Stability of the Metal Configuration in Chiral-at-Metal Half-Sandwich Compounds

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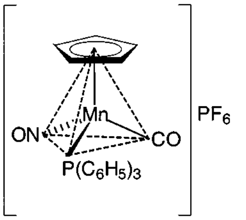
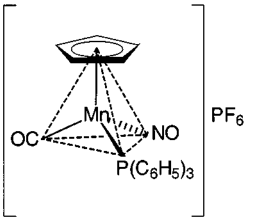
Half-sandwich compounds with a three-legged piano-stool geometry are prominent examples of optically active chiral-at-metal complexes. In these compounds, the configuration at the metal atom may be stable or labile in solution. Configurationally stable compounds can be used for the elucidation of the stereochemical course of substitution reactions and for organic synthesis in ligand transformation reactions. With configurationally labile compounds, the rate of change of the metal configuration can be measured, which sets an upper limit with regard to the handling of the compounds in solution. Surprisingly, in a number of recent papers the lability of the metal configuration has been overlooked resulting in misinterpretations and wrong conclusions.

Introduction

Organometallic compounds of the transition elements with chiral metal atoms can be resolved with respect to the metal configuration for many different ligand combinations and geometries.[1−21] As discussed in a recent review,[1] pseudo-tetrahedral half-sandwich complexes with a three-legged piano stool geometry, as in ***R***$_{\mathrm{Mn}}$-**1** and ***S***$_{\mathrm{Mn}}$-**1**,[22,23] are prominent examples. For the specification of the metal configuration, see refs.[24,25]



R$_{\mathbf{\mathit{Mn}}}$**-1**



S$_{\mathbf{\mathit{Mn}}}$**-1**

In a classical resolution procedure, a racemic mixture is converted into a pair of diastereomers by introducing an enantiomerically pure auxiliary. The auxiliary is then removed from the separated diastereomers to give the resolved enantiomers. The ultimate goal of such a resolution is to obtain both enantiomers in pure form. Enantiomers have mirror image chiroptical properties but give identical NMR spectra; their NMR differentiation is only possible with the help of chiral shift-reagents.

Diastereomers differ in their physical properties, such as solubility, and usually also in their ^{1}H NMR spectra. Therefore, the progress of the diastereomer separation can be monitored by NMR spectroscopy and the diastereomer ratio can be determined by the integration of suitably resolved signals. Thus, the NMR spectrum of a given diastereomer shows whether the "other" diastereomer is present or absent, without the need for the addition of a chiral shift-reagent. As far as NMR differentiation is concerned, diastereomers thus contain more information than enantiomers.

In most of the organometallic compounds described herein, the optically active auxiliary is part of one of the ligands. Usually, it is not easy to remove the chiral auxiliary after diastereomer separation. Therefore, resolution proced-

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ures frequently stop after separation of the diastereomers, which differ only in the configuration at the metal atom.

In solution, the chiral-at-metal compounds behave differently. Some of them prove to be configurationally stable; their metal configuration does not change even at higher temperatures. Others are labile with respect to the metal configuration; the isomers interconvert at various rates. The solution behavior is in contrast to the behavior in the solid state. All of the organometallic compounds discussed herein are configurationally stable at the metal atom in the solid state, even those which are configurationally labile in solution. This fact was already emphasized in the very first study.[22] It is the configurational stability at the metal center in organometallic compounds in solution which is the key aspect of this Microreview. The configurational stability sets an upper limit with regard to the handling of a given compound in solution and to the conditions for its reactions in which the stereochemical course with respect to the metal center is to be elucidated. It also determines the accessible temperature range for measuring the kinetics of the change of the metal configuration. Another reason for taking up the issue of the stability of the metal configuration in this Microreview is its misinterpretation in a number of recent papers, which has led to wrong conclusions (see later).

Measurement of the Change of Configuration at the Metal Atom

The configurational change at the metal atom can be monitored by polarimetric measurements. In such measurements, enantiomeric complexes that contain only chiral metal atoms approach the 1:1 racemization equilibrium. Figure 1 shows the decrease in the optical activity and the approach to the racemization equilibrium $\boldsymbol{R}_{\text{Mn}}$-**2** $\leftrightarrows$ $\boldsymbol{S}_{\text{Mn}}$-**2**.[26]

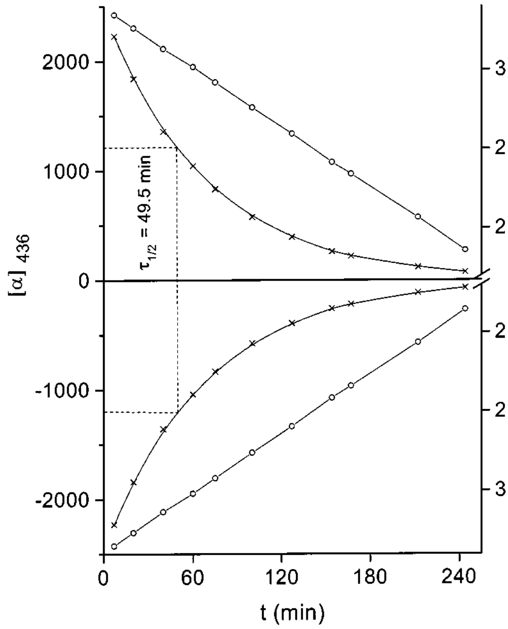
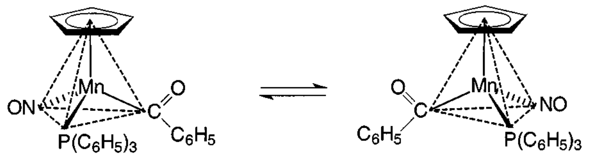


