Study of the Configuration Stability of the Carbon – Zinc Bond, Direct Measurement of Enantiomeric Ratios, and Tentative Assignment of the Absolute Configuration in Secondary Organozinc Halides**

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The determination of the stereochemical features of reactions involving organometallic species is a long-standing issue, which is still to be appropriately addressed. The study of the stereochemistry of products after a reaction of an organometallic species with a suitable electrophile has been the most commonly used strategy,[1] and often the only possible approach.[2] However the term "suitable electrophile" is intrinsically imprecise. The reaction of an organometallic reagent with an electrophile is always a possible source of interference when the goal is to study the organometallic compound itself. The degree of retention/inversion/loss of stereochemical integrity is highly specific for each organometallic – electrophile pair and is therefore not available in many cases. Different electrophiles can give rise to a different distribution of products with partial (or complete) retention (or inversion) of their configurations.[3] Even though retention of configuration is the most common reaction pathway, the exact behavior of each particular system is, at the present time, simply unpredictable.[4, 5]

Among the different organometallic reagents utilized in organic chemistry, organozinc compounds occupy an intermediate position in terms of the electronegativity of the metal and hence reactivity. As a general trend for organometallic reagents devoid of functionality, the more covalently bonded species are those which display high energy barriers to inversion of the carbon center (or topoisomerization barriers),[6] and vice versa. Thus, activation energies for inversion in primary organometallic compounds of the type R_nM increase in the order $M = Li < Mg < Zn$, and the inversion of Al and Hg compounds is slow on the NMR time scale.[7a,b] In general, NMR spectrometers are designed to operate between 200 °C and -100 °C or less, which allows the study of a wide range of systems with activation energies ranging from approximately 5 to 25 $kcal\,mol^{-1}$.[8] When the experimental conditions permit the observation of coalescence the information obtained is very valuable.[7a–e] However, in the cases in which the inversion is slow on the NMR time scale, the ultimate question about the preservation of the configurational integrity of the organometallic species on a macroscopic time scale remains unanswered. This is the case for most secondary organometallic compounds, which are, otherwise, far more interesting than primary ones for possible synthetic applications. It is not surprising that secondary organozinc bromides invert slowly under the conditions of the experiment (200 MHz ^1H NMR, 1.5 M in THF, 150 °C) since the inversion rates for secondary organolithium or Grignard reagents could not be obtained in this way.[7f,g] Stereocontrolled preparation and reaction of organozinc compounds is, however, a very active field of research. Diastereomeric cyclic secondary organozinc halides were prepared as mixtures of isomers that appear to be configurationally stable under the experimental reaction conditions used (RZnI; $E^+ = I_2$, Bu_3SnCl).[9] The distribution of products was found to be dependent on the electrophile E^+. Other cyclic and acyclic diastereomerically enriched mixed diorganozinc species have also been prepared and their stereochemistry studied after reaction with electrophiles (RZn*i*Pr; $E^+ = D_2O$, $CuCN \cdot 2\,LiBr$ + allyl bromide).[10] In other studies, benzylic secondary organozinc halides were found to be labile at ambient temperature under the reported reaction conditions (RZnX; $E^+ = D_2O$).[11]

We have attempted to observe the configuration of organozinc halides directly by NMR spectroscopy by employing chiral solvating agents.[12, 13] After a survey of different chiral ligands (including mono- and diamines, protected diols and binaphthols, diphosphanes, boranes, and alkaloids) some chiral bis(oxazoline) ligands (box-ligands) were identified that displayed two sets of signals in the ^1H NMR spectrum of complexed 2-butylzinc bromide. This organozinc substrate was chosen for its simplicity, with the aim of developing a general method applicable to the measure of enantiomeric excesses in more complex systems. Several 2,2′-bis(oxazoline) and methylene, isopropylidene, and 2-indanylidene 2,2′-bis(oxazoline) ligands, all C_2 symmetrically substituted (for example, 4,4′-Ph_2, -Bn_2, -*t*Bu_2, or 4,4′,5,5′-Ph_4) were tested. Among them, (+)-2,2′-isopropylidene-bis((*R*)-4-phenyloxazoline) ((*R*)-**1** or (+)-**1**) gave the best results in terms of $\Delta\Delta\delta$ values. The dynamic behavior of organometallic compounds in solution involves inversion at the carbon atom bonded to the metal center, carbon – metal exchange, and ligand – metal coordination exchange. A fast dynamic equilibrium in solution, a product of these last two processes, generates surprisingly simple NMR spectra at room temperature (Scheme 1a, Figure 1a – c). The fact that two sets of signals occur, which correspond to the two enantiomers of the organozinc reagent (1:1 ratio), indicates by itself that inversion of configuration is slow on the NMR time scale. This observation has little significance from a synthetic point of view,[14] and could be inferred from data in the literature.[7] The search for a different test to determine the limits of the configurational robustness of the C-Zn bond in organozinc bromides was undertaken. Under fast equilibrium conditions two racemic reagents will generate only one set of signals, even though two pairs of diastereomers are formed. Indeed, the use of a racemic ligand afforded a single set of signals, as expected for a fast complexation equilibrium (Figure 1d and

