Non-racemic (scalemic) planar-chiral five-membered metallacycles: routes, means, and pitfalls in their synthesis and characterization†

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This *critical review* provides a systematic classification of the synthetic routes to planar-chiral five-membered metallacycles into several routes, namely C–H bond activation, oxidative addition, transmetallation and optical resolution. As a characteristic of these bulk compounds is that they are synthesized as binary mixtures of enantiomers in proportions varying from the racemate to enantiopure, a review of absolute-configuration determination of the title planar-chiral scalemates is presented. This review is of interest to organic and organometallic synthetic chemists involved in asymmetric synthesis (97 references).

Introduction

Planar chirality[1] is a potential intrinsic property of those cyclometallated aromatics in which the chelate is missing a plane of symmetry as is generally the case in heterodisubstituted cyclophanes and metallocenes (Fig. 1). Non-racemic (scalemic) planar-chiral cyclometallated aromatics are highly modular, in terms of steric and/or electronic properties. Basic investigation of the mechanisms of assisted *ortho*-metallation[2] and on the reactivity of the carbon–metal bond have been supplemented with innovative applications in various fields of chemistry. The versatility of cyclometallated aromatics and their increasing importance in metal-mediated synthesis,[3] homogenous catalysis,[4] photophysics[5] and in the emerging fields of molecular sensing[6] and bioorganometallic drug design[7] is evident from a survey of recent literature.

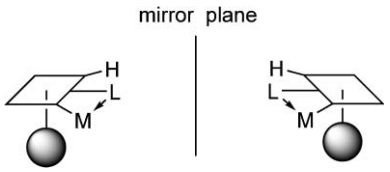

Fig. 1 Planar-chiral metallacycles: the sphere located on a single side of a planar aromatic ring (represented here by a square) represents either a π-coordinated metal-centred or any other moiety that may lift the mirror symmetry of the plane of the chelate.

Planar-chiral homo- or hetero-chelates of transition metals constitute a valuable pool of chiral catalysts particularly for their ability to induce high enantioselectivities by virtue of the driving role of planar chirality in the stability of transition states.[8] With planar-chiral metallacycles, chemical discrimination of the vicinal ligands bound to the metal centre is also effective (Fig. 2): in square-planar complexes, equatorial ligands L_1 and L_2 are affected by different *trans* influences from the [L,C] heterochelating ligand and in octahedral

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Jean-Pierre Djukic

Jean-Pierre Djukic, born in 1967 in Courbevoie (France), obtained a PhD in 1992 from Paris VI University under the guidance of E. Rose. He was associate researcher with L. K. Woo at Iowa State University from 1993 to 1994 and an Alexander von Humboldt fellow with K. H. Dötz at the University of Bonn from 1996 to 1997. Djukic is currently heading the research effort in organometallic chemistry at the CNRS in Strasbourg, which he joined in 1994.

Akram Hijazi

Akram Hijazi was born in 1980 in Houla (Lebanon). He graduated in organic synthesis in 2004 from the University Claude Bernard (Lyon). Since 2005 he has been a PhD student undertaking research on the stereoselective direct metallations of planar-prochiral complexes with asymmetric octahedral and tetrahedral transition metal complexes.

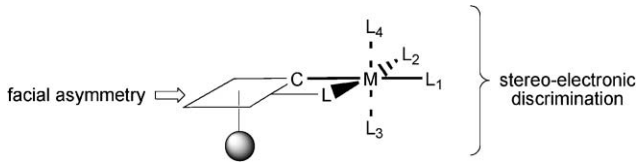


Fig. 2 The stereo-electronic asymmetry of planar-chiral [C,L]M chelates.

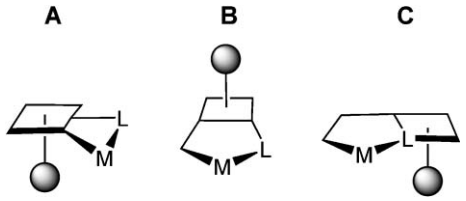


Fig. 3 The three classes of possible planar-chiral metallacycles according to Sokolov:[10] **A**, planar chirality at the carbanionic part of the chelating ligand; **B**, planar chirality at a bridging position between the carbanionic part and the donor atom; **C**, planar chirality at an heterocycle comprising the donor atom of the chelating ligand.

complexes axial ligands L_3 and L_4 are differentiated mainly by their diastereotopicity.

Therefore, by extrapolation, it is expected that these stereo-electronic effects may exert, to some degree, stereochemical control over the processes that take place in the coordination sphere of the chelated metal centre. It is to be understood that the chelating unit itself may possibly be deemed, in the chemical sense, a *non-innocent* "spectator" moiety as outlined by Delacroix and Gladysz.[9] These considerations are the basis for most of the recent applications to organic synthesis of this class of organometallic compounds and in this review these applications will not be described in detail, the reader being thus referred to the corresponding citations or to the recent survey by Carretero and co-workers published in 2006.[8]

In the late 1970's Sokolov predicted[10] that planar chirality could be introduced in 5-membered metallacycles by three separate ways: (1) at the carbanionic part of the [C,L] chelate (case **A**, Fig. 3), (2) at a bridging position between C and L (case **B**, Fig. 3), and (3) at L if the latter is part of a heterocycle (case **C**, Fig. 3). In the first part of the current article attention will focus on compounds of type **A** since these are the most prevalent in the literature to date, and will also review the most relevant synthetic routes that have been devised following the pioneering work of Sokolov at the Institute of Organo Element Compounds of the Russian Academy of Sciences in Moscow 30 years ago. We limit our review to the paths (*vide infra* Fig. 5) for synthesizing scalemic planar-chiral cyclometallated aromatics of transition-metal based complexes. In the second part of this review, the means used for the structural determination of the stereochemistries of the title compounds by X-ray diffraction techniques will be presented and followed by a critical discussion on the methodology applied to the structural determination of most of the complexes addressed herein.

Terminology and conventions used

Throughout this article, the basic terminology of stereochemistry recommended by IUPAC[11] is used with a few exceptions. The term 'scalemic' is used to mean binary mixtures of enantiomers in proportions other than the racemate and will be applied especially to those cases where the analytical proof of enantiopurity of a given compound has not been provided or has only been assumed. The term 'enantiopure' is applied to compounds with an enantiomeric excess (ee) equal to or higher than 98% so long as good direct or indirect experimental evidence is available. Diastereomeric distribution dd will be used in place of diastereomeric ratio dr to qualify the degree of diastereoselectivity in reactions leading to more than two products. The stereochemical chirality descriptor for planar-chiral arrangements as defined for metallocenes and other π-arene metal compounds by applying an extension of the so-called CIP rule[12,13] to substituted and metal-bound sp^2 carbons, is written as p*S* or p*R* and not S_p or R_p in order to prevent any confusion which might arise with phosphorus-related chirality descriptors S_P and R_P. This descriptor will always refer to the arene's carbon that bears the substituent of highest atomic number (Fig. 4). For consistency, the same notation p*S* and p*R* will be used for the stereochemical chiral descriptor of [2,2]-*para*-cyclophanes according to the *ad hoc* CIP selection rule (Fig. 4).[1]

Howard D. Flack

Howard Flack was born in Reigate (England) in 1943. He studied chemistry and obtained a PhD in crystallography from the University of London in 1968. On reading Rogers' publication on η refinement, the idea of the inversion-twin parameter for absolute-structure determination germinated in Flack's mind. Flack ran the committee on electronic publishing of the International Union of Crystallography for nine years. The IUCr recently won the 2006 ALPSP Award for publishing innovation.

Gérald Bernardinelli

Gérald Bernardinelli was born in Nice (France) in 1945. He studied chemical engineering and chemistry, and obtained a PhD in 1978 from the University of Geneva. Since 1983 he has been responsible for the structural determination of organic and organometallic compounds by X-ray diffraction for the schools of chemistry and biochemistry and of pharmacy at the University of Geneva. He is co-author of more than 400 scientific publications.

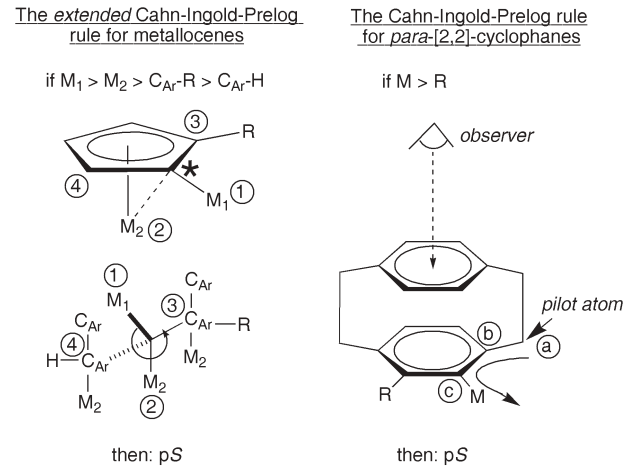


Fig. 4 Different definitions of the "p*S*" configuration in planar-chiral metallocenes and *para*-[2,2]-cyclophanes: the "p" prefix refers to the planar-chiral character of the moiety.

Material and classifications

As the literature on this topic is extensive and a wide variety of ways and means have been researched and used to prepare scalemic planar-chiral metallacycles (abbreviated here SPCMC), some means of classification was necessary to structure the information. We therefore decided to identify classes of synthetic strategies or "routes" which we chose to distinguish mainly on the basis of the elementary step responsible for the generation of the scalemic planar-chiral metal chelate moiety from either prochiral, racemic or scalemic substrates. The outlines of four types of synthetic approach were identified in the literature, each subdivided into sub-routes of transformations distinguished either by the type of reagents used or by their sequence of reactions (Fig. 5). To the reasonably-well documented routes **I**, **II**, **III**, and **IV**, and their related variations **Ia**, **Ic–d**, **IIb**, **IIIa–b** (*vide infra*), we added a few others considered as possible but for which, to our knowledge, no example has been reported to date in the literature; these are routes **Ib**, **IIa** and **Va–b**.

A systematic classification

The five main routes leading to SPCMC are namely (Fig. 5):

- Route **I**: SPCMC generation *via* so-called C–H bond activation with variations **Ia** (**a′** or **a″**), **Ib**, **Ic**, and **Id**,
- Route **II**: SPCMC generation *via* direct oxidative addition with variations **IIa** and **IIb**,
- Route **III**: SPCMC generation *via* transmetallation with variations **IIIa** (**a′** or **a″**) and **IIIb**,
- Route **IV**: SPCMC isolation by resolution of racemic or diastereomeric mixtures,
- Route **V**: SPCMC generation *via* stereoselective facial desymmetrization of a chelate.

From a practical point of view, route **I** is certainly the most appealing as it does not require extensive experimental effort; some considerable understanding of the underlying stereo-electronic and mechanistic issues of the cyclometallation reaction is nonetheless essential to reach partial or complete enantio- or diastereo-selectivity. Route **II** is restricted to transition-metal centres capable of undergoing oxidative addition of a carbon–halogen or carbon–hetero element bond. Route **III** directly depends upon one's ability to replace a metal introduced in a preliminary step either by "symmetric" transformation or by routes **I**, **II**, **IV** or **V**. Class **IV** transformations are extensions of Pasteur's so-called "optical resolution" method;[14] the separation of enantiomers requiring the mediation of a non-racemic auxiliary, preferably enantio-pure and labile in character. To our knowledge, route **V** has no known example in the literature although the principle of facial stereodiscrimination in the π-coordination of "planar prochiral" or chiral non-metallated aromatics itself is well documented.[15]

Occurrence in the literature

While evaluating the number of publications on an annual basis using the five above-mentioned routes classification, we noticed a discontinuity between the end of the 1980's and the mid 1990's, when this topic gained renewed interest with researchers. This increase in interest can be directly related to a new perception of this family of heterochelates, not only investigated as stoichiometric organometallic reagents but more generally as molecular objects endowed for instance with new functions such as catalysts. A pie chart illustrates the distribution of publications per routes (Fig. 6a); some references have been counted several times when more than one synthetic route was mentioned in a given article. It clearly shows the predominance of reports on route **I**. Among these, subclass **Id** is overwhelmingly represented whereas **Ia** remains surprisingly low (Fig. 6b). Reports on route **II** are quite rare and essentially focus on subclass **IIb**. Examples of route **III** are fairly frequent and essentially represented by subclass **IIIa**. Reports on route **IV** are relatively rare and those on route **V** non-existent (Fig. 6a).

It is worthy of note that a majority of reports are devoted to the preparation of planar-chiral [C,L]M chelates in which M is a d^8 metal lying in a square-planar coordination geometry *SP*-4[16] such as Pd(II) and to some extent Pt(II) (Fig. 7). Hg(II) complexes holding a linear coordination geometry *L*-2 (Fig. 7) are also frequently mentioned in the literature. Only a minority of reports describes other types of compounds, which combine a planar-chiral chelate and a chiral or prochiral metal centre[17] (Mn(I), Re(I), Ru(II), Te(II)) sitting either in an octahedral (*OC*-6), a real or pseudo tetrahedral (*T*-4) or a trigonal planar (*TP*-3) coordination environment (Fig. 7).

Among all the articles considered here, planar-chiral ferrocenes (Fc) have been the most studied especially in the early period between 1977 and 1995 (Fig. 8). Other types of planar-chiral complexes, such as representatives of (η^4-cyclobutadiene)(η^5-cyclopentadienyl) cobalt(I) (CbCpCo), (η^6-arene)tricarbonylchromium(0) (ATCCr) and [2,2]-para-cyclophane (PCPh) have shown up in the literature from 1997 onwards, thus opening a new era of development (Fig. 8).

