted indoles have been reported, they usually use 1,2,3-trisubstituted benzene derivatives as precursors (*27*), which are difficult to obtain. Overall, our methodology transforms substrates easily prepared from inexpensive, commercially available 2-bromoaniline to highly substituted indole and indoline species.

Scheme 14



A second application of this chemistry is in the efficient synthesis of the spirocyclic dienone **19** (*25*) (Scheme 15), related to the anticancer agent CC-1065 (*28*). Conversion of the readily prepared **20** to diiodide **21** can be efficiently accomplished with the method described above. Demethylation under standard conditions produced **22**, which can be cyclized to **19** by treatment with a suspension of NaH in THF.

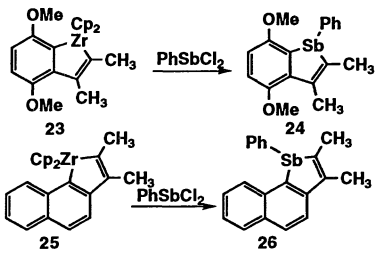
Scheme 15



Indoles and benzo[b]thiophenes are well known to organic chemists. In contrast, the corresponding benzo[b]stiboles had not been previously reported. A report by Fagan and Nugent in 1988 that zirconacycles could

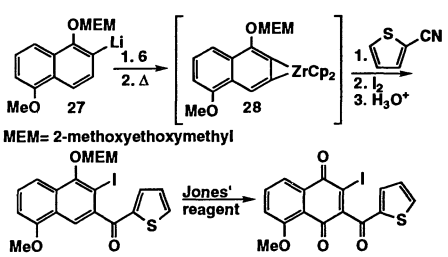
serve as excellent precursors to a number of main-group metallacycles (*29*) led us to combine this methodology with the zirconium chemistry we had developed. In this manner, a variety of interesting main-group compounds can be prepared. The chemistry of these main-group metallacycles has been studied in our laboratories for the last few years (*30*). Our first entry into this chemistry was to apply the Fagan-Nugent transmetallation procedure to zirconacycles of type **7** (*31*). For example, the treatment of zirconacycle **23** with $PhSbCl_2$ produced the first benzo[b]stibole (stibaindole) **24** (Scheme 16). In a similar fashion, zirconacycle **25** was converted to the tricyclic stibacycle **26**. These simple examples illustrate the utility of combining the versatility and efficiency of our zirconocene chemistry with the ease of transmetallation of the Fagan-Nugent procedure to prepare new classes of main-group compounds.

Scheme 16



Naphthalynes. Interest in the development of new methods for the synthesis of substituted naphthalenes (*32*, *33*) prompted us to determine whether the benzyne chemistry could be extended to the synthesis of zirconocene complexes of naphthalynes (*34*) (Scheme 17). Of particular interest was the potential to prepare highly substituted naphthalene derivatives that possess substitution patterns not easily accessible by conventional synthetic techniques. We focused on the preparation of dioxygenated systems, which we felt might be precursors to biologically active naphthoquinone derivatives (*33*). The addition of lithionaphthalene **27** to **6** followed by the addition of a nitrile substrate and iodination of the intermediate metallacycle led to the iodonaphthalene derivatives, with good chemo- and regioselectivity, presumably by way of the naphthalyne complex **28** (Scheme 17).

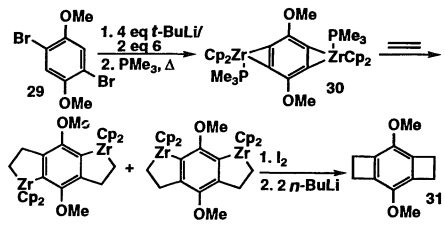
Scheme 17



The iodoacylnaphthalenes were transformed further by oxidation with Jones' reagent into the corresponding iodoacylnaphthoquinones.