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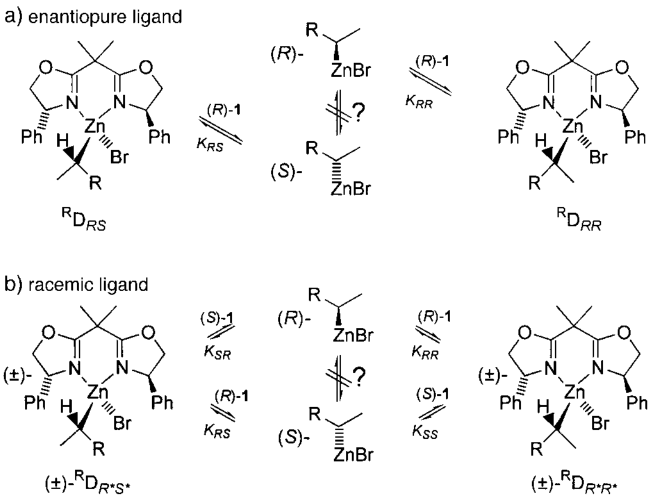


Scheme 1. Complexation equilibria of 2-butylzinc bromide (R = Et) or (1-phenylprop-2-yl)zinc bromide (R = Bn) with: a) (R)-**1**; b) (RS)-**1**. $K_{RS} = K_{SR} = K_{R^*S^*}$; $K_{RR} = K_{SS} = K_{R^*R^*}$. The ratio of the concentration of both diastereomers, measured in the racemic system, is the equilibrium constant between these diastereomers ($^{R}D_{RS} \rightleftharpoons {}^{R}D_{RR}$); $^{R}K = K_{RR}/K_{RS} = [^{R}D_{R^*R^*}]/[^{R}D_{R^*S^*}]$.

e). The equilibrium can be frozen at $-50\,^{\circ}C$ and two sets of signals, analogous to those observed using an enantiopure ligand but in the appropriate ratio, are again observed in the NMR spectrum (Figure 1 f). The ratio now corresponds to the *thermodynamic* equilibrium constant, which depends on the relative stabilities of both diastereomeric complexes, and is in general $\neq 1{:}1$. This ratio is $^{Et}K = K_{RR}/K_{RS} = 1.01{:}1$ for 2-butylzinc bromide at $-50\,^{\circ}C$ (R = ethyl, Scheme 1 b, Figure 1 f), which is right at the limit of the sensitivity of the integration.[15]

Differences in steric hindrance between Me and Et are not large and results in the equilibrium constant for $^{Et}D_{RR} \rightleftharpoons {}^{Et}D_{RS}$ (^{Et}K) being close to 1. Substitution of Et by Bn modifies the final equilibrium composition, with $^{Bn}K = 2.70$ (R = benzyl, Scheme 1, Figure 2 f) at $-30\,^{\circ}C$. The rate of inversion of the secondary C-Zn bond could be measured using this last organozinc bromide. The spectrum of (1-phenylprop-2-yl)zinc bromide in the presence of one equivalent of (R)-**1** showed two sets of signals in a 1:1 ratio (Figure 2 b). This is not a steady state. The rate at which the composition of the diastereomeric/enantiomeric mixture will spontaneously evolve from 1:1 to approximately 2.70:1, that is reach the thermodynamic equilibrium, will depend on the rate of inversion of the C-Zn bond.[16] In other words, the presence of a chiral ligand shifts the composition of the initial racemic mixture of the organozinc bromide from 1:1 to another value corresponding to the new thermodynamic equilibrium in that chiral medium. A good estimate of this new equilibrium is obtainable using the racemic ligand approach. From the rate laws of interconversion of both enantiomers, represented by Equation (a), the equations that describe the exponential approach to the final equilibrium can be easily deduced [Eqs. (b) and (c)]. In the simplest approximation to the

$$D_{RR} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} D_{RS} \qquad K = \frac{k_1}{k_{-1}} \tag{a}$$