The most frequent ancillary ligands explored for the preparation of SPCMC are tertiary amines, pyridines, imines and oxazolines and to a limited extent phosphines.

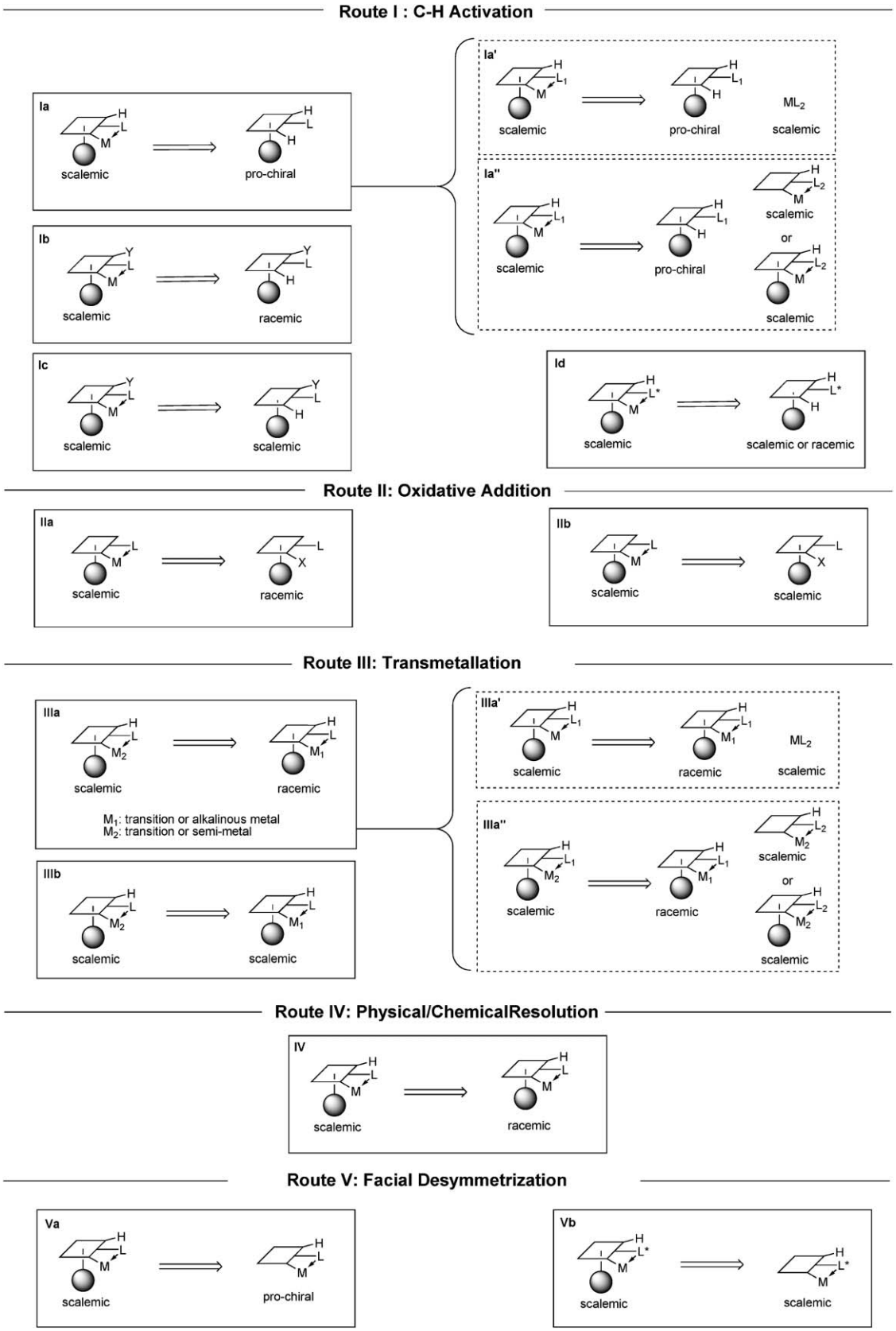


Fig. 5 Description of the five synthetic routes for the synthesis of scalemic planar-chiral metallacycles with their variations: route **Ia** (enantioselective *ortho*-metallation of a prochiral ligand), **Ib** (enantioselective *ortho*-metallation of a racemic ligand), **Ic** (*ortho*-metallation of a scalemic planar-chiral ligand) and **Id** (diastereoselective metallation of a scalemic or racemic ligand); route **IIa** (enantioselective oxidative addition) and **IIb** (oxidative addition at a scalemic ligand); route **IIIa** (transmetallation by a scalemic metal complex and resolution) and **IIIb** (transmetallation of a scalemic planar-chiral metallacycle); route **IV** (resolution of a racemic metallacycle); route **Va** (enantioselective facial desymmetrization) and **Vb** (diastereoselective facial coordination).

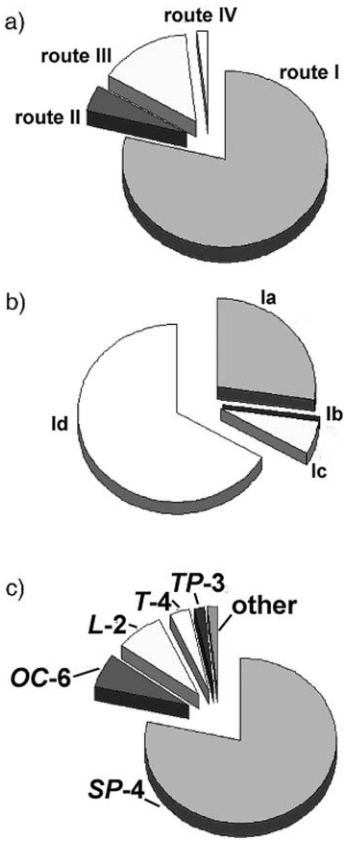


Fig. 6 Distribution in the literature of (a) routes **I**–**IV**, (b) routes **Ia**–**d**, (c) the coordination geometries at the chelated metal centre.

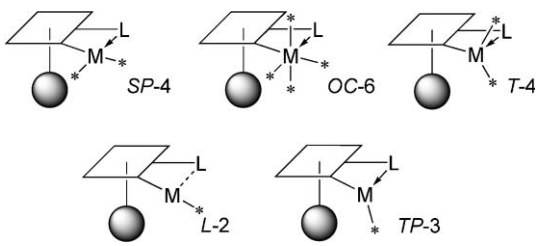


Fig. 7 Types of coordination geometries of scalemic planar-chiral metallacycles encountered in the literature.

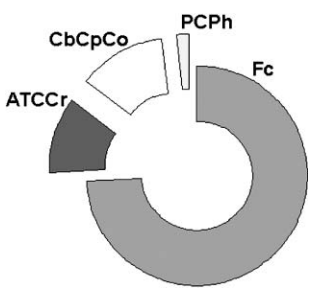
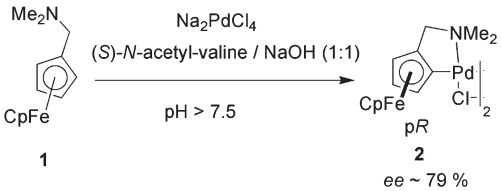


Fig. 8 Distribution in the literature of the type of planar-chiral or -prochiral ligands used in the syntheses of scalemic planar-chiral metallacycles.

Synthetic routes

Route I, C–H bond activation

Route Ia, enantioselective *ortho*-metallation of a prochiral ligand. The end of the 1970's witnessed the first attempts in the enantioselective *ortho*-palladation of prochiral metallocenes. This work was undertaken exclusively by the group led by Sokolov and was supplemented with various extensions and applications in the years following their initial report on the induction of chirality during the palladation reaction in the presence of enantiopure carboxylic acids such as lactic acid, mandelic acid and amino acids [eqn (1)].[18] These researchers clearly demonstrated that the *ortho*-palladation of *N*,*N*-dimethylaminomethylferrocene in the presence of a *N*-acetylated amino acid could produce new scalemic cyclopalladated ferrocenes.



With *N*,*N*-dimethylaminomethylferrocene[19] itself, it was stressed that an optimal induction of chirality leading to *ca.* 79% ee was reachable when the basicity of the reaction medium was maintained within a narrow range of pH, *e.g.* $7.9 < \text{pH} < 9.8$, ensuring a relative conversion of 50% with (+)-(*S*)-*N*-acetyl-valine as the chiral promoter and $PdCl_4^-$ as the metallation agent. A p*R* configuration for the major component of the scalemic palladacyclic product was reliably deduced from a chemical correlation consisting of a derivatization of the latter Pd(II) complex into a series of carboxy and carbonyl substituted ferrocenes, of which the respective specific rotations $[\alpha]_D$ were compared to those of presumed enantiopure reference compounds. The authors assumed that all the reactions involving the C_{Fc}–Pd bond occur with retention of configuration. A transition state involving a partial coordination of Pd(II) by both the ferrocene's amine and the amino acid was put forward to explain the observed enantioselectivity (Fig. 9). This assumption is somewhat supported by later studies by Ryabov[2] and by Macgregor and Davies[20] on the peculiar role of the carboxylate ion in *ortho*-palladation: the ambiphilic palladium carboxylate intermediate provides electrophilic activation of a C–H bond and acts as an intramolecular base for the deprotonation. If extended to the case of the asymmetric palladation of **1**, enantioselectivity could likely arise, as suggested by Sokolov, from the coordination of the deprotonated amino-carboxylate to the palladium centre in the early stage of the reaction.

Many variations of this enantioselective amino acid promoted palladation reaction were reported with an emphasis on applications in organic synthesis: the synthesis of ferrocene analogues of prostaglandins[21] and scalemic glycerides,[22] the desymmetrization of prochiral 1,2-dihydroxycymantrene[23] and the synthesis of scalemic ferrocenyl alkenes.[24] More recently[25] Ryabov reported the synthesis of a pair of (+) and (−) scalemic ferrocenyl carboxylic acids from scalemic *ortho*-palladated *N*,*N*-dimethylaminomethylferrocene **2** obtained by

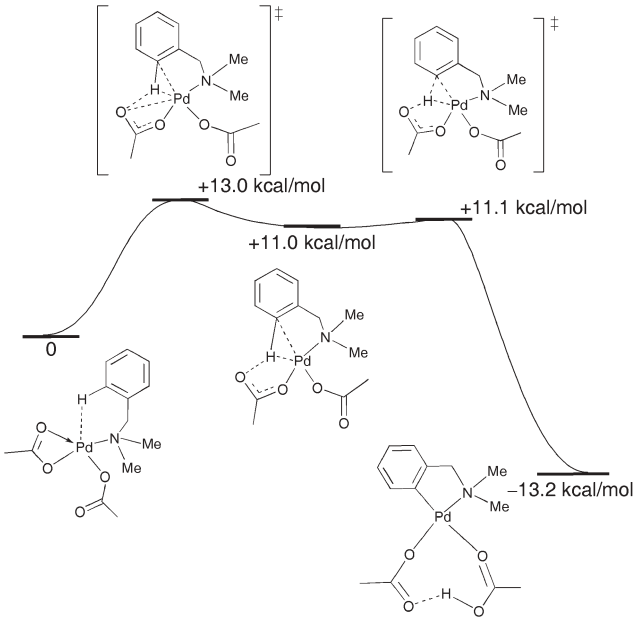
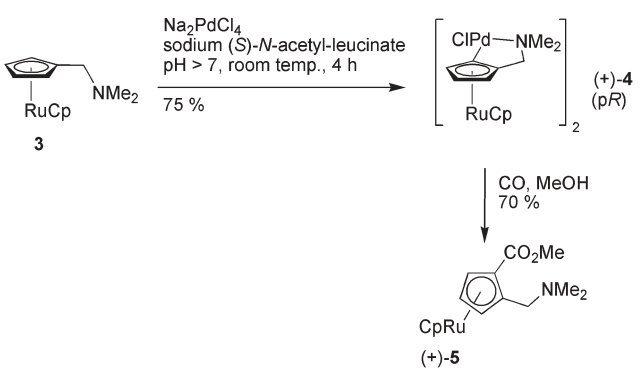


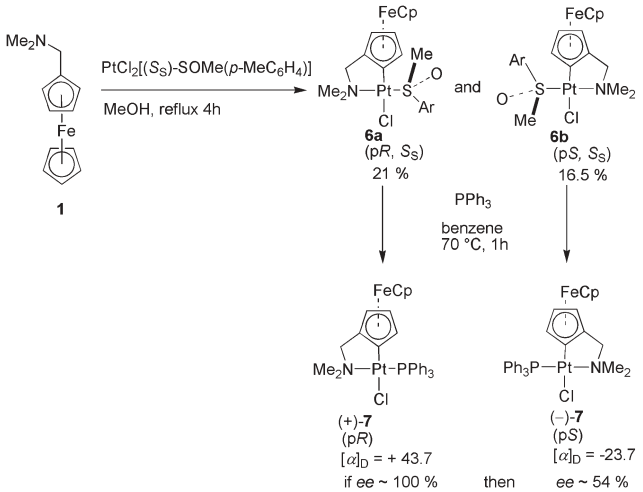
Fig. 9 Computed reaction profile for the cyclometallation of $Pd(OAc)_2[C_6H_5CH_2N(CH_3)_2]$ according to Davies, Donald and Macgregor, *cf.* ref. 20.

palladation with $PdCl_4^-$ with the mediation of (*S*) and (*R*)-*N*-acetyl-leucine. For the (+) product the enantiomeric excess spanned from 69% (mother liquor) to 80% (crystalline precipitate) of the p*R* enantiomer for a palladation carried out at pH 7.85. *N*,*N*-Dimethylaminomethylruthenocene **3** was also successfully *ortho*-palladated with the use of (*S*)-*N*-acetyl-leucine to synthesize the scalemic palladacyclic product (+)-**4** reportedly with a 75% yield of the p*R* enantiomer (Scheme 1).[26] The latter was further converted to ester **5** by carbonylation in methanol.