Figure 1. Racemization of $\boldsymbol{R}_{\text{Mn}}$-**2** and $\boldsymbol{S}_{\text{Mn}}$-**2** in toluene solution at 20 °C

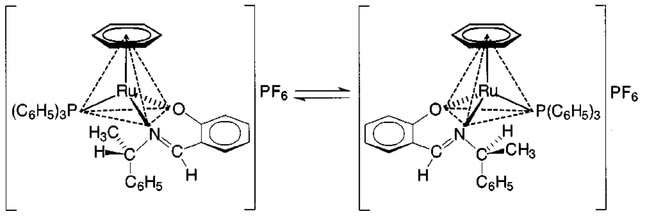


$\boldsymbol{R}_{\boldsymbol{Mn}}$-**2** $\boldsymbol{S}_{\boldsymbol{Mn}}$-**2**

If the diastereomers which are used in such polarimetric studies contain, besides the configurationally labile metal atom, configurationally stable asymmetric carbon atoms, the epimerization at the metal atom results in equilibria with nonzero optical rotations and equilibrium ratios displaced from 1:1. Under these circumstances, the equilibrium ratio of two diastereomers that differ only in the metal configuration gives a measure of the chiral induction of the enantiomerically pure ligand on the metal configuration under thermodynamic control.[15]

Because organometallic complexes of the transition elements are generally colored and absorb strongly in the visible region, the transparency in the polarimetric measurements is usually limited. Therefore, only dilute solutions can be studied, the air-sensitivity of which represents a possible source of error in such measurements.

Diastereomers such as $\boldsymbol{R}_{\text{Ru}}\boldsymbol{S}_{\text{C}}$-**3** and $\boldsymbol{S}_{\text{Ru}}\boldsymbol{S}_{\text{C}}$-**3** differ in their ^{1}H NMR spectra.[27,28] Thus, the kinetics of the configurational change at the metal atom can be followed by time-dependent integration of suitable signals. In this technique, the quantities to be used are larger, the possibilities for the exclusion of air are better and, therefore, the results are more reliable than those obtained from polarimetry. Figure 2 shows the change in the concentration of the complexes $\boldsymbol{R}_{\text{Ru}}\boldsymbol{S}_{\text{C}}$-**3** and $\boldsymbol{S}_{\text{Ru}}\boldsymbol{S}_{\text{C}}$-**3** as a function of time, as measured by ^{1}H NMR spectroscopy, during approach of the epimerization equilibrium $\boldsymbol{R}_{\text{Ru}}\boldsymbol{S}_{\text{C}}$-**3**/$\boldsymbol{S}_{\text{Ru}}\boldsymbol{S}_{\text{C}}$-**3** = 95.8:4.2 in $CDCl_3$ solution, and its interpretation according to first-order kinetics.[27,28]



$\boldsymbol{R}_{\boldsymbol{Ru}}\boldsymbol{S}_{\boldsymbol{C}}$-**3** $\boldsymbol{S}_{\boldsymbol{Ru}}\boldsymbol{S}_{\boldsymbol{C}}$-**3**

In most cases, the configurational change at the metal atom is a first-order process. Therefore, a convenient measure of the configurational stability is given by the half-life $\tau_{1/2}$. The half-life for the approach to the racemization equilibrium of complexes $\boldsymbol{R}_{\text{Mn}}$-**2** and $\boldsymbol{S}_{\text{Mn}}$-**2** in toluene at 20 °C is 49.5 min,[26] while the half-life for the approach to the epimerization equilibrium of complexes $\boldsymbol{R}_{\text{Ru}}\boldsymbol{S}_{\text{C}}$-**3** and $\boldsymbol{S}_{\text{Ru}}\boldsymbol{S}_{\text{C}}$-**3** (Figure 2) in $CDCl_3$ at 12 °C is 25 min.[27] Thus, a