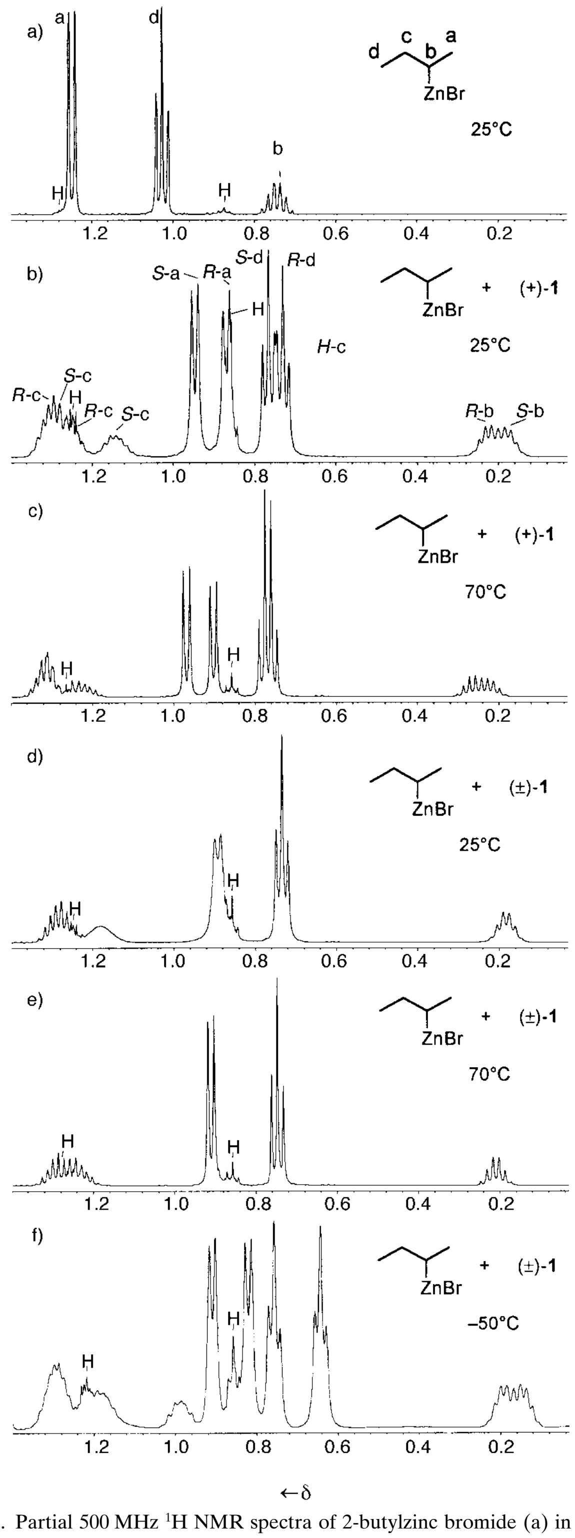


Figure 1. Partial 500 MHz ^{1}H NMR spectra of 2-butylzinc bromide (a) in the presence of one equivalent of (R)-**1** (b, c) or its racemic counterpart (RS)-**1** (d–f) at several temperatures. The butane side product is represented by H. The peaks of the methylene protons c are not shown in spectrum (a) because they overlap with the solvent peak. Assignments of the absolute configurations were made on the basis of predicted anisotropic effects, and are illustrated in spectrum (b).