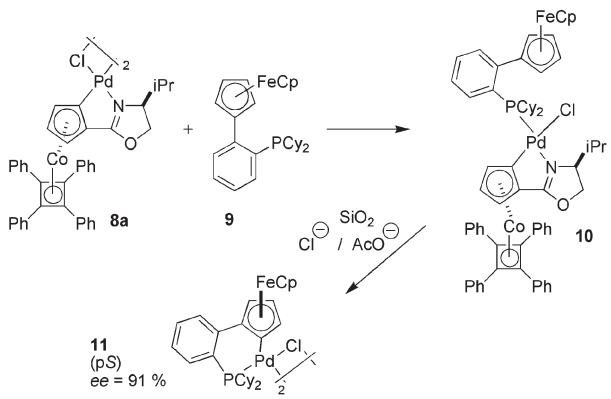
Chiral metallation reagents were also considered for the preparation of SPCMCs following subroutes **Ia′** and **Ia″**. A report by Ryabov on the *ortho*-platination of *N*,*N*-dimethylaminomethylferrocene **1** with an enantiopure Pt(II) complex of (S_S)-methyl-*p*-tolyl sulfoxide illustrates subroute **Ia′** (Scheme 2).[27] The platination reaction resulted in the formation of a quasi-equimolar mixture of two diastereomeric platinacyclic products **6a** and **6b** with an overall conversion of *ca.* 37%. Upon treatment of each separated diastereomer with PPh_3, scalemic planar-chiral (+) and (−) platinacycles **7** were



Scheme 1



Scheme 2



Scheme 3

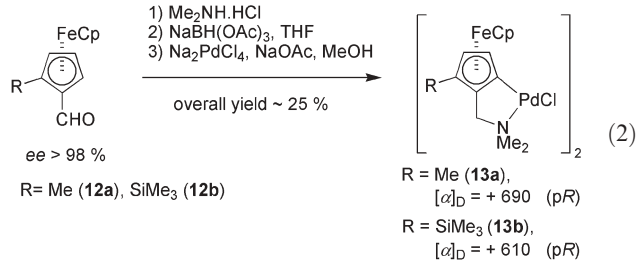
recovered quantitatively and their ee roughly evaluated to 100% of p*R* and 54% of p*S* respectively.

Recently, Richards reported on an elegant asymmetric application[28] of Ryabov's acid-catalysed transcyclopalladation reaction,[29] which illustrates subroute **Ia″** (Scheme 3). In this work the Pd(II) centre is formally moved from a planar-chiral 5-membered chelate **8a** to a 6-membered one in **11**, *via* the intermediate adduct **10**, by a relatively smooth SiO_2-promoted reaction with **9**. The treatment of 1-phosphino-2-ferrocenylbenzene **9** with other scalemic palladium diastereomeric complexes derived from substituted [1,2,3,4-tetraphenyl(η^4-cyclobutadiene)][oxazolyl(η^5-cyclopentadienyl)]cobalt(I) ligands of either p*R* or p*S* configurations (see route **Id**) resulted in the corresponding p*S* and p*R* 6-membered phosphapalladacycles respectively in high yields. Enantiomeric excesses (78% < ee < 95%) were deduced from ^1H and ^{31}P NMR analyses upon treatment of the μ-chloro or acetate dimers with excess enantiopure either (*S*) or (*R*) 2-*N*,*N*-dimethylamino ethylbenzene.

Route Ic, *ortho*-metallation of a scalemic planar-chiral ligand. Reports on the *ortho*-metallation of scalemic disubstituted planar-chiral ferrocenes are rare. Sokolov reported the *ortho*-palladation of a scalemic sample of 2-bromo-1-(1′-*N*,*N*-dimethylamino-6′-carboethoxyhexyl)ferrocene, which was

synthesized in two steps from 1-(1′-*N*,*N*-dimethylamino-6′-carboethoxyhexyl)ferrocene *via* route **Ia**.[21,30]

More recently Overman presented a three-step synthesis of 1,2,3-trisubstituted palladated ferrocenes **13a**–**b** from methyl and trimethylsilyl enantiopure ferrocenyl aldehydes **12a**–**b** [eqn (2)], which were subsequently probed for their activity as Lewis acids for the catalysis of the allylic rearrangement of imidates.[31]



(2)

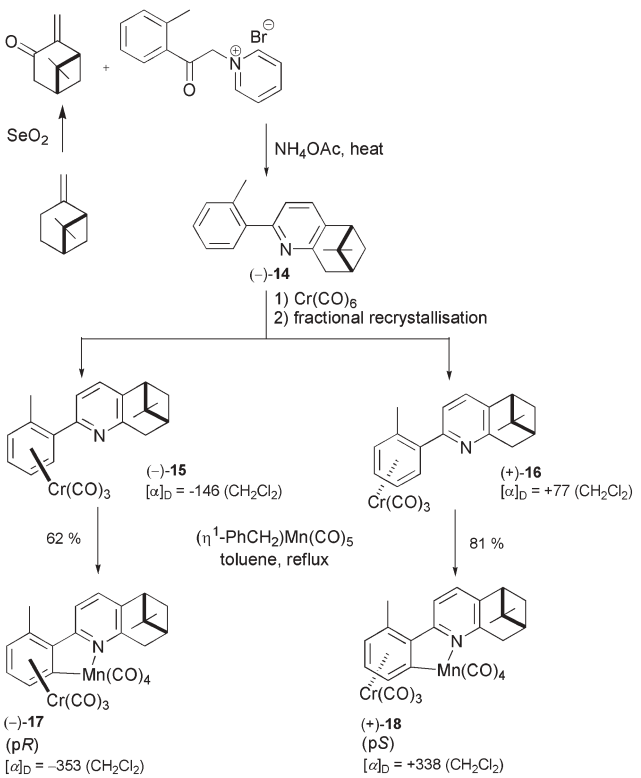
Isolated diastereomers of terpenic homologues of tricarbonyl[1-pyridyl,2-methyl(η^6-phenyl)]chromium **15** and **16** prepared from (*R*,*R*)-**14**, itself synthesized from commercially available enantiopure β-pinene, were efficiently *ortho*-metallated with (η^1-PhCH$_2$)Mn(CO)$_5$ to yield the resulting Mn(CO)$_4$ scalemic planar-chiral chelates **17** and **18** of p*R* and p*S* configuration in 62% and 81% yield respectively (Scheme 4).[32] These complexes were further used for the synthesis of organomanganese chiral-helical ''spiralenes''.

Route Id, diastereoselective metallation of a scalemic or racemic ligand. The metallation of a planar prochiral monosubstituted aromatic that contains a remote site of chirality on the ancillary ligand, as implied by route **Id**, is one of the most convenient ways to synthesize SPCMCs. However, this route raises the question of diastereoselectivity as the planar prochiral fragment may undergo metallation at two chemically equivalent stereogenic *ortho* positions. As a large number of reports deal with this issue, we will concentrate here on the main trends. Generally, when thermodynamic control does **not** prevail, like in most irreversible metallation processes, the degree of diastereoselectivity correlates with the conformational diversity of the metal-precoordinated ligand.

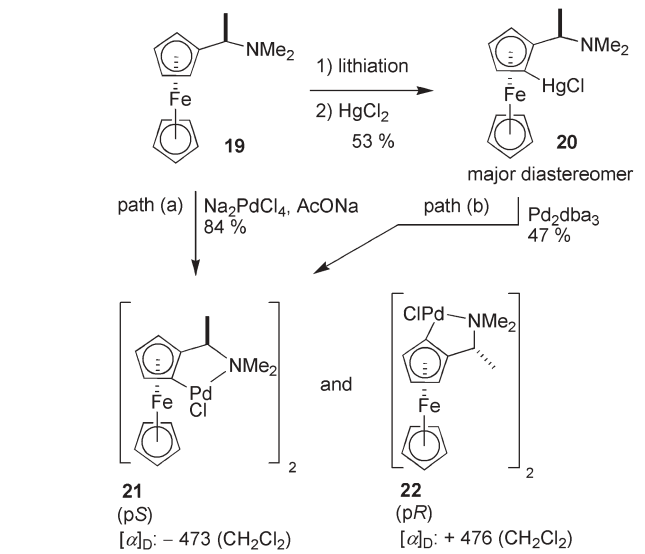
Recent molecular mechanics analyses of the diastereoselectivity towards lithiation in amido- and amino-ferrocenes[33] underlined the prevalence of the conformational energetics of the metal–ligand adduct in defining the preferred site of metallation: the adduct conformer with the shortest C–H···R–Li interaction being privileged.

With α-substituted tertiary alkylamines. The palladation of scalemic monosubstituted ferrocenes also follows this rule to some extent. For instance Sokolov[34] and later Overman[35] observed that the *ortho*-metallation of (*R*)-*N*,*N*-dimethyl-1-ferrocenylethylamine **19** could take place with a moderate diastereoselectivity producing compounds (−)-**21** and (+)-**22** (path (a), Scheme 5) with a 85 : 15 dr; scalemic **21** was also synthesized independently (path (b)) by transmetallation of **20** (*vide infra* route **IIIb**) to confirm its stereochemistry by X-ray diffraction analysis.

An opposing report by Lopez[36] for the same reaction with the *S* enantiomer claimed a dr of 100%. Reportedly, complete diastereoselectivity was observed in the *ortho*-palladation of (−)-*N*,*N*-dimethyl-1-ferrocenyl-1-trifluoromethyl-methylamine which yielded the palladated product with a p*S* configuration, an *R* configuration being assumed for the pseudobenzylic position on the basis of analogies found between the CD spectrum of this product with that of methyl-substituted homologues (CH$_3$ *vs.* CF$_3$).[37]



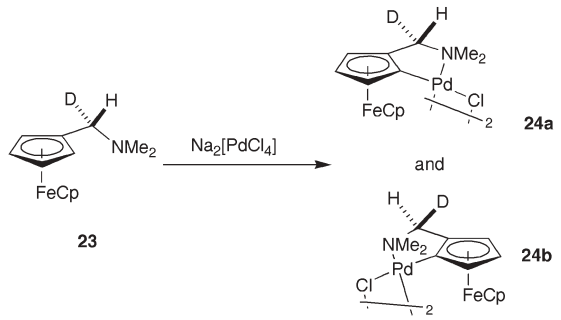
Scheme 4



path (a)	*dr*	85	:	15
path (b)	*dr*	100	:	0

Scheme 5

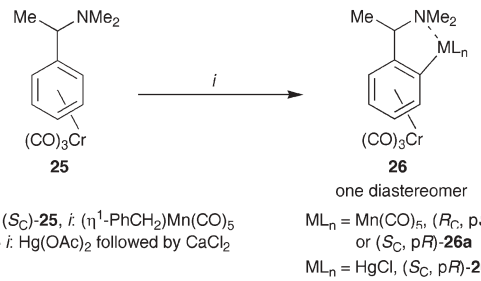
The importance of the conformational control over diastereoselectivity was supported by further investigations undertaken with scalemic (+)-(*S*)-*N*,*N*-dimethyl-1-deuterio-1-ferrocenylmethylamine **23**,[38] which resulted in the production of **24a**–**b** with very low asymmetric induction [eqn (3)].



(3)

1 % asymmetric induction

ortho-Manganation[39] with (η^1-$PhCH_2$)$Mn(CO)_5$ and mercuration[40] with $Hg(OAc)_2$ of either enantiopure (*S*) and (*R*) *N*,*N*-dimethyl-1-[tricarbonyl(η^6-phenyl)chromium]ethylamine **25** reportedly yielded single *ortho*-metallation products **26a**–**b** [eqn (4)].



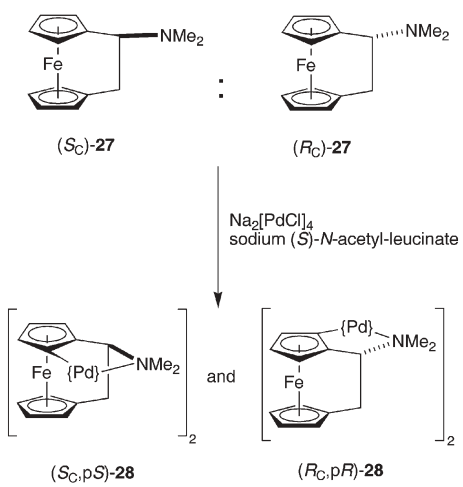
(4)

(R_C) or (S_C)-**25**, *i*: (η^1-$PhCH_2$)$Mn(CO)_5$
(S_C)-**25** *i*: $Hg(OAc)_2$ followed by $CaCl_2$

ML_n = $Mn(CO)_5$, (R_C, p*S*) or (S_C, p*R*)-**26a**

ML_n = HgCl, (S_C, p*R*)-**26b**

Interestingly, Sokolov, Gautheron and co-workers addressed the enantioselective palladation of racemic *rac*-1-dimethylamino[3]ferrocenophane **27**[41] [eqn (5)] using (*S*)-*N*-acetyl-leucine as the chiral promoter in the conditions optimized for route **Ia**. They outlined the character of "p*S* inducer" of (*S*)-*N*-acetyl-leucine in the formation of (p*S*)-**28** and the negative influence of conformational strains on the rate of palladation and diastereo- and enantio-selectivity.