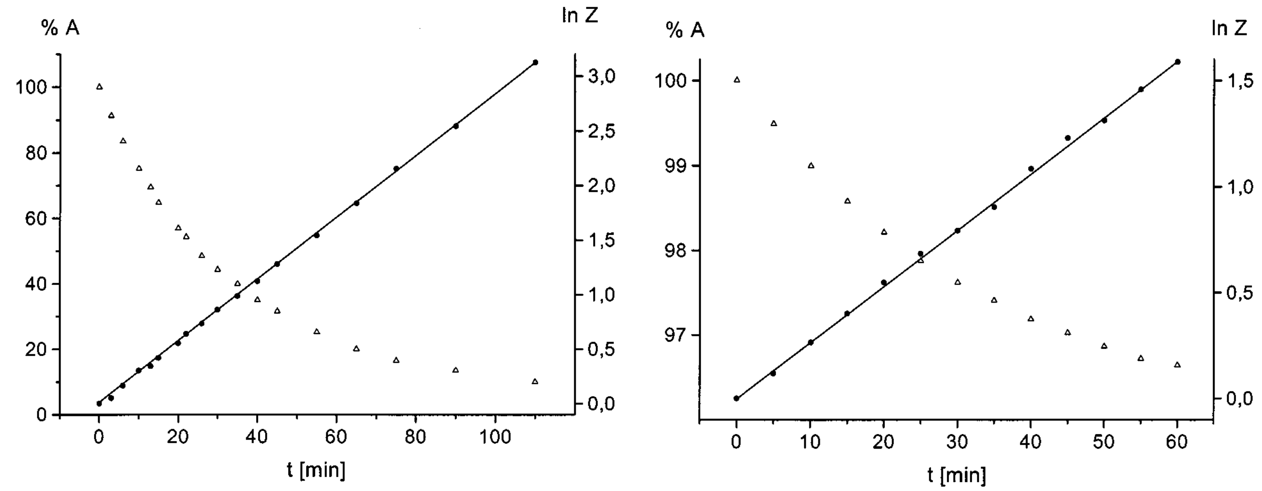


Figure 2. Epimerization of $R_{Ru}S_C$-**3** (left side) and $S_{Ru}S_C$-**3** (right side) in $CDCl_3$ solution at 12 °C; left ordinates: $[A_t]$ by ^1H NMR integration; right ordinates: ln$Z$, where $Z = ([A_o] - [A_\infty])/([A_t] - [A_\infty])$

change in the configuration at the metal atom takes place in solution in both cases, although this is much faster for $R_{Ru}S_C$-**3** and $S_{Ru}S_C$-**3** than for R_{Mn}-**2** and S_{Mn}-**2**.

As first-order reactions are not concentration dependent, the study of the racemization or epimerization kinetics is not restricted to pure enantiomers or diastereomers. Even samples only partly resolved, or those already partly racemized or epimerized, can be used to measure the change of a labile metal configuration, provided that the composition is sufficiently displaced from the equilibrium composition. The rate constant k, and from it the half-life $\tau_{1/2}$, are obtained from the function $\ln[(A_o - A_\infty)/(A_t - A_\infty)] = kt$, where A_o = starting concentration, A_t = concentration at time t, and A_∞ = equilibrium concentration after ten half-lives. By virtue of proportionality, instead of the concentrations A, the measured optical rotations of the sample or the integrals of suitable NMR signals can be used directly. For enantiomers, $A_\infty = 0$ and for diastereomers, $A_\infty \neq 0$. In order to dissect the first-order rate constant k for approach to equilibrium for diastereomers into k_1 and k_{-1} for the forward and backward reactions, respectively, and to determine the equilibrium constant K from the equilibrium optical rotation, the optical rotations of the pure diastereomers must be known. If the diastereomers differ in their ^1H or ^{31}P NMR spectra, these quantities can be directly determined by integration of the spectrum of an equilibrated sample. Thus, information concerning the change of the metal configuration can be obtained through studies of both the racemization of enantiomers and the epimerization of diastereomers.

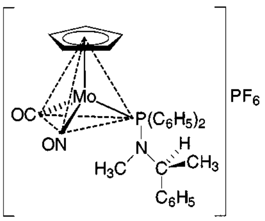
Half-Sandwich Complexes with Stable and Labile Metal Configurations

The first resolved organometallic compounds R_{Mn}-**1**/S_{Mn}-**1** are configurationally stable at the metal atom and do not undergo racemization in solution. They can be kept in CH_2Cl_2 for weeks without any decrease in the optical rotation.[23] On the other hand, the benzoyl compounds R_{Mn}-**2**/S_{Mn}-**2**, which are formed in the reaction of R_{Mn}-**1**/S_{Mn}-**1** with phenyllithium, are configurationally labile at the Mn atom (Figure 1).[26] Thus, compounds R_{Mn}-**1**/S_{Mn}-**1** and R_{Mn}-**2**/S_{Mn}-**2**, which were involved in the early studies of optically active organotransition metal compounds, are representative examples of the two alternatives, having stable and labile metal configurations, respectively. This makes it even more surprising that so many ambiguities have recently arisen regarding the stability of the metal configuration in similar compounds (see later).

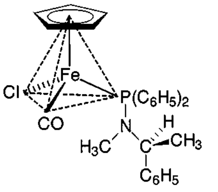
The configurational stability of the benzoyl complexes R_{Mn}-**2** and S_{Mn}-**2** can be tuned by *para*-substitution of the phenyl ring of the benzoyl ligand[26] and by *para*-substitution of the phenyl rings of the triphenylphosphane ligand.[29] An NMe_2 substituent on the benzoyl ligand reduces the half-life at 20 °C in toluene to 3.6 min, whereas a CF_3 substituent increases it to 418 min.[26] The same *para*-substituents have the opposite effect if they are attached to the phenyl rings of the triphenylphosphane ligand. As the benzoyl and triphenylphosphane ligands are on different sides of the critical bond, this indicates that it is the Mn−P bond that undergoes dissociation in the rate-determining step. CF_3 substituents in the *para*-position of the phenyl rings of the phosphane ligand give a half-life of 5.9 min, while OCH_3 substituents extend it to 337 min.[29] Hammett plots have been constructed for both series of compounds. Thus, a combination of an NMe_2 substituent on the benzoyl ligand and a CF_3 substituent on the triphenylphosphane ligand would give an extremely labile metal configuration, whilst the opposite combination should give the most stable compound in this series.[18] Obviously, knowledge of the half-life for the change of the metal configuration is important with regard to the handling of solutions of optically active compounds without appreciable loss of enantiomeric purity.