$$(1 + K)[D_{RR}] - 1 = \frac{K - 1}{2}\,e^{-(k_1 + k_{-1})t} \tag{b}$$

$$K - (1 + K)[D_{RS}] = \frac{K - 1}{2}\,e^{-(k_1 + k_{-1})t} \tag{c}$$

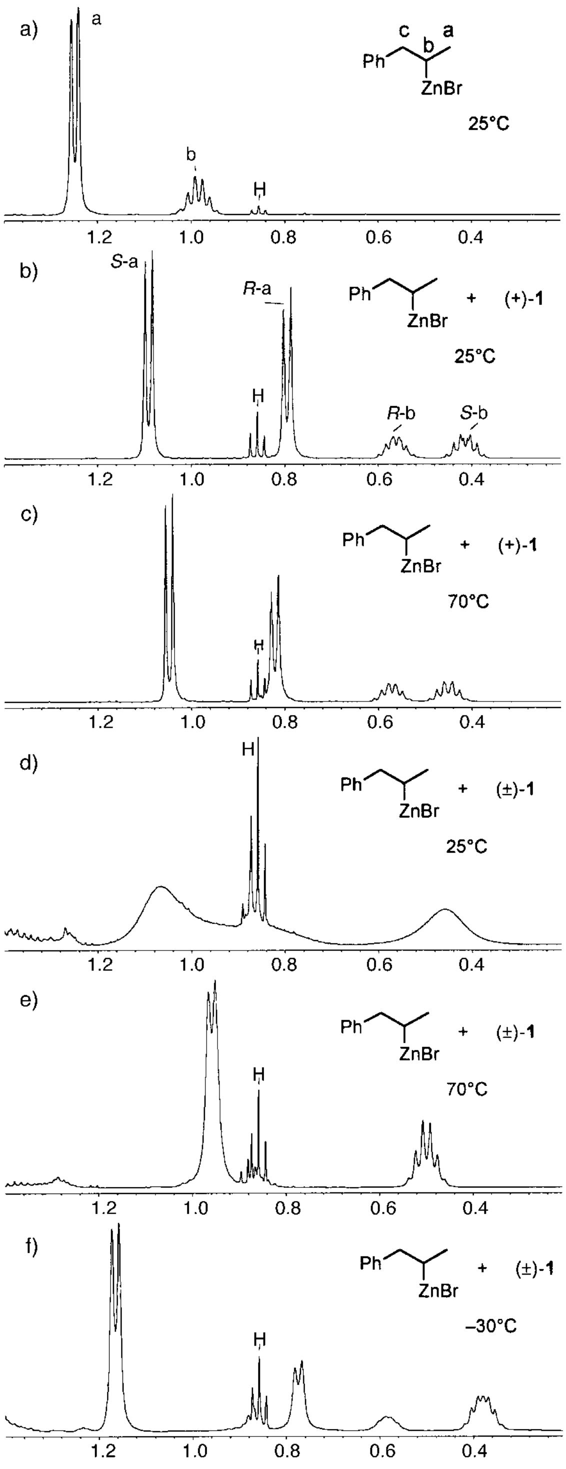


Figure 2. Partial 500 MHz ^{1}H NMR spectra of (1-phenylprop-2-yl)zinc bromide (a) in the presence of one equivalent of (*R*)-**1** (b, c) or (*RS*)-**1** (d–f) at several temperatures. The 1-phenylpropane side product is represented by H. Methylene protons (c: 2.75–2.95 (2H, m, CH_2) in spectrum (a) are not shown. Assignments of the absolute configurations were made on the basis of both free-energy criteria and predicted anisotropic effects, and are illustrated in spectrum (b).

mechanism of inversion, a monomolecular transition state is assumed.[7a] D corresponds to the averaged signal of the actual diastereomer and the free organozinc reagent in fast equilibrium, as observed by NMR spectroscopy. A sample of BnCH(ZnBr)Me + (*R*)-**1** was monitored by ^{1}H NMR spectroscopy over nine days. The evolution of both diastereomers was slow, but perceptible, as they grew towards the predicted ratio (^{Bn}K varies only slightly with temperature).[16] The results, plotted as a function of Equations (b) or (c) are represented in Figure 3. From the slope, $k_1 + k_{-1} = 0.00024\,h^{-1}$, a half-life of $t_{1/2} = 4.0$ months is obtained for the inversion of the secondary carbon atom. This value corresponds to a free energy of activation $\Delta G^{\neq} = 27.2\,kcal\,mol^{-1}$ at 25 °C. The data collected represents only the early stages of the system in reaching equilibrium. However, it also carries information about the final equilibrium. From the ordinate value at $t = 0$, we can also obtain a perhaps better determination of ^{Bn}K at room temperature as $^{Bn}K_{25^\circ C} = 2.60$.