(5)

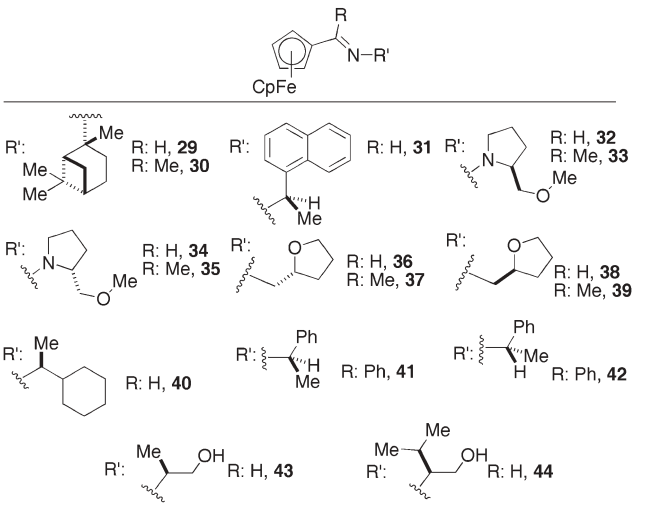
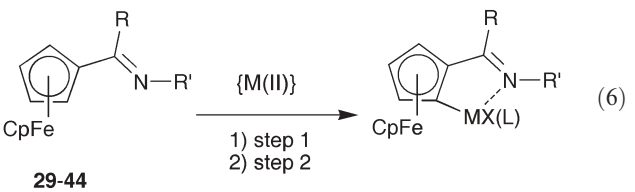


Chart 1

With chiral imines. The *ortho*-metallation of ferrocenyl imines prepared from racemic ferrocene aldehyde, acetylferrocene or benzoylferrocene and enantioenriched amines such as (−)-*cis*-myrtanylamine (**29** and **30**, Chart 1),[42] (*R*)-1-naphthylethylamine (**31**, Chart 1),[43] cyclic hydrazines (**32**–**35**, Chart 1),[44–46] (*R*) and (*S*)-tetrahydrofurfurylamine (**36**–**37**and **38**–**39**, Chart 1),[47] (*S*)-1-cyclohexyl-ethylamine[48] (**40**, Chart 1), (*S*) and (*R*)-1-phenyl-ethylamine[49] (**41** and **42**, Chart 1) and various β-amino alcohols such as (*S*)-2-amino-1-propanol (**43**, Chart 1), (*S*)-valinol (**44**, Chart 1),[50] or (*S*)-phenylalaninol[51] has been extensively investigated. Chart 2 displays the structures of the scalemic metallacycles which were formed *via* eqn (6).



(6)

From the data extracted from the literature and compiled in Table 1 the diastereoselectivity of the *ortho*-metallation of chiral imines may be deemed to depend on the nature of the metallation agents and to a limited extent to the bulkiness of the ancillary chiral organic fragment. High diastereoselectivities are noted for fifteen palladation reactions (entries 1, 4, 7 and 10–22, Table 1), and low or no selectivity for two *ortho*-mercuration (entries 23 and 24, Table 1) and two platination reactions carried out with $PtCl_2(dmso)_2$ (entries 25 and 26, Table 1). Interestingly, bidentation of the Pd(II) centre recedes in favor of tridentation in the case of the cyclopalladation of ferrocenylaldehyde-derived ligands **32** and **34**. In contrast, the palladation of the acetylferrocene-derived ligand **33** leads to the formation of conventional μ-chloro/bromo-bridged dimeric palladium chelates **33a–e** with a high degree of diastereoselectivity. The effect of the chiral imine moiety on diastereoselectivity has not yet been clearly rationalized. However, the diastereoselectivities obtained for acetate-promoted palladation reactions suggest that they operate under kinetic control as the nature of the transition states resulting

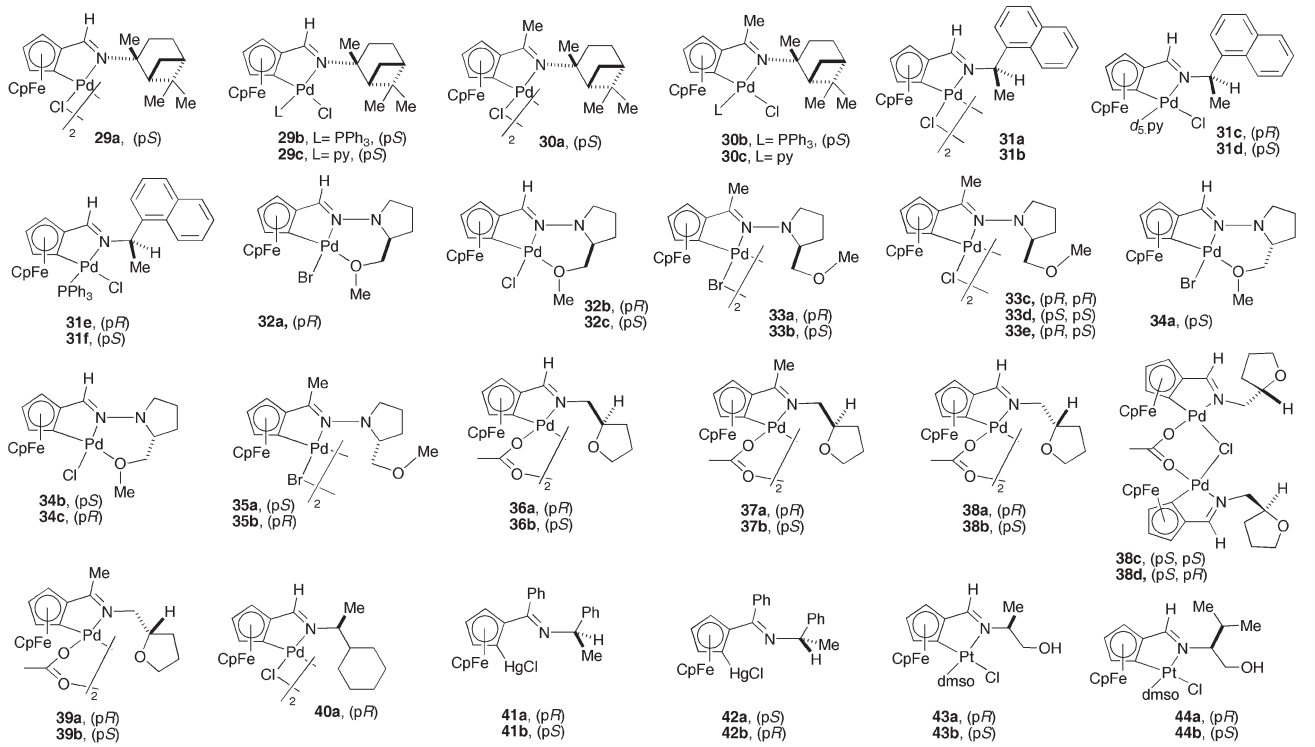


Chart 2 Planar-chiral ortho-metallated complexes resulting from the metallation of enantiopure chiral imines: absolute planar-chiral configurations are mentioned for those compounds which have been investigated structurally.

from the precoordination of the chiral imine to the Pd(II) centre may well be energetically discriminated by intrinsic conformational restrictions or by additional chelation by the remote chiral substituent binding the imine as outlined by Mak to rationalize the dd of compounds **36a–b–39a–b**. The less stereoselective mercurations of **41** and **42** (Table 1, entries 23 and 24) and the *ortho*-platinations of **43** and **44** (Table 1, entries 25 and 26) with $Hg(OAc)_2$ and $(dmso)_2PtCl_2$

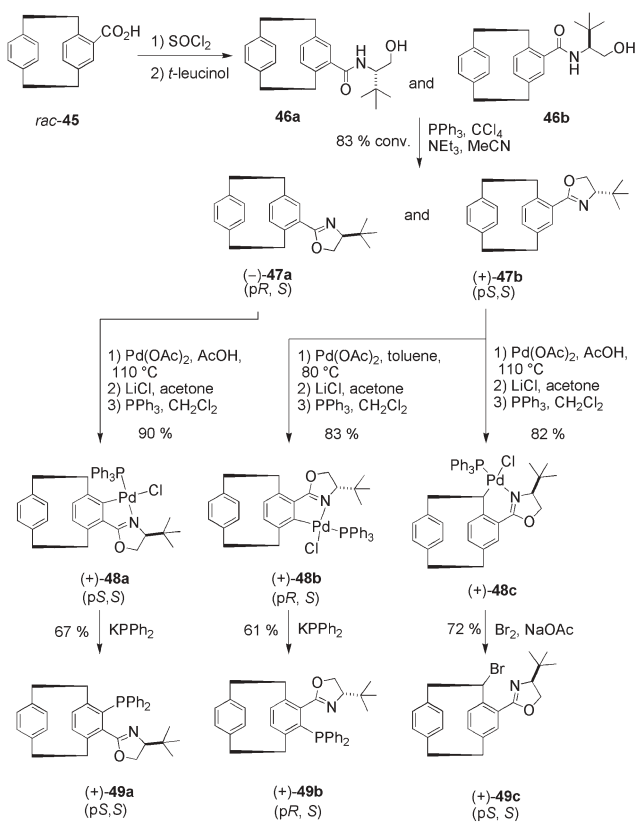
Table 1 *ortho*-Metallation of enantiopure imines **29–44**

Entry	Substrate	{M(II)}	Step 1	Step 2	MX(L)	Products (yield (%))	dr or dd	$[\alpha]_D$	XRD[a]
1	**29**[b]	Pd(II)	Na_2PdCl_4–NaOAc		μ-Cl-PdCl	**29a** (71)	100 : 0	+ 245	—
2	(**29a**)[b]			PPh_3	PdCl(PPh_3)	**29b** (57)		+ 29	**29b**
3	(**29a**)[b]			NC_5H_5	PdCl(py)	**29c** (60)		+76	—
4	**30**[b]	Pd(II)	Na_2PdCl_4–NaOAc		μ-Cl-PdCl	**30a** (77)	100 : 0	+160	—
5	(**30a**)[b]			PPh_3	PdCl(PPh_3)	**30b** (69)		−291	**30b**
6	(**30a**)[b]			NC_5H_5	PdCl(py)	**30c** (67)		+93	—
7	**31**[c]	Pd(II)	Na_2PdCl_4–NaOAc		μ-Cl-PdCl	**31a** : **31b** (58)	75 : 25		—
8	(**31a–b**)[c]			NC_5D_5	PdCl(d_5.py)	**31c** : **31d** (100)	75 : 25		—
9	(**31a–b**)[c]			PPh_3	PdCl(PPh_3)	**31e** : **31f** (80)	75 : 25	+98:−24	—
10	**32**[d]	Pd(II)	$Pd(OAc)_2$–NaOAc–LiBr		PdBr	**32a** (61)	100 : 0	+ 682	**32a**
11	**32**[e]	Pd(II)	Na_2PdCl_4–NaOAc		PdCl	**32b** : **32c** (77)	85 : 25	−3558:+ 2888	**32b**, **32c**
12	**33**[d]	Pd(II)	$Pd(OAc)_2$–NaOAc–LiBr		μ-Br-PdBr	**33a** : **33b** (72)	90 : 10	−3507:+ 2353	**33a**, **33b**
13	**33**[f]	Pd(II)	Na_2PdCl_4–NaOAc		μ-Cl-PdCl	**33c** : **33d** : **33e** (67)	80 : 10 : 10	+2685:−900:−2880	**33c**, **33d**, **33e**
14	**34**[d]	Pd(II)	$Pd(OAc)_2$–NaOAc–LiBr		PdBr	**34a** (66)	100 : 0	−681	**34a**
15	**34**[e]	Pd(II)	Na_2PdCl_4–NaOAc		PdCl	**34b** : **34c** (71)	75 : 25	+ 3461:−2885	**34b**, **34c**
16	**35**[g]	Pd(II)	$Pd(OAc)_2$–NaOAc–LiBr		μ-Br-PdBr	**35a** : **35b** (69)	90 : 10	+3510:−2359	**35b**
17	**36**[g]	Pd(II)	$Pd(OAc)_2$–NaOAc		(μ-OAc)$_2$ Pd	**36a** : **36b**	90 : 10	+2989:−370	
18	**37**[g]	Pd(II)	$Pd(OAc)_2$–NaOAc		(μ-OAc)$_2$ Pd	**37a** : **37b**	90 : 10	+1727:−584	
19	**38**[g]	Pd(II)	$Pd(OAc)_2$–NaOAc		(μ-OAc)$_2$ Pd	**38a** : **38b**	90 : 10	−2981:+376	**38a**, **38b**
20	**38**[g]	Pd(II)	Na_2PdCl_4–NaOAc		(μ-OAc)(μ-Cl)Pd	**38c** : **38d**	86 : 10	−385:−726	**38d**
21	**39**[g]	Pd(II)	$Pd(OAc)_2$–NaOAc		(μ-OAc)$_2$ Pd	**39a** : **39b**	90 : 10	−1743:+602	
22	**40**[h]	Pd(II)	Na_2PdCl_4–NaOAc		μ-Cl-PdCl	**40a** (76)	100 : 0	+ 409	—
23	**41**[i]	Hg(II)	$Hg(OAc)_2$–LiCl		HgCl	**41a** (22) : **41b** (20)	50 : 50	+493:−661	**41a**, **41b**
24	**42**[i]	Hg(II)	$Hg(OAc)_2$–LiCl		HgCl	**42a** (16) : **42b** (12)	50 : 50	−493:+ 660	**42a**, **42b**
25	**43**[j]	Pt(II)	$PtCl_2(dmso)_2$–NaOAc		PtCl(dmso)	**43a** (30) : **43b** (27)	50 : 50	nr[k]	—
26	**44**[j]	Pt(II)	$PtCl_2(dmso)_2$–NaOAc		PtCl(dmso)	**44a** (16) : **44b** (27)	37 : 63	nr[k]	**44b**