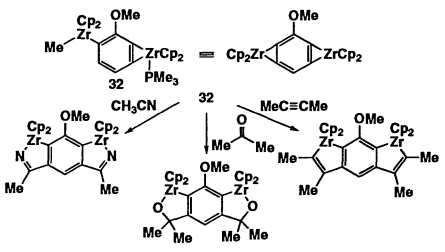
Benzdiyne. The lure of preparing zirconocene complexes of very high energy organic molecules induced us to see whether the chemistry we had developed could be extended to prepare a complex of benzdiyne (by benzdiyne, we refer to a doubly dehydrogenated benzene) (*15*, *35*). This species, in the free state, was calculated to have a strain energy of roughly 130 kcal mol^{-1} (*36*). After some initial experimentation, we found that treating a mixture of dibromide **29** and **6** with 4 eq of *t*-BuLi, adding excess PMe_3, and heating the resulting reaction mixture to 70°C caused the formation of the benzydiyne complex **30**, which subsequently crystallized from the reaction mixture

Scheme 18



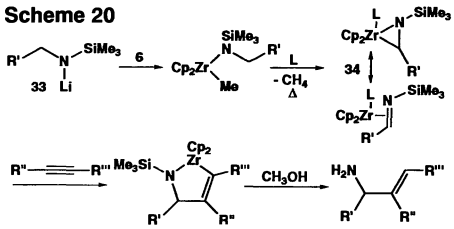
in moderate yield. Complex **30** participated in double insertion reactions, albeit with a low degree of regioselectivity. In one example, *bis*-benzcyclobutene **31** was prepared (Scheme 18). To prepare *bis*-metallacycles in a regiocontrolled fashion, complex **32**, the synthetic equivalent of the 3-methoxybenzdiyne, was prepared (*37*). When **32** was treated with a variety of unsaturated species, a net double insertion process took place to produce the desired *bis*-metallacycles regioselectively (Scheme 19).

Scheme 19



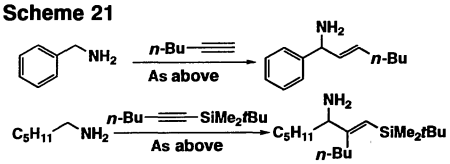
Zirconocene complexes of imines. The chemistry described above deals exclusively with complexes **1**, which contain only Zr-C bonds. Although the use of this methodology to prepare versions of **1** with Zr-heteroatom bonds seemed plausible, it was by no means obvious. We had no success preparing aldehyde complexes from alkoxy (Me) zirconocenes, but thioalkoxy (Me) zirconocenes were smoothly transformed to thioaldehyde complexes upon heating to 80°C in the presence of PMe_3 (*38*). From the viewpoint of organic synthesis, however, we felt that the analogous imine complexes would be more interesting. The desired imine complexes **34**, in fact, could be prepared from a wide variety of simple amine precursors (*4*). The most general protocol, shown in Scheme 20 (in which L represents a ligand), allowed the conversion of primary amines, through their silyl amide

Scheme 20



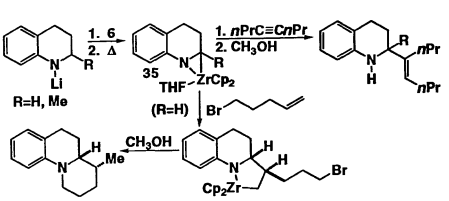
derivatives **33**, to **34**. The N-C bond distance of 1.41(1) Å in **34** (where R′ represents Ph), as seen from the x-ray crystal structure of its THF adduct (not shown), indicates that these molecules are best described as metallaaziridines. Two of the many transformations that could be accomplished are shown in Scheme 21 (*39*). In these, a primary amine and an alkyne are converted to a geometrically pure allylic amine product that is often formed with complete regiocontrol (*40*).

Scheme 21



Whitby and co-workers described the use of similar chemistry to prepare the zirconocene complex of the cyclic aldimine **35** derived from 1,2,3,4-tetrahydroquinoline (Scheme 22) (*41*). This complex was used to prepare a number of interesting heterocycles. This chemistry, which Whitby and colleagues extended to the preparation of ketimine complexes (*42*), has an added virtue in that it may effect the formation of a quaternary center.