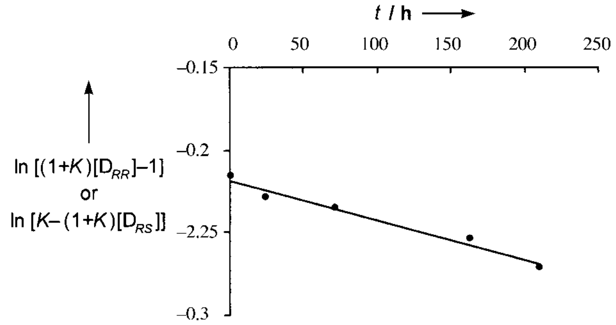


Figure 3. Kinetic plot showing the evolution of a mixture of (±)-$PhCH_2CH(ZnBr)CH_3$ + (*R*)-**1** towards the thermodynamic equilibrium, according to Equations (b) and (c). Slope: $k_1 + k_{-1} = 2.42 \times 10^{-4}\,h^{-1}$, ordinate origin: $\ln[(K-1)/2] = -0.22$, correlation coefficient = 0.98. The concentration of both diastereomers was obtained by averaging the Me and α-H signals. An approximately constant amount of phenylpropene was corrected for by normalizing the overall $D_{RR} + D_{RS}$ concentration to 1. The lifetime of the inversion process at 25 °C is 4130 h.

The scenario depicted so far requires an empirical model to perform NMR assignations of the absolute configuration in these organometallic compounds. Unfortunately no NOE could be observed at low temperature in this dynamic system, and other NMR experiments were also unsuccessful. Both inductive effects from the chelated Zn center and anisotropic effects from the phenyl group in the ligand explain the large upfield shifts observed. However, only the latter is responsible for the differences in the chemical shifts between the two diastereomers. The intrinsic geometric character of the anisotropic effect may certainly render some structural insights, provided that previous knowledge about the conformations involved is available. Conformational analyses on ^{Et}D and ^{Bn}D were best accomplished using PM3 semiempirical calculations.[17] These not only provided a reliable picture of the conformational equilibrium for each diastereomer, but also an excellent way to analyze differences in the energies in these organometallic complexes. The ligand (*R*)-**1** was used in all the analyses. Most of the structure in the complex is rigid, which limits considerably the number of degrees of freedom in the final conformational equilibrium and hence facilitates the analysis.

A rather simple scenario is found, which describes the geometry of the final set of conformers on the basis of two main characteristics: a) the metallacyclic subunit is slightly twisted from a flat conformation, with an approximately tetrahedral Zn atom. For (*R*)-**1**, only the (*P*)-twist (or (*R*)-twist, since the twist is a chiral conformation) is an energy minimum; b) three main conformations are observed, which correspond to the three rotamers of the α-carbon atom relative to the zinc center: C_H (H *anti* to Br, as in Scheme 1), C_{Me} (Me *anti* to Br), and $C_{Et/Bn}$ (Et or Bn *anti* to Br; Figure 4, Table 1). The conformations of the remaining bonds are mostly trivial. In general, these geometric patterns match those actually observed in the crystal structure of $[(S)\text{-}\mathbf{1}\cdot ZnCl_2]$.[18] Table 1 shows the thermodynamic description of the complexation process, as obtained from PM3 calculations. We include enthalpies $\Delta H^\circ = \Sigma_i n_i \Delta H^0_{i\,\text{form.}}$, and from them, calculated populations (n), entropies of mixing[19] ($S_{mix} = -R\Sigma_i n_i \ln n_i$), free energy ($\Delta G^0 = \Delta H^0 - T\Delta S^0$), and predicted $K_{25^\circ C}$ for the given equilibrium. The assignment of the NMR signals for R = Bn to nuclei in the *R* and *S* enantiomers was made on the basis of both free energy criteria and expected anisotropic effects. Energetic criteria are not applicable to 2-butylzinc bromide since the ratio of signals falls within the experimental error of the integration. On the other hand, anisotropic effects are more reliable for 2-butylzinc bromide since interferences from an intramolecular aromatic group (Bn) are not present. In general, the shielding provoked by the (*R*)-5-phenyl substituent, relative to the nonchiral complexation, is expected to be more intense in the group *anti* to the bromide ion in the first place, then in the β-group facing the phenyl ring, and, finally, weaker still in the β-group opposite to the phenyl ring (for example, α-H > β-CH$_2$ > β-CH$_3$ for C_H of $^{Et}D_{RS}$, Figure 4a). Table 2 summarizes the predicted relative anisotropic chemical shifts for the major conformation of each diastereomer displayed in Figure 4. The observed chemical shifts matched the predictions for α- and β-hydrogen atoms and allowed interpretation of the spectra in terms of absolute configurations. Indeed, this was confirmed by a COSY experiment performed at −50 °C, which revealed the expected correlation between the signals. Their absolute configuration assignments are indicated in Figures 1b and 2b.