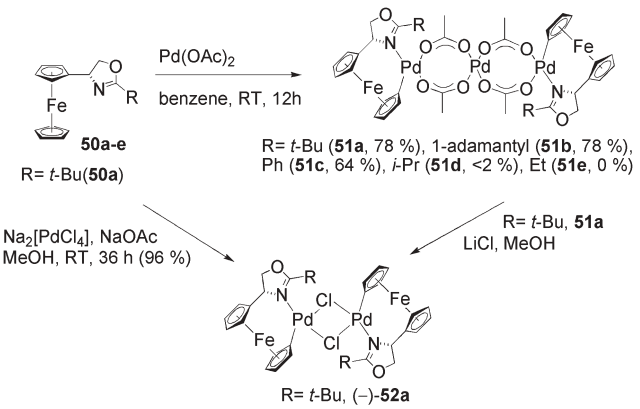
[a] Compounds for which absolute-structure determination by means of X-ray diffraction has been reported. [b] Ref. 42. [c] Ref. 43. [d] Ref. 44. [e] Ref. 45. [f] Ref. 46. [g] Ref. 47. [h] Ref. 48. [i] Ref. 49. [j] Ref. 50. [k] *nr*: not reported.

respectively could be deemed to stem from different mechanisms than that established for cyclopalladation. Neither is it possible to rule out thermodynamic control of these reactions. The structural assessment of the absolute configurations from X-ray diffraction analyses of those chiral ortho-metallated complexes mentioned in Table 1 were attempted by the resolution of the *absolute structures* (**32a–c**, **33a–e**, **34a–c**, **35b**, **38a–b**, **38d**, **41a–b** and **42a–b**, Chart 2, Table 1) and on indirect determinations from derivatives of the main metallation products. In the latter cases, the derivatives were obtained either by reactions of μ-halogeno-bridged dimers with a σ-donor ligand such as PPh_3 (**29b** and **30b**, Chart 2 and entries 1 and 5, Table 1) or by reaction with diphenylacetylene, which generally affords monomeric C-Pd bond alkyne-insertion products.[43,48,52]

With chiral oxazolines. An unusual use of scalemic cyclopalladated oxazolines was reported by Bolm and co-workers who took advantage of the inherent planar chirality of substituted [2,2]-paracyclophanes (Scheme 6).[53] In this work, *rac*-4-carboxy-[2,2]-paracyclophane **45** and *tert*-leucinol were the starting point of a multistep synthesis of enantioenriched P,N heterobidentate ligands *via* the intermediary formation and derivation of [2,2]-paracyclophanes **46a–b**, **47a–b** and cyclopalladated complexes **48a–b**. The key step of this strategy was the treatment of the latter Pd(II) complexes with $KPPh_2$, which produced the targeted heterobidentate ligands **49a–b**. It is worthy of note that diastereomeric p*R* and p*S* oxazoline ligands **47a–b** displayed quite different reactivities when treated with $Pd(OAc)_2$ at 110 °C in acetic acid. The p*R* diastereomer **47a** yielded the expected *ortho*-palladation product **48a** whereas the p*S* diastereomer underwent metallation at the vicinal ethylene bridge producing compound **48c**. C_{Ar}–H bond activation and cyclopalladation were eventually achieved by carrying out the reaction at 80 °C in toluene, which resulted in **48b**.



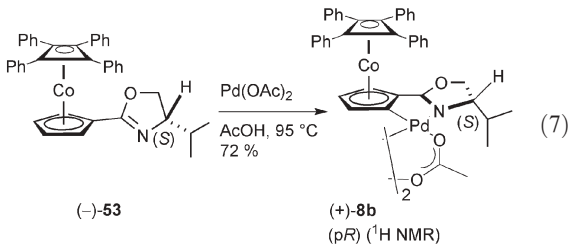
Scheme 6



Scheme 7

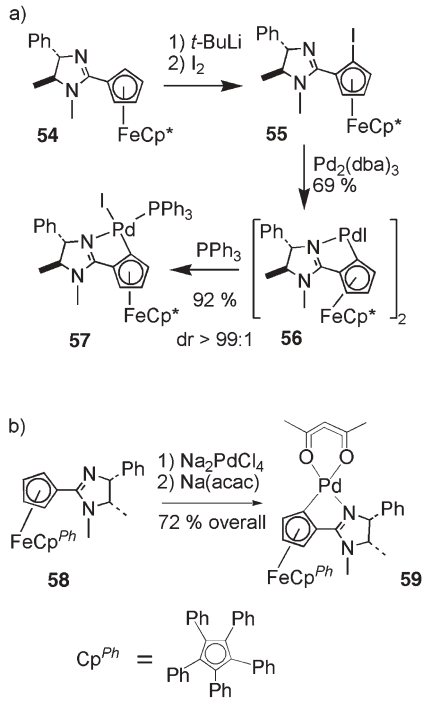
It is intriguing to note that the *ortho*-palladation of 2-ferrocenyl-1,3-oxazolines is reportedly impossible according to Moyano, Lopez and co-workers because of a competing redox process involving the Fe(II) centre with the Pd(II) reagent.[54] Nonetheless, as reported by these authors, the metallation of a series of scalemic homologues derived from *tert*-butyl, 1-adamantyl and phenyl-substituted 4-ferrocenyl-1,3-oxazoline **50a–e** with $Pd(OAc)_2$ or $Na[PdCl_4]$–NaOAc led to interannular cyclopalladation with yields ranging from 78% to 64% for products **51a–c**, and a yield of 96% for (−)-**52a** (Scheme 7). Compounds **51a–d**, which strictly-speaking are not planar-chiral, contain a core of three palladium atoms arranged linearly and linked by four acetate bridges.

Metallocene "molecular gears" applied to the stereochemical control of metallation. Stereochemical control of *ortho*-metallation by palladium salts was achieved by Richards, who extended the concept of conformation-restricted metallocene molecular gears[55] to the stereoselective preparation of new Pd-based Lewis acidic catalysts based on the (η^4-tetraphenylcyclobutadienyl)(η^5-cyclopentadienyl)cobalt(I) core. The palladation of enantiopure oxazoline complex (−)-**53** [eqn (7)] reportedly occurred with complete stereoselectivity yielding a unique product, the acetato-bridged analog of **8a**, *i.e.* (+)-**8b**.[56]



(7)

This result was rationalized by the cooperativity of the conformational relationship between the sterically demanding (η^4-tetraphenylcyclobutadienyl) fragment and the oxazolinyl-substituted cyclopentadienyl moiety, which predominantly contributes to orienting the metallation reaction at a single



Scheme 8

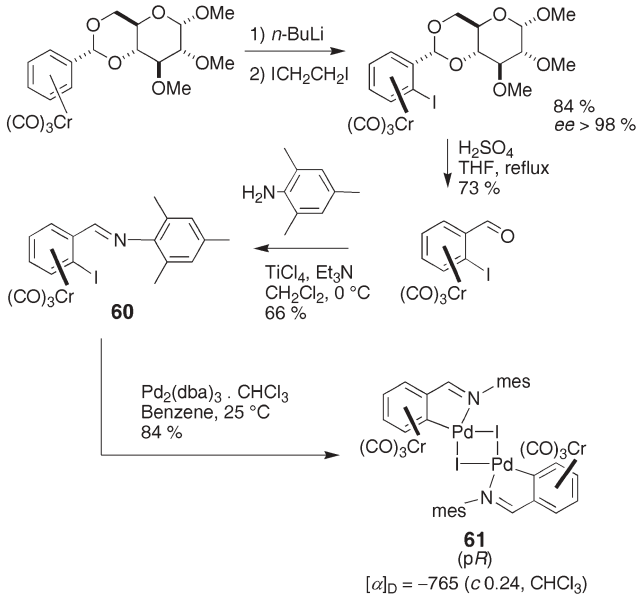
site. Identical results on the palladation of the same ligand were subsequently obtained by Overman and co-workers, who indirectly confirmed the p*R* planar-chiral absolute configuration of the product **8b** thanks to X-ray diffraction analyses of its acetylacetonate derivative.[57] This new class of palladacyclic compounds has in many instances proven its efficiency as promoters of the enantioselective allylic rearrangement of acetimidates[58,59] and esters.[60]

With chiral imidazoles and imidazolines. In their continued investigation of the concept of molecular gears[55] applied to the design of novel catalysts, Richards and co-workers studied the reactivity of (η^4-tetraphenylcyclobutadienyl)(η^5-cyclopentadienyl)cobalt(I) complexes containing a chiral imidazole. They suggested that the palladation with $Pd(OAc)_2$, which produces a single diastereomer of p*R* configuration at both short and long reaction times, was most certainly kinetically controlled.[61]

Recently, Peters and co-workers described the reactivity of scalemic [2-imidazolyl] pentamethyl and pentaphenylferrocenes, **54** and **58** respectively, towards palladation and pointed out a difference of reactivity of the Me_5 *vs.* Ph_5 complexes when treated with $Na_2[PdCl_4]$[62] (Scheme 8): the latter undergoes metallation with high diastereoselectivity (dr 16 : 1) to give **59**, whereas the former, *e.g.* **54**, does not metallate but rather decomposes by oxidation. The preparation of **56** and **57** (Scheme 8) required a different approach that corresponds to route **II**.

Route II, oxidative addition

The synthesis of scalemic planar-chiral cyclometallated compounds by the oxidative addition of a so-called low-valent



Scheme 9

metal to a planar-chiral halogeno-arene was attempted in a few cases, and mostly for the preparation of palladacycles.

Zipp and Overman described the multi-step preparation of enantiopure cyclopalladated (η^6-arene)tricarbonylchromium complexes by treatment of scalemic *ortho*-iodo substrates such as **60**, prepared following a method based on the work of Chung *et al.*[63], with $Pd_2(dba)_3{\cdot}CHCl_3$ (Scheme 9).[64] Most of the Pd(II) products, such as **61** whose planar-chiral configuration was established to be p*R*, were obtained in good yield. The same method of metallation using oxidative addition of Pd(0) to scalemic *ortho*-iodo ferrocenyl oxazolines was later reported by Overman and co-workers;[65] the products were found to have a remarkable catalytic activity as chiral Lewis acids for the promotion of Claisen rearrangements.[66]

Route **II** may therefore be deemed a convenient alternative to metallation by the so-called C–H activation route, even though a few additional synthetic steps are required. A good illustration of this is the synthesis of **56** by the oxidative addition of $Pd_2(dba)_3$ to an *ortho*-iodinated derivative of the Me_5 substrate **55** (Scheme 8).[62]

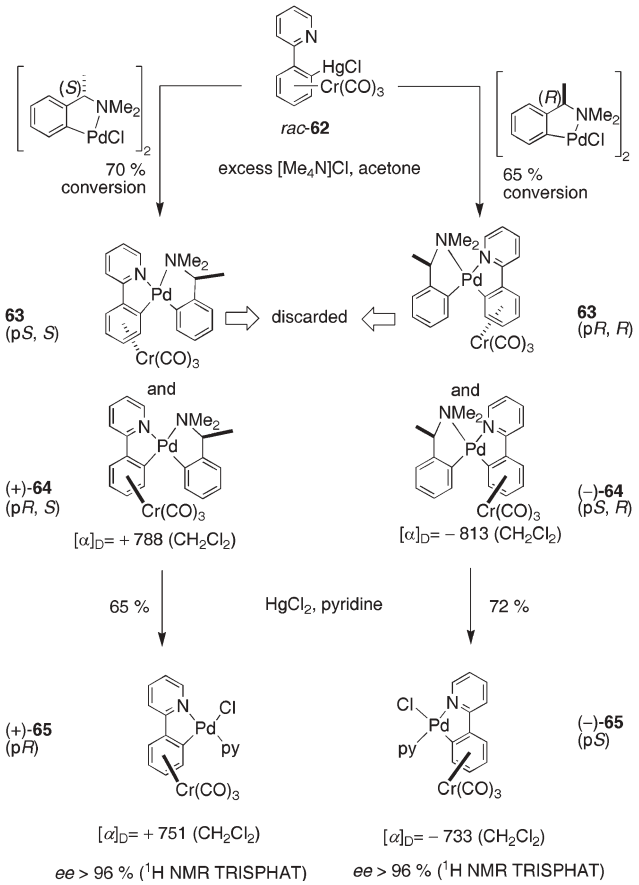
Route III, transmetallation

Transmetallation reactions, which can also be considered formally as intermetallic ligand cross-exchange, have been used in the synthesis of planar-chiral metallacycles starting from *ortho*-metallated substrates. One may distinguish two types of transformation, namely:

(1) the isohypsic[67] transmetallation of a racemic substrate with a scalemic metal complex auxiliary, followed sequentially by resolution of the resulting diastereomers and release of the chiral auxiliary (subroute **IIIa**),

(2) the oxido-reductive and the isohypsic metal exchange with scalemic substrates (subroute **IIIb**).