The aminophosphanes (S)-$Ph_2P-NH-CH(Me)(Ph)$ and (S)-$Ph_2P-N(Me)-CH(Me)(Ph)$ have proved to be versatile chiral phosphane ligands[30] akin to triphenylphosphane.[31]

The complex **$R_{\mathrm{Mo}}S_{\mathrm{C}}$-4**, containing (*S*)-$Ph_2P-N(Me)-CH(Me)(Ph)$ as the optically active auxiliary, is configurationally stable in solution even at higher temperatures.[32,33] In contrast, the chloro complex **$R_{\mathrm{Fe}}S_{\mathrm{C}}$-5**, a derivative of the same optically active aminophosphane ligand, is configurationally labile at the Fe atom. **$R_{\mathrm{Fe}}S_{\mathrm{C}}$-5** has a half-life of 181 min. at 20 °C in benzene solution, while the corresponding bromo compound epimerizes in the same solvent with a half-life of 185 min. at 45 °C.[34] With a half-life of 51 min. at 70 °C, the corresponding iodo compound has the highest configurational stability of the compounds CpFe(CO)Hal(aminophosphane).[35] The analogous compound CpFe(CO)Me(aminophosphane) epimerizes with respect to the iron configuration in benzene solution with a half-life of 70 min. at 70 °C.[36] However, the thermal epimerization of CpFe(CO)Me(aminophosphane) has to be distinguished from the epimerization induced by electron transfer (reaction with $[Cp_2Fe]PF_6$), which, at room temperature, is complete within five minutes.[36]

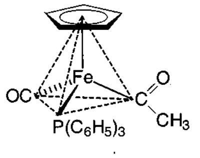


$R_{Mo}S_C$-4

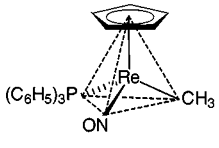


$R_{Fe}S_C$-5

The enantiomeric acetyl complexes **R_{Fe}-6** and **S_{Fe}-6**, which are configurationally stable at room temperature, have been developed as optically active auxiliaries for enantioselective organic synthesis.[7–11,37–40] These highly selective stoichiometric reagents are commercially available and allow the synthesis of a variety of compounds by virtue of the enolate chemistry of the acetyl substituent. Most of the $[CpRe(PPh_3)(NO)X]$ compounds[2,4,5] described by Gladysz, for example **S_{Re}-7**,[41] are configurationally stable at the metal atom, even at higher temperatures. However, it cannot be ruled out that one or other of the compounds, reported to be configurationally stable, will start to racemize or epimerize at higher temperatures before decomposition occurs.



R_{Fe}-6

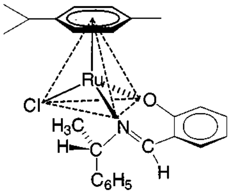


S_{Re}-7

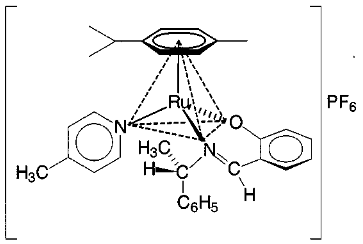
Whereas half-sandwich complexes of the three-legged piano-stool type racemize or epimerize through ligand dissociation, half-sandwich complexes of the four-legged piano-stool type, which are notoriously labile at the metal center, do so by intramolecular rearrangements without ligand dissociation.[1,3,14,17–19] These isomerizations at the metal atom can sometimes be investigated by ^1H NMR spectroscopy with the help of diastereotopic probes, a resolution with respect to the metal configuration being unnecessary. Such coalescence measurements are, however, restricted to relatively rapid reactions, in contrast to those that can be followed by time-dependent integration of suitable diastereomer signals. Half-sandwich complexes of the four-legged piano-stool type will not be considered further in this review.

Half-Sandwich (η^6-Arene)ruthenium Complexes

Recently, half-sandwich (η^6-arene)ruthenium(II) complexes have attracted much interest as catalyst precursors for organic transformations.[42] In 1991, Mandal and Chakravarty synthesized chiral-at-metal half-sandwich ruthenium compounds of the type $[(\eta^6\text{-cymene})Ru(LL^*)L']ClO_4$ and $[(\eta^6\text{-cymene})Ru(LL^*)Hal]$, with cymene = 1-isopropyl-4-methylbenzene and LL* = the anion of (*S*)-(1-phenylethyl)salicylaldimine. L′ was a unidentate ligand, such as triphenylphosphane or 4-methylpyridine, and Hal a halide ligand.[43] The complexes **$R_{\mathrm{Ru}}S_{\mathrm{C}}$-8** and **$R_{\mathrm{Ru}}S_{\mathrm{C}}$-9** are representative examples.