Scheme 22

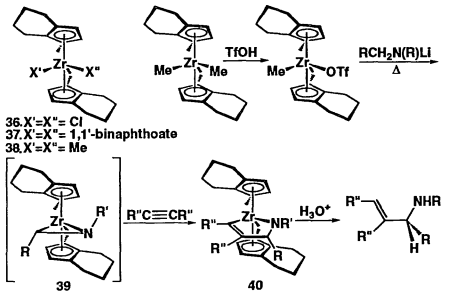


The importance of enantiomerically pure amines encouraged us to determine whether we could develop an enantioselective method to achieve the same type of C-C bond–forming reactions that had been seen by Whitby and co-workers and us with the zirconocene complexes of imines. This task required a chiral analog of zirconocene dichloride, a number of which had been

reported (*43*). Our work (*44*) began with the [1,2-ethylenebis(η^5-4,5,6,7-tetrahydro-1-indenyl)] $ZrCl_2$ (EBTHI $ZrCl_2$) **36** first prepared by Brintzinger (*45–47*) (Scheme 23), which had been synthesized previously in optically pure form (*46*). To obtain larger quantities, however, a new method was required. After a great deal of experimentation, a kinetic resolution method was developed in which enantiomerically pure 1,1′-binaphthyl-2,2′-diol was used (*44–47*). By this method, ~1-g quantities of the enantiomerically pure binaphthoate **37** were prepared. Beginning with **38**, (EBTHI)Zr(Me)OTf (where OTf is CF_3SO_3), a chiral version of **6**, was prepared in optically pure form (Scheme 23), which was used in situ to generate the enantiomerically enriched imine complex **39**. In the presence of internal alkynes, **39** was converted to the azazirconacyclopentenes **40**. The allylic amines were liberated by hydrolysis with aqueous HCl in ether; in most cases the allylic amines formed were found to have enantiomeric excesses ≥95%. The overall transformation is the coupling of a simple amine and an unactivated alkyne to produce a highly enantiomerically enriched and geometrically pure allylic amine (*44*).

To date, this chemistry is mostly of academic interest because of the difficulty in obtaining practical quantities of **38** and because of the stoichiometric nature of the transformation. What we believe is important, however, is the demonstration of a novel method for asymmetric C-C bond formation that uses extremely simple amine and alkyne substrates (*48, 49*). The development of more practical alternatives to **38** and of catalytic versions of this and related transformations are needed to increase the utility of this chemistry in organic synthesis.

Scheme 23

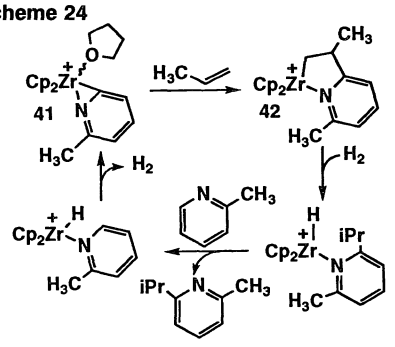


Future Directions

The chemistry described in this article involves the stoichiometric use of zirconocene reagents. Much of this chemistry derives from Cp_2ZrCl_2, a material that is stable in air, and relatively stable when exposed to moisture, and is commercially available at a modest price. There has been a growing emphasis on the development of methods in which a catalytic quantity of a transition-metal reagent is used (*48, 49*). This consideration is especially important when complexes of much more expensive metals are used, such as rhodium or palladium, or as in the case of **38**, when the preparation of the desired metal complex is quite involved.

During the past few years there have been several reports detailing catalytic methods of C-C bond formation that use early transition-metal complexes. For example, Jordan and Taylor reported the preparation of the cationic pyridyne complex **41** (*50*) (Scheme 24). In the presence of propene, **41** was converted to metallacycle **42**. Catalytic quantities of **42** could then be used, in the presence of ~1-atm H_2, to convert α picoline and propene

Scheme 24



to 2-isopropyl-6-methylpyridine. The ability to convert the initially formed metallacycle **42** to product by hydrogenation, with subsequent regeneration of **41** by ligand exchange and cyclometallation, allows this process to proceed in a catalytic fashion.

Other related catalytic processes that use chemistry related to method 1 (Scheme 1) have been reported by Dzhemilev (*51*), Waymouth (*52, 53*), Hoveyda (*54*), Negishi and Takahashi (*55*), Whitby (*56*), their co-workers, and ourselves (*57*). This flurry of activity, we believe, reflects one of the major future trends in this area of research.