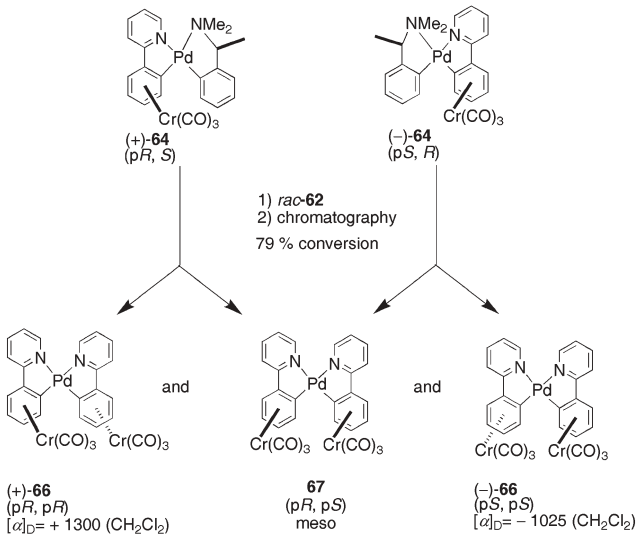
Route IIIa, transmetallation by a scalemic metal complex and resolution. Highly enantioenriched planar-chiral palladacyclic



Scheme 10

(η^6-arene)tricarbonyl complexes derived from 2-phenylpyridine have been prepared efficiently from an *ortho*-mercurated substrate, *e.g. rac*-**62** (Scheme 10).[68] The transmetallation step involves the reaction of a racemic chloromercurated substrate **62** with an enantiopure centro-chiral palladacycle derived from *N*,*N*-dimethyl-1-phenyl-ethylamine in the presence of a large amount of $[Me_4N]Cl$. The latter plays an important role in neutralizing $HgCl_2$, the main byproduct of the reaction, which may compromise, by virtue of its electrophilicity, the isolation of the targeted heteroleptic bischelated Pd(II) products **63** and **64**.[69] The release of planar-chiral cyclopalladated complexes was achieved after chromatographic separation of the 1 : 1 mixture of diastereomers **63** and **64** and subsequent treatment of either (+) or (−)-**64** with $HgCl_2$ and pyridine. The enantiopurities of enantiomers (+) and (−)-**65** were assessed by ^{1}H NMR using Lacour's TRISPHAT salts as a chiral shift reagent. The latter interacts with polar organometallic species to produce dipole–charge associations which may exert a significant shift of the ^{1}H NMR resonances.[70] Their absolute structures and configurations were established by X-ray diffraction analyses.

Furthermore, enantioenriched Pd(II) bis-chelates (+) and (−)-**64** (Scheme 11) have been used in the preparation of C_2 symmetric homoleptic Pd(II) bischelates (+)- and (−)-**66** and **67** by a ligand exchange reaction with racemic *ortho*-chloro-mercurated 2-[tricarbonyl(η^6-phenyl)chromium]pyridine, *rac*-**62**.[71] The difference of polarities existing between the *meso syn*-facial compound **67** and the scalemic *anti*-facial

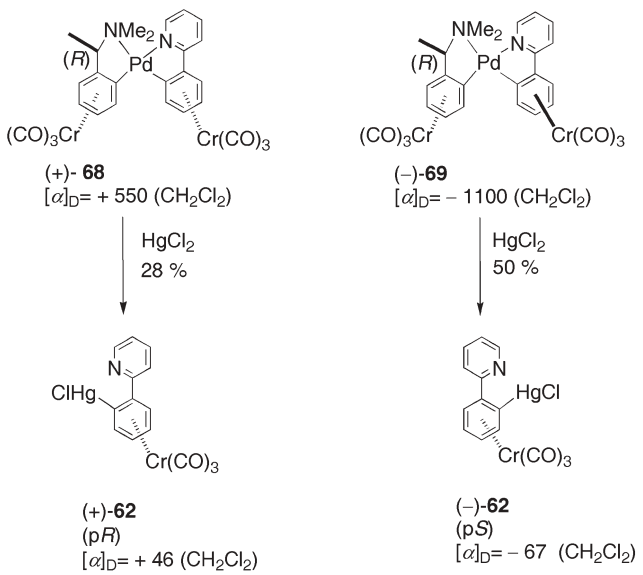


Scheme 11

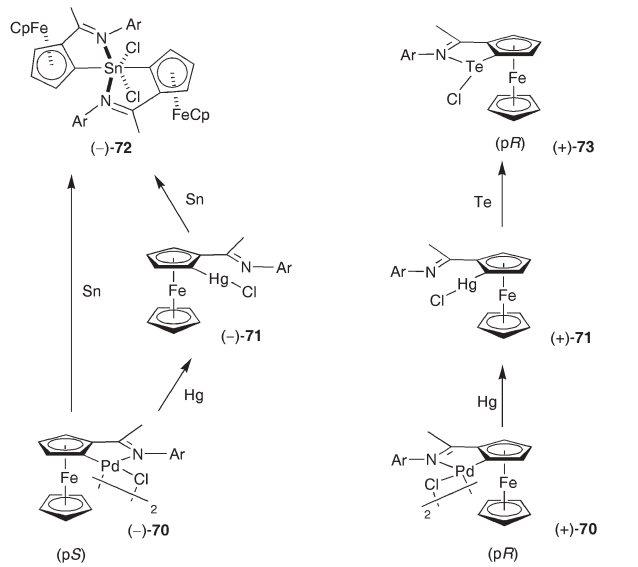
products, *i.e.* (+)-**66** and (−)-**66**, allowed their chromatographic separation.

Scalemic (+)-**62** and (−)-**62** *ortho*-chloro-mercurated 2-[tricarbonyl(η^6-phenyl)chromium]pyridine complexes were synthesized in 28 and 50% yield respectively by a reaction of scalemic diastereomers **68** and **69** with $HgCl_2$ (Scheme 12).

Route IIIb, transmetallation of a scalemic planar-chiral metallacycle. The first transmetallation reactions of scalemic planar-chiral metallacycles were initially reported by Sokolov and co-workers in the late 1970's for a sequential transformation of **19** into **20** and **21** (Scheme 5), which were deemed based on crystallographic evidence to proceed with complete retention of planar configuration.[72] Historically, the latter observation may be paralleled to the findings of Stille[73] in the same decade on the stereospecificity of the transmetallation reaction of chiral alkyl-mercury substrates.



Scheme 12



(–)-**71**, M= Hg

71a, Ar= *p*-$MeOC_6H_4$, 93 %, $[\alpha]_D$= – 678
71b, Ar= *p*-MeC_6H_4, 92 %, $[\alpha]_D$= – 677
71c, Ar= *p*-ClC_6H_4, 95 %, $[\alpha]_D$= – 653
71d, Ar= *m*-BrC_6H_4, 96 %, $[\alpha]_D$= – 556
71e, Ar= *o*-MeC_6H_4, 98 %, $[\alpha]_D$= – 535

(+)-**71**, M= Hg

71a, Ar= *p*-$MeOC_6H_4$, 95 %, $[\alpha]_D$= + 695
71b, Ar= *p*-MeC_6H_4, 94 %, $[\alpha]_D$= + 658
71c, Ar= *p*-ClC_6H_4, 93 %, $[\alpha]_D$= + 673
71d, Ar= *m*-BrC_6H_4, 92 %, $[\alpha]_D$= + 510
71e, Ar= *o*-MeC_6H_4, 96 %, $[\alpha]_D$= + 512

(–)-**72**, M= Sn

72a, Ar= *m*-$MeOC_6H_4$, 78 %, $[\alpha]_D$= – 1634
72b, Ar= *p*-MeC_6H_4, 81 %, $[\alpha]_D$= – 1776
72c, Ar= *p*-ClC_6H_4, 60 %, $[\alpha]_D$= – 1594
72d, Ar= *m*-ClC_6H_4, 74 %, $[\alpha]_D$= – 1680
72e, Ar= *o*-MeC_6H_4, 60 %, $[\alpha]_D$= – 1567

(+)-**73**, M= Te

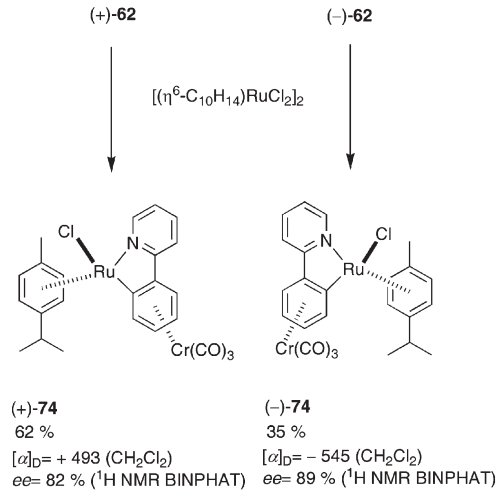
73a, Ar= *m*-$MeOC_6H_4$, 37 %, $[\alpha]_D$= + 2707
73b, Ar= *p*-MeC_6H_4, 27 %, $[\alpha]_D$= + 3190
73c, Ar= *p*-ClC_6H_4, 41 %, $[\alpha]_D$= + 3025
73d, Ar= *p*-BrC_6H_4, 23 %, $[\alpha]_D$= + 2141
73e, Ar= C_6H_5, 18 %, $[\alpha]_D$= + 3240

Scheme 13 "Redox transmetallations" of various *ortho*-metallated arylimines derived from acetyl-ferrocene with detailed nature of aryl group, yield and specific optical rotation.

Recently, the group of Wu reported an extensive series of redox transmetallations (Scheme 13) of cyclopalladated (compounds **70**) and mercurated imine complexes (compounds **71a–e**) with elemental metals or semi-metals such as Hg,[74] Sn[75] (compounds **72a–e**) and Te[76] (compounds **73a–e**). The authors demonstrated that the transmetallation of mainly p*R* and p*S* scalemic palladacycles (+) and (−)-**70** was ideally symmetric with Hg_{metal} resulting in (+) and (−)-**71** with specific rotations of similar absolute value for each pair of related enantiomers. With sound evidence produced by X-ray diffraction analyses of several scalemic compounds it was established that redox-type transmetallation reactions occurred with retention of planar configuration.

This stereospecificity of route **III** opens access, in principle, to a vast variety of scalemic planar-chiral metallacycles. For instance, the treatment of (+) and (−)-**62** with bis[dichloro(η^6-cymene)ruthenium] afforded scalemic *ortho*-ruthenated products (+) and (−)-**74** with enantiomeric excesses higher than 80% as determined by ^{1}H NMR spectroscopy using a BINPHAT salt,[77] an analogue of TRISPHAT, as a chiral NMR shift reagent (Scheme 14).

The transmetallation of arylmercury(II) substrates with alkyllithium reagents has also been reported to lead to the corresponding aryllithium intermediates with retention of the relative planar configuration.[40] For instance the sequential

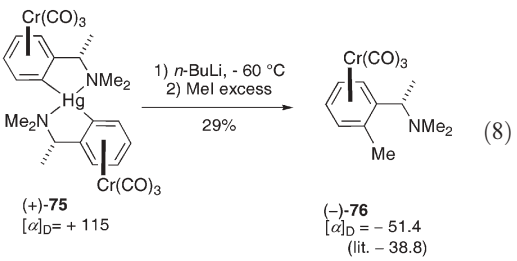


(+)-**74**
62 %
$[\alpha]_D$= + 493 (CH_2Cl_2)
ee= 82 % (^{1}H NMR BINPHAT)

(–)-**74**
35 %
$[\alpha]_D$= – 545 (CH_2Cl_2)
ee= 89 % (^{1}H NMR BINPHAT)

Scheme 14

treatment of scalemate (+)-**75** (8) with *n*-BuLi in THF and methyl iodide at low temperature resulted in scalemate (−)-**76** whose levorotatory property was consistent with that reported for the same compound by Davies and co-workers[78] few years earlier.



(+)-**75**
$[\alpha]_D$= + 115

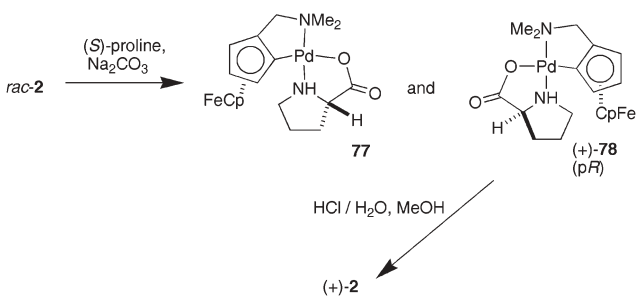
(–)-**76**
$[\alpha]_D$ = – 51.4
(lit. – 38.8)

(8)

Route IV, resolution of racemic or diastereomeric mixtures

The separation of enantiomers from a racemic mixture of a planar-chiral metallacycle by formation of diastereomers has been undertaken in only a few cases being mainly those of *SP*-4 Pd(II) complexes. This method requires the substrate to present a sufficient coordinative lability to allow the binding of an enantiopure auxiliary. Cyclopalladated μ-halogeno-bridged compounds are particularly suited as they may form, under mild conditions, diastereomeric heteroleptic bischelated complexes, when treated with stoichiometric amounts of enantiopure amino acids.