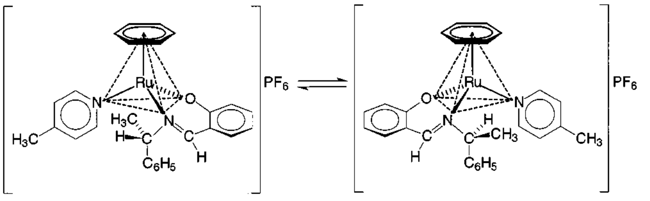


$R_{Ru}S_C$-8



$R_{Ru}S_C$-9

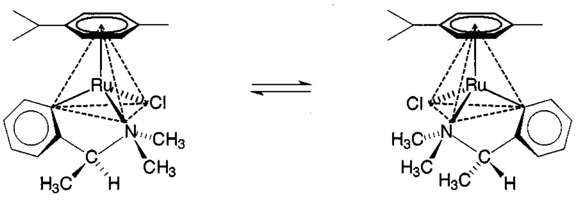
In subsequent studies, the stereochemistry of the substitution of the chloro ligand in **$R_{\mathrm{Ru}}S_{\mathrm{C}}$-8** by other ligands was investigated,[44,45] for example, by 4-methylpyridine in the reaction **$R_{\mathrm{Ru}}S_{\mathrm{C}}$-8** → **$R_{\mathrm{Ru}}S_{\mathrm{C}}$-9**. Through not taking into account the configurational instability of their compounds, Mandal and Chakravarty made serious misassignments. What they referred to as "retention or inversion stereochemistry of substitution reactions" had actually nothing to do with the substitution reactions themselves. It only reflected the different stabilities of the diastereomers in the diastereomer equilibria, which were rapidly established before and after the slow substitution reactions. The terms "retention" and "inversion" imply that the reactions under consideration are kinetically controlled and that there is no prior or subsequent epimerization. However, compounds of the type **$R_{\mathrm{Ru}}S_{\mathrm{C}}$-8** and **$R_{\mathrm{Ru}}S_{\mathrm{C}}$-9** are configurationally labile at the metal center. Thus, the diastereomers **$R_{\mathrm{Ru}}S_{\mathrm{C}}$-10** and **$S_{\mathrm{Ru}}S_{\mathrm{C}}$-10** of the benzene derivative $[(\eta^6\text{-}C_6H_6)Ru(LL^*)4\text{-}Mepy]PF_6$ interconvert through a change in the Ru configuration. The approach to the equilibrium **$R_{\mathrm{Ru}}S_{\mathrm{C}}$-10** $\leftrightarrows$ **$S_{\mathrm{Ru}}S_{\mathrm{C}}$-10** at −35 °C in acetone solution has a half-life of $\tau_{1/2}$ = 82 min.[46]



$R_{Ru}S_C$-10 **$S_{Ru}S_C$-10**

A similar equilibration is observed for [(η^6-cymene)Ru(LL*)4-Mepy]PF_6, the **$R_{Ru}S_C$-9/$S_{Ru}S_C$-9** equilibrium distribution at room temperature being 76:24 in [D_6]-acetone and 82:18 in $CDCl_3$.[47] These values do not prove predominant retention of configuration in the substitution of the chloro ligand by the 4-methylpyridine ligand in the reaction **$R_{Ru}S_C$-8** → **$R_{Ru}S_C$-9** as claimed by Mandal and Chakravarty. They give instead a measure of the different stabilities of the diastereomers in diastereomer equilibria such as **$R_{Ru}S_C$-10** $\leftrightarrows$ **$S_{Ru}S_C$-10**. After having uncovered these mistakes, the author's group published a corrigendum[47] including an appeal for the proper use of stereochemical terminology. Note that on going from **$R_{Ru}S_C$-8** to **$R_{Ru}S_C$-9** there is a change in the relative Ru configuration and simultaneously a change in the priority sequence of the ligands from cymene > Cl > O > N in **$R_{Ru}S_C$-8** to cymene > O > N(imine) > N(4-methylpyridine) in **$R_{Ru}S_C$-9**.

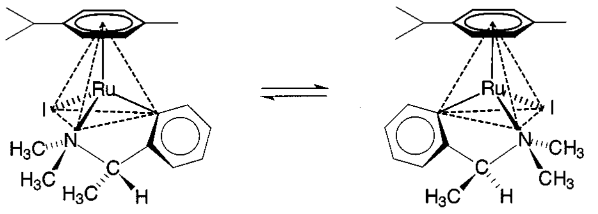
In 1995, Nelson and co-workers synthesized the compounds [(η^6-arene)Ru(LL*)Cl], with η^6-arene = benzene, toluene, cymene, and LL* = *ortho*-metalated (*S*)-*N*,*N*-dimethyl-1-phenylethylamine.[48] The parent compounds, from which all the other cymene complexes were derived, were the chloro complexes **$R_{Ru}S_C$-11/$S_{Ru}S_C$-11**.



$R_{Ru}S_C$-11 **$S_{Ru}S_C$-11**

The chloro complexes were obtained in a diastereomer ratio **$R_{Ru}S_C$-11/$S_{Ru}S_C$-11** = 87:13. Erroneously, the diastereomers **$R_{Ru}S_C$-11** and **$S_{Ru}S_C$-11** were described as being configurationally stable at the ruthenium center:[48] "the ^{1}H NMR spectra obtained in $CDCl_3$, [D_6]acetone, and CD_3NO_2 solutions.....are independent of time (days) and temperature (−20 to 50 °C), indicating their configurational stability". The authors must have used equilibrated samples for their NMR experiments at −20 °C, otherwise they would have noticed that it is in this temperature range that the Ru configuration starts to change. The author's group demonstrated that the half-life for approach to the equilibrium **$R_{Ru}S_C$-11** $\leftrightarrows$ **$S_{Ru}S_C$-11** at 4 °C in CD_2Cl_2 is 108 min. The half-life was found to be 9 min. at 11 °C, showing that solutions of the complexes cannot be handled at room temperature without rapid change of the metal configuration.[49]