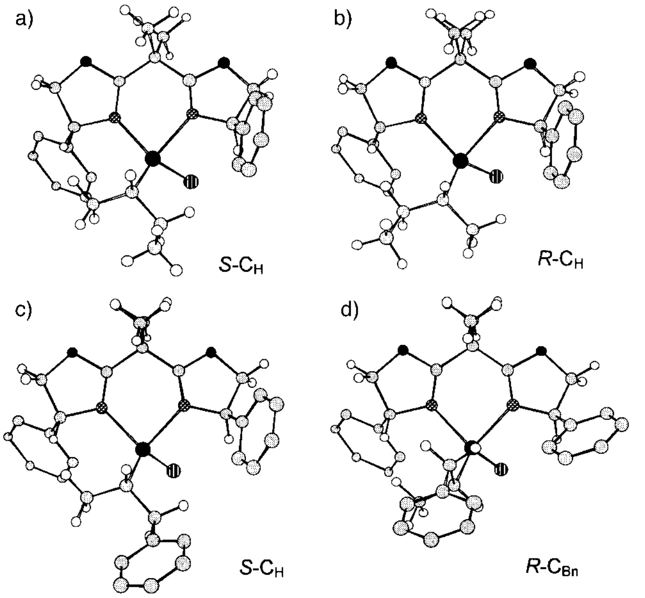
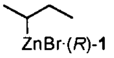
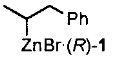


Figure 4. Major conformers of each diastereomer as obtained from PM3 calculations. Hydrogen atoms on the phenyl rings are omitted for clarity. Other conformations in Table 2 can be approximated by rotation of the α-C–Zn bond. Conformations without an α-hydrogen atom on the phenyl side are always high energy and other metallacyclic conformations may occur. In structure (d) the natural orientation of the phenyl ring is altered by the presence of the benzyl group.

Table 1. Thermodynamic description of the organozinc–ligand complexation at 25 °C based on PM3 energies.[a]

 ZnBr·(*R*)-1	$^{Et}D_{RR}$ (major)			$^{Et}D_{RS}$ (minor)		
Conformer	C_H	C_{Me}[b]	C_{Et}	C_H	C_{Me}	C_{Et}[b]
$\Delta H^0_{\text{form.}}$[c]	−25.02	−23.93	−24.74	−25.09	−24.58	−23.90
n[d]	0.560	0.090	0.349	0.640	0.273	0.087
$^{Et}D_{RS} \rightleftharpoons {}^{Et}D_{RR}$	$\Delta H^0 = 0.026$ kcal mol^{-1}; $\Delta S^0 = 0.11$ cal mol^{-1} K^{-1} $\Delta G^0 = -0.008$ kcal mol^{-1}; $^{Et}K_{25^\circ C} = 1.01$					
 ZnBr·(*R*)-1	$^{Bn}D_{RS}$ (major)			$^{Bn}D_{RR}$ (minor)		
Conformer	C_H	C_{Me}	C_{Bn}[b]	C_H	C_{Me}	C_{Bn}
$\Delta H^0_{\text{form.}}$[c]	6.62	8.24	8.49	8.10	8.38	7.36
n[d]	0.903	0.058	0.039	0.194	0.122	0.684
$^{Bn}D_{RR} \rightleftharpoons {}^{Bn}D_{RS}$	$\Delta H^0 = -0.84$ kcal mol^{-1}; $\Delta S^0 = -0.90$ cal mol^{-1} K^{-1} $\Delta G^0 = -0.57$ kcal mol^{-1}; $^{Bn}K_{25^\circ C} = 2.61$					

[a] Corresponding to isolated molecules. [b] In highly congested conformations, boatlike deviation geometries were found to have energies close to those of the twist ones, which only affects the thermodynamic parameters marginally. [c] Fully optimized $\Delta H^0_{\text{form.}}$ [kcal mol^{-1}] values were obtained after an exhaustive search for minima in the energy surfaces. [d] Populations based on a Boltzmann distribution.