Historically, this methodology was first reported in 1981 by Nonoyama for the resolution of *rac*-**2** (Scheme 15).[79] The



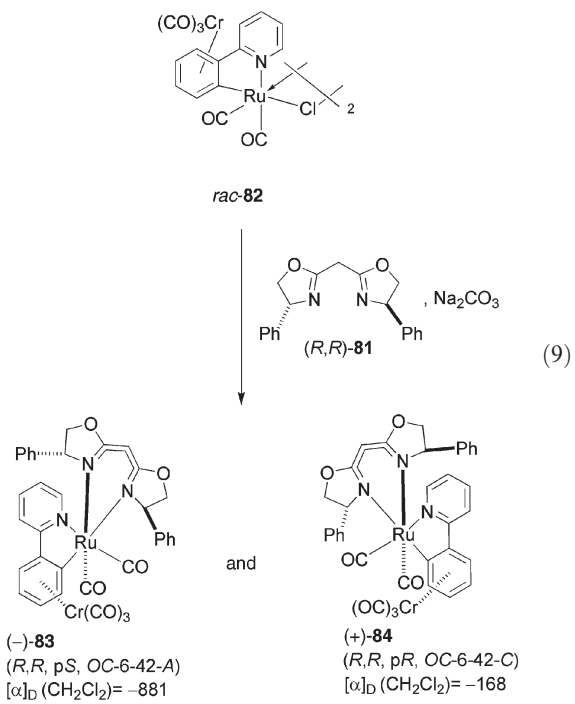
Scheme 15

resolution relied on the reversibility of the chelation of the Pd(II) centre by (*S*)-prolinate, the latter being assumed to chelate the Pd centre in a *trans* N,N fashion with respect to the [C,N] chelating ligand. The pair of diastereomeric bischelates **77** and **78** was separated by fractional recrystallization to yield crystalline (+)-**78** in 26% yield. The authors did not give any details of the purity of compound **77**. Nonetheless, (+)-**2** was efficiently recovered in 51% yield by treating (+)-**78** with dilute aqueous HCl in MeOH. The absolute planar configuration p*R* for (+)-**2** was proposed based on similarities both in the sign and intensity of Cotton effects observed in the CD spectrum of the former and in that of (p*R,S*)-**21**.

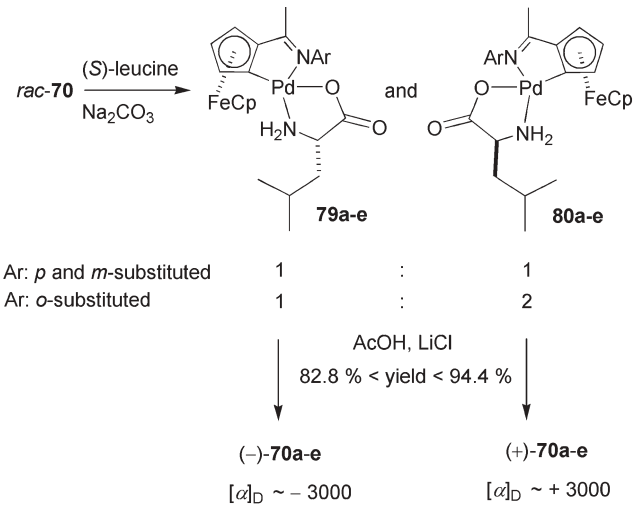
This method of resolution does not present major synthetic drawbacks apart from a single report on a suspected unusual mode of coordination of a Pd(II) ferrocene metallacycle with glycine.[80] Wu *et al.* applied this methodology to the preparation of imine complexes (+) and (−)-**70a–e** from *rac*-**70a–e** by using (*S*)-leucine as the chiral auxiliary (Scheme 16).[74] The intermediary diastereomers **79a–e** and **80a–e** were separated by preparative thin-layer chromatography.

Interestingly, large disparities in dr were noticed and correlated with the type of substitution on the aryl group that binds the imine nitrogen; *ortho*-substitution and steric hindrance induced the highest diastereoselectivities. Scalemates of **70a–e** were subsequently recovered by treatment with LiCl and acetic acid in yields ranging from 82 to 94%.

The use of other chiral bidentate ligands for the physical separation of diastereomeric planar-chiral metallacycles has only been sparsely reported to date. Enantiopure bisoxazolinylmethane (*R,R*)-**81** [eqn (9)] reacts under basic conditions with chloro-bridged *OC*-6 Ru(II) chelate *rac*-**82** to yield a 1 : 1 mixture of chiral-at-ruthenium diastereomers (p*S*)-**83** and (p*R*)-**84**, which were readily separated by conventional chromatography.[81]



(9)



Scheme 16

Crystal-structure and absolute-configuration determination of planar-chiral metallacycles

Troublesome scalemates

By its very nature a scalemate is a mixture, a binary mixture of enantiomers. Consequently in an absolute-configuration determination, one needs some physico-chemical (non-diffraction) characterization to identify unequivocally the enantiomer under investigation. An additional complication is that on crystallization of a scalemate, the enantiomeric composition of: (i) the domains within an individual crystal, (ii) the individual crystals, (iii) the bulk crystalline solid and (iv) the liquid phase, will not in general be identical, only the truly enantiopure bulk (ee = 100%) being an exception to this rule. So a major concern in the valid determination of absolute configuration from a scalemate arises from the specification of the enantiomeric composition of the one single crystal used for the X-ray diffraction experiment which may well not be characteristic of the bulk. The physico-chemical (non-diffraction) characterization required is that of the single crystal used for the diffraction experiment.

This part of the review commences with a short presentation of thermodynamic and structural properties, and the characterization of scalemates. Then follows a brief reminder of the current technology of absolute-configuration determination by single-crystal X-ray diffraction. We conclude, by way of an illustration of the foregoing, of the evaluation of the published crystal-structure determinations of those planar-chiral metallacycles cited in the earlier part of the review. For fuller details on absolute-configuration determination by X-ray diffraction the reader is referred to the works[82–85] and to Jacques, Collet & Wilen's monograph[86] for thermodynamic and kinetic information on the crystallization of scalemates.

Physico-chemical properties and characterization of scalemates

There are three basic types of binary phase diagram for scalemates:

(1) Racemic compound formation: the most frequent type of binary phase diagram corresponds to the formation of a

homogeneous crystal structure of the racemate, commonly called the racemic compound. The phase diagram contains symmetric eutectic points (minima) between the racemic and enantiopure compositions which themselves are maxima. According to the composition of the solution and the eutectic, one obtains either crystals of the racemic or the enantiopure compound. The melting temperature of the racemic compound may be higher, even much higher, or lower than that of the enantiopure compound. The crystal structure of the racemic compound may be either centrosymmetric or non-centrosymmetric achiral or non-centrosymmetric chiral. The crystal structure of an enantiopure compound is chiral.

(2) Racemic conglomerate formation: the type of phase diagram giving rise to spontaneous resolution is symmetric about a eutectic point (a minimum) at the racemic composition with maxima at the enantiopure compositions. Crystallization of a racemate gives equal quantities of enantiopure left- and right-handed chiral crystals known as a racemic conglomerate. The melting temperature of the racemic conglomerate is lower than that of the enantiopure compound. As always, the crystal structure of an enantiopure compound is chiral.

(3) Solid-solution formation: a rarely-studied type of phase diagram is that of a continuous solid solution which is sometimes known as a pseudoracemate. Their crystal structures are disordered.

There are three principal methods for the characterization of scalemates:

(OR) The specific rotation of the optical activity in solution. As the measurement of specific rotation is a single-wavelength technique, the presence and effect of impurities can easily go undetected. Moreover OR can not be applied to microgram quantities (one single crystal). Also OR can only provide a measure of ee if the specific rotation of the enantiopure compound is sufficiently strong and has been determined previously.

(CD) The visible and near-UV circular dichroism spectrum in solution. The presence and effect of impurities may be readily recognized in a CD spectrum. In favourable circumstances, CD may be applied to the single crystal used for diffraction measurements taken into solution. For compounds that racemize rapidly in solution, solid-state CD in a KBr disk may be applied to the bulk compound and perhaps even to a powdered single crystal.[87] One may expect vibrational CD, either IR or Raman, to be used increasingly in the future.

(EC) Enantioselective chromatography. This sensitive technique is applicable to microgram quantities and provides estimates of the ee. It is of course necessary to establish that under the chosen experimental conditions the two enantiomers are clearly separated. The retention times provide a satisfactory characterization of the two enantiomers.

Regrettably little use is made of differential scanning calorimetry (DSC) by synthetic chemists and structure analysts. Nevertheless the measurement of melting temperatures and enthalpies is a valuable technique for establishing the phase diagram of the scalemate. DSC measurements may be applied to the bulk.

Single-crystal X-ray diffraction techniques

The distinction by single-crystal X-ray diffraction of inversion-related models of a non-centrosymmetric crystal structure relies on the phenomenon of resonant scattering (anomalous dispersion) and is measured by the Flack parameter[83] whose underlying physical model is that of a crystal twinned by inversion.[88] A simple way of picturing the crystal twinned by inversion is to imagine a racemic conglomerate in which the crystals have stuck together at growth in a perfectly oriented manner giving diffraction patterns that look like those of a single crystal. Let X represent the model crystal structure as given by its cell dimensions, space group and atomic coordinates and $\bar{X}$ its inversion image in a point. The macroscopic crystal may be represented as $C = (1 - x)\,X + x\,\bar{X}$ for which the Flack parameter x measures respectively the mole fractions $(1 - x)$ and x of the two types of domain X and $\bar{X}$. When $x = 0$, there is only one domain in the crystal which is that of the model X. When $x = 1$, there is only one domain in the crystal which is that of the inverted model $\bar{X}$. When $x = 0.3$ both types of domain are present in the crystal in the proportion 70% of X to 30% of $\bar{X}$. The physically meaningful values of x are $0 \leqslant x \leqslant 1$ but due to statistical fluctuations and systematic errors, experimental values may lie a little outside of this range. A crystal of an enantiopure compound in the correct absolute configuration has a value of the Flack parameter of zero.

In crystallographic jargon one says that the Flack parameter measures the absolute structure of a non-centrosymmetric crystal and from this one may deduce the absolute configuration of the chiral molecules forming the crystal. There are conditions under which one may say that the absolute structure of the crystal has been determined satisfactorily. Firstly one wants to know whether the absolute-structure determination is sufficiently precise by looking to see whether the standard uncertainty u of the Flack parameter $x(u)$ is sufficiently small: in general u should be less than 0.04 but this value may be relaxed to 0.10 for a compound proven by other means to be enantiopure. Secondly the value of the Flack parameter itself should be close to zero within a region of three standard uncertainties *i.e.* $u < 0.04$ (or $u < 0.10$ for ee = 100%) and $|x|/\mu < 3.0$. Moreover the crystal and bulk need to have been characterized as described above. Once the absolute structure has been determined satisfactorily, it is only then the moment to see whether something can be said about the absolute configuration of its constituent molecules. The basic criterion is that the chiral molecule whose absolute configuration is to be determined should be present in the crystal structure at the enantiopure composition (ee = 100%). Two subsidiary, necessary but not sufficient, symmetry restrictions can be derived from this criterion: (i) the symmetry of the molecule in the crystal structure should not contain rotoreflection operations in its point group (*i.e.* the molecule is chiral) and (ii) likewise the space group of the crystal structure should not contain rotoinversion operations (*i.e.* the crystal structure is chiral). If these criteria hold, the absolute configuration of the molecule can be determined by examining a graphical representation of the molecule in the crystal structure. Some of the above criteria may be relaxed but such

studies need exceedingly careful, individual and expert evaluation.[84] A common alternative technique for absolute-configuration determination, not requiring resonant scattering, makes use of an enantiopure group, substituent or molecule of known absolute configuration.

One should bear in mind that a structure analysis may be erroneous. An error with which one should be familiar is the one in which the symmetry of a crystal structure has been incorrectly assigned to a non-centrosymmetric space group whereas the crystal structure itself is really centrosymmetric. In an erroneous non-centrosymmetric description of a crystal structure, the conditions for absolute-configuration determination may apparently be achieved which do not apply in the true centrosymmetric description.[85] Equally relevant to the study of scalemates are those cases of analysis in which an achiral crystal structure of a racemate (often disordered) with a space group containing rotoinversion operations has erroneously been assigned to a crystal which has in fact a chiral crystal structure of an enantiopure compound with a space group containing only rotation operations.[89] This latter case may arise when a bulk racemate crystallizes by spontaneous resolution and the structure analyst force-feeds the structure solution with a racemate.

Polar-dispersion errors[90] and partial-polar ambiguities[91] are of particular concern in crystal-structure studies of metallacycles. Under certain conditions of intensity measurement, data reduction and refinement strategy, biased (wrong) atomic coordinates along certain specific directions may occur. Such polar-dispersion errors are in general avoided by full refinement of the Flack parameter. In a crystal-structure solution suffering from a partial-polar ambiguity some of the atoms are correctly located but the others are images of the real atoms inverted in a point. One may be able to recognize these two types of error by a study of interatomic distances and angles.