Concluding Comments

The chemistry described herein represents a nontraditional means for effecting C-C bond formation in the synthesis of carbocyclic and heterocyclic systems. Its attractiveness stems from its use of simple, often commercially available substrates without the requirement of the normal polar activating groups. Particularly promising is the development of new methods in which an enantiomerically pure catalyst effects asymmetric C-C bond formation between two achiral substrates in chemistry related to that shown in Scheme 23. Careful consideration to functional group compatibility and generality must be made. To achieve success, a great deal of further research in synthetic and mechanistic organometallic chemistry involving metal complexes from all areas of the periodic table is needed. Information that we have gathered in the synthesis and study of **1** should be useful in the development of the chemistry of such complexes.

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RESEARCH ARTICLE

Crystal Structure of a Five-Finger GLI-DNA Complex: New Perspectives on Zinc Fingers

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Zinc finger proteins, of the type first discovered in transcription factor IIIA (TFIIIA), are one of the largest and most important families of DNA-binding proteins. The crystal structure of a complex containing the five Zn fingers from the human *GLI* oncogene and a high-affinity DNA binding site has been determined at 2.6 Å resolution. Finger one does not contact the DNA. Fingers two through five bind in the major groove and wrap around the DNA, but lack the simple, strictly periodic arrangement observed in the Zif268 complex. Fingers four and five of GLI make extensive base contacts in a conserved nine base-pair region, and this section of the DNA has a conformation intermediate between B-DNA and A-DNA. Analyzing the GLI complex and comparing it with Zif268 offers new perspectives on Zn finger-DNA recognition.

Zinc fingers, of the type found in TFIIIA (*1*), are one of the most common DNA-binding motifs in eukaryotic transcription factors. This family of zinc finger proteins is characterized by the consensus sequence X_3-Cys-X_{2-4}-Cys-X_{12}-His-X_{3-5}-His-X_4 (where X is any amino acid residue); more than a thousand such zinc finger sequences have been reported (*2*). The zinc finger forms a compact globular structure that contains a β sheet and an α helix held together by a central Zn ion (*3*). The two cysteines, which are in the β sheet region, and the two histidines, which are in the α helical region, are tetrahedrally coordinated to the Zn. Crystallographic studies of a complex containing the three Zn fingers from the Zif268 protein (*4*) revealed that the Zif fingers bind in the major groove and wrap partway around the double helix. Residues from the NH_2-terminal portion of each α helix contact the bases, and a conserved pattern of side chain-base interactions is observed in the Zif complex.

Although only a small number of the known Zn finger proteins have been characterized in detail, it is clear that this family of proteins can recognize a diverse set of DNA sequences. For example, the *Drosophila* Hunchback protein recognizes a site that includes the sequence AAAAA (*5*); the human Sp1 protein recognizes a site that includes the sequence GGGGGC (*6*); and the human glioblastoma (GLI) protein recognizes a site that includes the sequence TGGGTGGTC (*7*). Preliminary attempts to model other Zn finger complexes suggested that Zif might provide a reliable basis for modeling complexes formed by closely related proteins [such as Sp1 and WT1 (*8*)], but it did not appear that Zif would provide a satisfactory basis for modeling complexes formed by other, more distantly related Zn finger proteins.

To help understand how Zn fingers can recognize such a diverse set of binding sites, we have studied a complex that contains the five Zn fingers from the human *GLI* oncogene. The *GLI* gene was first discovered because it was amplified in human glioblastomas (*9*), and GLI was later found to be amplified in other tumors (*10*). In vitro studies have shown that the GLI protein, in conjunction with the adenovirus E1A protein, can transform primary rodent cells (*11*). GLI is a sequence-specific DNA-binding protein, and three high-affinity sites have been recovered from a pool of human genomic DNA (*7*). Our crystals contain the five Zn fingers of the human GLI protein (Fig. 1A) bound to a 21–base pair (bp) DNA fragment (Fig. 1B) that includes a high affinity DNA-binding site. We now describe the crystal structure of the GLI complex at 2.6 Å resolution, compare it with Zif, and consider the broader implications for our understanding of Zn finger–DNA interactions.

Overall structure of the GLI complex. The overall structure of the GLI-DNA complex shows that fingers 2 to 5 fit in the major groove and wrap around the DNA for a full helical turn (Fig. 2 and Table 1). Finger 1 surprisingly does not contact the DNA but instead makes extensive protein-protein contacts with finger 2. The overall arrangement of the other fingers is generally similar to that observed for the fingers in the Zif complex. The α helix of each finger fits into the major groove, and the NH_2-terminal portion of each of these α helices

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