Table 2. Predicted relative anisotropic chemical shifts.[a]

	$^{Et}D_R$		$^{Bn}D_R$	
Configuration[b]	*S*	*R*	*S*	*R*
α-H	up	up	up	down[c]
β-CH$_3$	weak	up	weak	up[d]
β-CH$_2$	up	weak	up[e]	down[c, f]
γ-CH$_3$	down[g]	up[g]	—	—
model	4a	4b	4c	4d

[a] Based on the major conformation for each diastereomer, which are represented in Figure 4. Up = upfield. [b] Configuration of the organozinc; the ligand is always *R*. [c] Downfield anisotropic chemical shift resulting from a group approximately coplanar to the phenyl ring. [d] Tentatively assigned to intramolecular shielding from the benzyl group. [e] Not shown: 1.84 (1 H, dd, J = 12.2, 10.4 Hz, PhCH*H*) and 2.24 (1 H, dd, J = 12.2, 6.7 Hz, PhC*H*H). [f] Not shown: 2.02 (1 H, dd, J = 13.3, 9.1 Hz, PhCH*H*) and 2.49 (1 H, dd, J = 13.3, 5.3 Hz, PhC*H*H). [g] Groups further than the β position do not seem to obey a simple scheme of anisotropic effects.

The procedure reported herein constitutes a straightforward way to measure enantiomeric ratios of reactive organometallic species directly by NMR spectroscopy[20] by using a chiral solvating reagent, as well as an easy way of testing for racemization in carbon–metal bonds without having to prepare an enantiomerically enriched organometallic reagent. Kinetic parameters for the inversion in the presence of the ligand can be calculated. The chemical shift of the α-hydrogen atom is conveniently separated from the main areas of solvent and other resonances; typical $\Delta\Delta\delta$ values for these and other signals range from 0.1–0.3 and increase as the temperature lowers. Finally, an empirical model based on PM3 conformational analysis permits a tentative assignment of configurations at the carbon atom α to the metal, relative ligand on the basis of both anisotropic effects and free energy criteria. Structural studies aimed at finding definitive proof for the assignment of the absolute configuration as well as studies of other organometallic species are underway.

Experimental Section

Organozinc bromides were obtained by reaction of active zinc with the corresponding bromides, previously distilled over P_2O_5, in dry THF at RT in an Ar atmosphere.[21]. (*R*)-**1** and (*S*)-**1** were purified by precipitation with $ZnCl_2$ (THF), extraction (0.2 M aqueous NaCN in $CHCl_3$), and vacuum distillation. (*RS*)-**1** ($[\alpha]_D^{25} = 0.0$) was prepared by mixing equal amounts of the former reagents. The concentration in all the NMR experiments was 0.5 M in THF/C_6D_6 (1/1), except for those performed at 150°C in which it was 1.5 M in THF/[D_8]THF (4/1). TMS was added as an internal standard.

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[15] Deconvolution and analytical integration of signals was performed throughout, both for superposed and nonsuperposed peaks. The ratios were compared for two sets of signals belonging to the same molecule (for example, Me and α-H), the deviation being $< 2\%$ in all cases.

[16] In conditions of intermediate exchange (for example, Figure 2d) the spectra obtained at ≤ 10°C showed broad signals for both diastereomers in a ratio only slightly smaller than that observed at −30°C.

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[20] For example, the 2-octylzinc bromide prepared from (*R*)-2-bromooctane in ref. [2b] has now been unambiguosly identified as racemic by using this method.

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Electrochemical Oxidation of Water to Dioxygen Catalyzed by the Oxidized Form of the Bis(ruthenium–hydroxo) Complex in H_2O**

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Much attention has been paid to the oxidation of water to dioxygen by homogeneous catalysts. Of particular interest are di- and tetranuclear transition metal complexes, since extended X-ray absorption fine structure studies have indicated that the O_2-evolving center (OEC) in photosystem II is composed of a tetranuclear Mn cluster with dimeric di-μ-oxo Mn units.[1] A variety of di- and tetranuclear metal complexes have been prepared as structural models of the OEC, and four-electron oxidation of water has been attained with only a few dinuclear metal (Mn, Ru) complexes.[2–4] The key intermediates for O_2 evolution in the OEC is thought to be high-valent metal–oxo complexes derived from aqua

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