Analysis of published crystal-structure determinations of planar-chiral metallacycles

The determination of absolute structure and absolute configuration are on the finer side of the study of crystal structures. To ensure that appropriate measurements have been undertaken and that these properties have been correctly estimated, one first needs to evaluate the more ordinary aspects of data measurement and structure determination. Furthermore the crystal structure determination needs to be reported in sufficient detail to have any scientific worth. So in our study we have taken a very broad view of the evaluation of the crystal structures of metallacycles and did not restrict our analysis only to chiral crystal structures but also harvested data on achiral (non-centrosymmetric and centrosymmetric) ones. Of course from the latter it is not possible to determine absolute configuration but chirality-related problems nevertheless appear.

All publications cited in the first part of this review were examined to see if they reported crystal-structure determinations of metallacycles not previously published. Crystallographic and chemical data for those 135 compounds published after 1985 were extracted from the primary publications and their supplementary material, from data in CIF format deposited with the CCDC or the ICSD, and by search in the CSD with Conquest. Authors were contacted only very rarely. A detailed table of the harvested data with full explanatory material is provided in the ESI.† On the chemical side we sought information on the characterization of the compound and crystal by the physico-chemical techniques mentioned above. For the crystallographic measurements we evaluated intensity-measurement region, data treatment, least-squares refinement, the final structure solution and its reporting. A major element in the latter evaluation is the checkCIF/PLATON service provided free-of-charge by the International Union of Crystallography.[92] In the following we discuss the general trends that were observed for these crystal-structure and absolute-configuration determinations giving an outline of the principal observations and shortcomings. Remarks particular to racemates are treated in a separate section. Individual structures are not discussed.

Principal observations

Publications in which crystal structures were well described tended to be accompanied by insufficient chemical and physico-chemical information. Conversely those papers in which the synthesis and physico-chemical characterization of the compound were well reported tended to be much weaker on the structure analysis. The worst cases of the latter are those that contain only an ORTEP plot of the crystal structure and claims of an absolute-configuration determination but next to no crystallographic data *e.g.* no cell dimensions, no atomic coordinates and no value of the Flack parameter.

The main method of physico-chemical characterization of the metallacycles was measurement of the specific rotation on the bulk product which was presented in 63% of studies. It was very encouraging to see that in a reasonable number of cases (30%) both enantiomers had been synthesized and had their specific rotation measured for comparative purposes. In 70% of these 30%, the crystal structures of both enantiomers had been determined. CD spectra of the bulk in solution were presented for 12% of the compounds and 1.5% reported that the single crystal used for the diffraction measurements had been taken into solution for CD measurement. There were no reports of a CD spectrum having been made on a powder in the solid state. Measurements of enantioselective chromatography on the bulk were presented in 4.4% of cases but there were no reports of the single crystal used for the diffraction study having been analysed. No DSC measurements were reported. Properly quantified values of ee (enantiomeric excess) with a standard uncertainty were never presented.

Despite the risk of mixtures of diastereoisomers being present in many of the bulk products, there were no reports of the simple expedient of comparing the X-ray powder diffraction pattern of the bulk product with that simulated from the results of a single-crystal study. Clearly although this technique is of no help for detecting racemic conglomerates, it is very helpful for other mixtures.

It is possible from calculations based only on the chemical composition of the compound[85,93] to make an *a priori* estimate of the capacity of single-crystal X-ray diffraction measurements to distinguish between inversion-related models and to

give an *a priori* estimate of the experimental value of the standard uncertainty of the Flack parameter. Thus calculation of $\chi.10^4$ (Friedif)[93] established that the resonant-scattering contribution to the diffraction from all these structures was sufficient for absolute-structure and absolute-configuration determination. This is hardly surprising for a set of metallacycles. For the non-centrosymmetric crystal-structure determinations 58% had an adequate (>50%) Friedel coverage and 84% reported a Flack parameter with its associated standard uncertainty. We can not stress sufficiently[85] that for new non-centrosymmetric crystal structures of metallacycles it is essential to measure all pairs of Friedel opposites (*i.e.* reflections $h\ k\ l$ and $\bar{h}\ \bar{k}\ \bar{l}$) and to use them separately in the least-squares refinement to obtain a meaningful value of the Flack parameter and its associated standard uncertainty.

No examples of a polar dispersion error or a partial polar ambiguity were recognized in the metallacycle structures studied here.

From an analysis of the atomic coordinates and cell parameters, checkCIF/PLATON may provide an alert that a space group of too low symmetry has been chosen. The most common situation is that it may be possible to add a centre of symmetry to the chosen space group. This proposition should be rejected if there is strong evidence to show that the compound is enantiopure in the crystalline state. With the metallacycle structures, there were eight cases where a higher symmetry was suggested of which six involved the addition of a centre of symmetry. Of these six cases: (a) for four of them the authors had commented and explained the nature of the pseudo-symmetry in the publication, (b) for the fifth the chemical evidence made it clear that the compound was enantiopure and (c) for the sixth one there was no mention of the pseudo-symmetry in the publication but, on our prompting, the authors have confirmed that the structure is indeed centrosymmetric by undertaking the appropriate least-squares refinement on the original intensity data.

Principal shortcomings

Regrettably 26% of the crystal-structure determinations suffer from an incompatibility between the chemical and the crystallographic evidence. Our careful study of these structures shows that they all display the same characteristics and consequently the incompatibility has the same cause. In general, the chemical evidence was adequate to convince us that the bulk products had a composition close to enantiopurity. The crystal structures were determined as being chiral but with values of the Flack parameter close to 0.5, with a low standard uncertainty, indicative of a crystal twinned by inversion with an overall composition near to that of the racemate in contradiction to the chemical evidence. All these structures were measured using the same model of diffractometer and the same software. Our attention was drawn to the use of software implementing an empirical absorption correction which was not used in any of the other structure determinations. We hypothesize that for the incompatible crystal-structure determinations that either the data-reduction software averaged Friedel opposites or that the particular empirical absorption correction procedure tends to eliminate intensity differences between Friedel opposites. These structure determinations run the risk of suffering from a polar-dispersion error. It is standard practice in our laboratory to calibrate every diffractometer after a hardware or software modification with a well-defined reference material of a chiral crystal structure and containing a sufficient amount of resonant scattering. We use enantiopure potassium hydrogen (2*R*,3*R*)-tartrate [$\chi.10^4$ (Friedif) MoKα = 174]. With such a test material, structure solution must give a Flack parameter very close to zero for the (2*R*,3*R*) configuration of the acid tartrate anion. A further calibration[94] with an untwinned sample of an achiral non-centrosymmetric crystal would be useful to detect other types of software errors but we have as yet been unable to identify a suitable test material. In particular software initially written for the treatment of biological materials but subsequently adapted to more general cases should be treated with the greatest suspicion.[94]

There were frequent disparities amongst the various sources of information on a crystal structure (journal publication, its supplementary material, the deposited CIF, checkCIF/PLATON and the CSD) concerning Z (the number of molecules in the unit cell) and Z' (the number of molecules in the asymmetric unit). Our analysis led us to regard the CSD as providing the most reliable and consistent source of such information. The underlying problem is that of deciding what exactly is (are) the molecule(s) that is (are) being counted. Seemingly molecular symmetry, molecular association or dimerization, partial occupancy of solvent molecules in the crystal structure, *etc*. all combine to lead to different interpretations of Z and Z'. Standardization of definitions and usage is required. Furthermore we noticed several cases in the metallacycle publications and data of incompatibility between the various CIP chirality indicators[1,13] used for a molecule and the absolute configuration of the crystal-structure determination, the chemical schema, diagrams and crystal-structure drawings.

Study of individual crystal-structure determinations and evaluation studies such as the present one, rely on the crystal data being available in a suitable form. At present only a CIF can fulfil these requirements. However the mere existence of a CIF does not ensure the communication of the relevant values. A good proportion of the available CIFs of the metallacycles produced a considerable number of alerts on running checkCIF/PLATON. Minor modifications to the data treatment, analysis and reporting could have been undertaken by the structure analyst to reduce the number of alerts and to explain the remaining major alerts. In order to improve the current situation the importance of producing a detailed and accurate CIF file, for the benefit of all, must be emphasised at all levels and journals must be encouraged to ensure that referees analyse the CIF files presented in detail. The occurrence of incompatibilities between the CIF and textual, tabular and diagrammatic information in the main body of a publication could suggest that the latter are not being generated automatically from the CIF itself but produced by other means with many possibilities for transcription errors. Files such as the CIF need to be understood and used as the primary source of data from which all other compilations are

treated as secondary presentations. The real electronification of chemical journals has still a long way to go.

Another obstacle to the evaluation of published crystal structures is the lack of the availability of X-ray diffraction intensity data in a computer-readable format. Unfortunately, at present, few journals require this information as part of the publication procedure but as the scope of electronic submissions increases, and computer storage becomes cheaper and more accessible, it is hoped that this situation may change. In two cases described in this review we had to contact the authors directly.

CIF is the only widely-used way of transferring crystallographic data. At the structural level it deals with asymmetric units of atoms, atom-types, atomic positions and interatomic distances and angles. It neither directly provides a way of transmitting molecular information such as molecular symmetry, chemical numbering, bond types, graphical representation of atoms and bonds, chirality, charge, mapping to atoms present in a crystal structure nor of making a relation between a CIF and some other file containing the chemical molecular information. Indeed there does not appear to be any public-domain molecular file structure in common usage in the chemical-publication industry. Consequently molecular software operating from a CIF give variable and contradictory interpretations and representations. The CIP indicators are particularly sensitive to this lack of molecular information.

Racemates

There are several problems with racemates and we have already touched upon one of them in the section above on single-crystal X-ray diffraction. On the chemical side, for none of the bulk compounds nor for any individual single crystals of metallacycles coming from a synthesis which was expected *a priori* to be non-enantiospecific, were measurements of specific rotation, CD or enantioselective chromatography undertaken. Put briefly, there was no chemical confirmation that either the bulk or the single crystal was a racemate. In fact 'racemates' need the same attention to be paid to their characterization as any scalemate or enantiopure compound to avoid crystal structures being described wrongly with a space-group symmetry which is too high. At present checkCIF/PLATON does not attempt to identify such cases. In principle[95] study of the intensity statistics of weak reflections should allow non-centrosymmetric–centrosymmetric ambiguities to be resolved. However until a systematic study of real cases relating physico-chemical to X-ray diffraction evidence is made available, these intensity statistics should not be relied upon in practice. It is the physico-chemical characterization of the sample which is essential. In the metallacycle structures we noticed one structure solution presented as a disordered racemate in a centrosymmetric space group lacking any evidence of the enantiomeric composition of the bulk or single crystal. Upon our prompting, the authors observed that although the intensity statistics of the weak reflections gave a moderate indication that the structure might be non-centrosymmetric, no non-centrosymmetric refinement seemed to them or to us more convincing than the published centrosymmetric one.

Incorrectly naming compounds can hinder use of databases[96] and racemates seem to be particularly prone to misnaming. Frequently the IUPAC recommendations on stereochemistry[11] are not followed. Often authors give no indication in the compound name that it is a racemate and it is policy at the CCDC to carry the compound name given by the author into the CSD. It seems not to be generally realized that conformance to the IUPAC recommendations[11] has repercussions on the choice of which molecules to select as the asymmetric unit of the crystal structure to ensure compatibility. The ones to be chosen are the ones named by the recommendations.

Concluding remarks

This review has presented an evaluated compendium of synthetic methods and routes developed since the early 1970's. The level of development and effort given over to each of these routes is unequal. The extensive amount of work on route **I** and particularly that of route **Id** shows that the initial overriding objective was to establish a quick and efficient means to synthesize scalemic species to be used mostly as catalysts in metal-promoted reactions and in a few cases as stoichiometric chiral resolving agents.[97] It is therefore quite surprising that only a handful of studies dating mostly from the 1970's have looked at the enantioselective metallation of racemic planar-prochiral ligands as defined by route **Ia**. From this standpoint, the recent work by Richards *et al.* is a remarkable event[28] which might trigger some renewed interest in this important reaction. More generally, if routes **Id**, **II** and **IV** offer a convenient and practical means to synthesize scalemic complexes, knowledge of the underlying stereochemical and mechanistic aspects is still lacking in most cases. Molecular-engineering approaches, such as the one used in the synthesis and application of molecular gears,[55,56] hold out promise. It has also to be noted that few reports have been devoted to *ortho*-metallation by metal complexes of geometries different than *SP*-4. This is a challenging topic which should certainly deserve attention in the future, as planar-chiral octahedral *OC*-6 and pseudo-tetrahedral *T*-4 planar-chiral metallacycles may readily find applications in chemistry and at its boundaries with other disciplines. Characterization of scalemic complexes can nowadays call on a large variety of very powerful analytical techniques but these are still not systematically used by experimentalists to assess enantiomeric excess. By itself structure determination by X-ray diffraction is insufficient to determine the enantiomeric purity of a given batch of scalemate with consequences in absolute-configuration determination. Our critical study of the synthetic and analytical aspects of the synthesis of scalemic SPCMCs has convinced us that chemists and crystallographers have much to gain by raising the standard of structure determination.

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