The wrong assumption of configurational stability was repeated by Nelson's group in a paper published in 1996[50] and in three papers published in 1999.[51−53] Fatally, it was used as a basis for stereochemical assignments in substitution reactions, which were inevitably wrong. The authors cited our warning in ref.[47] but did not take it into account. For example, on addition of NaI to complexes **$R_{Ru}S_C$-11/$S_{Ru}S_C$-11** the iodo complexes **$R_{Ru}S_C$-12/$S_{Ru}S_C$-12** are formed in a reaction for which "predominant retention of configuration at ruthenium", was claimed.[50] This is true only in a strictly formal sense. However, as the authors presented associative, dissociative, and ring-slippage mechanisms at length, they definitely addressed the substitution reaction itself, which was as unjustified as it was in the case of Mandal and Chakravarty's work.



$R_{Ru}S_C$-12 **$S_{Ru}S_C$-12**

The iodo complexes turned out to be even more configurationally labile than the chloro complexes. Their half-lives were found to be 62 min. at −15 °C and 15 min. at −4 °C in CD_2Cl_2.[49] Therefore, no conclusions regarding the stereochemistry of the substitution reaction **$R_{Ru}S_C$-11/$S_{Ru}S_C$-11** → **$R_{Ru}S_C$-12/$S_{Ru}S_C$-12** can be drawn, because the diastereomer ratios of the starting material (chloro complexes **$R_{Ru}S_C$-11/$S_{Ru}S_C$-11**) and the products (iodo complexes **$R_{Ru}S_C$-12/$S_{Ru}S_C$-12**) have nothing to do with it. The diastereoselectivities only reflect the different stabilities of the diastereomers in the respective diastereomer equilibria. Arguments such as those invoking total retention of configuration in the reaction of the major diastereomer **$R_{Ru}S_C$-11** and partial retention and inversion in the reaction of the minor diastereomer **$S_{Ru}S_C$-11** to account for the observed diastereoselectivities are inherently flawed.[50,51]

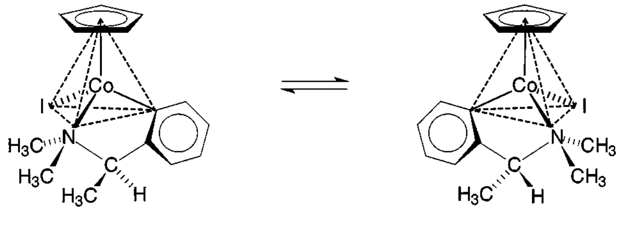
A single-crystal X-ray structure analysis had been carried out for the diastereomer **$R_{Ru}S_C$-11**. It was assigned to the major diastereomer of the 87:13 pair **$R_{Ru}S_C$-11/$S_{Ru}S_C$-11** because "the crystals of this species have a higher chance of being isolated from a mixture" assuming "that each bulk-crystallized sample is a solid mixture of the two diastereomers in a ratio equal to that observed in their solutions" — a strange argument implying a 13% statistical chance of being wrong![48,51] The author's group dissolved the crystals obtained from the 87:13 mixture of **$R_{Ru}S_C$-11/$S_{Ru}S_C$-11** at −80 °C and showed by ^{1}H NMR spectroscopy that they consisted of the pure diastereomer **$R_{Ru}S_C$-11**.[49] It was only in the temperature range around 0 °C that the minor diastereomer **$S_{Ru}S_{C}$-11** began to appear due to the onset of epimerization. Thus, from an 87:13 mixture of diastereomers under the aforementioned crystallization conditions, a single diastereomer crystallized exclusively and was removed from the equilibrium. Through re-establishment of the equilibrium, all the material was converted into a single pure diastereoisomer, a process referred to as an asymmetric transformation of the second kind.[54] If the Ru configuration were stable, the composition of the solid obtained on evaporation of the solvent would have been the same as that in solution (Nelson's conclusion).[48,51] However, after recognition of the configurational lability at the Ru center, the formation of a single pure isomer on crystallization can be understood. Consequently, there was no danger of picking a crystal of the minor diastereomer and of making a wrong configurational assignment.

In recent papers by Nelson's group,[52,53] further chiral-at-metal (η^6-arene)ruthenium complexes have been reported as being obtained through substitution of the chloride ligand in compounds of the type **$R_{Ru}S_{C}$-11/$S_{Ru}S_{C}$-11** by azide, nitrite, thiocyanate, cyanate, and other ligands. It will have to be checked whether these compounds really are "configurationally rigid in solution under mild conditions" and whether or not "these ligand substitution reactions proceed with predominant retention of configuration at ruthenium".

CpCo Complexes

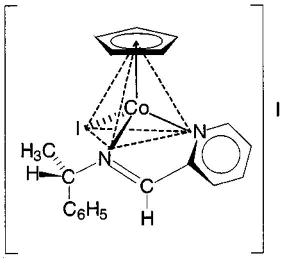
At the end of 1999, a paper was published by Pfeffer et al.[55] concerning a series of cobaltacyclic compounds of the type [(η^5-C_5H_5)Co(LL′)I] differing in the configuration at the metal. With the optically active ligands LL′H = (R_C)-(+)- and (S_C)-(−)-*N*,*N*-dimethyl-1-phenylethylamine, a mixture of the two diastereomers, **$R_{Co}R_{C}$-13**, **$S_{Co}R_{C}$-13** and **$S_{Co}S_{C}$-13**, **$R_{Co}S_{C}$-13**, respectively, in a 19:1 ratio (91% *de*) was obtained. This ratio "could not be improved by fractional crystallization or column chromatography" and "^{1}H NMR studies indicate that the compounds are configurationally stable at the cobalt center". Moreover, "no epimerization could be observed in solution, for instance, over a period of seven days at room temperature in either $CDCl_3$ or [D$_6$]acetone". Although the diastereomers "displayed comparable crystallization rates so that the bulk sample from which X-ray quality crystals were obtained contained the same ratio of both diastereomers as determined above", the crystal structure of **$R_{Co}R_{C}$-13** was assigned to the major diastereomer on the basis that "the crystals of this species have a higher statistical chance of being isolated from a mixture of diastereomers". Thus, the same (wrong) argumentation was used as for the (η^6-arene)ruthenium complexes discussed above.[48,50−53]

The author's group synthesized the complexes **$R_{Co}R_{C}$-13/$S_{Co}R_{C}$-13** according to the published procedure[55] using [(η^5-C_5H_5)CoI_2]$_2$ and *ortho*-lithiated (R_C)-(+)-*N*,*N*-dimethyl-1-phenylethylamine. Dark-green needles were obtained, the ^{1}H NMR spectrum of which in CD_2Cl_2 solution at room temperature exhibited signals due to both diastereomers **$R_{Co}R_{C}$-13** and **$S_{Co}R_{C}$-13** in a 96:4 ratio (92% *de*), in agreement with ref.[55] However, when a sample of crystals was dissolved in CD_2Cl_2 and the ^{1}H NMR spectrum was recorded at −40 °C, only the signals of the major diastereomer were seen.[49] Measurements at −20 °C, 0 °C, and +21 °C revealed that the minor diastereomer **$S_{Co}R_{C}$-13** was formed only at higher temperatures.

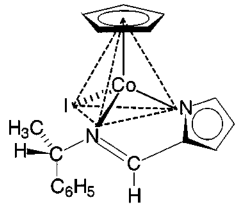


$R_{Co}R_{C}$-13 **$S_{Co}R_{C}$-13**

The half-life for the conversion of **$R_{Co}R_{C}$-13** into the equilibrium mixture **$R_{Co}R_{C}$-13** $\leftrightarrows$ **$S_{Co}R_{C}$-13** was estimated to be between 20 and 25 min. in CD_2Cl_2 solution at +1.4 °C. The accuracy of these measurements is limited by the fact that the equilibration of the major diastereomer involves only a small concentration change to give the equilibrium mixture major diastereomer/minor diastereomer = 96:4. Clearly, the major diastereomer **$R_{Co}R_{C}$-13** cannot be handled at room temperature without a rapid change in the metal configuration. The measurements leading to the postulation of configurational stability at the cobalt center[55] were thus most probably carried out with epimerized samples. Interestingly, it has been demonstrated previously that the configuration at cobalt is labile in compounds **$R_{Co}S_{C}$-14** and **$R_{Co}S_{C}$-15**.[56] However, the latter compounds, which are very similar to compounds **$R_{Co}R_{C}$-13/$S_{Co}R_{C}$-13** and are subject to the same stereochemical problem of the cobalt configuration, were not mentioned in ref.[55]



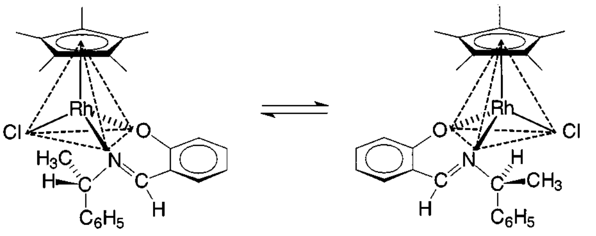
$R_{Co}S_{C}$-14



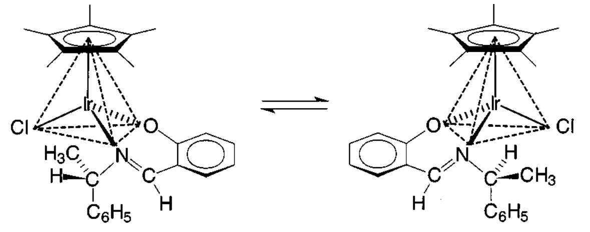
$R_{Co}S_{C}$-15

Cp*Rh and Cp*Ir Complexes

In 1997, Loza, Parr, and Slawin synthesized the compounds [Cp*M(ON)Cl] (**$R_{Rh}S_{C}$-16/$S_{Rh}S_{C}$-16** and **$R_{Ir}S_{C}$-17/$S_{Ir}S_{C}$-17**), where ON was the anion of (+)-*N*-[(*S*)-1-phenylethyl]salicylaldimine.[57] A high diastereomeric excess was claimed as, in the room-temperature ^{1}H NMR spectra, only one isomer was seen in each series. The compound **$R_{Ir}S_{C}$-17** was characterized by X-ray structure analysis, as a result of which the (R_{Ir},S_C)-configuration was assigned to the only diastereomer observed in solution. These conclusions turned out to be wrong or unreliable because the authors had overlooked the configurational instability at the metal center in these complexes.[58]



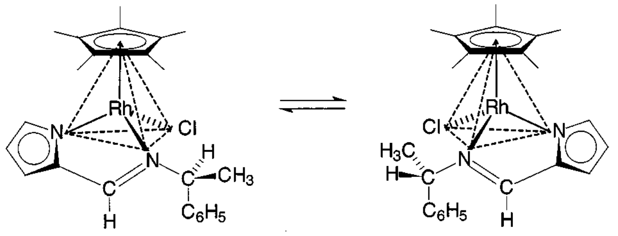
$R_{Rh}S_C$-16 **$S_{Rh}S_C$-16**



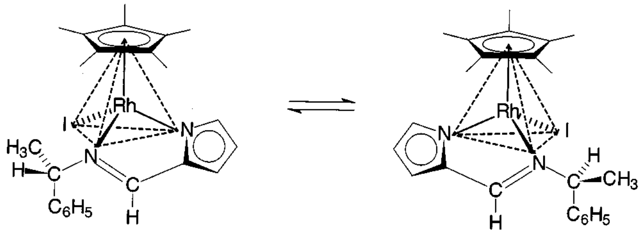
$R_{Ir}S_C$-17 **$S_{Ir}S_C$-17**

The author's group confirmed that the ^{1}H NMR spectra of **$R_{Rh}S_C$-16/$S_{Rh}S_C$-16** and **$R_{Ir}S_C$-17/$S_{Ir}S_C$-17** featured only one set of signals. However, it was found that the room temperature ^{1}H NMR spectra were the averaged high temperature limiting spectra (fast-exchange regime of two diastereoisomers in their diastereomer equilibria). At low temperatures, interconversion of the two diastereomers of each pair became so slow that the diastereomers gave separate signals that could be integrated. The ratios were found to be 81:19 at −80 °C in CD_2Cl_2 in the rhodium series **$R_{Rh}S_C$-16/$S_{Rh}S_C$-16** and 85:15 at −50 °C in $CDCl_3$ in the iridium series **$R_{Ir}S_C$-17/$S_{Ir}S_C$-17**. As equilibration with respect to the metal center in these compounds is fast even at −80 °C, the transfer of the absolute configuration found in the solid state to the major isomer in solution, as assumed in ref.[57], does not have any sound basis.

It cannot be taken for granted that it is always the *major* isomer that crystallizes from a dynamic diastereomer equilibrium. In the series of chloro complexes **$R_{Rh}S_C$-18/$S_{Rh}S_C$-18**, the diastereomer equilibrium distribution in CD_2Cl_2 was found to be **$R_{Rh}S_C$-18/$S_{Rh}S_C$-18** = 87:13 at room temperature. In this case, it was definitely the *minor* diastereomer (13% content only!) that crystallized. This was proven by X-ray crystallography and low-temperature NMR spectroscopic analysis of the crystals dissolved at −80 °C. For the iodo system **$R_{Rh}S_C$-19/$S_{Rh}S_C$-19**, the reverse was found to be true. From the 87:13 equilibrium mixture, the *major* isomer crystallized in a diastereomerically pure state. Due to the rapid isomerization of the compounds **$R_{Rh}S_C$-16/$S_{Rh}S_C$-16** and **$R_{Ir}S_C$-17/$S_{Ir}S_C$-17**, the NMR test at −80 °C is not available. Therefore, no unequivocal configurational assignment of the diastereomers in solution can be made.



$R_{Rh}S_C$-18 **$S_{Rh}S_C$-18**



$R_{Rh}S_C$-19 **$S_{Rh}S_C$-19**

Low Temperature NMR Spectra in Solution — A Solution for the Aforementioned Problems

Diastereomers differing only in the metal configuration may be formed under kinetic control or under thermodynamic control.[15] In both cases, the diastereomer ratios can be close to 1:1 or may reach high values.[15] Irrespective of the ratio, the isolation of diastereomerically pure samples or at least diastereomerically enriched samples (relative to the starting composition) should be possible by means of fractional crystallization or chromatography including zone cutting, provided that the diastereomers are configurationally stable at the metal center. If a diastereomer mixture resists separation or enrichment whatever its composition (as in refs.[48,55] etc.), the reason may be configurational instability at the metal atom. In such cases, the configurational stability/lability should be checked by all the available techniques, including the dissolution of samples crystallized at low temperatures and the measurement of low-temperature NMR spectra without prior warming. Provided that the equilibration between the two diastereoisomers is slow under the conditions of dissolution, this technique shows whether a crystallized sample consists of a pure diastereoisomer or a mixture of the two diastereomers. Depending on the crystallization conditions and the epimerization rate, both situations may be encountered.

In the previous paragraphs, several publications by different groups in good journals have been discussed, where the conclusions drawn were either partly or wholly wrong. At present, there are high standards as far as the publication of preparative work and X-ray structure analyses is concerned.

However, with respect to stereochemistry and mechanisms the quality standards are not so high, as demonstrated herein for the narrow field of half-sandwich ruthenium, cobalt, rhodium, and iridium complexes. Confusion results and corrections are required. In the worst case reinvestigations are necessary some time later to avoid contradictions. In most of the cases discussed, low temperature NMR experiments, easily available with modern equipment, would have proved or disproved the ideas, assumptions, and conclusions put forward. Why is this technique not used more frequently?

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